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Performance of an implantable automatic atrial fibrillation detection device: impact of software adjustments and relevance of manual episode analysis

Charlotte Eitel†, Daniela Husser†, Gerhard Hindricks, Manuela Frühauf, Sebastian Hilbert, Arash Arya, Thomas Gaspar, Ulrike Wetzel, Andreas Bollmann, and Christopher Piorkowski*

Heart Center, Department of Electrophysiology, University of Leipzig, Strümpellstrasse 39, 04289 Leipzig, Germany

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Aims Implantable loop recorders (ILRs) with specific atrial fibrillation (AF) detection algorithms (ILR-AF) have been developed for continuous AF monitoring. We sought to analyse the clinical value of a new AF monitoring device and to compare it to serial 7-day Holter.

Methods and results Sixty-four consecutive patients suffering from paroxysmal AF were included in this prospective analysis and received an ILR-AF. Manual electrogram analysis was performed for each automatically detected episode and each was categorized into one of three possible diagnoses: 'no AF', 'definite AF', and 'possible AF' (non-diagnostic). Analysis was performed separately before and after a software upgrade that was introduced during the course of the study. A subgroup of patients (51 of 64) underwent AF catheter ablation with subsequent serial 7-day Holter in comparison with the ILR-AF. A total of 333 interrogations were performed (203 before and 130 after software upgrade). The number of patients with AF misdetection was significantly reduced from 72 to 44% following the software upgrade ($P = 0.001$). The number of patients with non-diagnostic interrogations went from 38 to 16% ($P = 0.001$). Compared with serial 7-day Holter, the ILR-AF had a tendency to detect a higher number of patients with AF recurrences (31 vs. 24%; $P = 0.125$).

Conclusions The rate of AF detection on ILR-AF may be higher compared with standard AF monitoring. However, false-positive AF recordings hamper the clinical value. Developements in device technology and device handling are necessary to minimize non-diagnostic interrogations.

Keywords Atrial fibrillation • Implantable loop recorder • ECG monitoring

Introduction

Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia, resulting in significant morbidity and cost to the healthcare system.[1] Asymptomatic or silent arrhythmia is a frequent condition in patients suffering from AF.[1,2] It is observed in a substantial number of patients suffering from cryptogenic stroke.[3] Due to the inability to reliably detect asymptomatic AF recurrences,

† These authors contributed equally.

*Corresponding author. Tel: +49 341 865 1410; fax: +49 341 865 1460, Email: piorkowskic@yahoo.de

clinical and scientific uncertainty remains for fundamental treatment decisions such as rate vs. rhythm control or the need for oral anticoagulation.[4]

Several methods have been described to improve rhythm monitoring in AF patients.[3,5–7] In general, these data have shown an increased AF detection rate with longer monitoring durations.[6,8] However, even with serial 7-day Holter electrocardiograms (ECGs) or daily plus symptom-activated transtelephonic ECG monitoring, it is estimated to detect only ~70% of all recurring AF episodes.[9]

To provide continuous AF rhythm monitoring, implantable leadless loop recorders with specific AF detection algorithms (ILR-AF) have been developed. In patients with paroxysmal AF, the XPECT trial evaluated the detection performance of an ILR-AF (Reveal XT) against a specialized surface ECG Holter device over a short monitoring period of 46 h. The results of the study indicated a high sensitivity of 96.1% for detecting AF. However, specificity (85.4%) was limited by falsely stored AF episodes in 15% of the patients.[10]

The purpose of this study was to analyse the performance of the implantable continuous AF detection device in a clinical setting before and after introduction of a software upgrade with monitoring periods covering several months and to compare it with standard monitoring based on serial 7-day Holter.

Methods

Patient population and study design

Between September 2007 and February 2008, 64 consecutive patients (69% male, mean age 60 ± 9 years) suffering from paroxysmal AF were included into this prospective analysis. Thirteen patients (20%) suffered from lone AF and 45 (70%) from arterial hypertension with a mean left atrial diameter of 43 ± 7 mm and a left ventricular ejection fraction of 61 ± 9%.

All of the patients had received an ILR-AF (Medtronic Reveal XT™ model 9529) during the course of the XPECT study.[10] After termination of the XPECT study, the patients were included into routine clinical follow-up. Our data represent an analysis of the ILR-AF performance during a longer and clinically relevant AF monitoring period of an average of 57 days (75% range: 23–98 days).

Due to a high amount of AF misdetection, mostly caused by oversensing of myopotentials and artefacts, a software update (see below) was introduced in June 2008 during the course of the study. Interrogations were analysed with the use of manual EGM analysis (see below) and results before and after software update were compared.

During the course of the study, a subgroup of patients ($n = 51$, 79%) underwent circumferential pulmonary vein isolation and was followed with serial (post-ablation, after 3 months, after 6 months, after 12 months) 7-day Holter recordings (Lifecard CF, DelmarReynolds Medical Inc, Irvine, CA, USA) in addition to the ILR-AF interrogations. The physician performing the Holter analysis was blinded with regard to patient name, date of ablation, and the patient's symptom log. Based on the ILR-AF detection algorithm (see below), AF recurrence was defined as a documented AF episode lasting longer than 2 min to allow for comparison between ILR-AF and 7-day Holter monitoring results.

Implant procedure

The ILR-AF was implanted in a left parasternal position. Optimal orientation of the device axis was determined prior to implantation. For that, the vector check tool was used (Medtronic, Minneapolis, MN, USA), which allows testing for the highest R-wave amplitude obtained from a single lead recording in different locations/orientations on the body surface. During implantation, the device was pushed into the subcutaneous tissue without prior pocket preparation, in order to assure close tissue-device contact and to prevent mobility of the device within the pocket. The device was fixated within the pocket.

Software and device description

The AF detection algorithm operates through an assessment on the regularity of RR intervals (Lorenz plot) within a 2 min time window.[11] Once AF is diagnosed, it is stored as a sustained AF episode within the automatic episode counter, showing date and time of occurrence as well as episode length. After detection, the device is capable of storing 2 min of each AF episode as electrogram (EGM) with a total storage capacity of 49.5 min. Once storage is exhausted, older EGMs are overwritten with newer ones. However, the automatic episode counter is not overwritten until the next interrogation.

The mentioned upgraded software aims at a reduction of noise-induced false-positive AF episodes by reducing the noise rejection threshold from 60 to 5 s. In this way, episodes containing >5 s of noise in a 2 min window are not considered for classification.

As additional device tools, an external assistant box (Medtronic Reveal XT™ patient assistant model 9539) allows patients to tag and store symptomatic episodes by activating a recording button; furthermore, the patient can check whether EGM storage capacity is exhausted by activating an interrogation button. Nevertheless, this alarm was not activated in our patients.

In addition to AF detection, the device also detects and classifies other types of arrhythmias, e.g. asystole, bradycardia, and tachycardia. However, storage of non-AF episodes was disabled unless individual patient history warranted detection of other arrhythmias. In these cases, storage of those episodes was permitted; however, only AF episodes were analysed.

Interrogations and follow-up

All patients were integrated in the routine follow-up within the pacemaker/implantable cardiac defibrillator clinic with quarterly visits and additional visits upon request. Interrogation of the ILR-AF is similar to pacemaker interrogations and requires the Medtronic programmer (Medtronic CareLink programmer model 2090, software model SW007). The standard setting for R-wave sensing was 0.05 mV. Depending on the occurrence of under- or oversensing, it was adjusted during follow-up accordingly.

From a clinical perspective, each interrogation was classified according to the diagnosis derived from automatic AF detection and manual analysis of all stored EGMs (*Figure 1A* and *B*). Automatically stored AF episodes were judged by an experienced physician as adequate if there was an irregular RR pattern in the absence of P-waves throughout the EGM recording. With that approach, an interrogation could lead to the diagnosis: (i) no AF; (ii) definite AF; (iii) possible AF (non-diagnostic interrogation) (*Table 1*). The diagnosis of 'no AF' was made in cases where the automatic AF counter was zero.

Statistics

The data were tested for normal (Gaussian) distribution using Kolmogoroff–Smirnov test. Normally distributed continuous variables are presented as mean ± standard deviation (SD). In case of a non-Gaussian distribution, median and quartiles are given. Categorical variables are expressed as number and percentage of patients and interrogations, respectively.

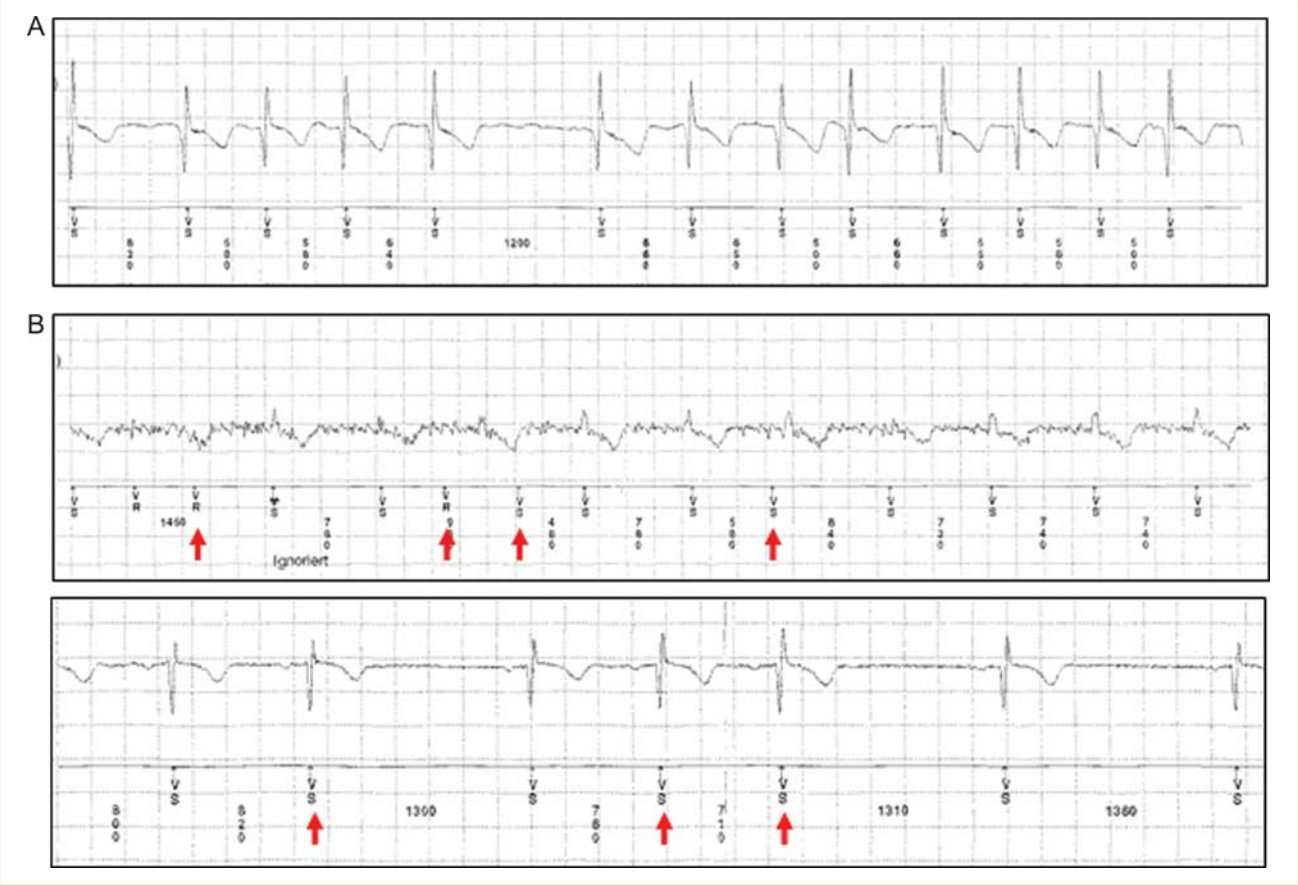

Figure 1 (*A*) Device stored electrogram with correctly classified atrial fibrillation. (*B*) Device stored electrogram with misclassified AF (red arrows) due to myopotentials (upper panel) and PAC (lower panel).

Table 1 Definition of clinical diagnosis of interrogations based on manual electrogram analysis

Automatic episode counter	no AF episodes	limited AF episodes (EGM for all episodes)		multiple AF episodes (EGM not for all episodes)	
Manual EGM analysis	–	Only SR	With AF	With AF	Only SR
Diagnosis	No AF	No AF	Definite AF	Definite AF	Possible AF (non-diagnostic)

Differences between continuous normally distributed data before and after the software upgrade were tested for statistical significance using the paired *t*-test. In case of continuous data with a non-Gaussian distribution the Wilcoxon test was used. Differences between categorical data before and after the software upgrade as well as the rate of AF detection on ILR-AF and on 7-day Holter were tested for statistical significance using the McNemar test.

All analyses were performed using SPSS for Windows, Release 12.0. A *P*-value of <0.05 was considered statistically significant.

Results

No complications occurred during or after implantation, no persistent discomfort was reported and no explanations of the device were necessary during follow-up. Among the 64 patients, a total of 333 interrogations were performed. Of those, 203 interrogations occurred before and 130 interrogations occurred after the software upgrade. Results of manual interrogation analysis are displayed separately for interrogations before and after the software upgrade in *Figure 2A* and *B*.

Details on distribution of interrogations, number of AF episodes, length of follow-up period, mean R-wave amplitude, length of clinical follow-up, and amount of storage overflow are summarized in *Table 2*.

Non-diagnostic interrogations

Interrogations with automatically stored AF episodes containing only EGMs with sinus rhythm and artefacts leading to AF

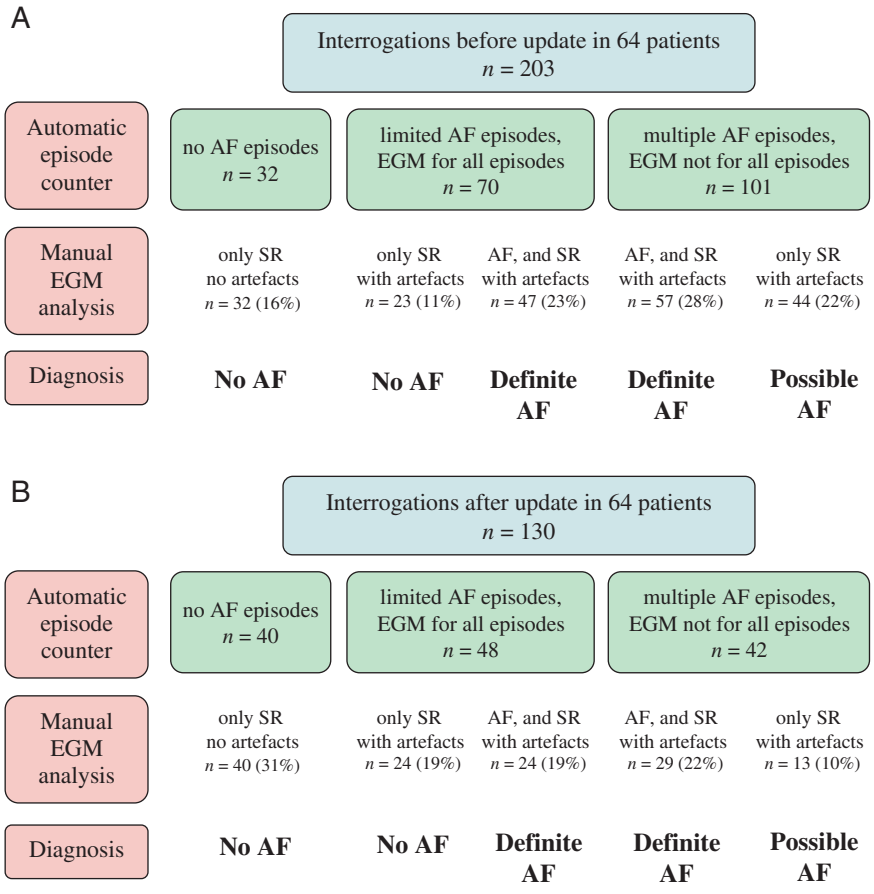

Figure 2 (*A* and *B*) Clinical classification of interrogations before and after software upgrade.

misdetection could be found in 22% of interrogations prior and 10% after the software upgrade, respectively (*Figure 2A and B*). For these interrogations, however, it is unclear whether AF was present among the remaining automatically stored AF episodes without available EGM.

Causes of atrial fibrillation misdetection

Before and after software upgrade, reasons for AF misdetection were the occurrence of myopotentials/noise in 70/203 interrogations (35%) vs. 28/130 (22%), T-wave oversensing in 3/203 (1.5%) vs. 1/130 (1%), frequent premature ventricular or atrial complexes (PVCs/PACs) in 28/203 (15%) vs. 26/130 (20%), as well as R-wave undersensing in 9/203 (4%) vs. 7/130 (5%), respectively.

Individual patient analysis before and after software upgrade

The length of follow-up intervals between consecutive interrogations did not vary before and after software upgrade [49 (23; 98) vs. 68 (25; 98) days; $P = 0.276$]. However, the length of total clinical follow-up before and after software upgrade was significantly longer prior software upgrade (193 $\pm$ 85 days prior upgrade vs. 141 $\pm$ 54 after upgrade; $P < 0.001$).

Table 2 Characteristics of interrogations before and after software upgrade

	Before software upgrade	After software upgrade	*P*-value
Total number of interrogations, *n*	203	130	
Number of interrogations per patient[a]	2.6 $\pm$ 1.8	1.9 $\pm$ 1.3	<0.001
Number of AF episodes, *n*[b]	27 (3; 125)	5 (1; 20)	<0.001
R-wave amplitude, mV[b]	0.7 (0.4; 0.8)	0.7 (0.5; 0.9)	0.166
[c]Monitoring period, days[b]	49 (23; 98)	68 (25; 98)	0.276
[d]Length of clinical follow-up[a]	193 $\pm$ 85	141 $\pm$ 54	<0.001
[e]Interrogations with storage overflow, *n* (%)	101 (50%)	42 (32%)	

[a]Data given as mean and standard deviation.
[b]Data given as median and quartiles.
[c]Monitoring interval between two subsequent ILR-AF interrogations.
[d]Length of clinical follow-up was defined as total monitoring time before and after software upgrade.
[e]Interrogations with storage overflow were defined as interrogations including automatic episodes without available EGM.

Overall, introduction of the new software upgrade significantly reduced the number of patients with any misdetection of AF [46/64 (72%) vs. 28/64 (44%); $P = 0.001$]. This reduction was mainly attributable to a significantly lower number of patients having AF misdetection due to myopotentials or noise [32/64 (50%) vs. 15/64 (23%); $P < 0.001$]. On the other hand, the occurrence of R-wave undersensing [6/64 (9%) vs. 5/64 (8%); $P = 1.0$], T-wave oversensing [3/64 (5%) vs. 1/64 (2%); $P = 0.625$], misdetection of PVC [3/64 (5%) vs. 1/64 (2%), $P = 0.625$], and PAC [20/64 (31%) vs. 14/64 (22%), $P = 0.238$] were not significantly improved with the introduction of the software upgrade.

The number of patients with clinically non-diagnostic interrogations was significantly reduced [24/64 (38%) vs. 10/64 (16%); $P = 0.001$] (*Figure 3*). A detailed evaluation of the 10 patients with non-diagnostic interrogations despite the software upgrade revealed the following reasons of frequent AF misdetection: myopotential oversensing ($n = 7$), frequent PACs ($n = 5$), R-wave undersensing ($n = 3$). Simultaneous over- and undersensing occurred in three patients, posing a challenge for the adjustment of R-wave sensing.

Atrial fibrillation detection on implantable loop recorder compared with 7-day Holter

Out of 64 patients, 51 (80%) underwent circumferential PV isolation. With serial 7-day Holter monitoring, 12 of 51 (24%) patients had documented episodes of AF recurrences. In all of these patients, AF was correctly identified by the ILR-AF. In four additional patients, AF recurrences were detected by the ILR-AF which was not seen on 7-day Holter. Therefore, the rate of documented AF recurrence had a tendency to be higher on ILR-AF, but failed to reach statistical significance [16/51 (31%) vs. 12/51 (24%); $P = 0.125$].

Discussion

Main findings

This is the first study to evaluate the implantable continuous AF detection device in long-term clinical routine based on a manual analysis of automatically stored AF episodes. Compared with high-quality standard measures of AF monitoring such as serial 7-day Holter, the device increased the total number of patients with AF detection. However, we also found a high rate of false-positive AF recordings mainly caused by oversensing of myopotentials and noise. Together with an only limited EGM storage capacity that led to non-diagnostic interrogations in 38% of the patients. Following software upgrade, the specificity of the device improved with non-diagnostic interrogations in 16% of the patients.

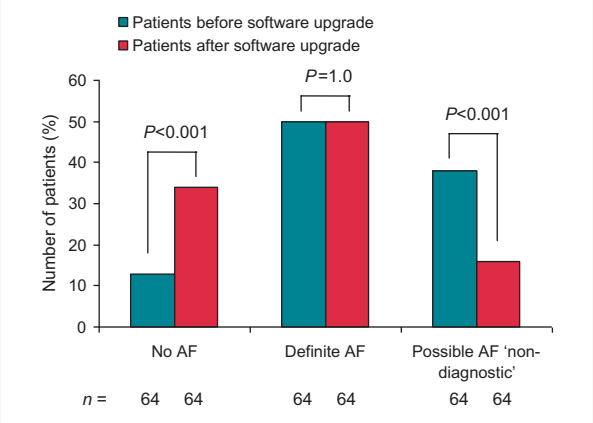

Figure 3 Clinical classification of patients before and after the software upgrade.

Role of implantable loop recorders in atrial fibrillation detection

Implantable loop recorders have become an important diagnostic tool for the patient with unexplained syncope and are well established for this purpose.[12] In how far this monitoring strategy is useful for rhythm follow-up in patients with AF remains to be evaluated.

During an initial validation study, a high sensitivity of 96.1% for detecting AF was found, while specificity was limited by falsely stored AF episodes in 15% of the patients.[10]

Recently, a second study has compared the AF detection rate obtained from ILR-AF against three-monthly 24-h Holter in patients after surgical ablation of AF over a 1-year follow-up. Exclusive usage of automatically detected AF episodes obtained with the old detection algorithm prior to the software upgrade together with the lack of any information on manual EGM analysis and the problem of AF misdetection limits the understanding on the true value of the ILR-AF for long-term continuous AF monitoring in this study.[13]

Our study is the first one using the ILR-AF as long-term continuous AF monitoring device in clinical routine and validating its diagnostic accuracy according to manual analysis of all automatically stored AF episodes. Some key findings need to be emphasized. The AF detection rate of the device tended to be higher compared with standard serial 7-day Holter ECG recordings. However, due to oversensing of myopotentials and subsequent AF misdetection, specificity is lacking. Similar results have been shown for other device-based rhythm monitoring, e.g. pacemaker or implantable defibrillators. In prospective randomized trials, the relative portion of misclassified AF episodes by an implanted dual-chamber pacemaker is ~26%.[14]

Oversensing of myopotentials, mostly from the pectoral muscle, was found to be the leading cause for false-positive AF annotation in our study. In order to minimize myopotential detection, a new and improved software algorithm was released during the course of the study. Our results show that using the updated algorithm the number of patients with non-diagnostic interrogations could be reduced from 38 to 16%. However, considering the invasive nature of the follow-up tool, this rate of non-diagnostic data sets has to be improved.

Measurements to reduce non-diagnostic interrogations

Besides further software developments, several measures can be discussed to reduce the number of non-diagnostic interrogations. To recognize false-positive AF episodes, all automatically detected

episodes need to be confirmed on manual EGM analysis. Therefore, it is necessary to prevent EGM storage overcrowding. That can be achieved with two methods. First, the patient assistant box has the ability to indicate full EGM storage through an alarm signal which should initiate a visit to the device clinic in order to retrieve and analyse all available EGMs. That in return would lead to individualized follow-up intervals. Secondly, remote monitoring techniques like the CareLink network allow patient initiated sending of diagnostic and monitoring information from home. This provides the possibility of regularly relieving the EGM storage and could enhance manual EGM analysis for all automatically stored episodes.

Prolongation of the detection period for sustained AF may be a different way to prevent episodes of AF misdetection, because false-positive AF episodes are rather short. Programming options of the ILR-AF include detection periods for sustained AF of 6 min and more. Clearly, shorter AF episodes will then be unrecognized. The clinical and scientific impact of such a change in definition of sustained AF remains to be evaluated.

The impact of the above-discussed measures on the accuracy of the ILR-AF in the clinical setting of continuous AF monitoring has to be assessed within further studies.

Study limitations

This study is an observational study reporting the first experiences with an implantable leadless continuous monitoring device for AF in a clinical setting. It needs to be emphasized, however, that patients' follow-up intervals were routinely integrated into the pacemaker clinic, i.e. follow-up intervals were not individualized for each patient since they were not based on patients' self assessment of remaining EGM storage capacity with the patient assistant. The CareLink system facilitating remote device interrogation with the aim of reducing storage overflow was also not available in our patients. Nevertheless, the importance of manual episode analysis and the problem of storage exhaustion due to false-positive AF episodes first arose from our experience with the device.

Variations in length of clinical follow-up and in frequencies of interrogations before and after software upgrade as well as performance of AF ablation during the course of the study might have impacted the results of the study.

Although the number of non-diagnostic interrogations was reduced after software upgrade, the lack of a gold standard for continuous AF monitoring over such extended follow-up periods prevents a conclusive assessment of diagnostic accuracy with respect to positive and negative predictive values. Therefore, decreasing the number or proportion of stored episodes with noise does not necessarily imply an actual improvement in AF detection accuracy from the users' perspective.

Although we could show that this device is valid, its relevance for clinical decision-making in patients with AF remains to be seen. As this device is mainly used for AF detection, other atrial and ventricular arrhythmias have not been evaluated in this study.

Conclusion

The ILR-AF is a first and promising tool for continuous AF monitoring. To incorporate this device into routine patient care, developments in device technology and device handling are still necessary to minimize the number of non-diagnostic interrogations.

Conflict of interest: none declared.

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