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CLINICAL RESEARCH

Atrial fibrillation detection using a novel three-vector cardiac implantable monitor: the atrial fibrillation detect study

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Aims Continuous rhythm monitoring is valuable for adequate atrial fibrillation (AF) management in the clinical setting. Subcutaneous leadless implantable cardiac monitors (ICMs) yield an improved AF detection, overcoming the intrinsic limitations of the currently available external recording systems, thus resulting in a more accurate patient treatment. The study purpose was to assess the detection performance of a novel three-vector ICM device equipped with a dedicated AF algorithm.

Methods and results Sixty-six patients (86.4% males; mean age 60.4 ± 9.4 years) at risk to present AF episodes, having undergone the novel ICM implant (BioMonitor, Biotronik SE&Co. KG, Berlin, Germany), were enrolled. External 48-h ECG Holter was performed 4 weeks after the device implantation. The automatic ICM AF classification was compared with the manual Holter arrhythmia recordings. Of the overall study population, 63/66 (95.5%) had analysable Holter data, 39/63 (62%) showed at least one true AF episode. All these patients had at least one AF episode stored in the ICM. On Holter monitoring, 24/63 (38%) patients did not show AF episodes, in 16 of them (16/24, 67%), the ICM confirmed the absence of AF. The AF detection sensitivity and positive predictive value for episodes' analysis were 95.4 and 76.3%, respectively.

Conclusion Continuous monitoring using this novel device, equipped with a dedicated detection algorithm, yields an accurate and reliable detection of AF episodes. The ICM is a promising tool for tailoring individual AF patient management. Further long-term prospective studies are necessary to confirm these encouraging results.

Keywords Atrial fibrillation • BioMonitor • Continuous monitoring • Implantable loop recorder • Implantable cardiac monitor

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, increasing in prevalence with age, resulting in significant morbidity and cost to the healthcare system.[1] Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages.[2,3] The adverse events associated with AF are mainly correlated to the episodes' duration, frequency, and arrhythmia burden;[4–6] therefore, an appropriate and continuous rhythm monitoring in AF patients is important to guide anti-thrombotic therapy for the prevention of embolic events.[7,8] Several methods have been described to detect AF episodes,[9–13] showing that a longer monitoring is associated with an enhanced arrhythmia identification rate.[12,13] In fact, it has been estimated that serial 7-day Holter electrocardiograms (ECGs) or daily plus symptom-activated transtelephonic ECG monitoring could miss roughly 30% of AF episodes.[14] To overcome this problem, the use of an implantable cardiac monitor (ICM) represents a reliable strategy for AF monitoring.[13,15,16] A novel subcutaneous leadless ICM (BioMonitor, Biotronik SE&Co. KG, Berlin, Germany) has

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What's new?

- The atrial fibrillation (AF) detection performance of the novel three-vector implantable cardiac monitor resulted in 95.6% sensitivity and 76.3% positive predictive value.
- The sensitivity, specificity, positive predictive value, and negative predictive value for identifying patients with any AF were 100, 67, 83, and 100%, respectively.
- All patients with AF episodes documented at ECG–Holter recordings were correctly classified by the device detection algorithm.

recently become available allowing long-term continuous remote monitoring (5–6 years) with fully automated daily transmission and a specific AF detection algorithm. In the present study, we sought to assess the AF detection performance of this novel ICM.

Methods

Study design

Between November 2013 and July 2014, 66 patients have been included in our institution. Patients with an implanted ICM (BioMonitor) and who (i) had documented AF episodes or symptoms attributable to AF, (ii) were scheduled for catheter ablation, and (iii) had undergone catheter ablation still experiencing AF-related symptoms were considered eligible for enrolment. All patients met at least one of the abovementioned criteria. Those presenting with long-standing persistent and permanent AF were excluded. The clinical study was conducted in accordance with the Declaration of Helsinki and the international standard for clinical investigation of medical devices in human subjects, ISO 14155. The ethics committee approved the study, and all patients gave written informed consent.

Aim of the study

The aim of the study was to determine the AF detection capability of this novel ICM in terms of sensitivity and positive predictive value (PPV) of the AF algorithm. Therefore, the ICM recordings were compared with external 48-h ECG Holter monitoring system performed 4 weeks after device implantation.

Device characteristics

The BioMonitor is a leadless implantable loop recorder that uses three electrodes located in the 53 × 42 × 7 mm can of the device to continuously monitor patients' subcutaneous ECG (sECG). The device is MRI conditional under 1.5 and 3 T static magnetic field.

The ICM memory can store a maximum of 35.8 min of sECG recordings. The BioMonitor offers remote monitoring (Biotronik Home Monitoring). The arrhythmia detection algorithms are all based on the identification of QRS signals. The AF detection algorithm analyses the stability of the R–R interval, based on the differences in consecutive pairs of QRS cycles. If the cycle length instability crosses a programmable threshold, the algorithm marks the onset of an AF episode. The episode is stored after a user programmable delay function, to filter short arrhythmic episodes, considered not clinically relevant by the physician. All data in this report are based on the standard detection algorithm with the following nominal parameters: instability threshold of 12.5% of the mean R–R interval and delay time of 2 min. All ICMs were inserted subcutaneously under local anaesthesia. No pre-implant signal mapping was performed. The site for the implantation was defined anatomically at the 4th/5th intercostal spaces, along the left emiclavear line.

Holter recordings

A long-term three-channel Holter ECG system (LifeCard, Spacelabs Healthcare, Snoqualmie, WA, USA) was used to store a continuous and simultaneous 48-h recording of three-lead ECG. Patients were asked to perform their usual daily activities.

Data analysis

The ICM detection performance was assessed compared with the established method of 48-h Holter recording. The Holter–ECGs were manually annotated for AF episode onset and termination and verified by independent cardiologists blinded to the ICM detections. The surface ECG of the external Holter ECG and ICM sECG were manually synchronized by sponsor personnel not involved in the data analysis. The 48-h Holter ECG signal was evaluated by at least two expert physicians blinded to ICM detections and patient-related information. Segments with non-interpretable Holter ECG due to noise or artifacts were excluded.

Episode classification and calculation of atrial fibrillation detection performance

All AF episodes detected by either ICM or Holter monitoring were directly compared on an episode-by-episode basis. Each event longer than 2 min (default ICM confirmation window) could be classified as true positive (TP), false positive (FP), or false negative (FN), as shown in *Figure 1*. A Holter AF episode without a concomitant ICM AF episode was classified as an FN, conversely an ICM AF event occurring without a concomitant Holter AF episode was classified as FP. True positive episodes were dissected into one of two types: a Holter AF episode coincident with at least one ICM AF episode was classified as a TP_{Holter}, while an ICM AF episode coincident with at least 1 Holter AF episode was classified as a TP_{ICM}. The AF episode classification underwent a final review by an ECG expert not involved in the previous analysis. Verified AF episode classification (TP_{Holter}, TP_{ICM}, FP, FN) for each participant was used to quantify the AF detection performances of the implantable device. They were quantified using sensitivity (the percentage of Holter AF episodes that were correctly identified by ICM) and PPV (the percentage of ICM AF episodes that correctly identified a Holter AF episode). Sensitivity and PPV were calculated as follows:

$$\text{Sensitivity}(\%) = 100 \times \frac{TP_{Holter}}{(TP_{Holter} + FN)};$$

$$\text{Positive predictive value (PPV)}(\%) = 100 \times \frac{TP_{ICM}}{(TP_{ICM}+FP)}.$$

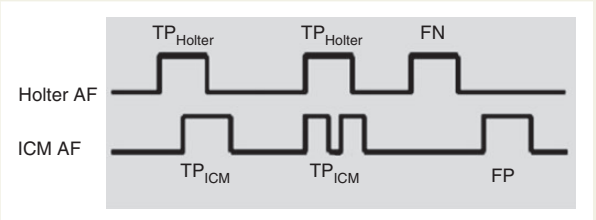

Figure 1 Classification of atrial fibrillation episodes. AF, atrial fibrillation; TP, true positive; FN, false negative; FP, false positive.

Statistical analysis

The sample size estimation is based on the sensitivity assessment using the exact binomial test and was carried out using PROC POWER in SAS (Version 9.3). Further prerequisites of this statistical assessment are $\alpha = 5\%$, $\beta = 20\%$, two-sided. The sensitivity of the ICM is estimated to be >80% even in a real world scenario (no data available). With a non-inferiority limit proposal of 60%, the sample size estimation yields 45 patients. The AF burden derived from the ICM and the Holter was described using the median and the percentiles and compare with the Mann–Whitney *U* test; the Pearson correlation coefficient was calculated between the two measurements.

Results

Study population

Sixty-six patients (mean age 60.4 ± 9.4 years) having undergone placement of ICM were included in this study. The mean body mass index (BMI) was 28.2 ± 4.2 kg/m^2, and the mean left ventricular ejection fraction (LVEF) was 53.9 ± 5.9%. The majority of patients were male (86.4), 62.1% had hypertension, and 4.5% had history of stroke or transient ischaemic attack (*Table 1*). No differences in the R wave sensing amplitude could be observed among male and female patients (males 0.49 ± 0.3 mV vs. females 0.53 ± 0.1 mV; $P = 0.69$). The indication for the ICM was AF episodes' detection and quantification for all patients. The clinical characteristics of the overall study population are listed in *Table 1*.

Patient-related atrial fibrillation detection performance

The AF episodes' classification, along with their associated sensitivity and PPV values, was provided for each patient. Sensitivity could not be calculated for patients without Holter AF episodes (TP_{Holter} or FN). Moreover, PPV could not be calculated for those without ICM AF episodes (TP_{ICM} or FP). The overall statistics episodes are listed in *Table 2*. Of a total of 66 participants with paroxysmal or persistent AF, 3 patients were excluded from the analysis because of Holter file conversion error ($n = 2$) or poor Holter recording quality ($n = 1$). No patients were excluded because of performance issues with the ICM. Of the remaining 63 patients, 39/63 (62%) showed at least one true AF episode during the 2-day Holter recording period (*Figure 2*), with a maximum of 30 definite episodes experienced by one patient. Among those experiencing AF episode at the Holter monitoring, the ICM was always able to detect at least one arrhythmic event. Therefore, all patients having AF episodes at the Holter recording were correctly classified by the ICM resulting in a 100% sensitivity per patient. Twenty-four (24/63; 38%) individuals were classified as not having AF in the Holter recording. In 16 (16/24, 67%) of them, the ICM confirmed the absence of AF episodes, resulting in specificity for identifying patients with no AF of 67%. The PPV and negative predictive value (NPV) of detecting AF episodes in a patient were 83% (39/47 patients) and 100% (16/16 patients), respectively. In 8 of the 24 patients (33%) not experiencing AF events during Holter monitoring, ICM detected FP episodes. Some patients had more than one type of FP recordings. Reasons of uncorrected classification of arrhythmic episodes were premature atrial contractions (PACs) or premature ventricular contractions (PVCs) in seven patients, signal noise in three, and irregular atrioventricular conduction in one (*Figure 3*).

Table 1 Patient characteristics

	Overall ($n = 66$)
Mean age, years	60.4 ± 9.4
Male gender, *n* (%)	57 (86.4)
Mean body mass index (BMI), kg/m^2	28.2 ± 4.2
LA dimension, mm	44.1 ± 5.4
Ejection fraction, %	54.1 ± 6.1
Hypertension, *n* (%)	41 (62.1)
Diabetes, *n* (%)	11 (16.7)
Heart failure, *n* (%)	0 (0)
Coronary artery disease, *n* (%)	3 (4.5)
History of stroke/TIA, *n* (%)	3 (4.5)
Valvular heart disease, *n* (%)	37 (56.1)
Dysthyroidism, *n* (%)	13 (19.7)
Number of previous AADs, *n*	1.4 ± 0.6

Data are expressed in mean ± standard deviation or absolute number and percentage.
TIA, transient ischaemic attack; AF, atrial fibrillation; AAD, anti-arrhythmic drug.

Atrial fibrillation episodes detection

In 63 Holter recordings, 2878 h of data were analysed, from which 146 AF episodes were identified. In the ICM memory, a total of 654 episodes were stored and analysed, 513 of them (78.4%) were classified as TP_{ICM} and 141 (21.6%) as FP. The latter episodes were incorrectly classified as AF, due to PACs or PVCs (102 of 141), signal noise (29 of 141), and irregular atrioventricular conduction (10 of 141) as confirmed by the manual analysis of the electrogram stored in the device memory. Thirty-seven FN AF episodes (i.e. true AF episodes undetected by ICM) occurred in five patients. In 3/5 patients with FN episodes, a marginal R–R interval variability could be observed in the Holter ECG, while in the remaining 2/5, despite detectable R–R variability during Holter recording, no BioMonitor snapshots were available during this time period (thus classified as FN). All patients with FN episodes had AF documented by the ICM in other episodes, and they were correctly identified as AF patients. The mean sensitivity and the mean PPV were 95.4 ± 13.3 and 76.3 ± 38.7%, respectively (*Table 2*). Of 39 available assessments, 37 were above 60% sensitivity (*Table 2*).

Atrial fibrillation burden

The AF burden is defined as the percentage of time spent in AF. No significant difference could be observed between the mean burden measured with the two systems. The mean ICM-registered burden was 27.4 ± 28.9%, whereas the mean Holter-registered burden was 28.0 ± 35.3% ($P = 0.76$). The Pearson coefficient between the two measurements was 0.90, showing a significant positive correlation ($P < 0.001$).

Discussion

Main findings

The major findings of the present study are as follows: (i) ICM monitoring with a dedicated algorithm is highly sensitive in the detection

Table 2 AF episode classification counts with sensitivity and PPV for each study patients

Patient	$TP_{Lifecard}$	$TP_{BioMonitor}$	FP	FN	Sensitivity (%)	PPV (%)	Lifecard episode evaluated
1	0	0	0	0	–	–	0
2	0	0	0	0	–	–	0
3	0	0	0	0	–	–	0
4	0	0	0	0	–	–	0
5	0	0	0	0	–	–	0
6	1	18	0	0	100	100	1
7	2	2	0	0	100	100	2
8	1	1	0	0	100	100	1
9	0	0	0	0	–	–	0
10	0	0	0	0	–	–	0
11	0	0	0	0	–	–	0
12	0	0	0	0	–	–	0
13	0	0	4	0	–	0	0
14	0	0	0	0	–	–	0
15	0	0	17	0	–	0	0
16	0	0	0	0	–	–	0
17	2	3	0	0	100	100	2
18	0	0	1	0	–	0	0
19	1	20	0	0	100	100	1
20	1	18	0	0	100	100	1
21	4	18	0	0	100	100	6
22	1	20	0	0	100	100	1
23	1	17	0	0	100	100	1
24	0	0	10	0	–	0	0
25	0	0	19	0	–	0	0
26	1	19	0	0	100	100	1
27	0	0	18	0	–	0	0
28	0	0	3	0	–	0	0
29	1	9	11	0	100	45	3
30	7	12	4	1	87	75	8
31	RAM corrupted						
32	1	19	0	0	100	100	1
33	1	19	1	9	199	95	1
34	6	18	1	3	67	95	21
35	16	17	2	14	53	89	30
36	1	18	0	0	100	100	1
37	1	17	0	0	100	100	1
38	8	20	0	1	89	100	17
39	1	19	0	0	100	100	1
40	0	0	0	0	–	–	0
41	1	19	0	0	100	100	1
42	1	19	0	0	100	100	4
43	7	15	4	9	44	79	19
44	1	1	0	0	100	100	1
45	0	0	0	0	–	–	0
46	0	0	0	0	–	–	0
47	1	19	0	0	100	100	1
48	2	4	2	0	100	67	2
49	1	6	0	0	100	100	1
50	1	4	7	0	100	36	1

Continued

Table 2 ***Continued***

Patient	$TP_{Lifecard}$	$TP_{BioMonitor}$	FP	FN	Sensitivity (%)	PPV (%)	Lifecard episode evaluated
51	0	0	0	0	–	–	0
52	1	18	0	0	100	100	1
53	3	3	0	0	100	100	3
54	1	20	0	0	100	100	1
55	1	2	0	0	100	100	1
56	2	20	0	0	100	100	2
57	1	19	0	0	100	100	1
58	2	5	15	0	100	25	2
59	RAM corrupted						
60	1	20	0	0	100	100	1
61	Poor quality of Holter recording						
62	0	0	20	0	–	0	0
63	0	0	0	0	–	–	0
64	1	11	0	0	100	100	1
65	1	1	0	0	100	100	1
66	1	3	2	0	100	60	1
Mean ± SD					95.4 ± 13.3	76.3 ± 38.7	2.3 ± 5.4

Dotted sensitivity entries reflect a lack of Holter episodes; dotted PPV entries refer to a lack of ICM episodes.

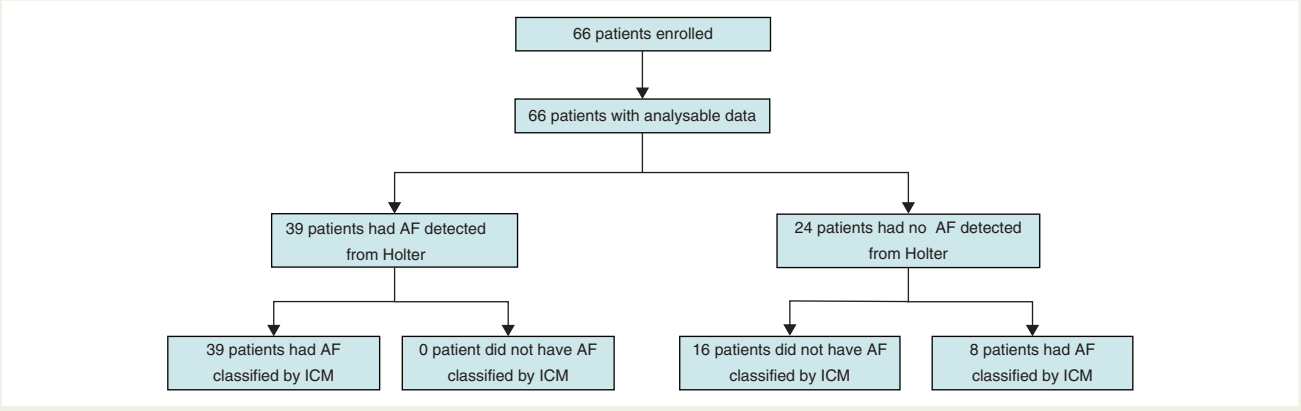

Figure 2 Flow chart of the study population showing the monitoring results of all enrolled patients.

of AF episodes providing a 95% sensitivity and 76% PPV; (ii) all patients with AF were correctly identified; and (iii) ICM is reliable in confirming freedom from AF.

Atrial fibrillation monitoring using implantable cardiac monitor

Atrial fibrillation is associated with a reduced quality of life and an increased number of adverse outcomes such as stroke, heart failure, increased number of hospitalizations, and mortality.[2] Arrhythmia adverse events are related to episodes' frequency and duration as well as to the AF burden.[4–6] The clinical management is mainly based on adequate identification of arrhythmic episodes to tailor the most appropriate treatment (i.e. anti-arrhythmic and anti-thrombotic). This concept has raised the need for long-term monitoring, since short-term monitoring (24-h Holter, 7-days or 30-days recording, patient-activated ECG recorders) yields an unsatisfactory estimation of the AF burden mainly due to the limited duration of the monitoring, the incidence of asymptomatic episodes, and poor patient compliance. Recent studies have shown that the AF detection rate is significantly increased by extending the monitoring duration.[6,12,16] However, the percentage of patients falsely diagnosed without AF by repetitive 7-day Holter recordings is unclear as well as the duration of continuous or intermittent recordings necessary to safely exclude the presence of AF.[14,16] Recent studies have demonstrated the beneficial value of continuous monitoring using an ICM capable to detect AF

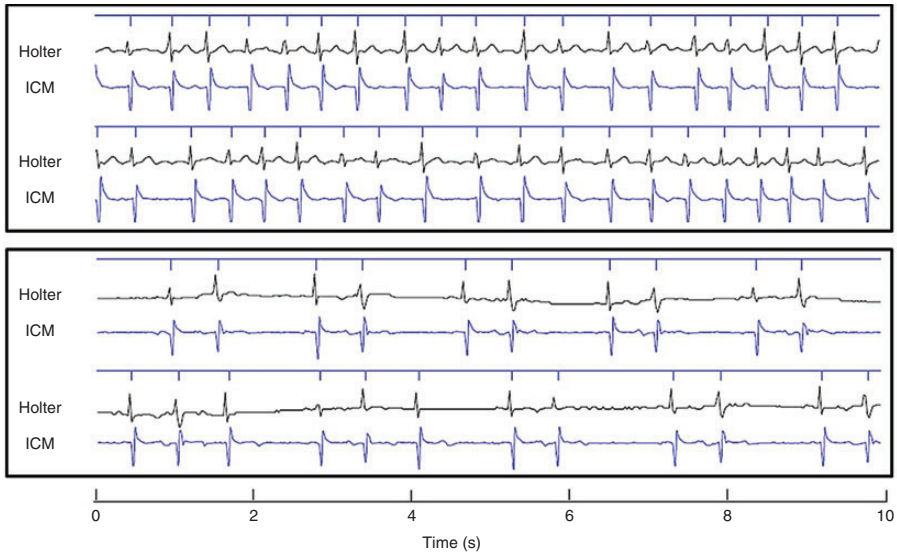

Figure 3 Examples of AF episodes snapshots stored in the ICM with the corresponding Holter recordings: in the top panel, a true positive episode (AF correctly identified by the ICM). In the bottom panel, a false positive episode due to sinus rhythm with frequent premature atrial contractions (PACs). First-line ICM markers (blue ticks); second-line Holter signal (black); third-line ICM sECG (blue).

episodes, overcoming the limitations of currently available external recording systems.[6,12,16,17] In addition, episodes' detection seems to be not enough, since the total amount of AF burden may identify patients at higher risk of thrombo-embolic events.[5–9] Despite the fact that a critical burden threshold has not been established so far, arrhythmia quantification may be relevant for its diagnostic and treatment implications. In the present study, the use of this novel subcutaneous leadless ICM equipped with a dedicated AF detection algorithm performed with high sensitivity and PPV in the identification of AF episodes. Compared with the reference of standard ECG–Holter monitoring, the ICM correctly identified all patients experiencing AF. The AF burden was correctly estimated by the ICM with a significant correlation with the ECG Holter reference (Pearson coefficient = 0.90). The latter may underline the reliability of the device in the AF detection compared with the standard ECG–Holter that still represents the most commonly used non-invasive monitoring system for the management of AF patients. The results of the current study are comparable to the ones reported in the XPECT trial,[15] in which the ICM Reveal XT (Medtronic, MN, USA) showed a sensitivity of 88.2% and a PPV of 75.9%, whereas in roughly 4% of it did not diagnose the arrhythmia. A novel miniaturized ICMs, i.e. Reveal LINQ (Medtronic, MN, USA), has been recently launched on the market. Compared with the latter, the main differences with the device used in the present study are two: the dimensions (Reveal LINQ is smaller) and the nominal battery life expectancy (2.5 years for the LINQ vs. 5–6 years for the BioMonitor). Therefore, although appealing for its technology and easy implantation technique, the performance of the LINQ ICM seems to be comparable to the one reported in the present study using the BioMonitor ICM.[18] Moreover, the longer battery life expectance of the latter proves it feasible for patients requiring longer rhythm monitoring, especially those undergoing or having undergone catheter ablation, or most importantly in those with cryptogenic stroke. Further studies are warranted to demonstrate the potential impact of ICMs on clinical care in other patient subgroups.

Pitfalls in the atrial fibrillation detection

Considering the risk of AF-related adverse events, a high detection sensitivity is crucial. The ICM correctly identified all patients experiencing AF, while 78.4% of all episodes stored in the memory were TP. Of note, none of patients with arrhythmic events at the Holter received an AF misdetection by the ICM. However, in 8/63 subjects (12.7%) without AF during Holter monitoring, the ICM falsely identified AF, which were predominantly associated with frequent ectopic beats, whereas only in a minority with signal noise. The incidence of automatically detected FP episodes was not negligible, accounting for roughly 22% of events, clearly underlining the need for physician manual analysis of the electrograms, as it may result in unnecessary treatments. Considering the storage capacity of every ICM device, the presence of high number of FP episodes might reduce the diagnostic accuracy, because such events may be overwritten due to memory limitation.[15,19] The new ICM with daily remote monitoring can overcome this issue, providing the possibility of daily and automatic data transmission from the ICM, allowing fully availability of all episodes in the remote monitoring system archive, even when a high number of events exceeds the storing capacity of the device. In addition, false negative AF episodes (i.e. true AF episodes undetected by the ICM), resulting in sensitivity values $<100\%$, were mainly attributed to R–R interval variability that, although non-zero in magnitude, did not exceed the ICM programmed limit of 12.5% for a sufficient fraction of intervals. To reduce the incidence of FN events, the R–R variability should be adjusted upon patients' characteristics, since it is programmable at 6.25%. Decreasing the rate variability may certainly minimize such episodes at the cost of a higher number of FP events that should

be easily identified by physician sECG analysis. In three out of five patients, FN episodes were associated with marginal R–R interval variability. Although the remaining two subjects showed R–R variability on the Holter signal, no ICM snapshots were available during this time period. The most likely reason for missing ICM snapshots might be due to noise detection on the signal, which results in temporary arrhythmic detection suspension, to save on device memory. Nevertheless, all patients with FN events had AF documented by the ICM in at least another one episode, thus allowing their identification as AF patients.

Limitations

Nowadays, the gold standard of cardiac rhythm monitoring is represented by permanent pacemakers.[20] Therefore, compared with the latter, the AF detection rate observed in the present study might be underestimated. However, our aim was to evaluate the performance of this novel three-sensing vector ICM compared with the ECG–Holter recording in the assessment of every detectable AF episode in the same patient (intra-individual comparison). The comparison of different ICMs performance with the gold-standard permanent pacemakers will be matter of future research. In this study, only AF episodes with at least 2 min duration were included in the analysis, potentially missing clinically important runs of AF. However, it is still unknown when AF, in terms of episode duration and burden, becomes significantly associated with co-morbidities (i.e. stroke). Data available in the literature seem to indicate that arrhythmic episodes should be considered clinically relevant, especially for anticoagulation therapy management, when they last >2 min.[5,6] Of note, the minimal duration for AF detection used in the present study is programmable as it might be adjusted upon the single patient characteristics by lowering the threshold up to 30 s. The comparison between ICM detected episodes and the ECG Holter recordings was limited to a 48-h period. Longer monitoring times might determine slightly different values of sensitivity, specificity, PPV, and NPV. However, while sensitivity and specificity for determining whether a patient has AF are more time dependent compared with PPV and NPV, which are related purely to the arrhythmia incidence. Based on the abovementioned considerations, the study was conducted in a specific patient population at higher risk of AF to have several arrhythmic events to assess the value of the ICM detection algorithm. Therefore, the results might not be generalized to other patient populations, which would certainly benefit from a long-term rhythm monitoring, especially post-AF ablation patients and those with cryptogenic stroke related to short runs of PAF.

The majority of study participants were male. However, the different anatomy might not have adversely influence the AF detection rate since there were no differences in the sensing amplitude. Two smaller and injectable ICMs (Reveal LINQ; BioMonitor2) have been recently launched on the market, potentially representing the next generation of subcutaneous recording device systems, and they may provide additional benefits compared with their predecessors.[18]

Conclusions

Continuous monitoring using the novel ICM, equipped with a dedicated AF detection algorithm, accurately detected AF episodes with 95.4% mean episode sensitivity and 76.3% mean episode PPV. The three-vector ICM is a promising and reliable tool in the accurate AF detection, potentially guiding clinicians to tailor individual AF patient's management. Further long-term prospective studies are needed to evaluate the clinical benefits of this novel device.

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