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Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: Results from the Reveal LINQ Usability Study

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BACKGROUND For clinicians, confidence in atrial fibrillation (AF) episode classification is an important consideration when electing to use insertable cardiac monitors (ICMs).

OBJECTIVE The purpose of this study was to report on the improved AF detection algorithm in the Reveal LINQ ICM.

METHODS The Reveal LINQ Usability Study is a nonrandomized, prospective, multicenter trial. The ICM has been miniaturized, uses wireless telemetry for remote patient monitoring, and its AF algorithm includes a new p-wave filter. At 1 month post-device insertion, Holter monitor data were collected and annotated for true AF episodes ≥2 minutes, and performance metrics were evaluated by comparing Holter annotations with ICM detections.

RESULTS The study enrolled 151 patients (age 56.6 ± 12.1, male 67%). Reasons for monitoring included AF ablation or AF management in 81.5% (n = 123), syncope in 12.6% (n = 19), and other indications in 5.9% (n = 9) of patients. Of the 138 patients with an analyzable Holter recording, a total of 112 true AF episodes were identified in 38 patients (27.5%). The overall accuracy of the ICM to detect durations of AF or non-AF episodes was 99.4%, and the AF burden measured by the ICM was highly correlated with the Holter (Pearson coefficient 0.995).

CONCLUSION The new AF detection algorithm in the Reveal LINQ ICM accurately detects the presence or absence of AF. Additionally, it showed high sensitivity in detecting AF duration in patients with a history of intermittent and symptomatic AF.

KEYWORDS Atrial fibrillation; Insertable cardiac monitor; Diagnosis; Long-term monitoring

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Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that affects millions of people worldwide, with an estimated 2.2 million people in the United States and 4.5 million in the European Union.[1] The causes of AF are numerous, varied, and multifactorial, and the symptoms range from nonexistent to severe (e.g., fatigue, palpitations, dyspnea, hypotension, syncope, heart failure).[2] AF is associated with an increased incidence of frequent hospitalizations, hemodynamic abnormalities, thromboembolic events (stroke and transient ischemia attack), and heart failure resulting in significant morbidity and mortality.[3,4] AF can be distinguished and classified as paroxysmal, persistent, long-standing persistent, or permanent based on the frequency and duration of

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episodes. It has been suggested that the adverse effects of AF have been correlated to episode duration and to the amount of time during which the heart is in AF, the so-called AF burden.[5–7] Therefore, such a characterization is clinically relevant with regard to the selection and outcome of the therapeutic approach.

Diagnosis of AF is usually based on the patient's clinical history and physical examination, and is confirmed by ECG. Patients suffering from symptoms have an increased likelihood that AF is diagnosed. However, studies have shown poor correlation between symptoms and occurrence of AF.[8,9] Because medical management of AF patients is currently primarily based on symptoms, there is concern that asymptomatic, undetected events of AF could expose patients to increased risk of ischemic stroke and thromboembolic events.[10] External cardiac monitors, such as Holter monitors and mobile cardiac telemetry, are among the most frequently used tests in cardiology. However, the yield of short-term monitoring is limited, and patient compliance with prolonged external monitoring is inversely proportional to the prescribed duration. Instead, continuous monitoring of AF is clearly superior and more efficient than any other method.[5,11]

Insertable cardiac monitors (ICMs) with dedicated AF algorithms have been introduced into clinical practice for the diagnosis and monitoring of AF in various clinical applications, such as recurrent AF diagnosis after surgical[12] or catheter AF ablation,[9,13,14] and cryptogenic stroke.[15,16] ICMs have been shown to have high accuracy in detecting AF burden using incoherence of R-R intervals over a period of time,[17,18] and high diagnostic accuracy due to the ability of long-term continuous 24/7 monitoring, particularly in patients with paroxysmal or asymptomatic AF.[12,19] Besides the improved AF algorithm,[18,20] the Reveal LINQ ICM is only 7 × 45 × 4 mm in size, making it 87% smaller than its predecessor. It has improved electrode coating and is inserted using a standardized technique that forms a tight pocket to improve the quality of the ECG signal. Our hypothesis is that the new p-wave enhanced AF algorithm should contribute to improve the quality of the signal and the performance of the device. Therefore, the main objective of this study was to assess the AF diagnostic, duration detection, and episode detection accuracy of the ICM.

Methods

Study design

The Reveal LINQ usability study is a prospective multicenter single-arm clinical study (ClinicalTrials.gov Identifier: NCT01965899). All patients provided written informed consent, and the study protocol was reviewed and approved by the Human Research Ethics Committee of each participating institution. The study was prospectively designed to have 2 phases, the first enrolling 30 patients with any indication for an ICM and the second enrolling 121 patients with a documented history of AF and ablation candidates.

Data collection

Patients were followed for 1 month after insertion of a Reveal LINQ ICM (Medtronic plc, Dublin, Ireland). Data were collected at baseline, insertion, and 1-month follow-up visit. At the 1-month follow-up visit, Holter monitoring was performed for 24 hours, during which the ICM continuously uploaded ECG and detected episode information to the Holter. The Holter monitor also stored 2 leads of surface ECG information, which was used to annotate the Holters along with the ECG recorded by the ICM. After the 1-month follow-up visit, patients were instructed to complete a manual transmission of the data stored in their devices at least once a month.

Device and AF algorithm

The AF detection algorithm is based on both an R-R interval and a P-wave evidence score. The P-wave evidence score reduces inappropriate AF detections in the original R-R interval pattern–based algorithm and leverages the evidence of a single P wave between two R waves using morphologic processing of the ECG signal. The algorithm makes a rhythm classification every 2 minutes. When an episode is detected at the end of a 2-minute detection period, the first 2 minutes of the ECG from that episode are stored in the device. The device can store up to 14 AF episodes with ECG; afterward, the earliest episode is overwritten by newer episodes. The longest AF episode detected (≥10 minutes) is always preserved in memory until a full manual transmission is done. Every night, the ICM wirelessly transmits the last 10 seconds of the 2-minute ECG segment for the longest episode of the day. In addition to the nightly wireless transmissions, the patient can manually transmit the full information on all episodes stored in memory at any given time.

Holter and episode annotation

Two reviewers interpreted both channels of the surface ECG and the Reveal LINQ ECG to annotate for the presence of atrial tachycardia (AT) or AF during the 24-hour recordings. All episodes > 10 seconds in duration were annotated during the review process. Segments in which the Holter was not interpretable on all 3 ECGs because of noise or motion artifact were marked as uninterpretable segments. The reviewers were blinded to the device episode detection information during the annotation process. No episodes recorded by the Holter were overwritten.

Statistical analysis

The baseline characteristics of all patients enrolled in the study are reported along with the indication for the ICM. The Holter annotations for true AF episodes were compared with the AF detections from the ICM device (Figure 1). Only true AF episodes that were annotated as ≥2 minutes in duration were used for data analysis. AT or atrial flutter episodes, uninterpretable segments, or periods with missing telemetry signals from the ICM were excluded from the data analysis.

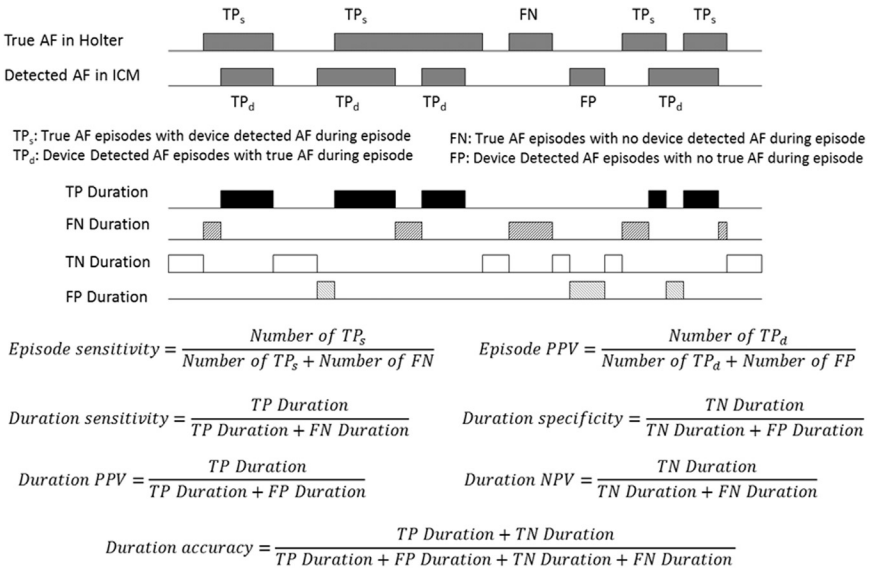

Figure 1 Definitions used for performance metrics. Definitions of true positive (TP), false positive (FP, false negative (FN), and true negative (TN) episode and duration used for computation of episode and duration detection performance metrics. AF = atrial fibrillation; ICM = insertable cardiac monitor.

Patient-, episode-, and duration-based standard performance metrics (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy) were evaluated by comparing Holter annotations with ICM detections. Duration-based metrics were calculated based on the overlap of the duration of time between periods annotated as AF and periods detected as AF by the ICM (Figure 1). Patient-based metrics, also called diagnostic metrics,[20] evaluate the ability of the ICM to detect the presence or absence of AF within a patient and were calculated as shown in Figure 2.

Episode-based metrics evaluated the proportion of true episodes and detected episodes that were appropriately identified. Generalized estimating equation estimates, which adjust for multiple episodes in a patient, and the possible correlation of AF detection performance on episodes from the same Holter recording, were also computed for episode detection sensitivity and PPV. Episode detection NPV and specificity could not be computed because a true negative episode cannot be defined. The AF burden determined by the ICM was compared with the reference AF burden by calculating the Pearson correlation coefficient between the paired measurements. The study required all inserted devices to be programmed at nominal settings. Results are reported for all patients "as programmed" during the Holter period.

Results

The study enrolled a total of 151 patients, of whom 1 patient was exited before 1 month without any Holter monitoring. The baseline characteristics of the enrolled patients are listed in Table 1. Mean age of patients was 56.6 ± 12.1 years, and 66.9% were male. There was a history of stroke or transient ischemic attack in 8.6%, paroxysmal AF in 66.9%, persistent

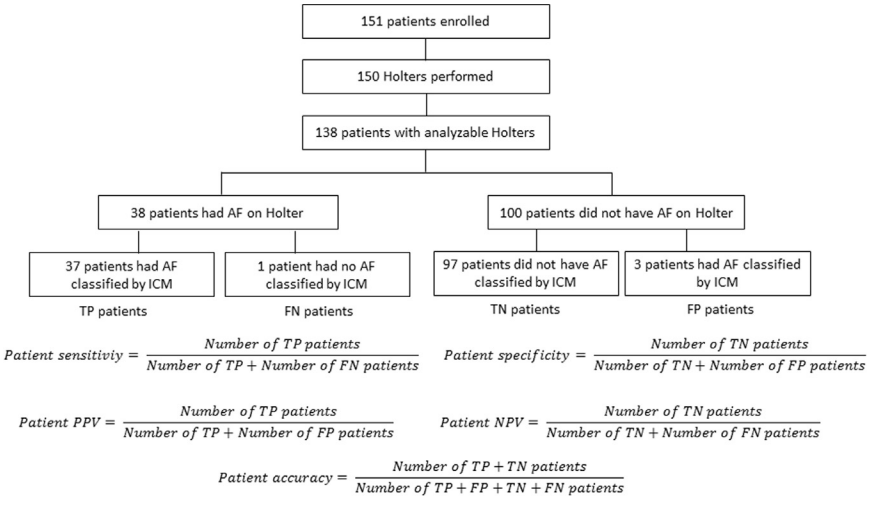

Figure 2 Definitions used for patient-based metrics. Definitions of true positive (TP), false positive (FP), false negative (FN), and true negative)TN) patients were determined by diagnosis based on Holter results compared to insertable cardiac monitor (ICM). AF = atrial fibrillation.

Table 1 Baseline demographics of patients enrolled in the study

Patient characteristics	Enrolled subjects (N = 151)
Gender	
Male	101 (66.9%)
Female	50 (33.1%)
Age (mean ± SD)	56.6 ± 12.1
Primary indication for implant	
Syncope	19 (12.6%)
Palpitations/suspected AF	7 (4.6%)
Cryptogenic stroke	1 (0.7%)
AF ablation monitoring/AF management	123 (81.5%)
Other	1 (0.7%)
Supraventricular tachycardia	130 (86.1%)
Atrial fibrillation	126 (83.4%)
Paroxysmal	101 (66.9%)
Persistent	27 (17.9%)
Permanent	2 (1.3%)
Atrial flutter/atrial tachycardia	24 (15.9%)
Stroke/transient ischemic attack	13 (8.6%)
Bradycardia–tachycardia syndrome	1 (0.7%)
Sinus node dysfunction	17 (11.3%)

Values are given as no. (%) unless otherwise indicated.
AF = atrial fibrillation.

AF in 17.9%, atrial flutter or AT in 15.9%, and brady–tachy syndrome in 0.7%. The indication for an ICM was syncope in 19 patients (12.6%), cryptogenic stroke in 1 (0.7%), palpitations or suspected AF in 7 (4.6%), and AF ablation or AF management in 123 (81.5%). A Holter was performed in 150 patients, of which 141 were suitable for analysis after excluding recordings with technical issues, such as loss of telemetry or inability to process the data. After exclusion of recorded segments with missing telemetry or uninterpretable surface ECG and periods of AT, a total of 3188 hours of valid recording time from 138 patients were analyzed, yielding a mean valid recording time of 23.1 hours per patient. True AF was observed in 38 of the 138 patients included in the data analysis, yielding a total of 112 true AF episodes ≥2 minutes and 450 hours of AF.

The ICM correctly identified 37 of the 38 patients with Holter-detected AF (diagnostic sensitivity of 97.4%) and 97 of the 100 patients without AF according to Holter analysis (diagnostic specificity of 97.0%). On the other hand, the ICM algorithm identified a total of 40 patients with AF, of whom 37 had Holter-detected AF (diagnostic PPV of 92.5%), and 98 patients without AF, of whom 97 also showed absence of AF by Holter (diagnostic NPV of 99.0%).

Table 2 lists ICM performance results, expressed as gross and patient averages. For every 100 hours of true AF, the algorithm correctly detected 98.4 hours as AF (gross duration sensitivity of 98.4%), and for 100 hours of normal sinus or other non-AF rhythms the algorithm inappropriately detected 0.5 hours as AF (gross duration specificity of 99.5%). The overall duration or AF burden accuracy, defined as the proportion of total correctly identified duration, was 99.4%. The AF burden detected by both ICM and Holter showed a high Pearson correlation coefficient of 0.995 (Figure 3). The ICM detected 109 of 112 episodes of true AF ≥2 minutes in duration (gross episode sensitivity of 97.3%), and of all 365 episodes detected by the algorithm across patients, 273 of them were true AF (gross episode PPV of 74.8%). Furthermore, for 100 patients with ICM detected episodes, 90 had at least 1 episode with true AF (patient averaged episode PPV of 90.4%).

During the Holter monitoring period, 5 patients (3.6%) had ≥1 inappropriate ICM-detected episode. Two patients (1.4%) accounted for nearly 92.4% of inappropriately detected episodes, whereas 2 patients had both appropriate and inappropriate detections. A total of 92 inappropriately detected episodes contributed to only 12.2 hours of detected duration, with a median episode duration of 4 minutes. For all detected episodes (≥2 minutes), the "gross" episode PPV was 74.8% and progressively improved to 83.8%, 97.1%, and 100% for detected episodes ≥6 minutes, 1 hour, and 6 hours respectively. The gross episode sensitivity improved from 97.3% for true episodes ≥2 minutes to 98.7%, 100.0%, and 100% for episodes 6 ≥minutes, 1 hour, and 6 hours respectively.

During the monitoring period, the Holters detected 134 AF episodes in 11 patients that were ≥30 seconds and <2 minutes. Of these 134 episodes, 17 overlapped with an episode indicated by the device and therefore were detected by the ICM. One patient had only 1 episode between 30 seconds and <2 minutes but no other episodes. Another patient had 2 episodes between 30 seconds and 2 minutes, but no episodes >2 minutes.

Discussion

For patients with diagnosed AF, guidelines exist to initiate therapy both with heart rate control and/or antiarrhythmic therapy, whereas in patients with stroke risk factors, anticoagulation treatment is recomended.[21] However, several factors can hinder AF diagnosis, including "silent AF," poor correlation between patient symptoms and AF episodes, intermittency, and brevity of episodes (e.g., paroxysmal AF), as well as the short duration of standard ECG monitoring. Several studies have effectively demonstrated a substantial incidence of previously undiagnosed AF in patients with cryptogenic stroke, and the presence and time course of recurrent AF after ablation by using an ICM.[9,13–16,22] A relationship between relatively short episodes of AF and an increased risk for thromboembolism has been shown as well.[7,23] In fact, one of the main challenges clinicians have is accurately identifying patients with AF and quantifying AF burden in order to implement the most appropriate therapeutic regimen and prevent complications such as stroke. The goal of ICMs is to overcome these challenges.

In this study, we measured the performance of the new p-wave enhanced AF detection algorithm of Reveal LINQ in a multicenter clinical trial for remote monitoring of patients with known or suspected arrhythmias. We report positive results with regard to (1) high sensitivity in detecting the presence of AF; (2) high specificity and PPV; (3) high reliability in confirming freedom from AF, as shown by the

Table 2 Duration and episode detection performance during the Holter monitoring period

Performance metrics	Reveal LINQ*	Reveal XT†
Patients with analyzable Holter	138	206
Duration-based results		
Sensitivity (%)		
Gross	98.4	98.1
Patient average	93.7	89.0
Specificity (%)		
Gross	99.5	98.5
Patient average	99.6	91.3
Positive predictive value (%)		
Gross	97.2	91.9
Patient average	90.6	75.2
Negative predictive value (%)		
Gross	99.7	99.7
Patient average	96.4	97.1
Accuracy (%)		
Gross	99.4	98.5
Patient average	99.4	98.5
Episode-based results		
Episode sensitivity (%)		
Gross	97.3	85.2
Patient average	97.2	87.9
GEE estimate (95% CI)	97.1 (97.1–97.2)	88.2 (82.0–92.5)
Episode positive predictive value (%)		
Gross	74.8	38.8
Patient average	90.4	73.6
GEE estimate (95% CI)	90.4 (77.6–96.2)	73.5 (64.5–81.0)
Patient-based results (%)		
Sensitivity	97.4	96.1
Specificity	97.0	85.4
Positive predictive value	92.5	79.3
Negative predictive value	99.0	97.4
Accuracy	97.1	89.3

CI = confidence interval; GEE = generalized estimating equation.

*Detection performance data from LINQ Usability Study.

†Detection performance data from XPECT Study.[17]

NPV; and (4) accurate assessment of AF burden. The Reveal LINQ correctly detected 98.4% of the total AF duration and 99.5% of the total normal sinus rhythm (Table 2). In addition, at the episode level, 74.8% of the detected AF episodes were correctly classified

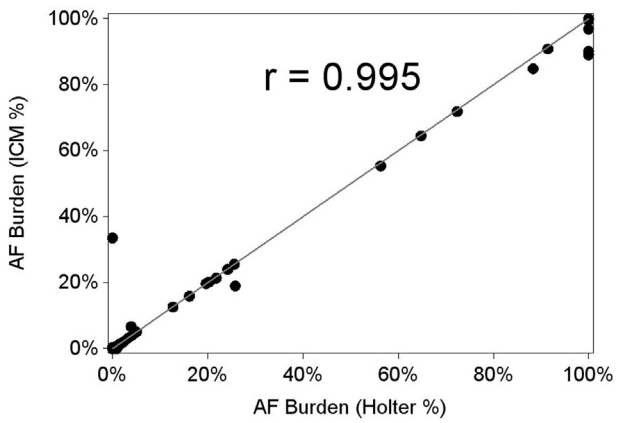

Figure 3 Comparison of atrial fibrillation (AF) burden by insertable cardiac monitor (ICM) and Holter. AF burden measured by the ICM compared with AF burden calculated from the annotated Holter recording for all patients. r = Pearson correlation coefficient.

(Table 2). The performance numbers are significantly better compared to the previous generation device (Reveal XT),[17,20] showing a clear improvement in terms of AF detection capabilities, particularly in reducing the number of false-positive events (Table 2).

The ability of the device to keep in storage the longest AF episode detected (≥10 minutes) between 2 full manual transmissions and also wirelessly transmit the longest episode of the day at midnight is an important feature, based on the higher accuracy of the device for longer episodes. Thus, there is a higher likelihood that a true AF episode will be stored for review without being overwritten. Based on these data, from a practical standpoint, physicians can confidently diagnose AF via either the full manual interrogation or the automatic transmission. The decision to take clinical actions for shorter or longer burden is at the physician's discretion. Our results showed an AF burden accuracy of 99.4% and an improvement of PPV with longer episode duration.

In addition to our results, the reduced size, improved electrode coating, and simplified insertion procedure that forms a tight pocket and improves the quality of the ECG signal position this new ICM as a reliable tool for diagnosis

of patients with asymptomatic AF and for long-term management of patients with a known history of intermittent and symptomatic AF.

Study limitations

One of the main limitations of this study is that the comparison between the Holter annotations and the device-detected episodes is limited to 24 hours. In addition, only AF episodes ≥2 minutes in duration were included in the analysis; therefore, the study results are not applicable to episodes that are shorter than 2 minutes. The study also focused on AF detection and did not address ICM performance with regard to AT and atrial flutter detection. Finally, most patients in the relatively small study cohort have a known history of AF, leading to a high disease prevalence. PPV and NPV values will differ in patient populations with a different disease prevalence. However, sensitivity and specificity will remain unaffected by disease prevalence.

Conclusion

The new AF detection algorithm in the Reveal LINQ ICM showed an improvement in terms of AF detection capabilities compared to its predecessor, showing high sensitivity, specificity, and PPV values. Reveal LINQ represents a valuable diagnostic tool in patients with suspected AF.

Acknowledgments

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