Clinical Impact of Oral Anticoagulation in Patients with Atrial High-rate Episodes

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Background: Atrial high-rate episodes (AHREs) are common in pacemaker patients. Our aims were to compare patients with AHREs to those without them and to assess if, in those with AHREs, the initiation of oral anticoagulation (OAC) has any clinical impact on the occurrence of ischemic and hemorrhagic events. *Methods:* From 2014-2017 we selected patients with pacemaker in whom AHREs were detected. AHREs were defined as episodes lasting more than 6 minutes if the electrogram was available or more than 6 hours if not. We used an age- and gender-matched population with pacemaker but no AHRE as a control group (observational study). Those with AHRE were referred to their assistant physician to decide OAC initiation, based on individual circumstances (interventional study). In interventional study, the primary outcome was a composite of systemic thromboembolism or major bleeding. Secondary outcomes were clinical relevant nonmajor bleeding, major and nonmajor bleeding, CV death, and death from all causes. *Results:* AHREs were detected in 86 patients: 69 patients initiated OAC and the remaining 17 patients did not. When comparing patients with and without AHRE, baseline characteristics were not different between the groups, except for indexed left atrium volume—40 mL (IQR: 34-50) in AHRE group versus 35 mL (IQR: 34-40) in control group ($P = .014$). AHREs were associated with future development of atrial fibrillation (AF) and the risk was higher if AHRE duration was superior to 6 hours. Death and cardiovascular (CV) death were not significantly different between the groups with and without AHRE. Primary outcome occurred in 4.9 per 100 person-year in OAC group versus 3.4 per 100 person-year in non-OAC group (HR 1.4, 95% CI .2-11.3, $P = .78$). Secondary outcomes were not significantly different in the groups. *Conclusions:* In this group of patients with pacemakers, the presence of AHREs was useful for predicting the future development of AF and the risk of AF was higher in those with a longer duration of AHRE. In the AHRE group, OAC therapy was not associated with a significant difference in the risk of thromboembolism or major bleeding.

Key Words: Atrial high rates episodes—subclinical atrial fibrillation—pacemaker—oral anticoagulation—bleeding—thromboembolic risk

Introduction

Current dual-chamber pacemakers are capable of automatically recording and storing episodes of spontaneous atrial tachyarrhythmias, according to programmable detection criteria. Such episodes, called atrial high-rate episodes (AHREs), may be recorded as interval data, local electrograms (EGM), or both. Due to the increasing number of implanted devices, a huge number of patients will have AHREs detected throughout life, but their clinical significance remains unknown.

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Latest studies demonstrated that stroke risk is higher in pacemaker patients with AHREs than in those without, but the available data also show that stroke risk in patients with AHREs is lower than in patients with atrial fibrillation (AF).[1–3] However, many strokes occur without a temporal relation to AHREs,[4–6] so it remains to clarify if AHREs, like AF, are the cause of stroke or a marker of a population at risk that would benefit from sustained anticoagulation. In a way or another, initiating oral anticoagulation (OAC) in patients with AHREs is controversial.

Also, the duration of AHREs from which the risk is increased is a matter of debate. Recent European Society of Cardiology guidelines stated >5-6 minutes[7] but different studies applied different cutoff values and many authors advocate more than 24 hours.[8,9]

The aims of this study were to compare patients with AHREs to those without them and to assess if the initiation of OAC in patients with AHREs lasting more than 6 minutes but less than 24 hours has any clinical impact in what concerns ischemic and hemorrhagic events.

Methods

Patients

This study enrolled adult patients who had received a dual-chamber pacemaker in whom AHREs were detected between January 2014 and January 2017. Age- and sex-matched controls with pacemakers but no AHREs were also evaluated.

Patients with a CHA_2DS_2VASc score≤1, previous diagnosis of AF or under previous treatment with OAC were excluded from the analysis.

The selection of patients for analysis is shown in the study flow diagram (Fig 1).

AHRE Definition

Dual-chamber pacemakers were programmed to detect an AHRE when atrial rate was superior to 190 beats per minute (bpm)[9] for 10 consecutive beats. Study personnel analysed all the AHREs detected. When EGM was available, AHREs were validated and confirmed if they lasted more than 6 minutes. If EGM was not available, episodes lasting more than 6 hours were considered AHREs.[9]

Study Design

An observational analysis was performed in the control group (patients with pacemakers but no AHREs). An interventional nonrandomized study was carried out in the AHRE group. When AHREs were confirmed, patients signed the informed consent and were referred to their assistant doctor to decide OAC initiation, based on individual circumstances. Clinical decision was left to physician consideration. If the patients missed the schedule consult with assistant doctor, but returned to the pacemaker consult, they were included in the non-OAC group and clock started in the day they had missed the consult.

Demographic data, cardiovascular (CV) risk factors, CHA_2DS_2VASc and HASBLED scores, transthoracic echocardiograms, and medications were recorded. Hypertension was defined as resting systolic or diastolic blood pressure ≥140/90 mmHg on 2 occasions or prescription of antihypertensive drugs. Diabetes mellitus was defined as a serum fasting glucose ≥7.0 mmol/L or prescription of antidiabetic medication. Smoking status was recorded as current smoker or nonsmoker. The CHA_2DS_2VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack (TIA), vascular disease, age 65-74 years, female) and HASBLED [hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)] scores were calculated. All patients underwent electrocardiogram (ECG) and 24 hour Holter after AHRE detection. All transthoracic echocardiograms available were collected and reviewed.

Outcome Measures

AHRE group versus control group

When comparing patients with and without AHREs, outcomes were AF diagnosis, CV death, and death from all causes. Stroke and bleeding were not compared since these outcomes would be directly influenced by OAC initiation, which occurred in only a proportion of AHRE patients.

AHRE group: OAC versus non-OAC group

Being an interventional study regarding OAC initiation, the primary outcome was a composite of thromboembolic event (ischemic stroke, (TIA), or systemic embolism) or major bleeding. Secondary outcomes were clinical relevant nonmajor bleeding (CRNMB), major and nonmajor bleeding, death from CV causes, and death from all causes. Whenever sustained AF was detected, OAC was initiated and patients were censored.

Definitions

Ischemic stroke was defined as a neurological deficit of sudden onset that persisted for more than 24 hours, corresponded to a vascular territory in the absence of primary hemorrhage, and that could not be explained by other causes (trauma, infection, and vasculitis). It was confirmed by computerized axial tomography or magnetic resonance imaging of the brain. TIA was defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. New occurrence of AF was defined as AF documented by a standard 12 lead ECG or a new 24-hour Holter monitoring. In accordance with the

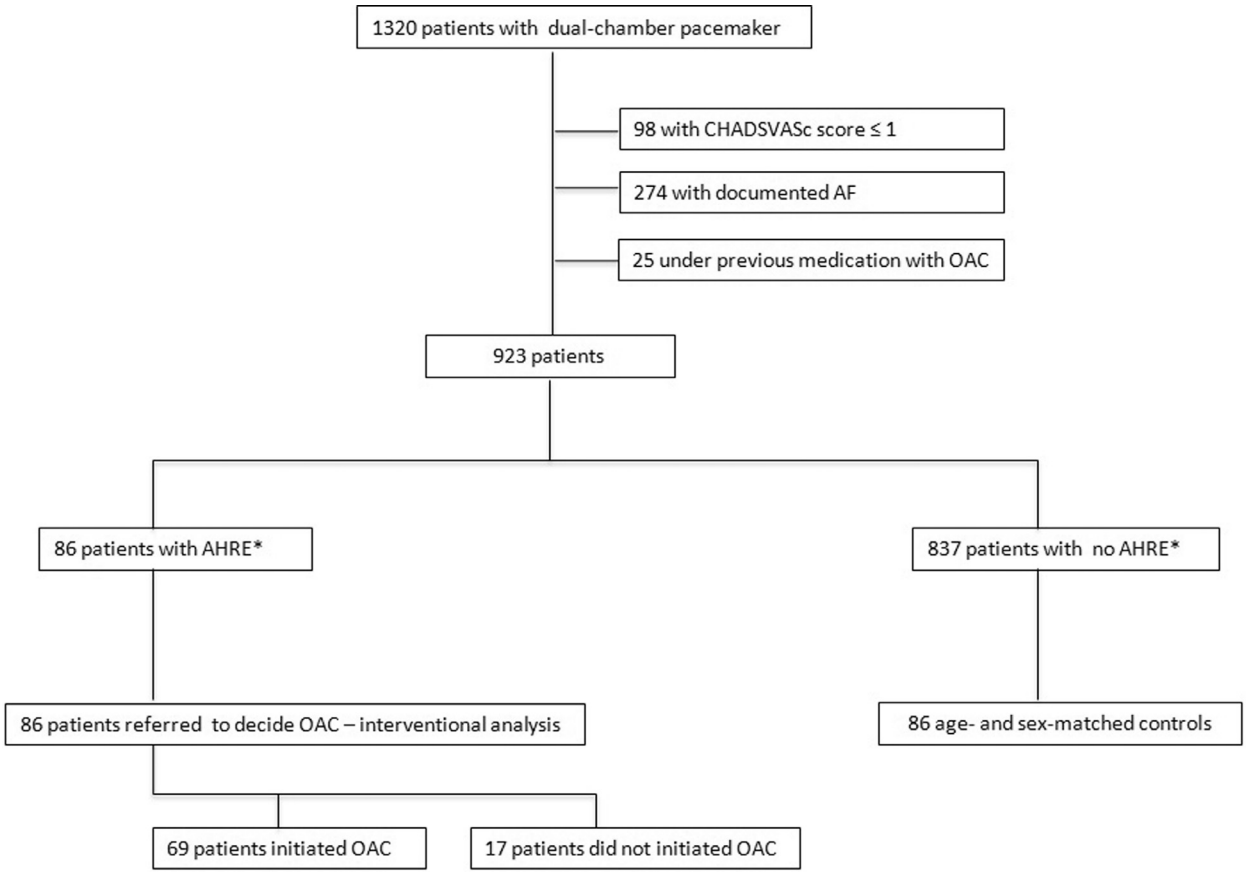

Figure 1. *Flow diagram of the study selection process.*
Flow diagram of patients included in analysis
*AHRE considered significant if episodes lasted >6 min if EGM was available or >6 h if it is not
AF, Atrial fibrillation; AHRE, atrial high-rate episode; EGM, electrograms; OAC, oral anticoagulation.

criteria of the International Society on Thrombosis and Haemostasis (ISTH), major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g/dL or more, led to a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death. CRNMB was also defined according to ISTH.[10] CV death included death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

Surveillance and follow-up

Patients were followed on a schedule visit every 6 months to the end of the study (June 2018) or until occurrence of AF, thromboembolic event, major bleeding, or death (whatever came first). Compliance with OAC was assessed in the OAC-group.

Ethics

All participants provided written informed consent. The Ethical Committee of our center approved the study. The study is in compliance with the Helsinki Declaration.

Statistics analysis

SPSS version 23 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Data is expressed as median (interquartile range) for continuous variables and as frequencies (percentages) for categorical variables. Baseline characteristics and outcomes were compared using the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Unadjusted and age- and gender-adjusted hazard ratios (HR) were calculated from a Cox proportional hazard model. A value of $P < .05$ was considered statistically significant.

Results

Study population

AHREs were detected in 86 (9.3%) patients with implanted pacemaker (n = 923) (AHRE group). Eighty-six age- and sex-matched controls with pacemaker but no AHRE were evaluated (control group). Median follow-up was 20 (IQR: 17-30) months. No patients were lost to follow-up.

Baseline characteristics of AHRE and control groups are presented in Table 1. There were no statistically significant differences between the 2 groups, except on indexed

Table 1. *Baseline characteristics of AHRE patients, comparing with a control age- and gender-matched population with no AHRE*

	AHRE group (n = 86)	Control group (n = 86)	*P* value
Demographic data			
Male gender, n (%)	48 (56)	48 (56)	.88
Age (y), median (IQR)	78 (72-83)	78 (72-83)	.88
Body mass index, Kg/m^2, median (IQR)	28 (23-30)	27 (22-29)	.64
Risk factors and history			
Hypertension, n (%)	67 (78)	51 (60)	.08
Diabetes mellitus, n (%)	22 (26)	16 (19)	.36
Current smoking, n (%)	16 (19)	8 (9)	.14
. Alcohol consumption >101g/wk, n (%)	4 (5)	1 (1)	.28
Coronary or peripheral arterial disease, n (%)	20 (23)	9 (10)	.09
Heart failure, n (%)	3 (3)	1 (1)	.70
Obstructive sleep apnea, n (%)	3 (3)	0 (0)	.32
Thyroid dysfunction, n (%)	1 (1)	0 (0)	.88
Laboratory			
Fasting glucose (mg/dL), median (IQR)	112 (91-143)	110 (90-147)	.65
Creatinine (mg/dL), median (IQR)	1.10 (.93-1.42)	1.12 (.89-1.39)	.87
LDL cholesterol (mg/dL) median (IQR)	138 (104-192)	135 (108-189)	.72
Echocardiographic parameters			
Left atrial volume/BSA, mL/m^2, median (IQR)	40 (34-50)	35 (34-40)	.014
Pacemaker indication			
Sinus node dysfunction, n (%)	37 (43)	27 (31)	.14
Atrioventricular block, n (%)	48 (56)	56 (65)	.29
Other, n (%)	1 (1)	3 (3)	.69
CHA_2DS_2VASc score*, median (IQR)	3.6 (1.1-4.8)	3.2 (1.1-4.2)	.68
HASBLED score, median (IQR)	1 (0-4)	1 (0-4)	.88

Values are presented as median [interquartile range (IQR)] and number(n) median [percentage (%)].

The CHA_2DS_2VASc score was calculated according to the presence of congestive heart failure/left ventricular dysfunction (1 point); hypertension (1 point); age ≥75 y (2 points); diabetes mellitus (1 point); history of stroke, TIA or thromboembolism (2 points); vascular disease (history of MI, PVD or aortic atherosclerosis) (1 point); age 65-74 years (1 point), and female gender (1 point).

The HAS-BELD score was calculated according to the presence of hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each).

*Age- and gender-matched group.

left atrial (LA) volume. LA volume/BSA was significantly higher in the AHRE group—40 mL (34-50) versus 35 mL (34-40) in the control group (*P* = .014).

In the AHRE group, 80% (n = 69) initiated OAC: 59 patients with non-vitamin K antagonist oral anticoagulant and the remaining (n = 10) with a vitamin K antagonist. Seventeen patients (20%) did not initiate OAC: due to doctor (n = 4) or patient-doctor shared decision (n = 9) and for missing the schedule consult to decide OAC initiation (n = 4). Baseline characteristics of patients who have or have not initiated OAC are presented in Table 2.

AHRE detection

The median time after pacemaker implantation to detection of the first AHRE was 41 months (15-93). In 4 patients (5%) AHREs were detected within 30 days after the procedure. The median number of AHREs was 3 (1-5). The median atrial rate was 250 bpm (205-389). Episodes were symptomatic in 8% (n = 7) of patients, most of them complained of palpitations (n = 5) and the remaining reported fatigue.

At the time of detection, median AHRE duration (*per* episode) was 2 hour (1-4). Forty-one patients (48%) had AHRE lasting more than 6 minutes but less than 6 hours and the remaining 45 (52%) had AHRE lasting more than 6 hours. These patients did not differ in baselines characteristics.

Outcomes

AHRE group versus control group

Comparison between patients with AHRE and control patients is presented in Table 3.

Atrial fibrillation

Diagnosis of AF occurred in 33 of the 86 patients who had had significant AHREs (38%) after 21 (10-34) months of the first detected AHRE. When comparing patients with and without AHREs, AF occurred in 21.1 per 100-person-years in the AHRE group, comparing with 5.2 per 100-person-years in the control group (HR 5.6, 95% CI 2.3-

Table 2. *Baseline characteristics in OAC and non-OAC groups*

	OAC (n = 69)	No OAC (n = 17)	*P* value
Demographic data			
Male gender, n (%)	39 (53)	8 (61)	.75
Age (y), median (IQR)	78 (71-84)	79 (76-85)	.54
Body mass index, Kg/m^2, median (IQR)	28 (22-29)	27 (21-29)	.19
Risk factors and history			
Hypertension, n (%)	57 (78)	10 (77)	.81
Diabetes mellitus, n (%)	19 (26)	3 (23)	.95
Current smoking, n (%)	14 (19)	2 (15)	.97
Alcohol consumption >101g/wk, n (%)	3 (4)	1 (8)	.95
Coronary or peripheral arterial disease, n (%)	18 (25)	2 (15)	.58
Heart failure, n (%)	2 (3)	1 (8)	.80
Obstructive sleep apnea, n (%)	2 (3)	1 (8)	.80
Thyroid dysfunction, n (%)	1 (1)	0 (0)	.27
Laboratory			
Fasting glucose (mg/dL), median (IQR)	111 (90-141)	114 (89-150)	.46
Creatinine (mg/dL), median (IQR)	1.07 (.92-1.40)	1.17 (.89-1.41)	.38
LDL cholesterol (mg/dL) median (IQR))	141 (105-191)	132 (110-195)	.10
Echocardiographic parameters			
Left atrial volume/BSA, mL/m^2, median (IQR)	39 (31-44)	38 (30-46)	.46
Pacemaker indication			
Sinus node dysfunction, n (%)	31 (45)	6 (35)	.64
Atrioventricular block, n (%)	37 (54)	11 (65)	.58
Other, n (%)	1 (1)	0 (0)	.27
AHRE duration			
Hours, median (IQR)	2.0 (1.0-4.0)	2.0 (1.8-2.3)	.07
>6 h, n (%)	39 (56)	6 (35)	.12
CHA2DS2VASc score, median (IQR)	3.6 (1.1-4.8)	3.2 (1.1-4.7)	.14
HASBLED score, median (IQR)	1 (0-4)	1 (0-4)	.98

Values are presented as median [interquartile range (IQR)] and number (n) median [percentage (%)].

The CHA_2DS_2VASc score was calculated according to the presence of congestive heart failure/left ventricular dysfunction (1 point); hypertension (1 point); age ≥75 y (2 points); diabetes mellitus (1 point); history of stroke, TIA or thromboembolism (2 points); vascular disease (history of MI, PVD, or aortic atherosclerosis) (1 point); age 65-74 y (1 point), and female gender (1 point).

The HAS-BELD score was calculated according to the presence of hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 y), drugs/alcohol concomitantly (1 point each).

AHRE, Atrial high-rate episodes; OAC, oral anticoagulation.

13.4, $P < .001$). After adjustment for indexed LA volume, AHRE remained significantly related with AF (HR 4.8, 95% CI 1.9-11.7, $P = .001$). Duration of AHRE was related with AF. AHRE lasting more than 6 hours confers an almost 3-fold increase in the risk of developing AF during follow-up (nonadjusted HR 2.6, 95% CI 1.2-5.6, $P = .012$).

Death

Death from all or CV causes were not different between the 2 groups. CV death occurred in 3.9 per 100-person-years in the AHRE group, comparing with 3.4 per 100-person-years in the control group (HR 1.1, 95% CI .3-3.8,

Table 3. *Event rate, hazard ratio (HR), and 95% confidence interval (CI) for atrial fibrillation and death according to the presence of AHRE*

	Rate per 100 person-years			
	All (n = 172)	AHRE (n = 86)	Control (n = 86)	HR (95% CI)
Atrial fibrillation	14.2	21.1	5.2	5.6 (2.3-13.4)
Death from CV causes	3.7	3.9	3.4	1.1 (.3-3.8)
Death from all causes	8.9	8.5	9.5	.8 (.4-2.0)

Abbreviations: CV, cardiovascular.

$P = .90$). Death occurred in 8.5 per 100-person-years in the AHRE group, comparing with 9.5 per 100-person-years in the control group (HR .8, 95% CI .4-2.0, $P = .70$).

AHRE group: OAC versus non-OAC

Occurrence of primary and secondary outcomes in patients with AHRE who had or had not initiated OAC is presented in Table 4.

Primary outcome

The composite outcome of ischemic and major bleeding events occurred in 4.9 per 100-person-years in the OAC-group, comparing with 3.4 per 100-person-years in the non-OAC group (age- and sex-adjusted HR 1.6, 95% CI .2-13.4, $P = .68$).

Ischemic stroke occurred in 1 patient. This patient had AHRE duration >12 hours and AF was present at the time of hospital admission due to stroke. He had a CHA_2DS_2-VASc = 4. TIA and systemic embolism did not occur in any patient. No ischemic events occurred in the OAC-group.

Major hemorrhagic complications occurred in 6 of 69 patients in the OAC group (9%): 4% per year. One hemorrhagic nonfatal but disabling stroke; 1 subarachnoid hemorrhage after a fall, and 4 episodes of bleeding leading to transfusion of 2 or more units of whole blood or red cells (1 fatal hemorrhagic shock). No hemorraghic events occurred in the non-OAC group.

Secondary outcomes

Clinical relevant nonmajor bleeding. Sixteen patients who initiated OAC (23%) had a CRNMB (13 per 100-person-years): needing a face to face evaluation (n = 8); requiring medical intervention by a healthcare professional (n = 5) or leading to hospitalization or increased level of care (n = 3). Those with nonmajor bleeding did not develop major bleeding during follow-up. In non-OAC group no ISTH relevant nonmajor bleeding occurred.

The proportion of ISTH major and CRNMB is significantly higher in OAC (32% in OAC-group versus 0% in non-OAC group, $P = .05$). However, using Cox proportional hazard model, no statistically significant differences were found between the groups (age- and sex-adjusted HR 3.1, 95% CI .7-13.3, $P = .13$).

Cardiovascular death. During the follow-up, CV death occurred in 4.1 per 100-person-years in OAC group, comparing with 3.4 per 100-person-years in non-OAC group (age- and sex-adjusted HR .5, 95% CI .1-3.8, $P = .49$). Of note, 1 patient died from hemorrhagic shock in the OAC-group and 1 patient died from ischemic stroke in the non-OAC group.

Death from all causes. Death occurred in 8.1 per 100-person-years in OAC group, comparing with 10.3 per 100-person-years in non-OAC group (age- and sex-adjusted HR .9, 95% CI .2-3.2, $P = .82$).

Discussion

Modern cardiac pacemakers function as permanently implanted cardiac monitors, detecting clinically silent atrial and ventricular arrhythmias. The incidence of AHREs in patients without a history of AF is variable according to the definition of AHRE and the study population, but it is generally high: 10%-15% of patients in the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT),[1] approximately 25% after 1 year and 35% after 2 years of follow-up in other studies.[1,11] In our study, results were similar: 9.3% of patients with dual chamber pacemakers had significant AHREs. Thus, it is of paramount importance to clarify what is the optimal management of patients in whom AHREs were detected.

Devices´ automated algorithms alert to the occurrence of AHREs, but these episodes do not always correspond to short atrial tachyarrhythmias. The currently accepted "minimal duration" of AHREs, 5-6 minutes, is based on technicalities related to the adequate diagnosis of true AHREs and their distinction from artifacts and other arrhythmias, rather than on biological processes.[10–12] According to Kaufman et al,[13] by using a cutoff of >6 minutes and >190 bpm, the rate of false-positive AHREs is 17.3%, making physician review of EGM essential. For AHREs lasting >6 hours, the rate of false positives is 3.3%, making physician review less crucial. Indeed, in our study we used the cutoff of 190 bpm for atrial rate and duration >6 minutes if EGM was available but >6 hours if it was not. Since AHREs can reflect other arrhythmias than AF or artifacts, the authors judiciously reviewed device EGM (if available) to determine whether it corresponded to an atrial arrhythmia. Only in cases of a high suspicion, the patients were referred to decide OAC initiation. When EGM was unavailable, a period of more than 6 hours was necessary to avoid incorrect diagnosis, as previously explained. Although clinical AF was not confirmed in ECG or Holter, OAC was considered in patients with AHRE after a careful evaluation of perceived benefits and risks, as stated in the current guidelines.[7]

It has been suggested that AHREs may be a transient phenomenon related to lead implantation.[14] In fact, in SAFE registry, some patients had AHREs only within the first 30 days after implantation, suggesting the possibility of transient atrial proarrhythmia related to lead insertion.[15] However, in our study it is not the case since only 5% of patients with significant AHRE had its detection within 30 days after the procedure and in all of them AHREs remained during follow-up.

It seems more reasonable to consider that risk factors for AHRE can be similar to risk factors for AF. When comparing AHRE group with control group, a higher indexed LA volume occurred in AHRE group, raising the suspicion that atrial remodeling had a role in the genesis of these atrial episodes. Although not statistically significant, there were a trend to a higher incidence of hypertension and coronary or peripheral arterial disease in AHRE group ($P = .08$ and .09, respectively). Pacemaker indication did not differ between AHRE and control groups, which are not in accordance with previous studies. In ASSERT trial, the prevalence of sinus node disease was higher among patients with AHRE.[1]

Some authors state that AHREs can be considered as an early manifestation of AF and apply the term "subclinical" AF.[9] Indeed, the detection of AHREs correlates well with electrocardiographic documentation of AF[16] and recent data from Boriani et al (2018) suggested that approximately 24% of patients had an increase in AF burden to up to 23 hours during follow-up.[17] In the present study, the presence of AHRE was associated with more than 5-fold increase in the risk of developing AF and the higher the duration of AHRE, the higher the risk, confirming that AHREs may be a predictor of AF. Importantly, after adjustment for indexed LA volume, which was higher in AHRE patients, AHREs remained associated with an increased risk of AF.

Two possible mechanisms may explain the occurrence of stroke in patients with AHREs. The hypothesis of causation is less plausible than in patients with paroxysmal AF. In patients with pacemakers, we are aware of all AHREs and there is not always a relationship between AHRE and stroke occurrence, as demonstrated in ASSERT trial.[1] An alternative hypothesis is that AHREs are just a marker of stroke risk. AHREs may indicate myocardial hypertrophy or fibrosis, valve or structural heart disease, or even a proinflammatory state, such as that associated with diabetes or the metabolic syndrome. In our study, it was not possible to demonstrate a cause-effect between AHREs and stroke when comparing patients with and without AHRE, because an interventional analysis was performed in patients with AHRE (OAC initiation). When comparing patients with AHRE who initiated OAC with those who did not initiate it, we did not find significant differences in stroke events, probably because the study was underpowered to find such differences.

While the lack of OAC is related to an increased risk of cardioembolic stroke in AF patients, the use of OAC has an inherent risk in all patients: bleeding. Major bleeding occurs in approximately 2%-3% per year in clinical trials and may be more in real world. In our study, major bleeding occurred in 9% of patients in OAC group (4% per year) which is in accordance with previous studies, highlighting the "price to pay" for this therapeutic intervention. OAC therapy could have avoided 1 stroke, but it was also responsible for a high incidence of major bleeding. When considering the combined endpoint of stroke and major bleeding, no significant differences were found between OAC and non-OAC group, probably due to the reduced number of patients.

In previous observational studies, the rates of CRNMB CRNMB varied between 10% and 20%,[18–20] while in our study, it was 22%. Although associated with a lower mortality, there is an independent increased risk of death and subsequent major bleeding associated with CRNMB,[21,22] suggesting that physicians should balance the risk of bleeding, even if nonmajor. On the other hand, CRNMB seems more important to patients and it could be related with drug compliance. Although CRNMB was more frequent in our study, it was not significantly associated with OAC initiation.

CV death and death from all causes were not different between AHRE and control groups. In the ASSERT trial, the authors did not find an increased risk of CV death in AHRE patients,[1] while in the MOde Selection Trial (MOST), an increased risk of overall death occurred in AHRE patients. The most plausible reason for these different results is the longer follow-up in the MOST trial (6 years) compared to the ASSERT (2.5 years) and to our study (2 years).

Duration of AHRE is probably one of the most important questions to address in the decision of OAC initiation. In patients with AHREs, the presence of an episode lasting 1 hour is not the same as an episode lasting 20 hours, since the risk of thromboembolic complications is probably a quantitative function of AF burden. Recently, Camm et al[8] suggested that only AHREs lasting more than 24 hours should deserve consideration about OAC therapy initiation, probably due to the findings of Gelder et al. These authors, in a subanalysis of ASSERT study, found that the risk of embolic events (stroke or systemic embolism) in patients with AHREs between 6 minutes and 24 hours was not significantly different from patients without AHREs, while episodes lasting >24 hours were associated with a significant increased risk of embolic events (adjusted HR 3.24, 95% CI 1.51-6.95, $P = .003$).[23] We studied this group of patients (AHRE lasting between 6 minutes and 24 hours), but an interventional study was performed, so we were not able to take conclusions about the risk of embolic events comparing to those with no AHRE.

The present study demonstrates that in real world the net benefit of initiation of OAC is at least debatable, despite current guidelines.[12] Understandably grossly underpowered to make any conclusion, our study is illustrative of the need to conduct adequately powered RCTs. Ongoing clinical trials like the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes trial (NOAH-AFNET 6)[24] and Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA)[25] trials will provide robust information on the effect of OAC in patients with AHREs detected by implanted devices. In NOAH-AFNET 6 trial, patients aged ≥65 with AHRE ≥6 minutes and ≥180 bpm

Table 4. *Event rate, hazard ratio (HR), and 95% confidence interval (CI) for primary and secondary outcomes according to OAC initiation in AHRE group*

	Rate per 100 person-years			Nonadjusted HR (95% CI)	Age- and sex- adjusted HR (95% CI)
	All (n = 86)	OAC (n = 69)	Non-OAC (n = 17)		
Primary composite outcome	4.6	4.9	3.4	1.4 (.2-11.3)	1.6 (.2-13.4)
Ischemic stroke	.7	0	3.4	.001 (.0-2.9 × 10^{13})	.001 (.0-5.5 × 10^{13})
Major ISTH bleeding	3.9	4.9	0	1.1 (.1-9.8)	1.3 (.1-11.4)
Secondary outcomes					
Nonmajor ISTH bleeding	10.5	13.0	0	4.9 (.6-37.3)	4.7 (.6-35.8)
Major and nonmajor ISTH bleeding	14.5	17.9	0	3.0 (.7-12.8)	3.1 (.7-13.3)
Death from CV causes	3.9	4.1	3.4	.5 (.1-2.9)	.5 (.1-3.8)
Death from all causes	8.5	8.1	10.3	.6 (.2-1.9)	.9 (.2-3.2)

Abbreviations: CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis.

documented by the implanted device and stored digitally and at least 2 stroke risk factors are randomized to edoxaban (according to standard AF dosing) versus placebo or aspirin (if clinically indicated).[24] In ARTESiA, participants aged ≥55 and with risk factors for stroke are randomized to receive either apixaban (according to standard AF dosing) or aspirin 81 mg daily if they have AHRE ≥6 minutes and average >175 bpm.[25]

Overall, our study addressed the key question of OAC initiation in patients with AHREs lasting less than 24 hours. Studies showing a benefit of OAC in reducing the risk of stroke among patients with AHREs in a manner similar to the studies performed in AF patients are lacking. Adverse effects and complications associated with OAC therapy are not neglectable, and our study suggests that the risk of bleeding with OAC is high. Due to the increased risk of AF during the follow-up, the authors propose that these patients must be followed on a more regular basis (eg: every 2 months or through remote monitoring, if available) in order to detect AF earlier. Probably, OAC initiation must be considered only at the time of AF diagnosis. In other words, AHRE detection provides a chance to detect AF earlier, instead of an indication for OAC treatment *per si*.

Study limitations

It was a single center, nonrandomized study and it is not large enough to derive comparisons of event rates. Outcomes were not adjudicated or blinded. The absence of a significant difference in outcomes can be related to the small number of patients. Also, it is arbitrary to classify as nonsignificant AHRE between 6 minutes and 6 hours simply because there is no EGM, although it is useful to avoid false positive AHRE. In those with no EGM, the diagnosis of AF could be underestimated because the ECG and 24 hour Holter has a low sensitivity for AF detection.[26]

Conclusions

In these groups of patients, the presence of AHREs predicted the future development of AF and the risk was higher in those with a longer duration of AHRE. In the AHRE group, OAC therapy was not associated with a significant difference in the risk of systemic thromboembolism or major bleeding. More investigation in this field is needed to decide the best clinical management of these patients.

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