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ORIGINAL PAPER

Atrial high-rate episodes and risk of major adverse cardiovascular events in patients with cardiac implantable electronic devices

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Abstract

Background Patients with atrial high-rate episodes (AHREs) are at higher risk of thromboembolic events and mortality. The risk of major adverse cardiovascular events (MACE) in these patients is unknown.

Objective To investigate the risk of MACE in patients implanted with cardiac implantable electronic devices (CIEDs) developing AHREs

Methods and results We included 852 consecutive patients undergoing CIEDs implantation. Primary outcome was a composite endpoint of MACEs occurring after AHREs ≥ 5 min. AHRE was defined as > 175 bpm and lasting ≥ 5 min. We also performed a subgroup analysis in patients with the longest AHRE lasting ≥ 24 h. Cox regression analysis with time-dependent covariates was used to investigate the relationship between AHREs and MACEs.

Mean age was 70.0 ± 13.6 years, and 39.3% were women: 325 patients developed AHREs ≥ 5 min [incidence rate (IR) 13.1% year 95% confidence interval (CI) 11.7–14.6] and 124 patients developed AHREs ≥ 24 h (IR 3.7%/year 95% CI 3.1–4.5). During a median follow-up of 37.0 months (IQR 19.0–64.3, 316,132 patient-years), 152 MACEs occurred (IR 4.85%/year, 95% CI 4.11–5.68). The IR of MACE occurring after AHREs onset was higher in patients developing AHREs ≥ 24 h (IR 1.13%/year) than AHREs ≥ 5 min (IR 0.63%/year, $p = 0.030$).

Multivariable Cox regression analysis showed that AHREs ≥ 5 min (HR 1.788, 95% CI 1.247–2.562, $p = 0.002$), diabetes (HR 1.909, 95% CI 1.358–2.683, $p < 0.001$), heart failure (HR 2.203, 95% CI 1.527–3.178, $p < 0.001$), and coronary artery disease (HR 1.862, 95% CI 1.293–2.681, $p = 0.001$) were associated to MACE. This association was even stronger for AHREs ≥ 24 h (HR 2.390, 95% CI 1.481–3.857, $p < 0.001$).

Conclusions Patients implanted with CIEDs developing AHREs show a significant risk for MACE, which is dependent on AHREs burden. Cardiovascular prevention strategies in this patient population are warranted.

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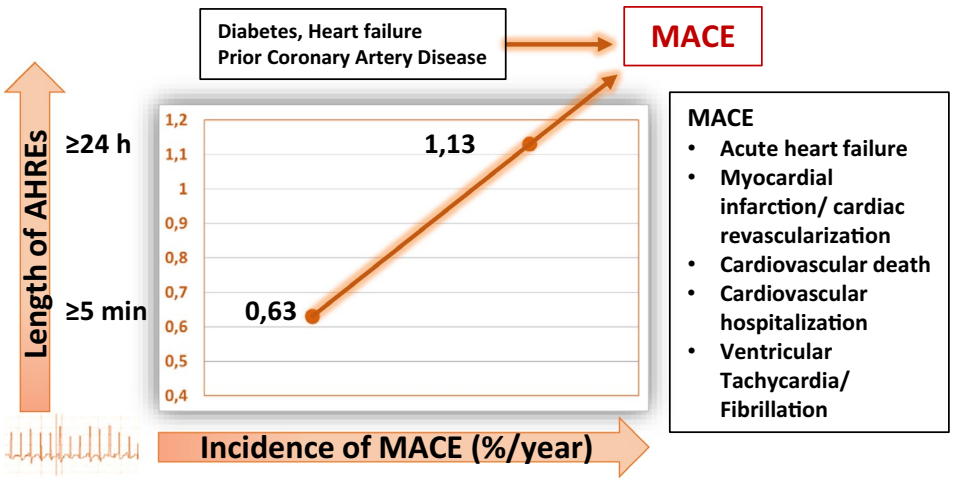
Graphic abstract



Keywords AHREs · CIED · MACE · Implantable device · Pacemaker · Atrial fibrillation · Myocardial infarction · Cardiovascular risk

Introduction

The use of cardiac implanted electronic devices (CIEDs) has significantly improved the detection of atrial high-rate episodes (AHREs) over conventional diagnostic methods, such as resting electrocardiogram and Holter monitoring [1–3]. The early detection of AHREs is clinically relevant considering that they have been shown to be associated to an increased risk of thromboembolic events [4–7] and death [8], i.e., 1.8%/year in the IMPACT trial [9].

AHREs lasting > 5 min are considered as clinically relevant, and current guidelines indicate that in patients presenting with AHREs, the presence of thromboembolic risk factors should be regularly assessed [10].

This increased risk of thromboembolism is not surprising considering that AHREs are closely linked to atrial fibrillation (AF). Indeed, AHREs are now referred to as 'subclinical AF' [1], and a recent consensus document from the European Heart Rhythm Association (EHRA) suggested that clinicians perform stroke risk stratification in patients with subclinical AF using the CHA_2DS_2-VASc score, and anticoagulation should be considered when patients presented with AHRE > 5.5 h and at two additional stroke risk factors [1].

An increased risk of cardiac events including myocardial infarction (MI) has been described in patients with AF [11], mostly conferred by the atherosclerotic burden characterizing this population [12]. It is also arguable that these AHRE patients may have an increased risk of major adverse cardiovascular events (MACEs) given the similar pathogenetic pathways linking AHREs with AF. However, no data about the risk of MACE in patients with AHREs are available.

Thus, aim of our study was to specifically investigate the incidence of MACE in a cohort of consecutive patients who had underwent CIEDs implantation, in relation to their developing AHREs or not during follow-up.

Methods

We included all consecutive patients with CIEDs (Medtronic) including permanent pacemaker, implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT) device, attending the Cardiology Department of Sandwell and West Birmingham Hospitals NHS Trust (Sandwell General Hospital and City Hospital) in Birmingham, United Kingdom from December 2010 to August 2017. We excluded patients with single-chamber VVI devices. Atrial sensitivity was programmed to 0.5 mV with bipolar sensing.

At baseline, personal medical history and information on co-morbidities were retrospectively collected. In particular, patients were classified as having AF at the moment of CIED implantation if AF was documented by ECG. The primary endpoint for the study was the occurrence of MACEs, including myocardial infarction/cardiac revascularization, acute heart failure and life-threatening arrhythmias defined as follows: sustained ventricular tachycardia (VT) > 30 s, VT required shock therapy or anti-tachycardia pacing, ventricular fibrillation (VF), cardiac arrest and cardiovascular hospitalization (pulmonary embolism, new onset AF and peripheral artery disease/aneurysm repair).

Only the first event occurring after the onset pf AHRE was used for the survival analysis. An AHRE was defined as > 175 bpm and lasting ≥ 5 min, as previously described [13]. We also performed a subgroup analysis in patients with the longest AHRE lasting ≥ 24 h. This study was conducted in accordance with the EU Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

We audited records for consecutive patients undergoing CIED implantation in our hospital, and we collected data from devices recordings. Data were retrieved anonymously, and patients were assigned to a code number. Patients were not involved in the study or contacted in anyway, and therefore an ethical approval was not necessary.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were expressed as numbers and percentages. The Pearson χ^2 test was used to compare proportions.

Indicators of AHRE ≥ 5 min and ≥ 24 h were used separately as time-dependent covariates in Cox proportional hazards regression, to compute hazard ratios (HR) and adjusted HR in multivariable models including clinical variables. In the multivariable model, oral anticoagulation and antiplatelet were not included as they maximally reflected patients with AF or MI, respectively.

Statistical significance was set at < 0.05. All tests were two-tailed and analysis was carried out using computer software packages (IBM SPSS 20.0 for Windows®, SPSS Inc. and R v. 3.4.0).

Results

Characteristics of patients according to the occurrence of AHREs ≥ 5 min or ≥ 24 h are reported in Table 1. Mean age was 70.1 ± 13.6 years and 39.3% women. The most common indication for CIED implantation (Table 1) was atrio-ventricular block (41.6%), followed by sick sinus syndrome (26.6%), HF (16.1%), VT/VF (9.4%) and syncope/symptomatic bradycardia (6.2%). Description of CIED type according to prior AF and HF status is reported in Table 2.

During follow-up, 325 patients developed AHREs ≥ 5 min [incidence rate (IR) 13.1%/year, 95% confidence interval (CI) 11.7–14.6], and 124 patients developed AHREs ≥ 24 h (IR 3.7%/year 95% CI 3.1–4.5). Patients developing AHREs during follow-up were older with a higher prior AF at baseline, while no difference in other cardiovascular risk factors was seen (Table 1).

AHREs and MACE

Patients who were lost at follow-up were excluded from the analysis ($n = 7$). Thus, the final cohort was composed of 856 patients. During a median follow-up of 37.0 (IQR 19.0–64.3) months yielding 3161.32 patient-years of observation, we recorded a total of 152 MACEs (IR 4.85%/year, 95% CI 4.11–5.68) (Table 3). Patients with a history of AF at baseline had a higher incidence of MACE compared to those without, of borderline significance (IR 6.14%/year 95% CI 4.48–8.22 vs. 4.41%/year 95% CI 3.61–5.32, respectively, $p = 0.06$).

When considering only MACE with time relationship to AHREs (i.e., occurring after AHRE onset), the incidence rate of MACE was higher in patients developing AHREs ≥ 24 h (IR 1.13%/year) than AHREs ≥ 5 min (IR 0.63%/year, $p = 0.030$).

On univariate Cox regression analysis. AHREs ≥ 5 min were significantly associated with the occurrence of MACE (HR 1.96, 95% CI 1.40–2.73, $p < 0.001$).

Multivariable Cox regression analysis (Table 4, model A) demonstrated that AHREs ≥ 5 min (HR 1.788, 95% CI 1.247–2.562, $p = 0.002$), diabetes (HR 1.909, 95% CI 1.358–2.683, $p < 0.001$), heart failure (HR 2.203, 95% CI 1.527–3.178, $p < 0.001$), coronary artery disease (HR 1.862, 95% CI 1.293–2.681, $p = 0.001$) were independently associated with MACE.

In the subgroup of patients with AHREs ≥ 24 h, ununivariate Cox regression analysis showed that AHREs ≥ 24 h were significantly associated with MACE occurrence (HR 3.43, 95% CI 2.19–5.09, $p < 0.001$). As with the analysis above, multivariable Cox regression analysis also demonstrated that AHREs ≥ 24 h, diabetes, heart failure and coronary artery disease were independently associated with MACE (Table 4, model B).

Discussion

In this study our principal finding was a previously unrecognized increased risk of cardiac adverse outcomes in CIED patients developing AHREs. This association was evident in patients developing AHREs lasting both ≥ 5 min and ≥ 24 h.

The relationship between AHREs and 'non-thromboembolic' events has been investigated only in a previous retrospective study including 377 patients with CRT, which showed that the cumulative burden of AHRE during the first year of follow-up was associated with worse long-term clinical outcomes of death, heart transplant or appropriate shock therapy [14].

In our study, we found an annual rate of cardiac adverse events of 1.83% including ischaemic heart disease and cardiovascular death, with this risk rising to 3.76% when

Table 1 Clinical characteristics of patients according to the occurrence of AHREs ≥ 5 min or ≥ 24 h

	Overall	AHREs ≥ 5 min		*p* value	AHREs ≥ 24 h		*p* value
	(*n* = 856)	No (*n* = 531)	Yes (*n* = 325)		No (*n* = 732)	Yes (*n* = 124)	
Women (%)	39.3	39.2	39.4	0.951	40.7	30.6	0.037
Age (years)	70.1 ± 13.6	68.7 ± 14.1	72.3 ± 12.4	< 0.001	69.6 ± 13.9	72.9 ± 11.1	0.010
Prior atrial fibrillation (%)	24.8	15.6	39.7	< 0.001	19.4	56.5	< 0.001
Hypertension (%)	70.4	69.1	72.6	0.281	69.4	76.6	0.111
Diabetes (%)	28.2	29.6	25.8	0.273	28.1	28.2	0.985
Heart failure (%)	25.0	26.7	22.2	0.143	23.9	31.5	0.092
Prior coronary artery disease (%)	36.3	37.1	35.0	0.558	35.2	42.7	0.108
Prior stroke/TIA (%)	10.7	10.0	12.0	0.365	10.2	13.7	0.271
Oral anticoagulation (%)	19.7	12.7	30.8	< 0.001	15.7	41.5	< 0.001
Antiplatelet (%)	51.4	53.6	47.8	0.121	51.8	49.2	0.618
ACE inhibitors/ARBs (%)	56.7	54.3	60.5	0.095	54.8	66.9	0.015
Beta blockers (%)	35.5	35.3	35.7	0.915	35.0	38.1	0.512
Calcium channel antagonists (%)	23.8	22.8	25.3	0.418	23.9	22.9	0.806
Digoxin (%)	4.9	3.4	7.5	0.011	3.7	11.9	< 0.001
Diuretic (%)	35.8	34.0	38.9	0.169	35.3	39.0	0.440
Amiodarone (%)	7.7	7.0	8.8	0.360	7.4	9.3	0.464
Statins (%)	66.0	64.8	68.0	0.354	64.9	72.0	0.134
Device type				0.031			0.870
Pacemaker	74.6	71.4	80.0		74.7	74.2	
ICD	10.4	12.2	7.4		10.7	8.9	
CRT	14.9	16.4	12.6		14.6	17.0	
Indication for CIED				0.008			0.205
Sick sinus syndrome	26.6	22.8	32.9		25.5	33.1	
Atrio-ventricular block	41.6	42.4	40.3		42.2	38.1	
Heart failure	16.1	18.1	12.9		15.8	17.8	
VT/VF	9.4	10.8	7.1		9.6	8.5	
Syncope/symptomatic bradycardia	6.2	5.9	6.8		6.8	2.5	

AHREs atrial high-rate episodes, *CIED* cardiac implanted electronic device, *CRT* cardiac resynchronization therapy, *eGFR* estimated glomerular filtration rate, *ICD* implantable cardioverter defibrillator, *MACE* major adverse cardiac event, *TIA* transient ischaemic attack, *VT/VF* ventricular tachycardia/fibrillation

Table 2 Type of CIED according to prior atrial fibrillation and heart failure status

Type of CIED	Prior atrial fibrillation	Heart failure
PM (*n*, %)	149 (70.3%)	34 (15.9%)
ICD (*n*, %)	18 (8.5%)	54 (25.2%)
CRT (*n*, %)	45 (21.2%)	126 (58.9%)
Total	212 (100%)	214 (100%)

considering also acute heart failure events. These findings demonstrate that the risk of cardiovascular events is increased in patients with CIED developing AHREs.

The increased risk associated with ischaemic heart disease may have a multifactorial pathogenesis, including a mismatch between blood request and supply during the arrhythmic high-rate episode. Thus, in patients with pre-existing coronary atherosclerosis, the occurrence of AHREs, especially in case of sustained or frequent arrhythmic events, may lead to overt ischaemic damage and heart failure. Nevertheless, future larger studies are needed to explore characteristics of cardiac damage in patients with AHREs (i.e., ST vs non-ST elevation MI, or type 2 or type 1 MI). Another mechanism may be represented by embolization from left atrium/appendage to coronary arteries, as recently described in patients with AF [15].

This increased cardiovascular risk in patients with AHREs is in keeping with that described in patients with AF [16], reinforcing the concept that AHREs and AF are likely to represent a clinical continuum in the spectrum of atrial tachyarrhythmias. Of note, we found that the incidence of MACE after AHREs onset was almost doubled in patients developing AHRE ≥ 24 h than patients with AHREs lasting ≥ 5 min. This association was still evident

Table 3 Type and incidence of MACEs in the whole cohort

Type of events	Number of events	Incidence rate (100 patient-years)	95% confidence interval
Acute heart failure	61	1.93	1.48–2.48
Myocardial infarction/cardiac revascularization	31	0.98	0.67–1.39
Cardiovascular death	27	0.85	0.56–1.24
Cardiovascular hospitalization	15	0.48	0.27–0.79
Ventricular tachycardia/ventricular fibrillation	18	0.57	0.34–0.91
Total	152	4.85	4.11–5.68

Table 4 Cox proportional hazard regression analysis with time-dependent covariates for MACE predictors in patients with AHREs ≥ 5 min (model A) and AHREs ≥ 24 h min (model B)

	Hazard ratio	95% confidence interval	*p* value
Model A. AHREs ≥ 5 min			
Age	1.010	0.995–1.026	0.197
Female sex	0.940	0.656–1.348	0.738
Prior atrial fibrillation	1.195	0.814–1.754	0.362
AHREs ≥ 5 min	1.788	1.247–2.562	0.002
Arterial hypertension	1.438	0.934–2.214	0.099
Diabetes	1.909	1.358–2.683	< 0.001
Heart failure	2.203	1.527–3.178	< 0.001
Prior stroke/TIA	0.886	0.521–1.509	0.657
Prior coronary artery disease	1.862	1.293–2.681	0.001
Model B. AHREs ≥ 24 h min			
Age	1.012	0.996–1.027	0.149
Female sex	0.924	0.638–1.338	0.675
Prior atrial fibrillation	1.066	0.706–1.608	0.761
AHREs ≥ 24 h	2.390	1.481–3.857	< 0.001
Arterial hypertension	1.312	0.849–2.028	0.222
Diabetes	1.887	1.336–2.665	< 0.001
Heart failure	2.174	1.503–3.144	< 0.001
Prior stroke/TIA	0.963	0.564–1.643	0.890
Prior coronary artery disease	1.863	1.284–2.703	0.001

on multivariable Cox hazard regression analysis. These results suggest that "AHRE burden" is associated with cardiovascular risk in patients with CIED. Hence, our study suggests that comprehensive management of atherosclerotic risk factors for coronary events is needed in CIED patients presenting with AHREs.

In this context, the use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AHREs may be of interest not only in the view of optimizing the thromboprophylaxis strategy [17], but also for reducing cardiac complications, given that NOACs, as compared to warfarin, may reduce the incidence of ischemic heart disease [18]. For example, in an observational cohort of 31,739 patients, the incidence rate of MI was 1.6%/year in patients treated with VKA, 1.2%/year for apixaban and dabigatran (risk difference − 0.4%), and 1.1%/year for rivaroxaban (risk difference − 0.5%) [18].

In addition to ischaemic events, patients implanted with CIED have also arrhythmic complications, such as VT/VF and sudden cardiac death [19, 20]. Thus, in our cohort VT/VF represented an indication for ICD implantation in about 10% of patients, and during follow-up, 18 patients developed VT/VF (0.57%/year). Recent evidence suggests that the use of sacubitril/valsartan in patients with HF equipped with ICD did not affect AF burden but significantly reduced the rate of VT/VF, suggesting a potential benefit in this population [21].

Limitations

This was a single-centre study performed in hospital-based setting. Given the observational design of the study, we cannot determine a causality between AHREs and cardiac adverse outcomes.

In conclusion, patients implanted with CIEDs developing AHREs show a significant risk for MACE. This risk is already increased in patients with AHREs ≥ 5 min. Cardiovascular prevention strategies in this patient population are warranted.

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Compliance with ethical standards

Conflict of interest None related to this paper.

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