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ORIGINAL ARTICLE

Early evaluation of atrial high rate episodes using remote monitoring in pacemaker patients: Results from the RAPID study

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Abstract

Aim: Remote monitoring (RM) of implantable cardiac devices has enabled continuous surveillance of atrial high rate episodes (AHREs) with well-recognized clinical benefits. We aimed to add evidence on the role of the RM as compared to conventional follow-up by investigating the interval from AHRE onset to physician's evaluation and reaction time in actionable episodes.

Methods and Results: A total of 97 dual-chamber pacemaker recipients were followed with RM (RM-ON group; $N = 64$) or conventional in-office visits (RM-OFF group; $N = 33$) for 18 months. In-office visits were scheduled at 1, 6, 12, and 18 months in the RM-OFF group and at 1 and 18 months in the RM-ON group. The overall AHRE rate was 1.98 per patient-year (95% confidence interval [CI], 1.76–2.20) with no difference between the two groups (RM-ON vs. RM-OFF weighted-HR, 0.88; CI, 0.36–2.13; $p = .78$). In the RM-ON group, 100% AHREs evaluated within 11 days from onset, and within 202 days in the RM-OFF group, with a median evaluation delay 79 days shorter in the RM-ON group versus the RM-OFF group ($p < .0001$). Therapy adjustment in actionable AHREs occurred 77 days earlier in the RM-ON group versus the control group ($p < .001$). In the RM-ON group, there were 50% less in-office visits as compared to the RM-OFF group ($p < .001$).

Conclusions: In our pacemaker population with no history of atrial fibrillation, RM allowed significant reduction of AHRE evaluation delay and prompted treatment of actionable episodes as compared to biannual in-office visit schedule.

KEYWORDS
atrial fibrillation, atrial high rate episodes, atrial tachyarrhythmias, pacemaker, remote monitoring

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

1 | INTRODUCTION

Atrial high rate episodes (AHREs) are defined as atrial tachyarrhythmia episodes (atrial fibrillation, atrial flutter, or atrial tachycardia) that are detected by cardiac implantable electronic devices as pacemakers, implantable cardioverter defibrillators, or implantable loop recorders. Current devices offer the option of being monitored remotely with automatic transmissions of diagnostic data from the devices to the referring clinic through a central service center.[1–3] Remote monitoring (RM) represents a useful tool for continuous surveillance of atrial rhythm with automatic alerts for relevant events, including AHREs and/or subclinical atrial fibrillation, allowing early detection and prompt reaction. This may be significant benefit considering recent evidence on the relationship between AHREs/subclinical atrial fibrillation and increased risk of stroke or systemic embolism.[1,4,5] However, few studies have investigated time from episode onset to investigator evaluation in detail during routine care of pacemaker patients by comparing regular in-person visit schedule with alert-based RM follow-up. The objective of the RAPID (RM of Atrial High Rate Episodes in Pacemaker Patients) study was to provide additional information about the role of the RM as compared to conventional follow-up for early detection and clinical management of AHREs in patients without prior documented atrial arrhythmias who received a dual-chamber pacemaker.

2 | METHODS

The RAPID study was a multicenter, prospective, nonrandomized, noninterventional trial comparing RM versus conventional follow-up for early detection of AHREs and subsequent medical intervention in patients with implanted pacemaker. The trial rationale, design, and protocol have been described previously.[6] In order to balance study arms, participating centers were selected basing on their predisclosed practice of providing RM to pacemaker recipients or not. After implant, patients who fulfilled the inclusion/exclusion criteria were enrolled and followed with RM (RM-ON group) or conventional in-office visits (RM-OFF group) according to center standard practice for 18 months. Specifically, all centers in the RM-ON group had a primary-nursing-based model of RM alerts management consisting of an experienced nurse reviewing RM data during working days and a responsible physician for supervision and medical intervention when appropriate.[7] The study was approved by the ethics committee of each participating site. All patients provided written informed consent for participation in the study.

Consenting >18-year-old patients who received a remotely monitored dual-chamber pacemaker for sick sinus node dysfunction or atrio-ventricular block were eligible. Exclusion criteria were the presence of atrial arrhythmias at the time of enrolment, prior documented or symptomatic episodes of atrial arrhythmias, replacement or upgrading of previous devices with already recorded AHREs, pregnancy, severe valvular disease, and previous valvular prosthesis.

The primary study endpoint was the AHRE evaluation delay, defined as the time from onset to physician evaluation of an adjudicated AHRE. Device AHRE detection was based on the high atrial rate criterion that was programmed with a threshold rate of 190 beats/min. Episodes were classified according to their duration: >30 s, >1 h (~5% of 24 h), and >6 h. Secondary endpoints included AHREs with associated patient-reported symptoms, and actionable AHREs defined as any appropriate AHRE leading to anticoagulation or antiarrhythmic drug initiation according to individual medical evaluation. AHRE electrogram recordings were adjudicated by an expert physician blinded to study groups.

2.1 | Implantation and device programming

All patients underwent implantation of a dual-chamber pacemaker programmed with an AHRE detection rate of 190 beats/min. Intracardiac electrogram recordings (IEGMs) were stored in the device memory and used for episode adjudication. AHRE duration was automatically provided by the device. For analysis consistency, all devices in the RM-ON group were equipped with the Home Monitoring technology (BIOTRONIK) capable of daily transmissions of device data and full arrhythmia-related diagnostics. RM data are available on a secure website for nurse and physician's review who automatically receive alert notifications about arrhythmias and technical issues. Event-triggered notifications are sent according to the alert-parameter set by the physician. Specifically, in this study, automatic RM notifications for AHRE detection were triggered by any transmitted IEGM for an AHRE; daily AHRE burden >5% (corresponding to cumulative duration of 1.2 h in a day); or long atrial arrhythmic episode >6 h.

2.2 | Follow-up

Patients in the RM-OFF group were followed in hospital at 1, 6, 12, and 18 months after discharge; subjects enrolled in the RM-ON group were remotely followed up and visited in hospital at 1 and 18 months only. Additional unscheduled in-office visits could be triggered by RM alerts in the RM-ON group. At each follow-up visit, data relative to device diagnostics and AHRE IEGM were collected and reported, as well as any adverse event and medical intervention. Investigators were requested to report the date they first became aware of any adverse event including any potential AHRE, regardless of their final adjudication, either during an in-person visit/device interrogation or a remote follow-up session. Confirmed AHREs were used for assessment of AHRE evaluation delay. Study participation terminated at the 18-month follow-up. Consent withdrawal, device removal, loss to follow-up, or death caused premature termination.

2.3 | Statistical analysis

The study was designed to test the null hypothesis that the probability of shorter AHRE evaluation delays in the RM-ON group

versus the RM-OFF group was 50%. The alternative hypothesis was based on an assumed 18% prevalence of AHRE-related symptoms[8] causing immediate patient-to-physician reporting, corresponding to 82% probability of a shorter AHRE evaluation delay in the RM-ON group. With 30% AHRE incidence at 18 months in both study groups we estimated that 104 enrolments (including 15% early dropouts) were needed to reject the null hypothesis with 80% statistical power.

During data analysis, we first assessed whether AHRE incidence did not differ between study groups to exclude potential biases induced by different underreporting rates between groups. We did this by using the propensity score with the method of inverse probability of treatment weighting[9] to adjust the hazard ratio (HR) of AHREs between study groups. Adjusting covariates were age, gender, New York Heart Association class, ejection fraction, QRS complex duration, hypertension, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, stroke or transient ischemic attack, indication to cardiac pacing. Propensity-score adjusted HR (weighted-HR) and 95% confidence interval (CI) were reported.

Then, we assessed AHRE evaluation delays reporting medians (25th–75th percentiles) of intervals from onset of adjudicated AHREs to physician evaluation and to medical intervention in both the RM-ON and RM-OFF groups. Comparisons were performed in a per-episode analysis with multivariable shared-frailty proportional hazard Cox models to control for within-subject correlation of multiple episodes. We included symptoms as an adjusting covariate. Cumulative distributions of AHRE evaluation delays were plotted by study groups.

Summary statistics for all continuous variables were presented as median and interquartile range. Categorical data were reported as absolute and relative frequency. Between-group differences in baseline characteristics were analyzed using the Wilcoxon rank-sum test for continuous variables and Fisher's or chi-square test, as appropriate, for binary or categorical variables.

A value of $p < .05$ was considered statistically significant. STATA (version 12; Stata-Corp LP) and R (version 4.0.0; R Foundation for Statistical Computing) with PSweight version 1.1.4 package were used for the statistical analysis.

3 | RESULTS

3.1 | Study population and in-person follow-ups

Of the 104 enrolled patients, 64 patients were in the RM-ON group and 40 in the RM-OFF group. Five patients of the RM-OFF group were lost with no follow-up. The remaining 97 patients (RM-ON 66%, RM-OFF 34%) completed the study follow-up and were analyzed. Table 1 summarizes baseline patient characteristics. Most patients were men (60%) with a median age of 78.5 (71.0–85.0) years. A dual-chamber pacemaker was implanted for one or more of the following indications: sinus node dysfunction (44%), any syncope (53%), and any form of atrio-ventricular (AV) block (49%). Baseline variables were similar in the two groups except for hypertensive cardiomyopathy and renal disease whose imbalance was successfully corrected during propensity score analysis. Two patients in the RM-OFF group died for noncardiovascular causes; no hospitalizations for worsening heart failure or cerebrovascular thromboembolic events were reported.

3.2 | AHRE occurrence and therapy adjustments

During a median follow-up of 18.3 (17.5–18.8) months, 298 atrial episodes from 33 patients (34%) were detected. Of them 239 were adjudicated as AHREs: 121 (51%) were atrial fibrillation (AF), 97 (40%) atrial flutter, and 21 (9%) atrial tachycardia (Figure 1). Most episodes were asymptomatic (61%) with a median duration of 2.6 (0.6–43.3) min. The overall AHRE event rate was 1.98 (CI, 1.76–2.20) per patient-year. AHREs required medical interventions (mainly anticoagulant or antiarrhythmic drug initiation) in 20 patients (21%). Most of actionable AHREs were atrial fibrillation (57.6% with a median duration of 3.3 [0.9–144.0] h) and atrial flutter (39.4% with mean duration of 0.2 [0.1–4.1] h).

At propensity score weighting analysis, the 18-month incidence of AHREs did not differ between study groups: 22.0% (CI, 9.2–30.0) in the RM-ON group versus 28.5% (CI, 7.4–44.7) in the RM-OFF group (weighted-HR, 0.88; CI, 0.36–2.13; $p = .78$).

In total, 132 and 124 in-hospital follow-ups were performed in the RM-OFF and in the RM-ON groups, respectively. The median number of in-person evaluations per patient was significantly lower with RM (RM-OFF group: 4 [4–4]; RM-ON group: 2 [2–2]; $p < .001$).

3.3 | Timing of AHRE evaluation

The count of AHREs and their evaluation delays are reported in the Table 2 by study groups and by class of duration and actionability, along with the type of reactions. The median evaluation delay was significantly shorter in the RM-ON group than in the RM-OFF group (2 [2–4] vs. 81 [23–103] days) the difference being highly significant after adjusting by symptoms and controlling for multiple episodes in individuals ($p < .0001$, shared-frailty Cox model). Statistical significance was also reached after filtering sustained episodes ≥1 h ($p < .0001$) or ≥6 h ($p = .04$). The difference was confirmed also by considering only the subset of episodes requiring medical intervention (3 [2–4] days in the RM-ON group vs. 80 (53–150) days in the RM-OFF group, $p < .001$). Cumulative distributions of AHRE evaluation delays are plotted in Figure 2 showing that in the RM-ON group with automatic alerts, all AHREs were evaluated by physicians within a maximum of 11 days from onset, regardless of duration and episode actionability. Conversely, the biannual in-person visit schedule in the RM-OFF group required a maximum of 202 days for all episodes and 166 days for actionable episodes to be evaluated.

TABLE 1 Baseline patient characteristics

Characteristic	RM-ON, *N* = 64	RM-OFF, *N* = 33	*p*-value
Age, years	79.0 (73.0, 84.0)	78.0 (68.5, 85.5)	.7
Males	41 (64%)	17 (52%)	.3
Cardiomyopathy			
None	53 (82.8%)	23 (69.7%)	.8
Dilated	2 (3.1%)	2 (6.1%)	.6
Hypertensive	3 (4.7%)	7 (21%)	.029
Ischemic	9 (14%)	7 (21%)	.5
NYHA class			.4
I	31 (56%)	14 (70%)	
II	24 (44%)	6 (30%)	
LVEF, %	60.0 (58.0, 64.0)	60.0 (55.0, 62.0)	.3
QRS complex duration, ms	90.0 (87.0, 115.0)	90.0 (87.8, 90.5)	.2
Comorbidities			
Heart failure	2 (3.2%)	0 (0%)	.9
Hypertension	58 (91%)	29 (88%)	.7
Renal disease	9 (14%)	0 (0%)	.026
Diabetes	18 (28%)	5 (15%)	.2
Stroke/TIA	3 (4.7%)	0 (0%)	.5
Cardiac pacing indication			
Sick sinus syndrome	40 (62%)	19 (58%)	.64
II–III AV block	21 (33%)	7 (21%)	.23
Others	3 (5%)	7 (21%)	-
Therapy			
ACE	27 (42%)	12 (38%)	.8
Sartans	18 (28%)	12 (36%)	.5
Statins	10 (16%)	5 (18%)	.9
Beta-blockers	17 (27%)	7 (21%)	.7
Diuretics	27 (42%)	13 (39%)	.9
Calcium antagonists	27 (42%)	10 (31%)	.4
Antiplatelet	9 (14%)	10 (30%)	.1
Class IC antiarrhythmic	0 (0%)	0 (0%)	-
Amiodarone	0 (0%)	0 (0%)	-
Sotalol	0 (0%)	0 (0%)	-

Abbreviations: ACE, angiotensin converting enzyme; AHRE, atrial high rate episode; AV, atrioventricular; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; RM, remote monitoring; TIA, transient ischemic attack.

4 | DISCUSSION

We tried to investigate in detail the delay from AHRE onset to physician evaluation (and subsequent reaction if necessary) in a pacemaker population without history of atrial fibrillation. We compared a follow-up strategy solely based on RM with automatic notifications and a conventional biannual schedule of in-person visits. The comparison was performed in the context of routine care in centers following up pacemaker patients either with remote monitoring or in-hospital visits. Although overall prevalence of AHREs was similar in the study groups after 18-month follow-up, the use of RM allowed reduced time from episode onset to physician evaluation and prompt treatment of clinically relevant events. In the RM-ON group AHRE evaluation delay was 79 days shorter than in the RM-OFF group, with medical therapy adjusted 77 days earlier. Our findings are in line with previous studies.[10–13] In the TRUST (The Lumos-T Safely Reduces Routine Office Device Follow-Up) trial, detection of arrhythmic events was anticipated by >30 days as compared with conventional follow-up schedule.[10] The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial reported a reduction in the median time from atrial episodes to medical reaction in the RM group versus the control group (4.6 vs. 22 days, respectively).[11] Similarly, in the SETAM (Early Detection and Treatment of Atrial Arrhythmias Alleviates the Arrhythmic Burden in

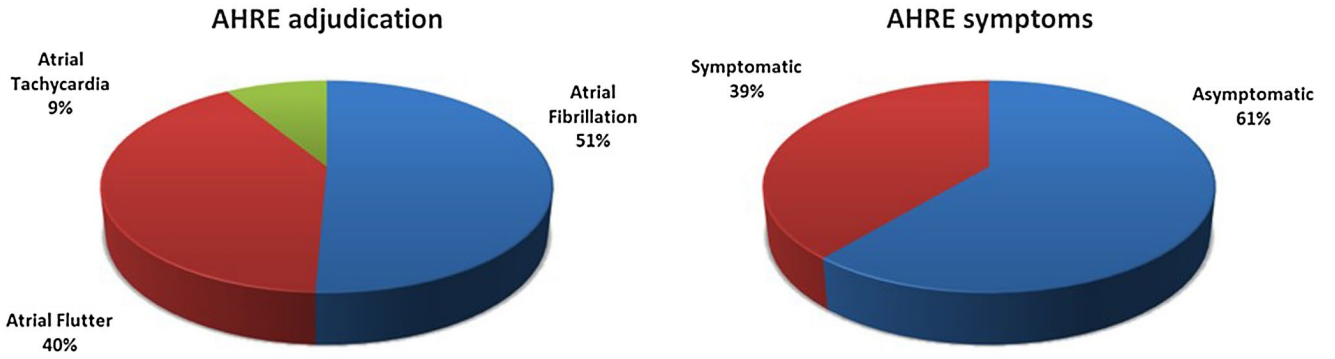

FIGURE 1 Classification of atrial high rate episodes and related symptoms

TABLE 2 AHRE count and time from onset to physician's evaluation (evaluation delay) by study groups

	RM-ON	RM-OFF	*p*[a]
AHRE evaluation delay (days)			
All episodes			
No. of episodes	155	84	
Evaluation delay (days)	2 (2–4)	81 (23–103)	<.0001
Actionable episodes			
No. of episodes (%)	23 (15%)	10 (12%)	
Evaluation delay (days)	3 (2–4)	80 (53–150)	<.0001
AHRE >1 h			
No. of episodes (%)	54 (35%)	12 (14%)	
Evaluation delay (days)	2 (2–3)	103 (38–156)	<.0001
AHRE >6 h			
No. of episodes (%)	25 (16%)	1 (1%)	
Evaluation delay (days)	2 (2–3)	121 (121–121)	.04[b]
Initiated therapies (*n*, % of patients)			
Anticoagulation	12 (18.7%)	7 (21.2%)	
Rhythm control	8 (12.5%)	2 (6.0%)	
Rate control	4 (6.2%)	1 (3.0%)	
Any therapy introduction	13 (20.3%)	7 (21.2%)	

Abbreviations: AHRE, atrial high rate episode; RM, remote monitoring.

[a]Results of per-episode analysis based on proportional hazard Cox model with shared frailty to control for multiple episodes in individual patients and using study group as independent variable and symptoms as covariate.

[b]Logrank test.

Paced Patients) study recruiting only pacemaker patients, the delay in the RM-OFF group was 110 days with respect to the RM-group.[13] Differences in AHRE evaluation delay reflect different in-person visit schedules used in the control group and heterogeneity of selected populations (prevalently with implantable defibrillators or cardiac resynchronization therapy devices). We adopted a biannual schedule for in-person visits in the RM-OFF group that is quite intensive for a pacemaker population as compared with common practice.[14] Therefore, our estimations of AHRE evaluation delay without RM are conservative.

We focused on pacemaker recipients as few studies have been conducted so far in this population, which is still underrepresented in the current cohort of remotely monitored devices, mainly because of costs and reimbursement issues.[15] Nonetheless benefits of RM, including early detection of AHREs and prevention of thromboembolic events, are at least equally relevant in this large population.

It is well established that even asymptomatic AHREs are associated with a higher risk of thromboembolic events in patients without prior history of atrial fibrillation.[1,16] A recent sub-analysis of the ASSERT study showed a direct correlation between AHRE duration and increased risk of stroke or systemic embolism.[17] Additionally, in patients with no clinical history of atrial fibrillation, the presence of AHREs at device interrogation was frequently associated with transitions to high thresholds of atrial fibrillation burden during follow-up.[18]

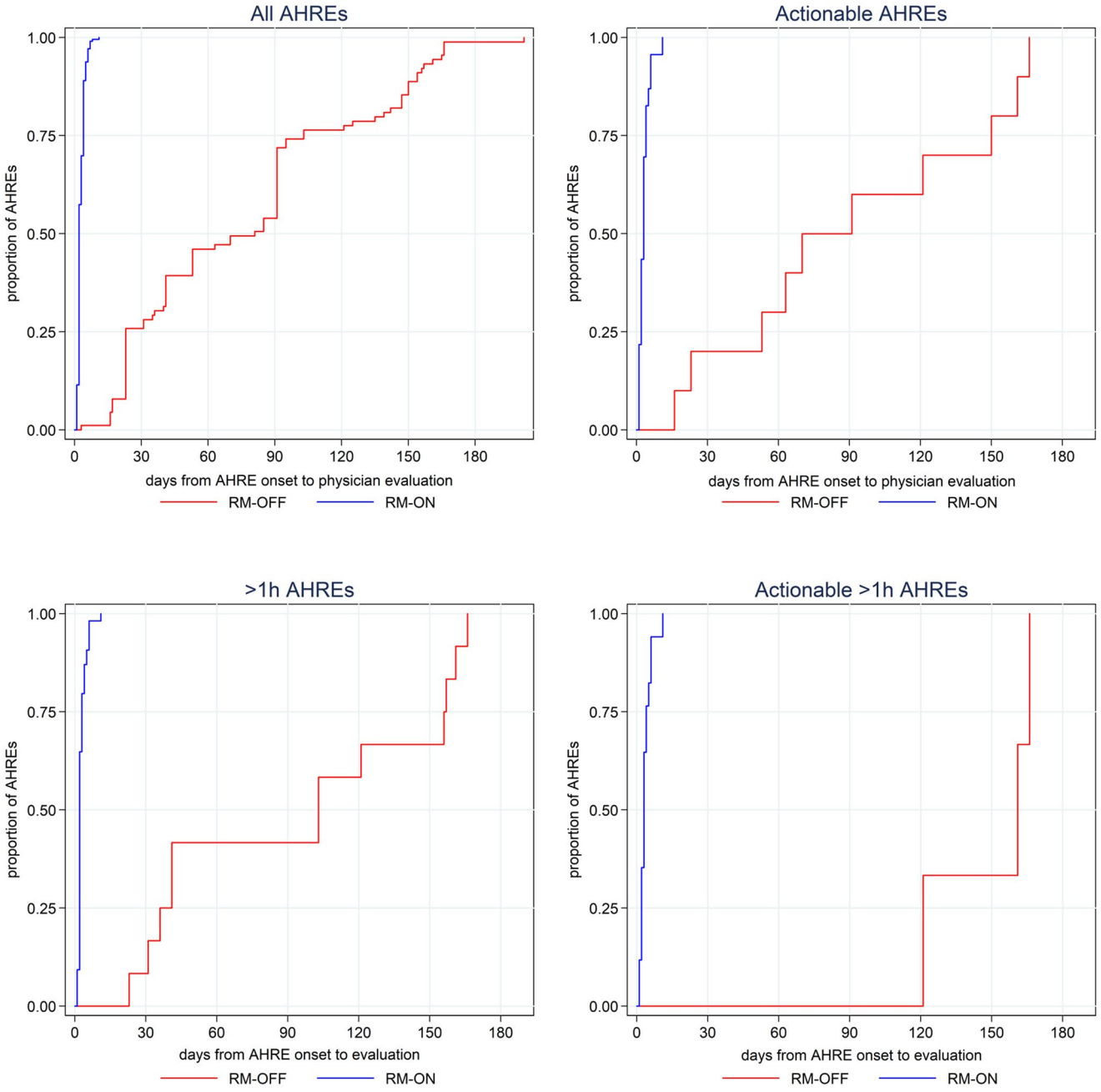

FIGURE 2 Cumulative distributions of time from AHRE onset to physician's evaluation (AHRE evaluation delay) by study groups, episode actionability, and duration. In the RM-ON group, with automatic notifications, 100% of AHREs, including episodes requiring medical interventions, were evaluated by physicians within a maximum of 11 days. In the RM-OFF group with biannual in-hospital visits, maximum evaluation delays were 202 days for all episodes, 166 days for actionable episodes. Similar distributions were observed in the subset of AHRE lasting ≥1 h. AHRE, atrial high rate episode; RM, remote monitoring

Therefore, AHREs should be efficiently monitored to keep overall arrhythmia burden under close medical control.[18] It may be worth noting that anticoagulation therapy was initiated in about one of five assessed actionable AHREs. This is likely explained by the lack of a generally agreed cutoff of AHRE burden to initiate the therapy and some hesitation in relation to associated side effects.[12,18–20] Remarkably enough, the recently published LOOP study[21] showed that not all device-detected atrial arrhythmias may be worth initiating anticoagulation, as the threefold increase in detection of atrial fibrillation incidence and anticoagulation did not result in a significant reduction in the risk of stroke or systemic arterial embolism. There are great expectations from the ongoing ARTESIA (Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation) and NOAH-AFNET 6 (Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes) studies, which will hopefully provide the missing pieces of the jigsaw.[22,23]

As a last remark, the 40-fold shorter AHRE evaluation delay obtained in the RM-ON group versus the RM-OFF group should

be appreciated in view of the almost 50% reduction in in-person visits we observed in the remotely monitored patients. This is additional prove that RM dramatically increases efficiency of healthcare systems. Previous studies have shown RM to reduce in-person visit burden without compromising safety.[10,12,24] In this regard, our study adds further evidence to support routine long-term follow-up of pacemaker patients entirely based on RM and automatic alerts, suppressing predetermined schedule of regular in-hospital device interrogations. Time may be ripe to investigate this option in more detail.

5 | LIMITATIONS

This is a nonrandomized albeit controlled study. Therefore, our estimations may be biased by uncontrolled confounders. We tried to mitigate this limitation by selecting investigational sites basing on their practice of providing RM to pacemaker patients in routine care (two sites with, one site without RM). We also used the propensity score to correct imbalances between study groups during analysis. The relatively small sample size should be mentioned among study limitations as it prevented any investigation and further analyses on thromboembolic events and heart failure hospitalizations, which still represent the main medical target. Also, interventions for actionable AHREs were left to individual medical evaluation, as therapeutic requirements for AHREs is presently unclear, according to the latest European guidelines for the diagnosis and management of atrial fibrillation.[19] However, sample size was justified by the study hypotheses and relative statistical power calculation.

6 | CONCLUSIONS

Our study showed that RM of patients with a dual-chamber pacemaker and without history of atrial arrhythmias provides earlier detection of AHRE gaining time to the management of clinically actionable events as compared to conventional in-hospital follow-up. Further studies are necessary to evaluate how to manage the introduction of anticoagulation therapy in patients with AHRE/subclinical atrial fibrillation basing on RM alerts.

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CONFLICT OF INTEREST

P.N. is an employee of BIOTRONIK Italia. The other authors have no major conflict of interest to disclose.

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