Early Detection and Treatment of Atrial Arrhythmias Alleviates the Arrhythmic Burden in Paced Patients: The SETAM Study

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Background: *Remote monitoring (RM) can remotely detect atrial tachyarrhythmias (ATAs). The benefit of RM compared to conventional follow-up in the detection and management of ATA was assessed in recipients of dual-chamber pacemakers.*

Methods: *The multicenter randomized SETAM study enrolled 595 patients in sinus rhythm with a CHA_2DS_2-VASc score ≥2, without ATA history and untreated with antiarrhythmics and antithrombotics, randomly assigned to RM (RM-ON; n = 291) versus ambulatory follow-up (RM-OFF; n = 304) during 12.8 ± 3.3 months. ATA occurrence, burden, and management were analyzed together with adverse clinical events.*

Results: *Patients were 79 ± 8 years old, 63% men, with a CHA_2DS_2-VASc score of 3.7± 1.2. ATA were detected in 83 patients (28%) in the RM-ON versus 66 (22%) in the RM-OFF group (P = 0.06). The median time between the pacemaker implantation and the first treated ATA was 114 days [44; 241] in the RM-ON versus 224 days [67; 366] in the RM-OFF group (hazard ratio [HR] = 0.56; 95% confidence interval [CI]: 0.37–0.86; P = 0.01). Therapies for ATA were initiated in 92 patients and the time to treatment of ATA was shortened by 44% in the RM-ON group (HR = 0.565; 95% CI: 0.37–0.86; P = 0.01). Over the last 4 months of follow-up, the mean ATA burden was alleviated by 4 hours/day (18%) in the RM-ON group. The rate of adverse clinical events was similar in both groups.*

Conclusion: *Remotely monitored patients were diagnosed and treated earlier for ATA, and subsequently had a lower ATA burden. (PACE 2017; 40:527–536)*

supraventricular tachyarrhythmia, atrial tachyarrhythmia burden, atrial fibrillation, remote monitoring, stroke

Introduction

Atrial fibrillation (AF) is the source of fatal and nonfatal clinical events, thromboembolic in particular.[1,2] Since it is often asymptomatic, its diagnosis may be challenging and its prevalence underestimated,[3] though its early detection is expected to improve the clinical outcome.[4] In

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contrast to the weak correlation observed between symptoms and episodes of atrial tachyarrhythmias (ATAs), the atrial tachyarrhythmic burden recorded by implanted devices has been found to be a sensitive and accurate measure of AF.[2,5–7] In recipients of implantable devices, the integrated Home Monitoring® technology (Biotronik SE and Co. KG, Berlin, Germany) provides, among a host of pertinent medical information, a detailed daily log of the atrial tachyarrhythmic burden, defined as the percentage of time spent at an atrial rate above a programmed value. Remote monitoring (RM) is a safe and reliable alternative to conventional monitoring of pacemaker or cardioverter defibrillator recipients[8,9] and, in observational studies, it shortened the time to first intervention for AF and lowered the incidence of adverse arrhythmic events.[10]

The French, multicenter, randomized "Strategy of Early Detection of Atrial Arrhythmias with Home Monitoring" (SETAM) trial was designed to examine the impact of RM on the detection and clinical management of ATAs.

Methods

Study Objectives

The primary objective of the study was to assess the superiority of RM compared to conventional follow-up in the detection and management of ATAs. The time between device implantation and the first ambulatory visit during which a treatment for ATAs was administered was compared in both groups. The secondary endpoints of the study included the impact of RM on the atrial arrhythmic burden and the incidence of ATAs and ATA-related adverse clinical events at 12 months.

Patient Selection

Patients were eligible for enrollment in the study if they (1) had an indication for a first implantation or replacement with an Evia® DR-T dual-chamber pacemaker (Biotronik), as defined in the practice guidelines issued by the European Society of Cardiology,[11] with activated RM; (2) had a CHA_2DS_2VASc score ≥ 2[12]; (3) were in sinus rhythm when enrolled; and (4) were able to comply with the clinical investigation plan and sign an informed consent form. The main exclusion criteria were (1) patient already treated with a class I or III antiarrhythmic drug, dual antiplatelet therapy, or long-term oral anticoagulation; (2) contraindication to these treatments; and (3) previously documented history of atrial arrhythmias.

RM System

RM uses a transmitter to automatically transmit daily data from the implantable cardiac device to the Biotronik service center over a wireless global system for mobile communication network. The data are analyzed automatically and posted on a secure Web site accessible to the physician responsible for the patient's care. Notifications are issued by the service center to the designated recipient in case of clinical, technical, or both types of messages. The RM notifications related to ATAs were programmed for an optimal detection of ATAs as follows: long atrial arrhythmic episode >6 hours, ATA burden >10% per 24 hours, and duration of mode switch episode >30% per day. The settings of other notifications were at the physicians' discretion.

Study Design

This randomized, single-blind, trial enrolled patients at 57 centers from the French National College of Hospital Cardiologists (Appendix). The study was sponsored by Biotronik SE and Co. KG, which contributed to the study design and data monitoring. The investigational plan complied with the guidelines of the Declaration of Helsinki and was reviewed and approved by the pertinent Ethics Committees. All patients provided their written informed consent before randomization.

Patients who fulfilled the inclusion criteria at the time of discharge from the hospital were randomly assigned 1:1 to an active group monitored by RM (RM-ON) versus a control group followed in a standard fashion (RM-OFF), each for 1 year. The randomization scheme was stratified by center, in blocks of 10 patients, who were unaware of their assignment. A transmitter was provided to all patients regardless of their random assignment to preserve the single-blind design and allow retrospective between-groups comparisons at the end of the study. However, the notifications were deactivated in the RM-OFF group. Crossover from one study group to the other was not allowed.

Patients in both groups were seen in the ambulatory department at 1–3 months and at 12 months after device implantation to comply with the professional practice guidelines.[13] Additional follow-ups were left to the physicians' discretion. Patients in the RM-ON group were monitored daily by RM. In case of RM-detected health event or device dysfunction, the physician was notified by e-mail, prompting the rescheduling of the next follow-up visit, if necessary. The physician's reaction time to notifications was not specified by the protocol and the patients were duly informed that the data were only evaluated during office hours on weekdays.

Device Programming

The following settings were programmed to optimize the detection of ATAs: (1) program the high atrial and ventricular rate limit at >200 and 160 beats/min, respectively; (2) activate the mode switch for atrial rates >160 beats/min; (3) activate the automatic sensitivity control to automatically measure the P and R waves; and (4) activate the atrial capture control algorithm to automatically measure the atrial threshold and adjust the pacing output, if necessary. The other settings were left to the physicians' discretion.

Supraventricular Tachyarrhythmias

ATAs included episodes of AF, atrial flutter, or atrial tachycardia with an atrial rate >200 beats/min, confirmed by the analysis of the corresponding pacemaker-stored intracardiac electrograms. Depending on the study group, ATAs were diagnosed by RM or during ambulatory follow-ups. ATA episodes were defined as significant episodes if lasting >6 hours/day or if the ATA burden was >10% per day. A RM notification was sent as soon as these preplanned limits were achieved. Whatever the study group, all episodes were confirmed during ambulatory face-to-face follow-ups on the basis of device's stored electrograms or a routine electrocardiogram (ECG). ATAs occurring within 48 hours after device implantation were excluded from the analysis. The date of the first ATA episode was defined as the date of the in-office follow-up visit during which the ATAs were diagnosed or confirmed for the first time. An independent Clinical Events Committee (Appendix) reviewed the electrograms or 12-lead ECGs available to validate all ATAs. Episodes erroneously diagnosed as ATAs or without proper electrocardiographic documentation were excluded from the analysis. Patients in both study groups were treated for ATAs, when diagnosed, according to the European Society of Cardiology guidelines for the management of patients with AF.[11] The treatment was left at the discretion of their physician according to the patient's medical condition. The date of beginning of treatment was defined as the date of the therapeutic decision. Since the clinical decision can be based on successive ATA episodes instead of an isolated ATA event, a time from ATA onset to clinical decision could not be calculated. Subsequently, the delay between enrollment and the clinical decision was preferred.

Data Collection and Management

All fatal and nonfatal major adverse events were recorded by the investigators and reviewed and classified by the clinical events committee (Appendix) before their analysis.

Sample Size Calculation

Based on an estimated 10% yearly incidence of ATAs,[14] we calculated a sample of 500 patients to detect a difference of 8 days between the study groups,[15] with a two-sided 5% significance level and an 80% power. Further assuming a dropout rate of 15%, the enrollment of 595 patients was planned.

Statistical Analysis

Continuous data are expressed as means ± standard deviation or medians [interquartile range] and categorical data as counts and percentages. Categorical data were compared by the χ^2 test or Fisher's exact test, while continuous data were compared using Student's *t*-test or Mann-Whitney U test, as appropriate. The normal distribution of data was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests.

The primary endpoint was analyzed according to the intention-to-treat principle. The Kaplan-Meier method was used to measure the survival-free from treatment of first ATAs in both groups and compared, using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the difference in time between pacemaker implant and first treatment of ATAs between the two groups were calculated, using a Cox proportional hazards model. The rate of data transmission was calculated by dividing the number of transmission days by the number of days between device implantation and end of the study. The ATA burden was calculated as the total percentage of time per 24 hours spent at an atrial rate >200 beats/min, according to the per protocol principle. Patients whose study ended prematurely, whose transmission rate was equal to 0, or whose pacemaker was not programmed in a dual-chamber pacing mode were excluded from the analysis. The data were analyzed using the SPSS software for Windows, version 19.0 (IBM Corporation, Armonk, NY, USA) or the R statistical software package, version 2.14.1.

This article was composed according to the recommendations of the CONSORT statement for the report of randomized trials.[16]

Results

Patient Population and Follow-Up

Between July 2010 and June 2012, 595 patients (mean age = 79 ± 8 years, 63% men) were enrolled in the study at 57 French medical centers (Appendix), of whom 291 were assigned to the RM-ON and 304 to the RM-OFF group. The

Table I.

Characteristics of the Entire Population and of Each Study Group

	All Patients (n = 595)	RM-OFF (n = 304)	RM-ON (n = 291)
Age, y	79 ± 8	79 ± 8	79 ± 8
Men	373 (63)	186 (61)	187 (64)
CHA_2DS_2-VASc score	3.7 ± 1.2	3.7 ± 1.2	3.7 ± 1.2
Cardiac Pacing Indication			
Sinus node dysfunction	121 (20)	56 (18)	65 (22)
Atrioventricular block	455 (77)	238 (78)	217 (75)
Other conduction defects	19 (3)	10 (3)	9 (3.)
Implant Procedure			
First implant	515 (86.6)	254 (83.6)	261 (89.7)
Device replacement	80 (13.4)	50 (16.4)	30 (10.3)
Left Ventricular Ejection Fraction			
<30%	0 (0.0)	0 (0.0)	0 (0.0)
30–50%	39 (6.6)	20 (6.6)	19 (6.5)
>50%	314 (52.8)	158 (52.0)	156 (53.6)
CHA_2DS_2-VASc risk factors			
Hypertension	482 (81.0)	244 (80.3)	238 (81.8)
Age >75	431 (72.4)	212 (69.7)	219 (75.2)
Age 65–74	132 (22.2)	78 (25.6)	54 (18.5)
Female gender	222 (37.3)	118 (38.8)	104 (35.7)
Diabetes	175 (29.4)	86 (28.3)	89 (30.6)
Vascular disease	141 (23.7)	73 (24.0)	68 (23.4)
Stroke/Transient Ischemic Attack	60 (10.1)	31 (10.2)	29 (10.0)
Heart failure	50 (8.4)	28 (9.2)	22 (7.6)
Morbidity Factors			
Sleep apnea	22 (3.7)	7 (2.3)	15 (5.2)
Chronic pulmonary disease	26 (4.4)	11 (3.6)	15 (5.2)

Values are means ± standard deviation, or number (%) of observations. RM = remote monitoring.

characteristics of the entire population and each study group are shown in Table I. The mean CHA_2DS_2-VASc score was 3.7 ± 1.2 in both study groups. No patient had a history of atrial arrhythmia prior to device implantation, and 10.1% previously had stroke or transient ischemic attack, considered as cryptogenic or of noncardiac origin.

During a mean follow-up of 12.8 ± 3.3 months, 84 patients exited the study prematurely, including 15 versus 13 deaths, 11 versus 13 loss of follow-up, and three versus four device upgrade or explantation in the RM-ON and RM-OFF group, respectively. Follow-up was completed by 249 patients in the RM-ON and 262 in the RM-OFF group.

Use and Reliability of RM

The mean transmission rate was 87 ± 18% in the RM-ON group and 86 ± 18% in the RM-OFF group (ns). Five patients (2%) in the RM-ON and two patients (1%) in the RM-OFF group (ns) transmitted no data. The pacemaker ATA diagnosis was confirmed by the stored electrograms analysis in 93% of notifications, while 7% were finally classified as noise or nonsustained ventricular tachycardia.

Primary Endpoint Analysis

The median time between the pacemaker implantation and the first treated ATA was 114 days [44–241] in the RM-ON versus 224 days [67–366] in the RM-OFF group (HR = 0.56; 95% CI: 0.37–0.86; P = 0.01). The time to treatment of ATAs was shortened by 44% in the RM-ON group (HR = 0.565; 95% CI: 0.37–0.86; P = 0.01). The cumulative percentage over time of patients with treated ATAs in each study group, up to 600 days of follow-up, for the 92 patients who were finally treated, among 149 with ATAs, is shown in Figure 1.

ATAs were detected in 149 patients, 83 (28%) in the RM-ON versus 66 (22%) in the RM-OFF group (P = 0.06), based on the device's stored

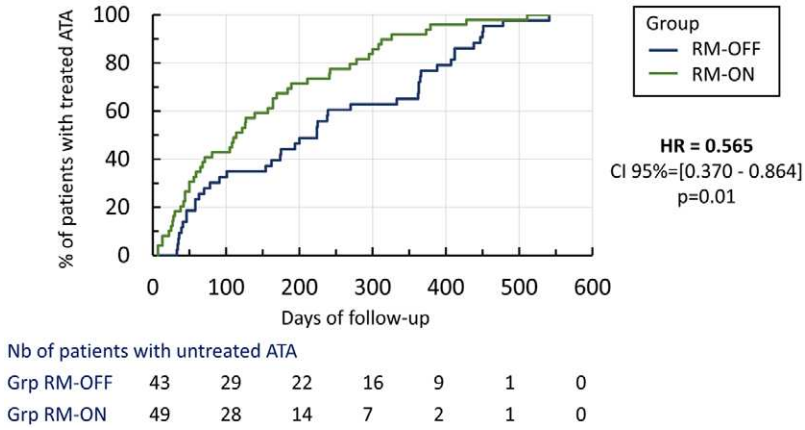

Figure 1. *Cumulative percentage of patients with treated atrial arrhythmias, for the 92 patients finally treated. [Color figure can be viewed at wileyonlinelibrary.com]*

electrograms or surface ECG. The analysis of clinical symptoms, in addition to that of routine ECG, did not provide any improvement for earlier diagnosis. In the overall population, 75.7% of ATAs were asymptomatic.

During follow-up, a treatment for ATAs, antiarrhythmic drug therapy, ablation, or cardioversion was only prescribed to 92 patients, 59% (49/83) from the RM-ON group versus 65% (43/66) from the RM-OFF group (ns), and anticoagulation therapy was initiated in 80% of all ATA patients (Table II). The ATA patients who did not receive a treatment related to ATAs had a significantly lower ATA burden compared with the patients who were prescribed a treatment for ATAs (0.04% ± 0.09 vs 10.1% ± 23.4; P = 0.002).

ATAs were more frequent in patients with sinus node dysfunction (27% vs 19%; P = 0.014), sleep apnea (7% vs 2%; P = 0.006), or a chronic pulmonary disease (7% vs 3%; P = 0.038).

Table II.

Initiated Therapies for ATA, in 92 of the 149 ATA Patients

	RM-ON (n = 49)	RM-OFF (n = 43)	P
Anticoagulation	37 (75.5)	37 (86.0)	0.31
Antiarrhythmic therapy	28 (57.1)	21 (48.8)	0.56
Rhythm control	22 (44.9)	15 (34.8)	0.44
Rate control	6 (12.2)	8 (18.6)	0.58
Antiplatelet therapy	2 (4.1)	2 (4.7)	0.70
ATA ablation	1 (2.0)	0 (0.0)	0.95
Cardioversion	1 (2.0)	0 (0.0)	0.95

Values are number (%) of observations. ATA = atrial tachyarrhythmia; RM = remote monitoring.

ATA Burden

At the end of the study, the mean ATA burden was 8 ± 26%/day in the RM-ON group versus 28 ± 43%/day in the RM-OFF group (P = 0.04) (Fig. 2).

The inset in Figure 2 shows the mean ATA burden in each group between 9 and 12 months of follow-up. The divergence of the ATA burden curves became statistically significant at the ninth month of follow-up. The mean burden was alleviated by 4 hours/day (18%) over the last 4 months of follow-up in the RM-ON group.

Adverse Clinical Events

Major cardiovascular events and deaths were comparable in the RM-ON and RM-OFF groups. In the RM-ON group, 39 patients (13.4%) experienced ≥1 hospitalization for cardiovascular adverse events versus 42 patients (13.8%) in

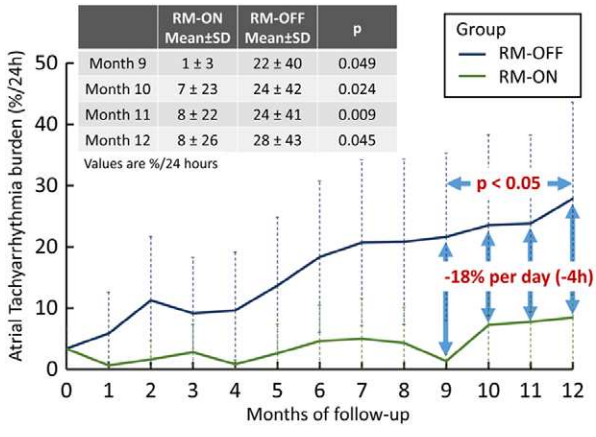

Figure 2. *Cumulative atrial tachyarrhythmia burden over 12 months of follow-up in each study group. [Color figure can be viewed at wileyonlinelibrary.com]*

Table III.

Patients with Ischemic Stroke during Follow-Up

	ATA Event (Delay) before Stroke	Antithrombotic Treatment at Time of Stroke	ATA at Time of Stroke	CHA2DS2-VASc Score
RM-ON	No	None	None	2
(n = 4)	Yes (7 months)	None	None	6
	Yes (3 months)	VKA	None	4
	Yes (4 months)	APA	Atrial fibrillation	4
RM-OFF	No	APA	None	5
(n = 7)	No	APA	None	3
	No	None	None	2
	No	APA	None	3
	Yes (16 months)	VKA	None	4
	Yes (9 months)	DOA	None	4
	No	APA, DOA	None	6

APA = antiplatelet agent; ATA = atrial tachyarrhythmia; DOA = direct oral anticoagulant; RM = remote monitoring; VKA = vitamin K agonist.

the RM-OFF group (ns). The mean duration of hospitalization was 10 ± 14 days in the RM-ON versus 11 ± 13 days in the RM-OFF group (ns).

No hemorrhagic stroke and one major bleeding, in a patient from the RM-ON group without anticoagulant therapy, occurred during follow-up. Ischemic strokes occurred in four patients (1.4%) in the RM-ON versus seven patients (2.3%) in the RM-OFF group (ns). Five patients presented with paroxysmal ATAs months before stroke occurred (Table III). Anticoagulation was not prescribed to two of them despite a CHA_2DS_2-VASc score of 6 and 4, and an HAS-BLED score of 3: in one case, a gastric angioma with a bleeding history might explain the medical decision; the second patient had a 22-minute ATA episode, without recurrence, and was reluctant to drug therapy. Six patients never presented with ATAs before stroke occurred, and only one patient was in AF at the time of stroke.

Discussion

The SETAM randomized prospective multicentric study confirmed the superiority of RM in the detection and management of atrial arrhythmias. Remotely monitored patients were diagnosed and treated earlier. Subsequently, compared with conventional follow-up, an alleviation of the atrial burden was observed, notably in the last 4 months of the study, among patients who had histories of ATAs.

AF is the most common arrhythmia, and its prevalence and associated mortality increases with age.[1,17] In our study, patients without known history of atrial arrhythmias, with a CHA_2DS_2VASc score ≥2, without ongoing antiarrhythmic or anticoagulant treatment and without contraindication to these treatments, were included, in order to be able to initiate such therapies in case of occurrence of significant atrial arrhythmias during follow-up.

In SETAM, the atrial arrhythmic episodes were counted when lasting >6 hours/day, or if the ATA burden was >10%/day. Despite this restrictive definition, the proportion of patients who developed ≥1 episode of ATA was quite high over the 1-year follow-up. The prevalence of AF was 28% in the group assigned to RM and 22% in the control group. This high incidence of arrhythmic episodes in pacemaker recipients is in support of an early detection and management strategy. It is worth noting that AV block patients were unusually prominent in the study population and this could have reduced the overall incidence of ATA and underpowered the study.

In pacemaker patients, RM is an acceptable alternative to usual follow-up, whether by its promotion of the early discharge of patients after device implantation[15] or as an alternative to regular ambulatory visits.[8] A retrospective analysis, which included >11,000 patients from 23 countries, found that RM advanced the detection of adverse events by a mean of 154 days, compared with a standard follow-up at 6-month intervals.[9] Subsequently published randomized multicenter prospective studies[8,18–23] demonstrated the early identification of events provided by RM (Table IV). In the RM-ON group of SETAM, the time to

Table IV.

Time of Event Diagnosis in Randomized Prospective Multicenter Studies on Remote Monitoring of Cardiac Implantable Electronic Devices

Study Name	Year	Number of Patients	Devices	Follow-Up (Months)	Events Detection or Intervention Delay in RM Patients vs Controls (Days)	ATA Incidence (%)	Time-Delay Until ATA Evaluation in RM Patients vs Controls (Days)
IMPACT[18]	2009	2718	DDD/CRT ICDs	24	3 vs 54 ($P < 0.001$)	34.8	NA
PREFER[19]	2009	897	VVI/DDD PMs	12.3	149 vs 191 ($P < 0.0001$)	NA	NA
TRUST[20]	2010	1,339	VVI/DDD ICDs	11.4	1 vs 35.5 ($P < 0.001$)	8.6	5.5 vs 40 ($P < 0.001$)
COMPAS[8]	2011	538	DDD PMs	18.3	17 vs 139 ($P = 0.001$)	NA	NA
CONNECT[21]	2011	1,997	DDD/CRT ICDs	15	4.6 vs 22 ($P < 0.001$)	10.6	3 vs 24
ECOST[22]	2012	433	VVI/DDD ICDs	24.2	5 vs 25 ($P = 0.04$)	1.4*	NA
EVOLVO[23]	2012	200	DDD/CRT ICDs	16	1.4 vs 24.8 ($P < 0.001$)	15	NA
SETAM	2017	595	DDD PMs	12.8	NA	25	114 vs 224 ($P = 0.01$)

ATA = atrial tachyarrhythmia; CRT = cardiac resynchronization therapy devices; DDD = dual chamber; ICDs = implantable cardiac defibrillators; NA = not available; PMs = pacemakers; RM = remote monitoring; VVI = single chamber.
*hospitalization for ATA.

diagnosis measured between the pacemaker implantation and the first treated ATA was reduced by 110 days. Silent AF episodes are common, and can occur together with symptomatic AF episodes.[24–26] In SETAM, 75.7% of the ATA episodes were silent, making the diagnostic value of RM obvious.

It has been suggested that an early management strategy for AF, with rhythm control combined with a vigorous detection and management of the associated disorders, might prevent a structural remodeling and halt the progression of ATA.[4,27] Since in our study RM detected ATA earlier, a prompt therapy could be initiated with a view to reduce recurrences. Shortening the delay in the diagnosis of AF and allowing an earlier initiation of antiarrhythmic therapy may explain the alleviation of the atrial burden observed in the last 4 months of the study in the patients with a history of ATA.

SETAM did not reveal significant between-groups differences in the rates of clinical events, notably cerebrovascular events, presumably because of an insufficient number of observations and a short follow-up, despite a reduction in AF burden. Ischemic strokes can also have a noncardiac origin and therefore cannot be anticipated by ATA detection via RM. In SETAM, six patients presented a stroke without any history of ATAs. In the COMPAS study, although its power was insufficient to compare the between-groups rates of clinical events, the rate of hospitalization for management of atrial arrhythmias or cerebral vascular accident was lower in the group followed remotely than in the group followed conventionally.[8] The SOS AF registry showed that the AF burden is a predictor of ischemic cerebral vascular accidents[28] and the Swedish AF cohort study[29] found that the anticoagulant treatment may have a net clinical benefit of 3.5% per year in terms of thromboembolic events in patients with AF. This matches with the results of SETAM, with a limited power, with four ischemic strokes in the RM-ON group versus seven in the RM-OFF

group. It must be emphasized that in SETAM the anticoagulant therapy was underprescribed in patients who presented with ATAs during follow-up, although it could have been indicated considering their average CHA_2DS_2-VASc score of 3.7 and no known contraindication to anticoagulation at study entry. However, indication for anticoagulation in case of ATA identified via cardiac pacemaker memory was still debated when the SETAM study was designed and initiated. Since then, it has been stated that anticoagulation is indicated for AF diagnosed in pacemaker recipients, as soon as the arrhythmia is confirmed by the device recordings.[30,31] In fact, only 75.5% and 86% of patients in the RM-ON and RM-OFF group, respectively, received anticoagulation following ATA occurrence. In two patients from the RM-ON group who suffered from an ischemic stroke, anticoagulation was not prescribed following ATA though it may have prevented the cerebrovascular event. Unfortunately, anticoagulation is often underprescribed to high-risk AF patients,[32] although clearly indicated by the recent guidelines.

Conclusion

The SETAM study demonstrates that the remote follow-up of dual-chamber pacemaker recipients, without history of AF and treated with neither anticoagulation nor antiarrhythmic drugs, enables an earlier diagnosis and management of atrial arrhythmias and subsequently reduces the AF burden. A larger study with a longer follow-up might be of particular value to determine whether RM lowers the incidence of AF-related cerebrovascular events via an earlier initiation of anticoagulant treatment, as clinically indicated.

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