Comparison of the Effect of Atrial Fibrillation Detection Algorithms in Patients With Cryptogenic Stroke Using Implantable Loop Recorders

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Occult atrial fibrillation (AF) can be the underlying cause for cryptogenic stroke (CS). Implantable loop recorders (ILRs) have become an important tool for long-term arrhythmia monitoring in CS patients. Office-based ILR implantation by nonelectrophysiologist physicians is increasingly common. To report the real world diagnostic yield and accuracy of remote ILR monitoring in high risk CS patients, we retrospectively analyzed 145 consecutive patients with CS who underwent ILR implantation between October 2014 and October 2018 at New York University Langone Health. A certified device technician and an electrophysiologist adjudicated all transmissions. The yield and accuracy of Reveal LINQ Intra Cardiac Monitor (ICM), a fourth generation device, was compared to that of TruRhythm Detection algorithm (fifth generation device). AF was diagnosed in 17 patients (12%) over a mean follow-up of 28 ± 12 months. The median time to diagnosis was 7.4 ± 21.3 months. A total of 1,637 remote transmissions (scheduled- and auto-triggered alerts: 756; patient-triggered: 881) were adjudicated. The positive predictive value for AF episodes in the scheduled interrogations increased from 4% in the Reveal LINQ ICM to 16% in the TruRhythm LINQ. Of 881 patient-triggered transmissions, none were found to be true positive. In the Reveal LINQ ICM, for scheduled transmissions, primary causes of false positive (FP) were atrial ventricular premature complexes (80%). In the TruRhythm LINQ, for scheduled transmissions, primary cause of FP were T-wave over-sensing (87%). In conclusion, the real world diagnostic yield of ILR for patients with CS remains suboptimal, with at least 84% of AF alerts being FP. Patient-riggered events did not correlate with arrhythmia and the necessity of patient triggering in this population should be questioned. Expert interpretation of recordings is critical to assure accurate diagnosis.
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Cryptogenic stroke (CS) represents 10% to 40% of ischemic strokes and is associated with significant morbidity and mortality and high risk of recurrence.[1−3] Thus, it is imperative to identify a definite cause and initiate treatment accordingly. Occult atrial fibrillation (AF) is an important cause of CS, and it is suspected to cause 1 of 3 CS cases.[4−6] Results from the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) study showed that monitoring with an insertable cardiac monitor (ICM) was superior to conventional follow-up for detecting AF after CS or transient ischemic attack (TIA) and that AF detection rate increased with the duration of monitoring.[7] The 2019 Heart Rhythm Society focused updated guidelines for the management of patients with atrial fibrillation recommend that in patients with cryptogenic stroke in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF (Class IIa; Level of Evidence B).[8] The diagnostic yield of ILR was recently demonstrated to be suboptimal, despite an algorithm update to the TruRhythm algorithm.[9] Even in the subpopulation of CS, where AF is relatively prevalent,[10] questions remain regarding the diagnostic yield of ILRs. In the present study, we aimed to investigate the real world diagnostic yield and accuracy of ILR based monitoring in high risk CS patients.

Methods

This is a retrospective study performed at a large tertiary care center (NYU Langone Health, New York, New York). We reviewed 145 consecutive adult patients who underwent implantation of ILRs at NYU Langone Health, between October 2014 and October 2018 for AF detection for the indication of CS. Medical records were reviewed to obtain epidemiologic characteristics, indications for implantation, tests done prior to the implantation of the ILR, and the type of ILR implanted (Medtronic Reveal XT/Medtronic Reveal LINQ, Medtronic, Minneapolis, Minnesota). Complications related to the implantation were recorded. The diagnostic

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information from the ILR leading to change in management was obtained during follow−up. Follow-up started on the day of implantation. The closing date of follow-up was October 31, 2019. The study was reviewed and approved by the Institutional Review Board in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, with a waiver of informed consent.

Loop recorder implants were all performed in an electrophysiology lab setting under sterile conditions with local anesthetic only, unless requested otherwise by the patient. The device was programmed according to the indication-specific nominal programming as suggested by the manufacturer for CS.[11]

All the implanted ILR devices were enrolled into the Carelink remote monitoring program (CareLink, Medtronic, Inc.) with automatic arrhythmia detection programs and P sense algorithms switched "ON" when available. All the records of ILR−detected abnormal rhythm and symptom episodes transmitted by the patient are evaluated by a device clinic professional with physician oversight. Specifically, our center employs full−time professionals (technicians, nurse practitioners) who respond to alerts when remote transmissions are received under the supervision of an attending cardiac electrophysiologist. Categorical variables were reported as percentages, and continuous variables were reported as mean and standard deviations. Continuous variables were compared between groups using analysis of variance (ANOVA) and categorical variables were compared using Chi-square test or Fisher's exact test. Kaplan-Meier curve and log rank test were used to describe mortality during the follow-up period. The length of follow up was described using the reverse Kaplan-Meier to generate median follow-up times censoring method interval were reported. All statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, Version 25.0, IBM Corp, released 2017. Armonk, New York) and R software (version 3.3.3, R Foundation for Statistical Computing, released 2017, Vienna, Austria).

Results

The baseline characteristics of the study cohort are presented in Table 1. A total of 145 patients were enrolled. The median (IQR) age of patients was 67 (53 to 70) years, and 83 (57%) were men. Pre-enrollment screening for atrial fibrillation consisted of Holter monitoring in 44% of patients and telemetry in 56% of patients. Follow-up duration was 28 ± 12 months. At study closure, all 145 patients had completed 12-months follow-up, 88 (61%) patients had completed 24-months follow-up, and 49 (34%) patients had completed 36-months follow-up.

AF was diagnosed in 17 patients (12%) with a median time to diagnosis of 7.4+ 12.3 months. AF detection increased progressively throughout the study and was 4.2-fold at 36 months as compared the first month (Figure 1). At 1 month, the rate of AF detection was 2.8% (n = 4); at 6 months, 5.5% (n = 8); at 12 months, 7.6% (n = 11); at 24 months, 9% (n = 13); and at 36 months, 11.7% (n = 17). Overall, 1,637 remote transmissions (scheduled- and auto-triggered alerts: 756; patient-triggered: 881) were adjudicated. The overall proportion of false positive (FP) transmissions was 96% (1,570/1,637). The proportion of FP patient-triggered transmissions was 100% (881/881). The cause and distribution of FP alerts are presented in Table 2 and Figure 2. A total of 891 transmissions were reviewed from patients with ILRs with TruRhythm algorithm (scheduled- and auto-triggered alerts: 307; patient-triggered: 584). The positive predictive value for AF episodes in the scheduled interrogations increased from 4% in the Reveal LINQ insertable cardiac monitor to 16% in the TruRhythm LINQ.

Table 1
Baseline demographic and clinical characteristics

Variable	(n = 145)
Stroke	120 (83%)
TIA	25 (17%)
Age (years)	67 ± 13
Men	83 (57%)
Coronary artery disease	37 (26%)
Valvular heart disease	12 (8%)
Myocardial infarction	6 (4%)
Heart failure	9 (6%)
Nonischemic cardiomyopathy	5 (3%)
Other cardiovascular disease	21 (14%)
Hypertension	106 (73%)
Diabetes	39 (27%)
CHADSVASC	4.6 ± 1.6
Left atrial volume Index (ml/m^2)	29 ± 9
Monitoring prior to ILR	64 (44%)
NIHSS score	4 ± 7 (62)
Time with ILR, months	28 ± 12

In the overall cohort, ILR findings resulted in an "actionable event" in 11 (5.2%) patients, for whom oral anticoagulation was initiated based on ILR findings. In 27 patients (18.5%) anticoagulant was started empirically before ILR implantation. Four patients had recurrent TIA, in none of them this event triggered initiation of anticoagulant and ILR interrogation was negative in all of them. Seven patients had recurrent Cerebrovascular accident − in 1 patient the ILR demonstrated brief AF episodes (up to 2 minutes), and anticoagulant was started. In all other 6 patients, the etiology was determined to be small vessel ischemic disease based on brain imaging findings and cardio embolism was thought to be less likely given negative ILR interrogation (Figure 3).

Discussion

With recent changes in reimbursement policy, ILRs have become a popular tool for long-term arrhythmia monitoring, and office-based ILR implantation by nonelectrophysiologist physicians are increasingly performed.[12] The present study provides evidence that in a "real-world" academic hospital setting with comprehensive device monitoring workflow, the diagnostic yield of ILRs for CS is lower than previously reported. Two pivotal randomized studies explored long-term monitoring versus shorter-term monitoring after cryptogenic stroke: CRYSTAL-AF[7] and EMBRACE.[13] Both studies showed that long-term monitoring is significantly more sensitive than standard arrhythmia monitoring for AF identification. In the CRYSTAL-AF,

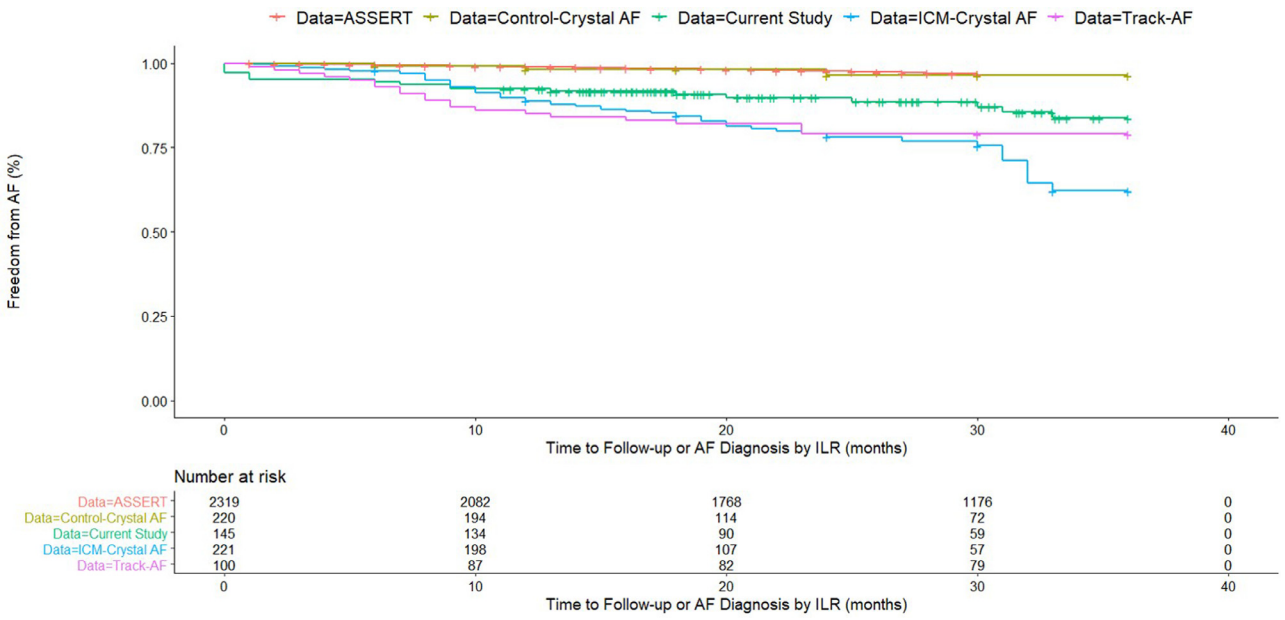

Figure 1. Kaplan Meier freedom from AF. The present study (green line) is plotted against the previous studies for comparison. (Color version of figure is available online.)

event was defined by >30 seconds of AF and was detected in 8.9%, 12.4%, and 30.0% of patients in the ILR arm and in 1.4%, 2.0%, and 3.0% of patients in the standard-of-care monitoring arm at 6, 12, and 36 months, respectively. In the EMBRACE study, the primary end point (detection of AF ≥30 seconds within 90 days) was met in 16.1% and 3.2% of patients in the ILR and control arms, respectively. In our cohort, AF was diagnosed at a lower rate of11.7% over a mean follow-up of 28 ± 12 months (Figure 1). To put this in perspective, when implanted for the diagnosis of unexplained syncope, 36% of patients experienced a recurrent event within 1 year.[14]

The lower AF detection rate in our study despite relatively high CHADS2VSAC2 score may be partially explained by the higher rate of TIA (vs stroke) indication for monitoring, which was 17% in our study versus 9% in CRYSTAL-AF.

The improved performance of the TruRhythm algorithm, with a corresponding significant decrease in false classification of sinus tachycardia is largely due to improved AF detection algorithm, with enhanced P-wave evidence score based on P-P interval regularity in addition to incoherence of R-R intervals.

Nevertheless, the incidence of FP during remote monitoring with nominal settings remains significant, ranging from 84% to 98% depending on the device generation and type of alert (scheduled versus patient triggered). Notably, none of the patient triggered transmissions, which were responsible for 54% of total transmissions, was found to be true positive AF nor other sustained arrhythmia. Adjudication of ILR transmissions require a considerable time commitment from electrophysiologists and device clinic personnel but is necessary to prevent misdiagnosis and potential errors in clinical management. In light of this, clinicians should be aware that although ILR implantation is a relatively noncomplex procedure, expert interpretation of the data is paramount. To partially mitigate the substantial volume of unrevealing readings, the exclusion of patient

Table 2
Reasons for false positive transmission during remote monitoring

Reason for FP	Reveal LINQ (n = 746)	TruRhythm LINQ (n = 891)	p Value
Scheduled interrogation			
Signal dropout/under sensing	0	50 (19%)	0.004
Atrial/ventricular premature complexes	346 (80%)	20 (8%)	0.0216
Over sensing (T waves)	0	224 (87%)	0.007
Noise	5 (1%)	6 (2%)	0.7
Sinus tachycardia	81 (19%)	2 (1%)	0.00052
Patient triggered alerts			
Signal dropout/under sensing	2 (0)	0	1
Atrial/ventricular premature complexes	78 (26%)	336 (58%)	0.0012
Over sensing (T waves)	0	0	1
Noise	0	23 (4%)	0.2
Sinus tachycardia	217 (73%)	225 (39%)	0.00062

Values are given as n (% of total FP) unless otherwise indicated.
n = Number of transmissions adjudicated.

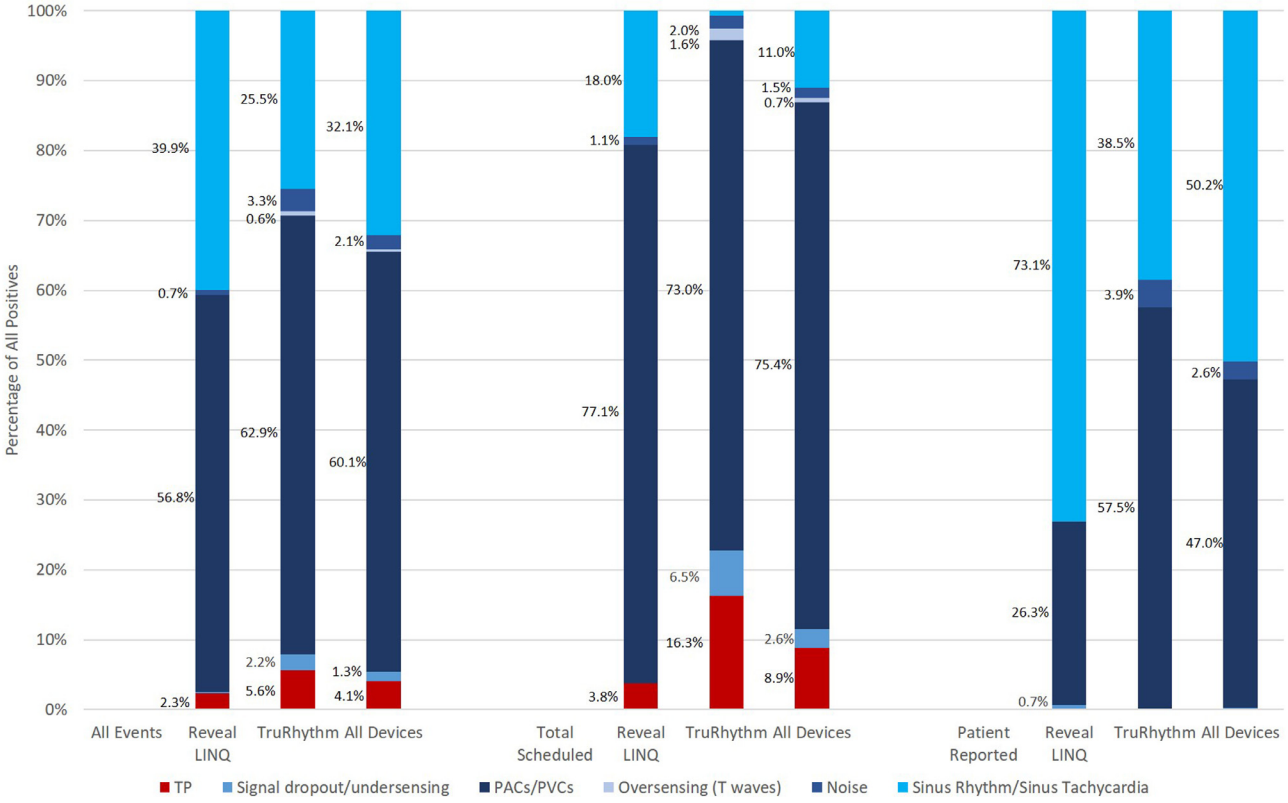

Figure 2. Events recorded by ILR in patients with CS. Events are stratified by the detection algorithm and by scheduled versus patient trigger.

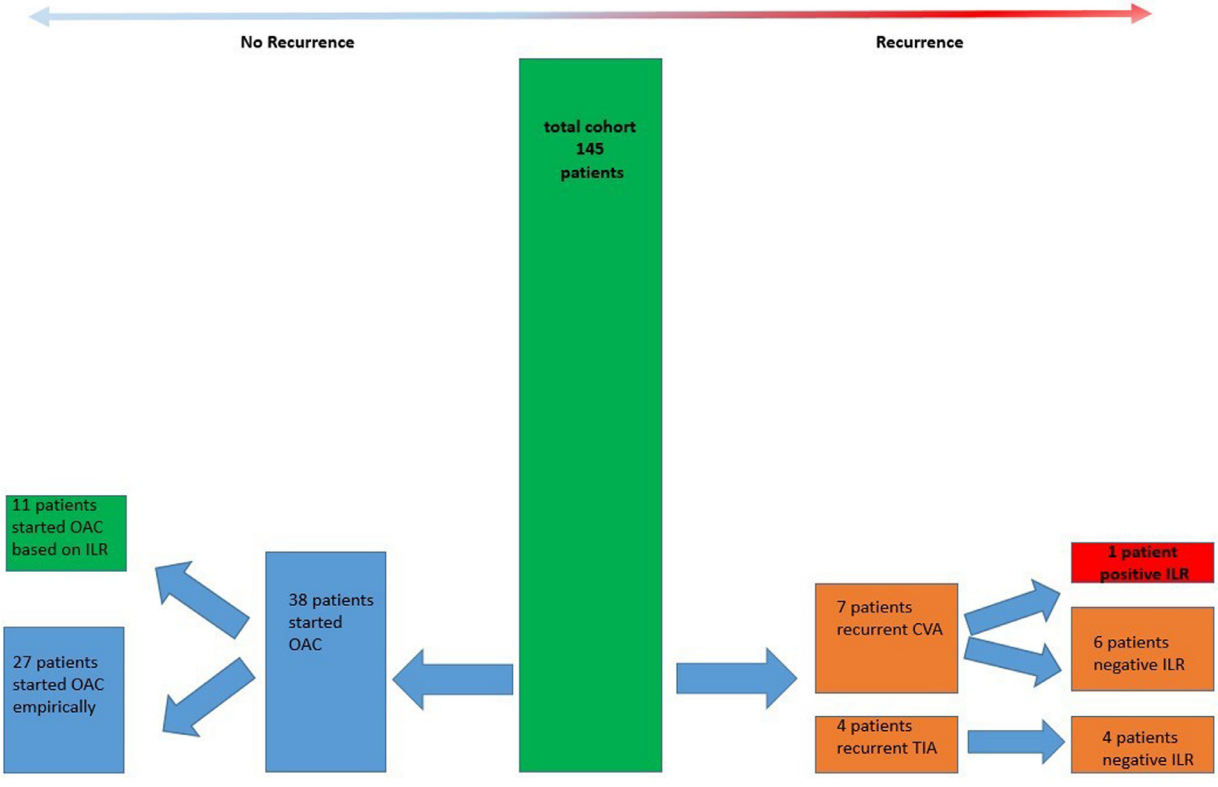

Figure 3. Graphic presentation of management changes and effectiveness of ILR in the current study.

triggering as a default in cases where CS is the sole indication for ILR implantation can be considered.

Our study has several limitations. This is a single-center, observational, retrospective uncontrolled study. Because of its retrospective nature, the study is subject to selection bias, and its results imply association, not cause and effect.

In conclusion, despite these limitations, this real world study from a high-volume device clinic provides insights into the limitations of remote monitoring with ILRs. The diagnostic yield of ILR for patients with CS remains suboptimal, and skilled adjudication of high volume ILR transmissions remains critical to avoid inappropriate treatment.

Disclosures

The authors have no conflicts of interest to disclose.

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