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54.8%

of first time ICD recipients were candidates for S-ICD.[1]

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REFERENCE
1. Friedman DJ, et al. Trends and In-Hospital Outcomes Associated with Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States. JAMA Cardiology 2016.

Rhythm Control and Its Relation to Symptoms during the First Two Years after Radiofrequency Ablation for Atrial Fibrillation

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Clinical Trial Registration: *URL: http://clinicaltrials.gov. Unique Identifier: NCT00697359.*

Objectives: *To evaluate rhythm control up to two years after atrial fibrillation (AF) ablation and its relation to reported symptoms.*

Background: *The implantable loop recorder (ILR) continuously records the electrocardiogram (ECG), has an automatic AF detection algorithm, and has a possibility for patients to activate an ECG recording during symptoms.*

Methods: *Fifty-seven patients (mean age 57 ± 9 years, 60% male, 88% paroxysmal AF) underwent AF ablation following ILR implantation. Device data were downloaded at the ablation and three, six, 12, 18, and 24 months after ablation.*

Results: *Fifty-four patients completed the two-year follow-up. Thirteen (24%) patients had no AF episodes detected by ILR during follow-up. Ten of 41 patients (24%) with AF recurrence were only detected by ILR and AF recurrences were detected earlier by ILR ($P < 0.001$). The median AF burden in patients with AF recurrence was 5.7% (interquartile range 0.4–14.4) and was even lower in patients with AF only detected by ILR ($P = 0.001$). Forty-eight % of the patients indicated symptoms via the patient activator but 33% of those recordings were not due to AF. Early AF recurrence (within 3 months) was highly associated with later AF recurrence ($P < 0.001$). AF burden >0.5% and longest AF episode >6 hours before the ablation were independent predictors of AF recurrence during intermittent but not continuous monitoring.*

Conclusions: *After AF ablation, the AF burden was low throughout the 24 months follow-up. Nevertheless, symptoms were commonly indicated but one-third of patient-activated recordings did not show AF. Continuous monitoring was superior to intermittent follow-up in detecting AF episodes and assessing the AF burden. (PACE 2016; 39:914–925)*

atrial fibrillation, catheter ablation, implantable loop recorder, monitoring, symptoms

Introduction

Current guidelines recommend catheter ablation of atrial fibrillation (AF) after failure of at least one antiarrhythmic drug (AAD) but can be considered as initial therapy in selected cases.[1] Success rates after AF ablation are currently based on symptoms, intermittent standard electrocardiogram (ECG) recordings, and ambulatory long-term monitoring. However, asymptomatic AF is common,[2] and the proportion of recurrent asymptomatic compared to symptomatic AF episodes increases after ablation.[3] Based on these current follow-up strategies, the success rates of AF ablation might be overestimated, and continuous long-term ECG monitoring for detection of AF with a possibility of symptom versus ECG correlation may provide more accurate information on rhythm status after ablation.

Disclosure: Björkenheim, Chemnitz, Magnuson, and Poçi have no disclosures. Brandes and Edvarsson are members of the Medtronic speaker bureau. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Continuous monitoring using cardiac implantable electronic devices found the duration of AF episodes to be associated with an increased risk of stroke.[4–7] Furthermore, Boriani et al. showed that the stroke risk was associated with the duration of the AF episodes in combination with $CHADS_2$ or CHA_2DS_2-VASc scores.[8] AF detection during continuous rhythm monitoring with a subcutaneously implanted loop recorder (ILR) was validated in the XPECT study.[9] ILRs have since been used in clinical studies for detection of AF after ablation with follow-up periods of up to 12 months.[10,11]

The aim of this study was to evaluate the rhythm control during the first two years after AF ablation, assessed by continuous monitoring using ILRs and intermittent monitoring, and its relationship with reported symptoms.

Materials and Methods

Patients who were scheduled for AF ablation between April 2009 and January 2013 at Örebro University Hospital, Sweden, and Odense University Hospital, Denmark, were eligible for inclusion in this prospective two-center study. All patients had symptomatic paroxysmal or persistent AF and provided written informed consent. The study protocol was approved by the appropriate ethical boards and was in compliance with the Declaration of Helsinki.

Device Characteristics, Implant Procedure, and Interpretation of AF Episodes

At least two weeks before the AF ablation, all patients received an ILR (Reveal® XT, Medtronic Inc., Minneapolis, MN, USA), which was implanted subcutaneously in the left parasternal area. The device has a battery longevity of up to three years. It automatically classifies and saves 30-s recordings of predefined arrhythmias (atrial tachycardia, AF, bradycardia, asystole, or fast ventricular tachyarrhythmia). The AF detection algorithm uses irregularity and incoherence in R-R intervals to identify and classify patterns in the ventricular conduction. The R-R intervals are analyzed within two-minute periods, and the difference in duration between consecutive R-R intervals (ΔR-R) is calculated. The variability of these ΔR-R intervals is subsequently calculated in a way similar to constructing a Lorenz plot.[12] When R-R intervals within the two-minute interval show a certain pattern of uncorrelated irregularity, the rhythm in this interval is classified as AF.[9] All patients were equipped with the Patient Assistant activator that enables the patient to save and store ECG in the ILR when experiencing symptoms of AF. The episode log shows up to 30 automatically detected AF episodes and up to 10 patient-activated episodes. In total, 49.5 minutes of ECG could be stored. When the memory is full, the first stored episode is overwritten by the latest episode. The ILR was interrogated at each outpatient visit. The episode log and recorded ECGs were all visually adjudicated by two experienced cardiologists (A.Br and A.Bj). The AF burden was calculated and reported based on all adjudicated AF episodes.

Catheter Ablation Procedure

The procedure was performed on uninterrupted oral anticoagulation with warfarin within the therapeutic international normalized ratio interval at least four weeks before ablation. Real-time 3D electroanatomic mapping was performed (CARTO Merge, Biosense Webster, Diamond Bar, CA, USA). Circumferential lines were produced around each pair of pulmonary vein (PV) ostia. The end point was the absence of PV signals for at least 15 minutes during sinus rhythm (SR). Direct current cardioversion was performed as needed. After ablation, all patients were observed on telemetry monitoring for 24–48 hours. AADs and warfarin were continued for three to six months after the ablation and then reevaluated. Withdrawal of AADs was guided by symptoms and intermittent ECG monitoring rather than the actual AF burden. Anticoagulation therapy was based on the CHA_2DS_2-VASc score regardless of arrhythmia status.

Follow-Up

The ILR was interrogated at ablation and during scheduled visits three, six, 12, 18, and 24 months after ablation or during unscheduled visits for presumed AF symptoms. A continuous Holter monitoring (SpaceLabs Healthcare, Snoqualmie, WA, USA) or a continuous external loop monitoring (R.TEST Evolution 3, NOVACOR, Rueil-Malmaison, France) for 48–96 hours was performed at each visit. A 12-lead ECG was recorded at each visit. Transthoracic echocardiography was performed at baseline and six, 12, and 24 months after the AF ablation. Reablation was permitted at the investigator's discretion without excluding the patient from the study. All patients were followed for a minimum of two years from the first ablation.

Outcome Measures

The outcome measures included time to first AF recurrence and AF burden over time. AF recurrence was defined as a 30-second episode of AF when detected on Holter or continuous external loop monitoring and an adjudicated two-minute episode when detected by ILR. AF burden was calculated from the ILR data as the percentage of

time in AF between visits. All symptoms reported via the patient activator of the ILR were compared with simultaneously recorded rhythm strips.

The rhythm analysis was performed with and without a three-month blanking period after ablation. We used two AF burden cut-off limits, 0% and <0.5%, at each scheduled visit, the latter previously suggested to classify patients as responders versus nonresponders.[13]

Statistical Analysis

Categorical variables are presented as percentages and continuous variables as mean ± standard deviation (SD) or median and interquartile range (IQR), when appropriate. Boxplots were used to visualize number of AF episodes, longest AF episode, and AF burden between time intervals of six months up to 24 months. For a few missing data within these time intervals, we used the "Last Observation Carried Forward" method. Friedman's test was applied to evaluate differences between time intervals. The McNemar test was used to evaluate differences between time intervals for categorical variables and the paired *t*-test to evaluate echocardiographic parameters. The Mann-Whitney U-test and Wilcoxon paired rank sum test were used to evaluate AF burden. Time to first AF recurrence was visualized with Kaplan-Meier curves between ILR and intermittent monitoring and was evaluated by Cox regression for clustered observations, which gives hazard ratios (HR) with a 95% confidence interval (CI) as the association measure.

Logistic regression was used to evaluate predictors of AF recurrence detected with intermittent monitoring and ILR, respectively. All variables in Table I were considered as potential predictors but for the multiple regressions only variables measured before ablation were included. History of AF, AF burden, and longest AF episode were evaluated on categorical and on a log linear scale and left atrial diameter and body mass index on both a linear scale and categorized as normal weight, overweight, and obese using the World Health Organization standard. A P value of <0.05 was considered statistically significant. All statistical analyses were done using SPSS version 22 (IBM Corp., Armonk, NY, USA) or STATA release 11 (StataCorp, College Station, TX, USA).

Results

Baseline Characteristics

Fifty-nine patients were included in the study, 57 of whom underwent AF ablation. Following ILR implantation, one patient withdrew and one was excluded before ablation because of no AF documentation during symptoms. One patient withdrew directly after the ablation due to sepsis, one patient was excluded at 12 months because of a severe neurological disorder, and one patient was excluded because of cancer, from which the patient died 18 months after ablation. Fifty-four patients completed the 24-month follow-up. The baseline characteristics are shown in Table II. The ILR was implanted 57 ± 37 days (range 18–218 days) before the ablation procedure. During this period, the median AF burden was 0.9% (IQR 0–5.3). Twenty-three (43%) patients had a reablation procedure a mean of 11 ± 4 months after the first procedure. The use of class IC or class III antiarrhythmic drugs decreased significantly during the study period, while the proportion of patients on β-blockers and anticoagulation treatment did not change significantly during follow-up (Fig. 1).

Rhythm Control up to 24 Months

Figure 2A shows the time to the first recurrence of AF detected by ILR. Ninety percent of patients with AF recurrence after the blanking period also had a recurrence during the blanking period compared with 15% of patients without recurrence after the blanking period ($P < 0.001$). After the blanking period, at least one AF recurrence was detected by the ILR in 41 (76%) patients and by intermittent follow-up in 31 (57%) patients (Fig. 2B). All AF recurrences identified by intermittent follow-up were also detected by ILR. Moreover, the ILR detected AF recurrences significantly earlier than intermittent follow-up (hazard ratio 1.51 [95% confidence interval: 1.22–1.87], $P < 0.001$). The median AF burden after the blanking period up to the 24-month follow-up was significantly lower when AF was only detected by ILR (n = 10), 0.11% (IQR 0.003–0.92), compared with when detected by both intermittent monitoring and ILR (n = 31), 5.7% (IQR 0.4–14.4) $P = 0.001$.

Thirteen (24%) patients had no AF episodes at all detected by ILR after the end of the blanking period and up to 24 months after ablation, while at least one AF episode was detected by ILR in 41 (76%) patients, corresponding to a median AF burden of 1.2% (IQR 0.3–12.3). Eleven of the 13 patients with no AF recurrence detected by ILR had paroxysmal AF at baseline.

The proportion of patients without recurrence of AF detected by ILR during the past six-month period was 48% at six months, 43% at 12 months, 43% at 18 months, and 43% at 24 months, i.e. fairly constant over time but the rhythm varied between AF and SR among 13–19% of the patients from one six-month period to the other, meaning that the concordance between successive time intervals was 81–87% (Fig. 3A). Using an AF

Table I.

Analysis of Predictors of AF Recurrence after AF Ablation with Logistic Regression

	Recurrence 3–24 Months (n = 41)	No Recurrence 3–24 Months (n = 13)	Unadjusted		Adjusted	
			OR (95% CI)	P	OR (95% CI)	P
Continuous Monitoring						
Age, mean ± SD, OR per year	58 ± 10	55 ± 9	1.035 (0.969–1.106)	0.31	1.076 (0.961–1.205)	0.20
Female sex	39%	38%	1.02 (0.28–3.69)	0.97	0.53 (0.10–2.91)	0.53
BMI, mean ± SD, OR per unit	29.0 ± 5.2	29.1 ± 3.6	0.998 (0.876–1.136)	0.97	1.073 (0.899–1.208)	0.44
BMI < 25	20%	0%	Reference	0.18†		
BMI 25–29	39%	62%	NE			
BMI ≥ 30	41%	38%	NE			
History of AF in months, median (IQR), OR per unit log scale	72 (IQR35–120)	72 (IQR30–168)	0.65 (0.12–3.58)	0.62	0.34 (0.04–3.05)	0.34
History of AF > 72 months	46%	46%	1.01 (0.29–3.52)	0.99		
AF burden before ablation, median (IQR), OR per unit log scale	1% (IQR0–9)	0% (IQR0–4)	2.15 (0.66–7.06)	0.20	2.67 (0.60–11.8)	0.20
AF burden >0.5% before ablation	68%	46%	2.43 (0.67–8.82)	0.18		
Longest AF before ablation in hours, median (IQR), OR per unit log scale	5 (IQR0–33)	0 (IQR0–15)	2.05 (0.85–4.92)	0.11		
Longest AF > 6 hours before ablation	46%	31%	1.91 (0.50–7.33)	0.34		
Persistent AF	12%	15%	0.76 (0.13–4.50)	0.77	0.25 (0.02–2.56)	0.24
Hypertension	42%	39%	1.13 (0.32-4.07)	0.85	0.76 (0.16–3.57)	0.73
LA diameter, mean ± SD, OR per unit	42 ± 8	41 ± 5	1.05 (0.42–2.59)	0.92	0.60 (0.16–2.29)	0.45
LA diameter < 40 mm	49%	61%	0.60 (0.17–2.13)	0.42		
Early AF recurrence < 3 months	90%	15%	50.9 (8.2–316)	**<0.001**		
Early ILR activation < 3 months while AF	54%	8%	13.9 (1.65–117)	**0.015**		

(Continued)

Table I.

Continued

	Recurrence 3–24 Months (n = 31)	No Recurrence 3–24 Months (n = 23)	Unadjusted		Adjusted	
			OR (95% CI)	P	OR (95% CI)	P
Intermittent Monitoring						
Age, mean ± SD, OR per year	58 ± 9	55 ± 10	1.039 (0.980–1.102)	0.20	1.015 (0.926–1.112)	0.75
Female sex	32%	48%	0.52 (0.17–1.58)	0.25	0.35 (0.08–1.61)	0.18
BMI, mean ± SD, OR per unit	28.4 ± 5.1	29.9 ± 4.4	0.933 (0.831–1.047)	0.24	0.963 (0.828–1.121)	0.63
BMI < 25	23%	4%	Reference			
BMI 25–29	42%	48%	0.17 (0.02–1.59)	0.12		
BMI ≥ 30	36%	48%	0.14 (0.02–1.36)	0.09		
History of AF in months, median (IQR), OR per unit log scale	84 (36–120)	48 (24–120)	1.86 (0.43–8.06)	0.41	2.13 (0.33–13.6)	0.43
History of AF > 72 months	52%	39%	1.66 (0.56–4.96)	0.36		
AF burden before ablation, median (IQR), OR per unit log scale	2% (1–36)	0% (0–3)	4.06 (1.29–12.8)	**0.017**	4.90 (1.13–21.3)	**0.034**
AF burden > 0.5% before ablation	82%	39%	6.8 (1.9–24.7)	**0.003**		
Longest AF before ablation in hours, median (IQR), OR per unit log scale	10 (3-100)	0 (0–4)	4.52 (1.66–12.3)	**0.003**		
Longest AF >6 hours before ablation	59%	22%	5.24 (1.50–18.3)	**0.010**		
Persistent AF	16%	9%	2.02 (0.36–11.5)	0.43	0.59 (0.07–5.27)	0.64
Hypertension	45%	35%	1.54 (0.51–4.70)	0.44	1.63 (0.41–6.49)	0.49
LA diameter, mean ± SD, OR per unit	42 ± 8	41 ± 6	1.23 (0.56–2.70)	0.60	0.95 (0.31–2.94)	0.93
LA diameter < 40 mm	45%	52%	Reference			
LA diameter < 40 mm	55%	48%	1.32 (0.45–3.91)	0.61		
Early recurrence < 3 months	16%	0%	NE	0.06†		
Early ILR activation < 3 months while AF	61%	17%	7.52 (2.05–27.5)	**0.002**		

Adjusted for all variables except for longest AF before ablation, early AF recurrence and early ILR activation. Bold values are considered statistically significant (P values < 0.05).
†Fisher exact test.
AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; ILR = implanted loop recorder; IQR = interquartile range; LA = left atrial; NE = Not estimable; OR = odds ratio; SD = standard deviation.

Table II.

Baseline Patient Characteristics

	n = 57
Male sex	34 (60%)
Age, years (mean ± SD)	57 ± 9
BMI (mean ± SD)	29 ± 5
Paroxysmal AF	50 (88%)
Persistent AF	7 (12%)
Months from first AF episode (median, IQR)	57 (IQR 36–120)
Days from latest perceived AF episode	29 (IQR 3–116)
EHRA I	20 (35%)
EHRA II	23 (40%)
EHRA III	13 (23%)
EHRA IV	1 (2%)
Concomitant cardiovascular disease	
Heart failure	2 (4%)
Hypertension	24 (42%)
Diabetes	2 (4%)
Coronary artery disease	1 (2%)
Previous CABG	1 (2%)
Valvular heart disease	1 (2%)
Stroke/transient ischemic attack	8 (14%)
$CHADS_2$ scores	
0	31 (54%)
1	14 (25%)
≥2	12 (21%)
CHA_2DS_2-VASc scores	
0	15 (26%)
1	20 (35%)
≥2	22 (39%)
Echocardiogram	
LVEF, % (mean ± SD)	60 ± 5
Left atrial diameter, mm (mean ± SD)	42 ± 7
Medications	
β-Blockers	37 (65%)
Class I AAD	16 (28%)
Class III AAD	16 (28%)
Warfarin	42 (74%)

Values are n (%), mean ± SD or median (IQR). AAD = antiarrhythmic drugs; AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke/transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥65 or 75 years, diabetes, prior stroke/transient ischemic attack, vascular disease, female sex; EHRA = European Heart Rhythm Association; IQR = interquartile range; LVEF = left ventricular ejection fraction; SD = standard deviation.

burden cut-off of <0.5%, 22 (41%) patients were responders from the end of the blanking period and up to 24 months after ablation, while AF recurrence was confirmed in 32 (59%) patients.

During intermittent monitoring, no AF was detected in 23 (43%) patients after ablation (Fig. 3B). The proportion of patients without recurrence of AF during the past six-month period was 74% at six months, 72% at 12 months, 68% at 18 months, and 65% at 24 months, i.e. considerably higher than with continuous monitoring.

The number of AF episodes ($P = 0.02$) (Fig. 4A) and the duration of the longest AF episode ($P = 0.04$) (Fig. 4B) decreased significantly over the two-year follow-up. The median AF burden was <1% before the ablation and was 0.09% during the 18–24 month interval (Fig. 4C).

The seven patients with persistent AF at baseline had a greater AF burden ($P = 0.001$) and longer duration of the longest AF episode ($P = 0.01$) than the 47 with paroxysmal AF before ablation, but the groups did not differ two years after ablation. Two patients had no AF recurrence at all during the long follow-up, as verified by ILR, while in four patients AF had become paroxysmal. Meanwhile, five (11%) patients with paroxysmal AF were in persistent/permanent AF at the end of follow-up.

Symptoms versus Arrhythmia Recurrence

Twenty-two (54%) patients with AF recurrence after the blanking period also had AF when reporting symptoms during the blanking period as compared to one (8%) patient without AF recurrence after the blanking period ($P = 0.003$). Twenty-six patients reported symptoms using the patient activator after the blanking period (Table III). Twenty-one (81%) of them had AF at least once when reporting symptoms, and five patients (19%) had no AF recurrence during the whole follow-up. Another three patients had AF recurrence but no reported symptoms during AF, but nevertheless reported symptoms at other times. Altogether the 26 (48%) patients reported symptoms on 341 occasions, of which 228 (67%) correlated with AF episodes. Five of the 13 patients (38%) without AF recurrence reported symptoms on 48 occasions after the blanking period. Twenty-one of 41 patients (51%) with AF recurrence reported symptoms at least once during the follow-up.

Twenty-five patients did not use the patient activator after the blanking period up to two years after ablation, but 17 (68%) of them had at least one ILR-detected AF recurrence and one patient underwent reablation.

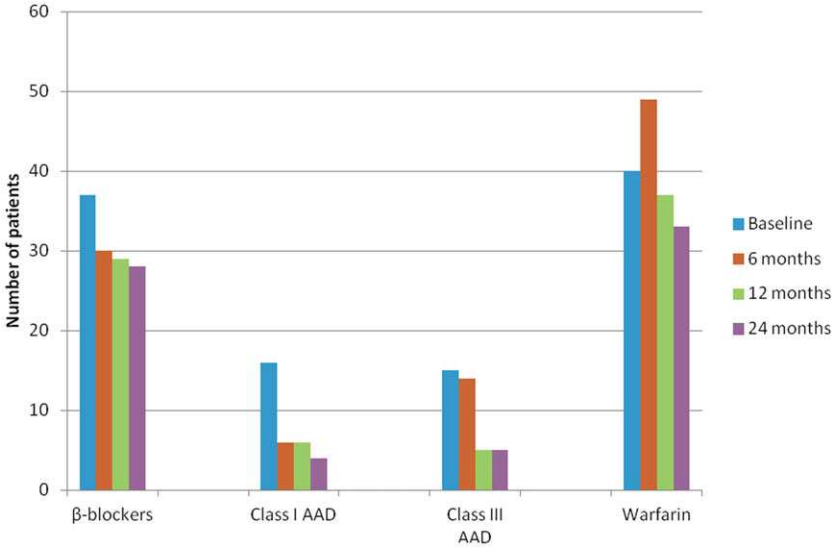


Figure 1. *Medications during the two-year follow-up. The change from baseline to 24 months after ablation was statistically evaluated with the McNemar test.*

Ten patients had AF recurrences after the blanking period detected only by ILR. Five of them indicated symptoms, three of them in connection with AF recurrence, and two at times when they did not have AF. The other five patients never indicated symptoms, but one of them nevertheless underwent a redo procedure for recurrent AF.

Seven of the 31 patients with AF recurrence detected both by ILR and intermittent monitoring never used the patient activator. The remaining 24 patients all reported symptoms and had at least one AF episode when reporting symptoms.

Patients without symptoms were younger (P = 0.02) than symptomatic patients and more often men (P = 0.03) (Table III). The majority of patients without symptoms were on AADs at the ablation (P = 0.001).

Analysis of Predictors of AF Recurrence

Eleven variables were considered as potential predictors of AF recurrence (Table I). For continuous monitoring, early recurrence (within the first 3 months) and early recurrence combined with patient symptoms were unadjusted significantly associated to recurrence after the blanking period.

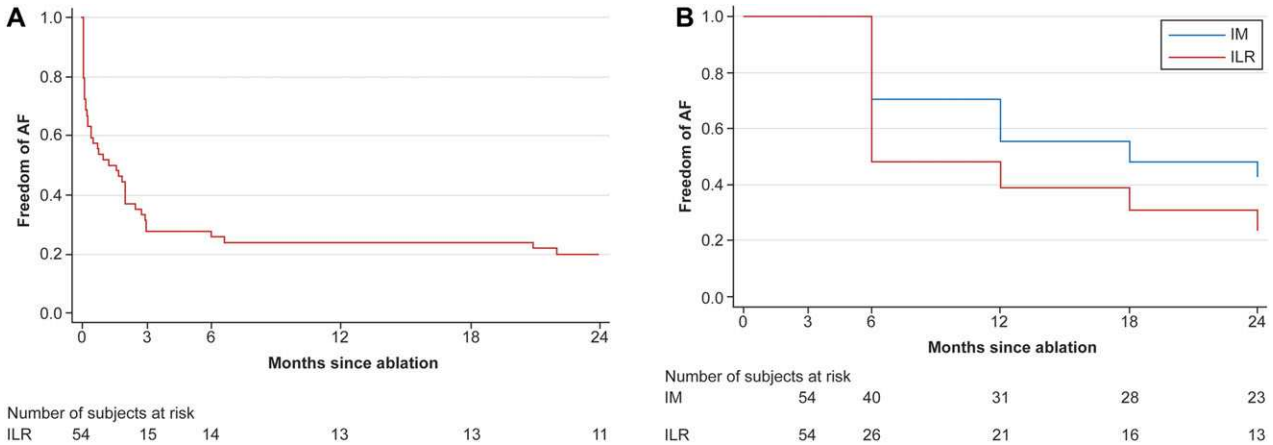
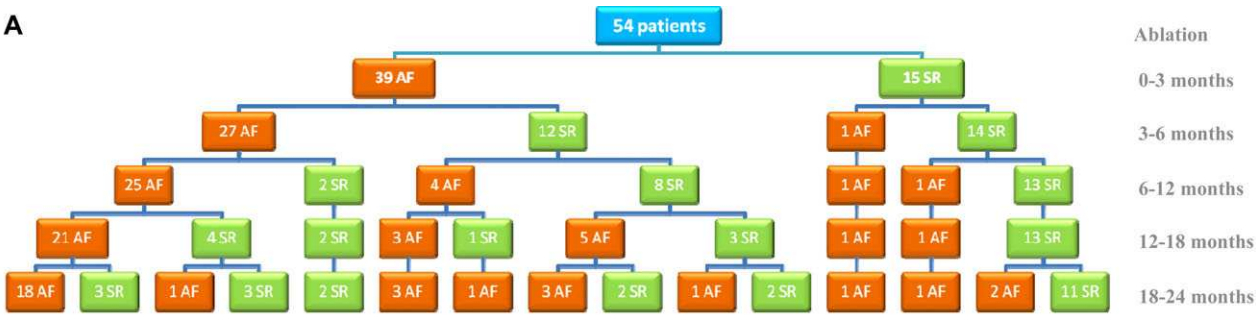
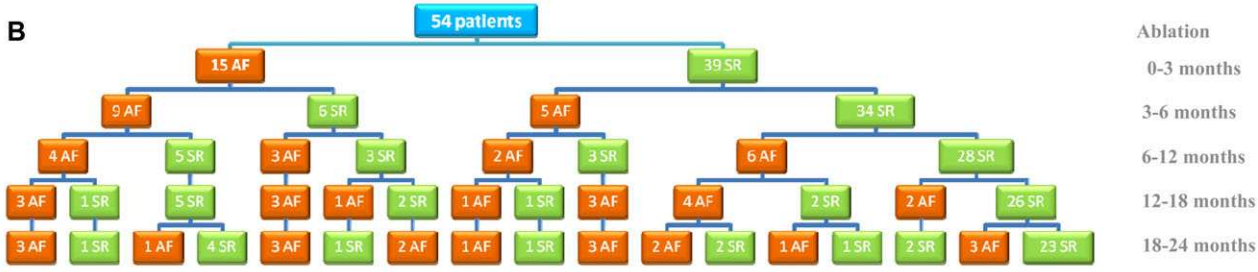


Figure 2. *Kaplan-Meier curves for freedom from atrial fibrillation after ablation showing (A) detection by the ILR at exact times 0–24 months, and (B) a comparison between ILR and IM at scheduled visits 3–24 months, excluding the blanking period from analysis, hazard ratio 1.51 (95% confidence interval: 1.22–1.87), P < 0.001. IM = intermittent monitoring; ILR = implantable loop recorder.*



	3-6 months		12 months	P*	18 months	P†	24 months	P‡
No recurrence of AF	48%		43%	0.45	43%	1.00	43%	1.00
Concordance AF + no AF		87% (26+21)		81% (26+18)		81% (26+18)		

* McNemar test comparing change of percentage of no AF between six months vs 12 months, † McNemar test comparing change of percentage of no AF 12 months vs 18 months, ‡ McNemar test comparing change of percentage of no AF 18 months vs 24 months



	3-6 months		12 months	P*	18 months	P†	24 months	P‡
No recurrence of AF	74%		72%	1.00	68%	0.75	65%	1.00
Concordance AF/no AF		68% (6+31)		81% (11+33)		78% (12+30)		

* McNemar test comparing change of percentage of no AF between six months vs 12 months, † McNemar test comparing change of percentage of no AF 12 months vs 18 months, ‡ McNemar test comparing change of percentage of no AF 18 months vs 24 months

Figure 3. *Number of patients with AF and SR measured at clinical visits after AF ablation (A) by ILR and (B) by intermittent monitoring. No recurrence of AF = AF burden 0%. Concordance of AF or no AF = SR + SR or AF + AF in two adjacent visits. Last observation carried forward was used for a few missing values. AF = atrial fibrillation; ILR = implantable loop recorder; SR = sinus rhythm*

AF burden and longest AF before ablation were highly correlated, $r = 0.93$ (Spearman) and only AF burden was considered in the multiple regression together with other variables measured at baseline. No variables were significantly associated to recurrence in the multiple regressions.

In intermittent monitoring, early recurrence combined with patient symptoms were unadjusted significantly associated to recurrence after the blanking period as well as AF burden and longest AF before ablation. In the multiple regression, where only baseline variables were considered, AF burden before ablation was a

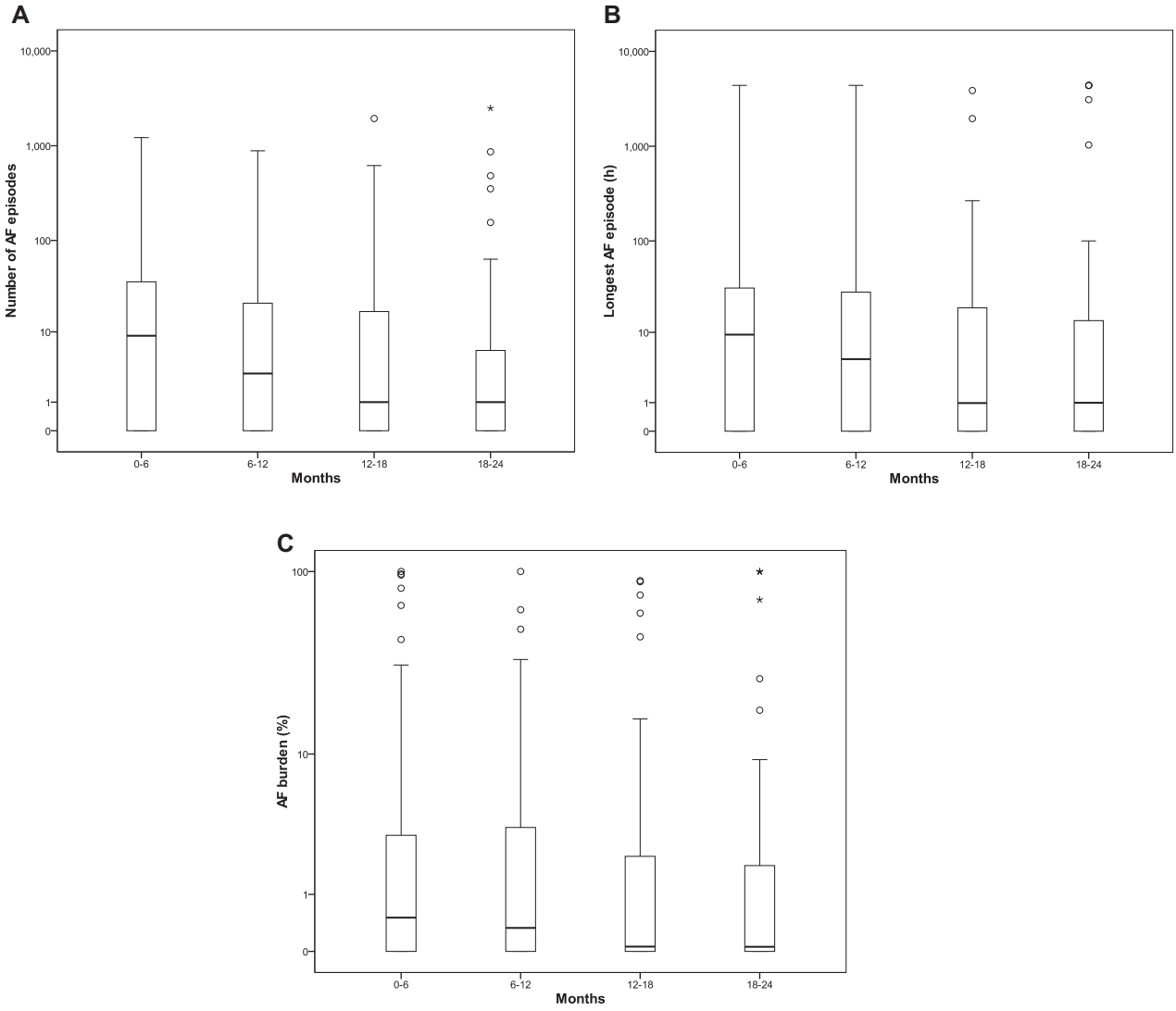


Figure 4. *Boxplot showing (A) the number of AF episodes that decreased significantly over time (P = 0.02), (B) the longest AF episode that decreased significantly over time (P = 0.04), and (C) AF burden that did not change significantly over time. Boxplot explanation: upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; the whiskers represents min and max if no outlier are present, outliers of more than 1.5 IQR or more than three IQR from the box are labeled as circles and asterisks. AF = atrial fibrillation.*

significant predictor, odds ratio (OR) 4.90 (95% CI: 1.13–21.3), P = 0.034. If duration of longest AF before ablation was included instead of AF burden, longest AF showed a significant association in the multiple regression, OR 6.30 (95% CI: 1.84–21.5), P = 0.003.

Discussion

The main findings of our study are that the AF burden was low after AF ablation and remained at a very low level during the 24-month follow-up period. Continuous rhythm monitoring was superior to intermittent follow-up in detecting AF recurrences, in particular in patients with a low AF burden and/or asymptomatic AF. AF burden >0.5% and longest AF episode >6 hours before ablation were, separately, independent predictors of AF recurrence detected by intermittent monitoring after ablation. Symptoms were reported at least once by half of the patients using the patient activator, but one third of these recordings did not show AF. More than half of the patients indicating symptoms by ILR activation confirmed to be due to AF during the blanking period, had a later

Table III.

Characteristics of Patients with AF Recurrence and No AF Recurrence and Symptoms Reported by Patient Activator

	AF Recurrence 3–24 Months		No AF Recurrence 3–24 Months		
	Symptoms (n = 21)	No Symptoms† (n = 20)	Symptoms (n = 5)	No Symptoms (n = 8)	P*
Age, mean ± SD	60 ± 9	55 ± 10	61 ± 7	51 ± 8	**0.02**
Male sex	48%	75%	40%	75%	**0.03**
BMI < 25	19%	20%	0%	0%	0.95
BMI 25–29	43%	35%	60%	63%	
BMI ≥ 30	38%	45%	40%	37%	
History of AF, months	75 (IQR39–126)	54 (IQR28–115)	72 (IQR24–204)	84 (IQR36–183)	0.48
Persistent AF	9%	15%	40%	0%	0.70
HATCH score, mean ± SD	0.6 ± 0.9	0.9 ± 1	1.2 ± 1.3	0.4 ± 0.5	0.94
AF burden before ablation	2% (IQR0.3–6)	1% (IQR0–34)	5% (IQR0, 3–52)	0% (IQR0–1)	0.06
Longest AF before ablation, hours	6 (IQR2–38)	5 (IQR0–186)	15 (2–64)	0 (IQR0–0.4)	0.07
Hypertension	38%	45%	40%	38%	0.74
β-Blockers baseline	67%	70%	80%	50%	0.70
Class I or III AAD baseline	33%	80%	40%	75%	**0.001**

*Patients with symptoms (n = 26) versus patients without symptoms (n = 28). Bold values are considered statistically significant (P values < 0.05).
†Three patients included with AF recurrence but no reported symptoms during AF, but symptoms at other times.
AAD = antiarrhythmic drugs; AF = atrial fibrillation; BMI = body mass index; HATCH score = hypertension, age older than 75 years, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, heart failure; SD = standard deviation.

recurrence of AF compared to 8% of the patients without an AF recurrence during the blanking period.

Continuous Monitoring by ILR versus Intermittent Monitoring

The AF detection algorithm in the Reveal® XT was evaluated in the XPECT trial, showing a sensitivity of 96.1% and a negative predictive value of 97.4% for identifying patients with any AF compared to Holter recordings, which makes it a suitable tool for detecting patients with AF.[9] In the present study, AF recurrences were detected significantly earlier and more often by ILR compared to intermittent follow-up, and one-fourth of them were only detected by ILR. This is in line with the ABACUS study where seven AF recurrences were detected by intermittent monitoring compared to 18 by ILR.[10] Several studies have demonstrated the correlation between the intensity of rhythm monitoring and the detection of AF recurrence[14,15] that is in favor of continuous monitoring. Long-term intermittent monitoring is also dependent on patient compliance, a problem that is overcome by ILRs although it is minimally invasive.

Most recurrences occurred early after ablation as expected, many of them within the first three months. If time to first recurrence of a 30 s AF episode had been used as the only criterion of success, the results of ablation would not have been impressive, whether a three-month blanking period was applied or not. However, the median AF burden was consistently low during the follow-up, and short-term AF recurrences did not preclude good long-term results for the patients. In our study, the AF burden in the 18–24-month interval was 10% of that before ablation, which is in line with the DISCERN AF study where the mean daily AF burden decreased from two hours per day to 0.3 hours per day[16] in 49 patients during a follow-up of 18 months. Thus, time to first recurrence of AF is not an appropriate measure of success after an intervention for AF. After ablation, the number of AF episodes and the duration of the longest AF episode decreased significantly during the 24 months of follow-up.

Symptoms versus Arrhythmia Recurrence

Half of the patients in our study reported symptoms, of which only two-thirds correlated with AF episodes. The other half of the patients did not report symptoms via the patient activator, which does not reliably mean that they did not have symptoms, supported by the fact that one of these patients underwent reablation because of symptomatic AF. Patients without symptoms were younger, more often male, and were on AADs

at ablation to a higher extent than patients with symptoms (Table III). Pokusholov et al. found, in a study of 129 patients ablated for paroxysmal and persistent AF, which only 32% of reported symptoms were due to AF.[13]

The main indication for AF ablation is symptomatic AF, and reduction of symptoms is important to the patients. However, asymptomatic AF is common even in symptomatic patients and its proportion increases after an ablation procedure.[3] In the DISCERN AF study using ILRs, a previous catheter ablation of AF was the strongest independent predictor of asymptomatic AF. The ratio of asymptomatic to symptomatic AF increased three times after ablation, and 12% of patients had only asymptomatic AF recurrences after the procedure.[16] Since asymptomatic AF carries the same risk of stroke as symptomatic AF, proper detection of any AF is necessary for prescription of subsequent adequate pharmacological treatment.

Predictors of AF Recurrence

Eleven variables were analyzed as potential predictors of AF recurrence (Table I). AF burden >0.5% and longest AF >6 hours detected by ILR before ablation, separately, were independent predictors of AF recurrence during intermittent monitoring. Because these two variables were highly correlated, they could only be included in the multiple regression analysis one at a time. Meanwhile, the same factors were not predictors of AF recurrence during continuous monitoring, implying that continuous monitoring was better than intermittent monitoring in detecting short AF episodes and a low AF burden. Continuous monitoring may also be useful in identifying patients who might benefit from reablation. Pokushalov et al. found that patients with AF recurrences at three months after ablation who underwent reablation had a significantly lower rate of AF recurrences at 12 months after ablation than patients randomized to medical therapy.[17] In our study, early recurrence was associated with later AF recurrence in the unadjusted analysis. Buiatti et al. also identified early recurrence as an independent predictor of AF recurrence after catheter ablation for lone AF in 855 patients, in addition to smoking and first-degree AV block.[18] In our study, early ILR activation while in AF was also associated with AF recurrences in the unadjusted analysis.

Is There a Need for Visual Validation of Device-Detected AF?

Visually adjudicated episodes not due to AF were not included in the adjudicated AF burden. False-positive AF episodes, e.g. due to atrial or in some cases ventricular premature beats during SR, occurred during short episodes and in patients with a low AF burden. Eventually, the difference between the device-measured and the adjudicated AF burden was insignificant. Hanke et al. showed that the risk for success misinterpretation by intermittent follow-up strategies increased in case of low AF burden, which is consistent with our results.[19]

Clinical Implications

In the present study as well as in others,[10,20] ablation resulted in a very low AF burden in most patients, and AF recurrence would have been missed in one fourth of patients based on intermittent follow-up. Patients should not be regarded as free of AF unless proven during a long and complete follow-up, and decisions regarding anticoagulation should not be based on intermittent rhythm analysis alone. Although symptomatic AF is the main indication for ablation, symptoms alone are an unreliable factor for determination of success given the poor correlation between reported symptoms and AF. Also, when using continuous monitoring, the continued indication for anticoagulants should be based on the risk score rather than on the remaining amount of AF. Previous reports have yielded variable results regarding the stroke risk and the need of anticoagulants after ablation, but even small amounts of AF have been found to increase the risk of stroke.[7]

Limitations

The number of patients was small, but they were all followed in great detail for two years after ablation. ILR data were downloaded at each visit but, in occasional patients with frequent and/or long-lasting AF recurrences, memory overflow occurred. However, all episodes defined as AF by the ILR appeared in the arrhythmia log, and the durations of the missing recordings were confirmed to be very short and contribute minimally to the AF burden.

Conclusions

After AF ablation the AF burden was low and remained low during the 24-month follow-up. Nevertheless, symptoms were commonly reported but were not a good indicator of AF without ECG confirmation as one-thirds of patient activated recordings did not show AF. Continuous monitoring was superior to intermittent follow-up in detecting especially short AF episodes and assessing the AF burden, and one-fourth of the patients had only device-detected AF recurrences, which has important clinical implications for

the selection of appropriate pharmacological treatment during subsequent follow-up.

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References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64:e1–e76.
2. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: Prevalence, prognosis, quality of life, and management. J Interv Card Electrophysiol 2000; 4:369–382.
3. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, Kottkamp H. Perception of atrial fibrillation before and after radiofrequency catheter ablation: Relevance of asymptomatic arrhythmia recurrence. Circulation 2005; 112:307–313.
4. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: Report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). Circulation 2003; 107:1614–1619.
5. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012; 366:120–129.
6. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G, Ricci R, et al. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. J Am Coll Cardiol 2005; 46:1913–1920.
7. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: The TRENDS study. Circ Arrhythm Electrophysiol 2009; 2:474–480.
8. Boriani G, Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Ricci R, et al. Improving stroke risk stratification using the CHADS2 and CHA2DS2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. Stroke 2011; 42:1768–1770.
9. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D, Rieger G, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: Results of the XPECT trial. Circ Arrhythm Electrophysiol 2010; 3:141–147.
10. Kapa S, Epstein AE, Callans DJ, Garcia FC, Lin D, Bala R, Riley MP, et al. Assessing arrhythmia burden after catheter ablation of atrial fibrillation using an implantable loop recorder: The ABACUS study. J Cardiovasc Electrophysiol 2013; 24:875–881.
11. Pokushalov E, Romanov A, Corbucci G, Bairamova S, Losik D, Turov A, Shirokova N, et al. Does atrial fibrillation burden measured by continuous monitoring during the blanking period predict the response to ablation at 12-month follow-up? Heart Rhythm 2012; 9:1375–1379.
12. Esperer HD, Esperer C, Cohen RJ. Cardiac arrhythmias imprint specific signatures on Lorenz plots. Ann Noninvasive Electrocardiol 2008; 13:44–60.
13. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Turov A, Shirokova N, Karaskov A. Ablation of paroxysmal and persistent atrial fibrillation: 1-year follow-up through continuous subcutaneous monitoring. J Cardiovasc Electrophysiol 2011; 22:369–375.
14. Kottkamp H, Tanner H, Kobza R, Schirdewahn P, Dorszewski A, Gerds-Li JH, Carbucicchio C, et al. Time courses and quantitative analysis of atrial fibrillation episode number and duration after circular plus linear left atrial lesions: Trigger elimination or substrate modification: Early or delayed cure? J Am Coll Cardiol 2004; 44:869–877.
15. Senatore G, Stabile G, Bertaglia E, Donnici G, De Simone A, Zoppo F, Turco P, et al. Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation. J Am Coll Cardiol 2005; 45:873–876.
16. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, Morillo CA, et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): A prospective, multicenter study. JAMA Intern Med 2013; 173:149–156.
17. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Turov A, Shirokova N, Karaskov A. Use of an implantable monitor to detect arrhythmia recurrences and select patients for early repeat catheter ablation for atrial fibrillation: A pilot study. Circ Arrhythm Electrophysiol 2011; 4:823–831.
18. Buiatti A, Kaess B, Reents T, Semmler V, Telishveska M, Bourier F, Kornmayer M, et al. Catheter ablation for "Lone" atrial fibrillation: Efficacy and predictors of recurrence. J Cardiovasc Electrophysiol 2016; 27:536–541.
19. Hanke T, Charitos EI, Stierle U, Karluss A, Kraatz E, Graf B, Hagemann A, et al. Twenty-four-hour Holter monitor follow-up does not provide accurate heart rhythm status after surgical atrial fibrillation ablation therapy: Up to 12 months experience with a novel permanently implantable heart rhythm monitor device. Circulation 2009; 120:S177–S184.
20. Tondo C, Tritto M, Landolina M, DE Girolamo P, Bencardino G, Moltrasio M, Dello Russo A, et al. Rhythm-symptom correlation in patients on continuous monitoring after catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2014; 25:154–160.