

**ORIGINAL ARTICLE**

# Prevalence of atrial high-rate episodes and the risk factors in Indian patients with cardiac implantable electronic devices: Real-world data

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## Abstract

**Background:** In patients with cardiac implantable electronic devices (CIEDs), atrial high-rate episodes (AHREs) are associated with an increased risk of developing atrial fibrillation (AF) and thromboembolism. We report here the characteristics of “real-world” patients that may be associated with the occurrence of AHREs.

**Methods:** This was an observational, cross-sectional, data collection study. Data of 234 patients with dual-chamber CIEDs, who visited our clinic over a period of 3 months, were evaluated. Occurrence of AHRE was defined as atrial tachyarrhythmia with an atrial rate of  $\geq 180$  beats/min lasting for  $\geq 5$  minutes. Multivariate logistic regression analyses were performed to evaluate clinical risk factors associated with AHRE.

**Results:** The mean age of the group was  $66.9 \pm 9.95$  years, and 25% were females. AHREs were recorded in 48 (21%) patients. Multivariate logistic regression analysis revealed that hypertension (HTN) (OR = 4.14; 95% CI: 1.74-9.85;  $P = .0013$ ) and type II diabetes mellitus (T2DM) (OR = 2.09; 95% CI: 1.04-4.23;  $P = .0392$ ) were significantly and independently associated with the occurrence of AHRE.

**Conclusion:** This real-world data report the prevalence of and risk factors associated with AHRE occurrence in Indian patients with dual-chamber CIED. Known risk factors for AF, such as HTN and diabetes mellitus, were also associated with AHRE occurrence, thus supporting the risk prediction for AF, stroke, or thromboembolism in such patient population.

## KEYWORDS

AHREs, atrial fibrillation, cardiac implantable electronic devices, hypertension, risk factors

## 1 | INTRODUCTION

Atrial fibrillation (AF), the most common type of sustained supra-ventricular arrhythmias, are known to increase the risk of cerebral stroke and all-cause cardiovascular mortality.<sup>1,2</sup> Clinical AF is often preceded by subclinical atrial tachyarrhythmia and asymptomatic or silent atrial high-rate episodes (AHRE); the later lasting >5 minutes are thought to be clinically relevant. It has been emphasized that these patients with AHREs should be assessed for overt AF as well as for the presence of other risk factors for stroke.<sup>3</sup>

While traditional methods like electrocardiogram (ECG) and Holter monitoring may not assist the detection of silent AHREs,<sup>4</sup> wearable ECG monitoring and novel technologies using smartphone have been shown to aid detection of tachyarrhythmias.<sup>5</sup> Moreover, cardiac implantable electronic devices (CIEDs), such as pacemakers, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), and loop recorders, offer early detection of atrial and ventricular arrhythmic episodes even in patients who are asymptomatic.<sup>6</sup> Patients with CIEDs are already predisposed to multiple comorbidities for developing AF and continuous monitoring may help in detecting silent AF episodes in such patients. In patients with implantable devices and with no history of AF, device-detected AHREs can predict long-term mortality outcomes and are known to be associated with increased risk of clinical AF, stroke, and thromboembolism.<sup>3,4,7-9</sup>

Several risk factors, including aging, hypertension (HTN), diabetes, heart failure, vascular disease, valve disease, and others, have been associated with increased incidences of AF; however, the association of these risk factors for predicting AHRE or subclinical AF is not fully understood.<sup>10-12</sup> Hence, this study was performed to evaluate the prevalence and risk factors associated with the occurrence of AHRE in Indian patients with dual-chamber CIEDs.

## 2 | METHODS

This was an observational, cross-sectional, data collection study conducted at a single, tertiary care center in Kolkata, India. Patients with dual-chamber CIED (dual-chamber pacemaker, ICD, CRT-P, and CRT-D), visiting the device clinic of our hospital during the period of May 2017 till July 2017, were eligible for this data collection protocol. Only patients who had their previous pacemaker interrogation done at least 12 months ago were considered for enrollment. Patients with single chamber devices without the capability for atrial sensing, those with a documented history of AF, and those with inadequate clinical data were excluded from the analysis.

Medical records and clinical data available for all eligible patients were collected. Devices were interrogated with the appropriate programmer of the device company. Data regarding AHRE were collected from the stored episodes and electrograms were corroborated regarding rate and duration. Intracardiac electrograms (EGM) were reviewed and adjudicated for episodes of AHRE. For the purpose of this study, an occurrence of AHRE was defined as

atrial tachyarrhythmia with an atrial rate of  $\geq 180$  beats/min lasting  $\geq 5$  minutes.<sup>3</sup> All the devices implanted were either Medtronic or St. Jude's devices. Although St. Jude's devices were programmed to detect atrial rate of  $\geq 180$  beats/min as AHRE, the detection level of Medtronic devices were set at  $\geq 175$  beats/min. For the later, we considered only atrial rates  $\geq 180$  beats/minute as AHRE.

The following data were collected: Age, sex, history of HTN, type II diabetes mellitus (T2DM), ischemic heart disease or ischemic stroke, left ventricular ejection fraction (LVEF), type of implanted device, indication for device implantation, year of implantation, and the presence of AHRE. The CHA<sub>2</sub>DS<sub>2</sub>VASc score was also calculated for all eligible patients.

Of the various risk factors for AF, the association of age, gender, HTN, T2DM, LVEF, ischemic heart disease, and stroke with AHRE was studied. Considering that the risk factors for AF closely parallel the risk factors for stroke, the relation of AHRE occurrence to CHA<sub>2</sub>DS<sub>2</sub>VASc score was also evaluated.

The study was approved by the Institutional Ethics Committee.

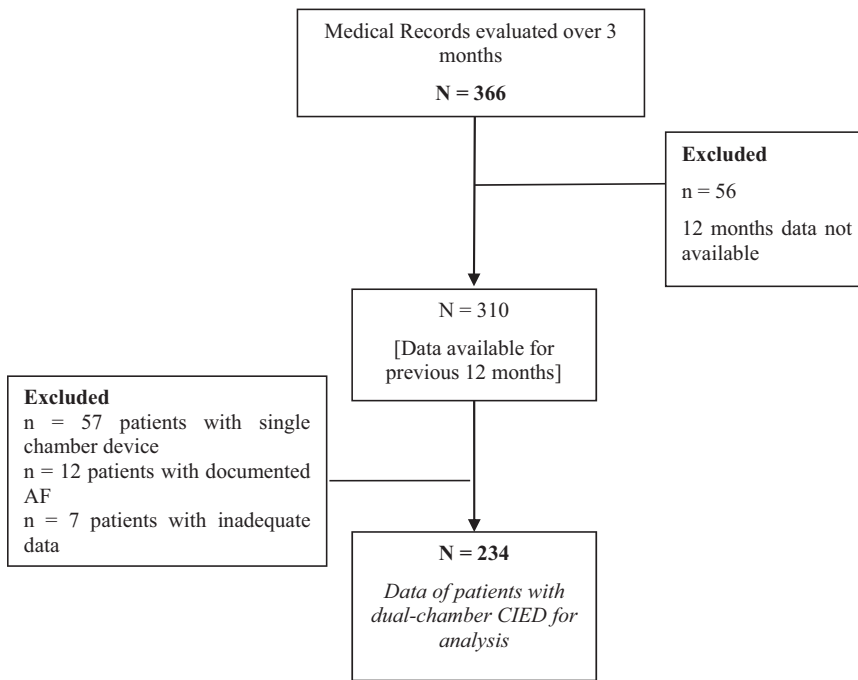
### 2.1 | Statistical analysis

Statistical analysis was performed using Statistical Analysis Software (SAS) version 9.4. Descriptive statistics were presented for baseline demographic clinical characteristics for the entire group, as well as for the subgroups of patients with and without AHRE. Continuous variables were presented as the number of patients (N), mean, standard deviation (SD), minimum (min), and maximum (max) and compared between subgroups using Unpaired Student's *t* test; while categorical variables were presented as frequency (N, percentage [%]) and compared using Pearson's chi-squared test.

A multivariate logistic regression model was carried out using a stepwise selection method to identify the prognostic factors for the occurrence of AHRE. In the first step, the intercept-only model was fitted and individual score statistics for the potential variables were evaluated. A significance level of .05 was used to allow a variable into the model. In stepwise selection, an attempt was made to remove any insignificant variables from the model before adding a significant variable to the model. Hosmer and Lemeshow test was used to evaluate "goodness of fit" in the selection model. Data from the multivariate logistic regression analyses were expressed as odds ratio (OR) and 95% confidence interval (CI), mean (SD), min-max, or frequency and percentages. Wald Chi-Squared probability values are reported, and a  $P < .05$  was considered statistically significant.

## 3 | RESULTS

During the study period of 3 months, 366 patients visited the pacemaker clinic; of which, 310 patients with implantable devices had data available for previous 12 months. Of these, 57 patients with single chamber devices without atrial sensing capabilities, 12 patients with documented AF, and seven patients with inadequate data were



**FIGURE 1** STROBE diagram for the patient population

excluded (Figure 1). Hence, data of 234 patients with a dual-chamber CIED were considered for this cross-sectional analysis. Of these, 225 patients had dual-chamber pacemaker, five patients had CRT-pacemaker, and four patients had dual-chamber ICD. Indications for device implantation included sinoatrial disease in 117 patients, atrioventricular block in 93 patients, heart failure in eight patients, ventricular tachycardia in one patient, and other (malignant vasovagal syndrome, hypersensitive carotid sinus syndrome) in six patients, while indication for implantation was not available in nine patients. None of the patients had moderate to severe mitral stenosis or prosthetic valve.

Demographic and clinical characteristics for all the patients are presented in Table 1. The group comprised of 175 males and 59 females, with a mean age of 66.9 years. The average duration post implantation was 3.74 years. Of the patients studied, 48 patients had at least one episode of AHRE which corresponds to a prevalence rate of 21% in the population studied. Patients with AHRE were comparable to that of the non-AHRE subgroup for all characteristics, except that the AHRE subgroup had a lower mean ejection fraction and a higher proportion of hypertensive patients ( $P < .05$  for both, Table 1).

**TABLE 1** Demographic and clinical characteristics of the patients

Patient characteristics	Statistics	All patients [N = 234]	Patients with AHRE (n = 48)	Patients without AHRE (n = 186)	P <sup>a</sup>
Age (years)	Mean (SD)	66.9 (9.95)	64.5 (11.70)	67.5 (9.38)	.066
	Min-Max	32-87	33-87	32-85	
LVEF (%)	Mean (SD)	52.8 (10.49)	49.9 (10.21)	53.6 (10.46)	.029*
	Min-Max	20-70	30-70	20-70	
Gender					
Male	N (%)	175 (74.8)	37 (77.1)	138 (74.2)	.681
Hypertension	N (%)	155 (66.2)	39 (81.3)	116 (62.4)	.0136*
Type 2 Diabetes Mellitus	N (%)	99 (42.3)	23 (47.9)	76 (40.1)	.377
Ischemic Heart Disease	N (%)	58 (24.8)	15 (31.2)	43 (23.1)	.245
Ischemic Stroke	N (%)	3 (1.3)	0 (0)	3 (1.6)	.376
CHA <sub>2</sub> DS <sub>2</sub> VASc Score	Mean (SD)	2.6 (1.33)	2.7 (1.22)	2.5 (1.36)	.386
	Min-Max	0-6	1-6	0-6	

Abbreviations: AHRE, atrial high-risk episode; LVEF, left ventricular ejection fraction; N, total number of patients; n (%), number of patients (percentage); SD, standard deviation.

<sup>a</sup>Comparison between patients with AHRE and without AHRE using Unpaired Student's *t* test (continuous variable) and chi-squared test (categorical variable), respectively.

<sup>b</sup> $P > .05$  = no significant difference. \* $P \leq .05$  statistically significant difference.

### 3.1 | Results from multivariate logistic regression: Patient characteristics associated with AHRE occurrence

The multivariate logistic regression model was carried out as described in the Methods section above. Prior to the first step, the intercept-only model was fitted and individual score statistics for the potential variables were evaluated. In Step 1, HTN was selected into the model, as it was the most significant variable. In Step 2, age was added as a variable, so that the model contained an intercept and HTN and age as variables. Both HTN and age continued to show significance ( $P < .05$  for both). In Step 3, T2DM was added; following which, all the three factors, that is, HTN, age, and T2DM showed significance ( $P < .05$  for all). Finally, none of the remaining factors met the entry criterion in the model, and hence, the stepwise selection was terminated. Results of the Hosmer and Lemeshow test confirmed the “goodness of fit” for the selected model ( $P = .7061$ ).

Results from the multivariate logistic regression are summarized in Table 2. The odds of prevalence of AHRE was 4.14 times more in patients with HTN as compared to nonhypertensive patients. Further, AHRE occurrence in diabetic patients was 2.09 times more as compared to nondiabetic patients. Age also appeared to be a significant covariate of AHRE in our model ( $P < .05$ ); however, the odds ratio of 0.95 [95% CI: 0.92–0.99] provides inadequate evidence for interpreting the association of increasing or decreasing age with AHRE occurrence.

## 4 | DISCUSSION

The main findings of this “real-world” analysis of Indian patients with CIED are: 21% of patients had device-detected AHREs; and HTN and diabetes were independently and significantly associated with AHRE occurrence.

The prevalence of device-detected AHRE in our study was defined as AHRE with the atrial rate of  $\geq 180$  beats/min and lasting  $\geq 5$  minutes. There are varying reports for the incidence of AHREs, ranging from 10% to 70%, owing to the different definitions used and time of follow-up.<sup>6,8,13–16</sup> One report identified AHRE of  $>5$  minutes as an independent predictor for silent ischemic brain lesions,<sup>7</sup> while other studies defined AHRE as episodes with atrial rate  $>180$  beats/min and/or of  $\geq 5$  minutes duration within 6 months of pacemaker implantation.<sup>8,13</sup>

**TABLE 2** Factors associated with the occurrence of AHRE using multivariate logistic regression

Odds ratio estimates*				
Effect	OR	95% CI		P
HTN	4.14	1.74	9.85	.0013
T2DM	2.09	1.04	4.23	.0395
Age	0.95	0.92	0.99	.005

Abbreviations: AHRE, atrial high-risk episode; CI, confidence interval; HTN, hypertension; OR, odds ratio; T2DM, type II diabetes mellitus.  
\*Significant risk factor for AHRE,  $P < .05$  as per Wald chi-squared test.

A recent “real-world” study reported AHREs as episodes with  $>175$  beats/min and lasting  $>5$  minutes in 35% of patients with CIEDs with a median follow-up of 16 months.<sup>6</sup> A retrospective report from patients without documented AF, pacemaker-detected AHREs of  $\geq 5$  minutes was reported in 29%.<sup>14</sup> In another study, subclinical atrial tachyarrhythmia episodes with atrial rate  $>190$  beats/min and for  $>6$  minutes were reported in 34.7% of patients with implantable devices, over a follow-up period of 2.5 years.<sup>16</sup> Patients with no history of AF who underwent dual-chamber pacemaker implantation reported AHREs of  $\geq 5$  minutes duration in 17% of patients within 6 months of pacemaker implantation.<sup>8</sup> In our study, we have observed only the prevalence of AHRE in the 12 months prior to patient enrollment.

While patient characteristics such as increasing age, HTN, diabetes, or vascular disease are already known to be independent predictors of AF,<sup>10,11</sup> the characteristics of “real-world” patients developing AHREs are poorly described. Association of the known risk factors of AF with the occurrence of AHREs may improve the predictability and detection of AHREs in patients with CIEDs; and also, further assist in predicting increased risk of stroke and systematic embolism through intense monitoring. Almost three decades ago, the landmark Framingham Heart Study has well-established HTN, aging, congestive heart failure, coronary artery disease, diabetes mellitus as independent risk factors for AF.<sup>10</sup> Multiple studies have, since then, consistently reported HTN and diabetes as significant independent predictors of AF, adjusting for age and other predisposing conditions.<sup>2,17–19</sup> Similarly, in our study too, we found significant association of HTN and diabetes with AHRE occurrence.

Aging has been a known risk factor for new-onset AF in both western as well as Asian patients.<sup>20</sup> However, while arrhythmia is observed frequently in older patients, it is also reported to be common in young people and those without any comorbidity.<sup>21</sup> Evidence for association of age with AHRE occurrence has been conflicting. Some studies have shown that the occurrence of AHRE increases with age,<sup>6,16</sup> while others have failed to show any significant relation between them.<sup>13,22</sup> In our analysis too, age appears to have a significant association with AHRE occurrence ( $P < .05$ ). However, an odds ratio ranging from 92% to 99% increase with a point estimate of 95% appears inadequate to strongly conclude if younger age is associated with AHRE occurrence in our study. Moreover, this outcome might be influenced by the fact that younger patients aged  $<60$  years comprised 80% ( $n = 187$ ) of the group, while only 20% of patients were  $\geq 60$  years. It is also worth mentioning that of the six patients less than 40 years of age, three patients had AHRE contributing to almost 50% of occurrence in the younger age range; hence the age-related association may be appearing skewed toward younger patients. Moreover, only patients with dual-chamber CIEDs were considered for this analysis, and these devices are more preferred in younger patients. The above, taken together, might have impacted the results leading to a borderline OR of  $<1.0$  for age and AHRE in our group; however, this evidence may not be considered strong enough to interpret the association of younger or older age with AHRE occurrence precisely.

Additionally, in concurrence with the real-world data that showed a limited value of clinical risk scores in predicting AHREs,<sup>6</sup>

the CHA<sub>2</sub>DS<sub>2</sub>VASc score in our analysis also did not show significant association with AHRE occurrence.

The current analysis does have some limitations. This was a cross-sectional analysis in a small number of patients; hence may not reflect upon all independent predictors for AHRE occurrence, and could have been impacted by other confounding risk factors, currently not collected. The generalizability of these results is also limited, as this was restricted to data from a single center. Although every effort was made to corroborate the marker channels with the EGM, the possibility of false detection of AHRE due to oversensing by the atrial lead<sup>9,23</sup> cannot be excluded.

Interrogation of implanted devices on a regular basis for AHRE is strongly recommended<sup>3</sup> so as to predict overt AF or risk of stroke. Patients with pacemakers present a high-risk population owing to the already underlying rhythm disturbances; and so, the prevalence of AHRE is higher than in general population.<sup>12</sup> Hence, detection of AHREs in these cases may offer helpful information on risk prediction and patient management.

To the best of our knowledge, this is a first report documenting the prevalence of AHRE in Indian patients with dual-chamber CIEDs. Known risk factors for AF, like HTN and diabetes mellitus, were also independently associated with the occurrence of AHRE, thus supporting the risk prediction for AF, stroke, or thromboembolism in this patient population.

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## CONFLICT OF INTERESTS

Authors declare no conflict of interests for this article.

## AUTHOR CONTRIBUTIONS

Suvro Banerjee: concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics, secured funding, and data collection. Suchit Majumdar: data adjudication, data interpretation, critical revision of article, approval of article. Aritra Konar: data collection, critical revision of article, approval of article.

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