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ORIGINAL RESEARCH

Development of New-Onset or Progressive Atrial Fibrillation in Patients With Permanent HIS Bundle Pacing Versus Right Ventricular Pacing: Results From the RUSH HBP Registry

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BACKGROUND: Conventional right ventricular pacing (RVP) has been associated with an increased incidence of atrial fibrillation (AF). We sought to compare the occurrence of new-onset AF and assessed AF disease progression during long-term follow-up between His bundle pacing (HBP) and RVP.

METHODS AND RESULTS: We included patients undergoing initial dual-chamber pacemaker implants at Rush University Medical Center between January 1, 2016, and June 30, 2019. A total of 360 patients were evaluated, and 225 patients (HBP, n=105; RVP, n=120) were included in the study. Among the 148 patients (HBP, n=72; RVP, n=76) with no history of AF, HBP demonstrated a lower risk of new-onset AF (adjusted hazard ratio [HR], 0.53; 95% CI, 0.28–0.99; *P*=0.046) compared with traditional RVP. This benefit was observed with His or RVP burden exceeding 20% (HR, 0.29; 95% CI, 0.13–0.64; *P*=0.002), ≥40% (HR, 0.31; *P*=0.007), ≥60% (HR, 0.35; *P*=0.015), and ≥80% (HR, 0.40; *P*=0.038). There was no difference with His or RV pacing burden <20% (HR, 0.613; 95% CI, 0.213–1.864; *P*=0.404). In patients with a prior history of AF, there was no difference in AF progression (*P*=0.715); however, in a subgroup of patients with a pacing burden ≥40%, HBP demonstrated a trend toward a lower risk of AF progression (HR, 0.19; 95% CI, 0.03–1.16; *P*=0.072).

CONCLUSIONS: HBP demonstrated a lower risk of new-onset AF compared with RVP, which was primarily observed at a higher pacing burden.

Key Words: Atrial fibrillation ■ atrial fibrillation progression ■ his bundle pacing ■ new-onset atrial fibrillation ■ right ventricular pacing

It is well recognized that conventional right ventricular (RV) apical pacing causes ventricular desynchrony and is associated with an increased risk of atrial fibrillation (AF) and development of cardiomyopathy.[1,2] Permanent His bundle pacing (HBP) provides a more physiological form of ventricular activation and has been shown to decrease or reverse some of the adverse clinical outcomes associated with RV pacing (RVP).[3,4] There might be some benefit of HBP in reducing onset and progression to persistent AF when compared with RVP. A study that compared HBP with RV septal pacing and RV apical pacing demonstrated that HBP showed a lower risk of progression to persistent or permanent AF.[5] However, the study included patients with and without prior history

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CLINICAL PERSPECTIVE

What Is New?

- In patients without a prior diagnosis of atrial fibrillation, His bundle pacing is associated with a lower incidence of a new-onset atrial fibrillation when compared with traditional right ventricular pacing.
- The lower risk of new-onset atrial fibrillation with His bundle pacing compared with right ventricular pacing was primarily driven by patients with a higher pacing burden.

What Are the Clinical Implications

- Patients with dual-chamber pacemaker implantations might benefit from His bundle pacing compared with traditional right ventricular pacing, through a reduction in the incidence of atrial fibrillation.
- Patients with a higher burden of pacing are more likely to benefit from His bundle pacing over right ventricular pacing.

Nonstandard Abbreviations and Acronyms

AAD	anti-arrhythmic drug
AHRE	atrial high rate episode
HBP	His bundle pacing
RVP	right ventricular pacing

of AF and did not evaluate the specific end point of a new diagnosis of AF. Whether HBP impacts the development of new-onset AF or affects the progression of AF has not been systematically evaluated in a large cohort of patients. It is unclear if a higher pacing burden with HBP is associated with a similar increase in the risk of new-onset AF and progression of AF when compared with RVP. This study was designed to assess the risk of new-onset AF or AF disease progression among patients with HBP as compared with conventional RVP. We also planned to perform a subgroup analysis based on the ventricular pacing burden to compare the incidence and progression of AF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

We performed a retrospective cohort analysis of successful dual-chamber permanent pacemaker implantations at Rush University Medical Center during the study period from January 1, 2016, through June 30, 2019, in patients with at least a 6-month duration of follow-up.

Subject Selection

Patients aged ≥18 years who had an indication for permanent pacemaker implantation based on current guidelines[6] and underwent successful initial dual-chamber permanent pacemaker implantation qualified for enrollment. Successful HBP implantation was defined as selective or nonselective HB pacing with paced QRS duration ≤130 milliseconds.[3,4]

Patients with valvular heart disease involving the mitral or aortic valve (moderate or severe stenosis or regurgitation), a history of open-heart surgery within the past 6 months, a known history of persistent or permanent AF at initial implant, a history of an atrioventricular node ablation or AF ablation, and those patients receiving a single-chamber pacemaker or cardiac resynchronization therapy device implant were excluded. The study was approved by the institutional review committee. Informed consent was waived, as this was a retrospective study.

Definitions

1. Paroxysmal AF: AF terminating spontaneously or with intervention within 7 days of onset[7,8,9].
2. Persistent AF: Continuous AF lasting ≥7 days.
3. Long-standing persistent AF: Continuous AF lasting ≥12 months.
4. Permanent AF: AF for which patients and clinicians chose not to employ a rhythm control strategy.
5. New-onset AF episode[7]: Device detection of a true AF episode (lasting ≥30 seconds) on intracardiac electrogram. Atrial high-rate episodes (AHREs) from device recordings were manually reviewed to confirm true AF and rule out other causes of AHREs. AHRE episodes were defined as episodes with an atrial intracardiac electrogram rate ≥190 bpm. AHRE episodes ≥6 minutes were also evaluated.
6. Progression of AF: Defined as an absolute increase in pacemaker reported average daily AF burden, by ≥10% from the initial device follow up evaluation at 1 to 2 months to subsequent device interrogations at 6-month intervals. Additionally, an increase in AF burden by ≥5% and ≥25% were also recorded.

Data Collection and Study Follow-Up

All patients had scheduled follow-up at 2 months after implant and every 6 months thereafter until the final follow-up or death. Data were collected on baseline patient characteristics such as age, sex, race, comorbidities, and other potential risk factors predisposing to AF, which could result in confounding. The

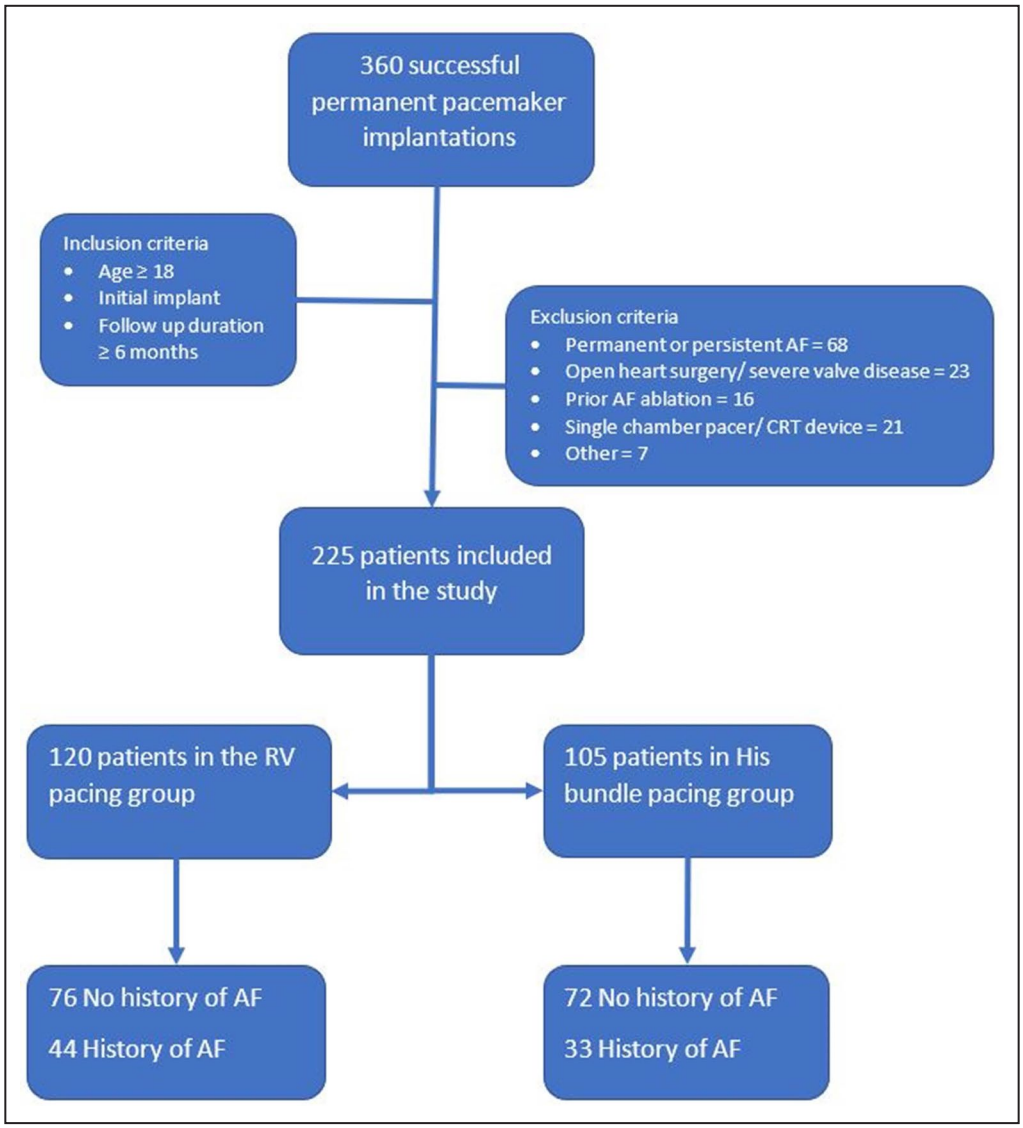

Figure 1. Flowchart demonstrating the patients included in the study as well as the inclusion and the exclusion criteria.
AF indicates atrial fibrillation; CRT, cardiac resynchronization therapy; and RV, right ventricular.

percentage of His or ventricular pacingand average daily AF burden at the initial 1- to 2-month follow-up visit and from each subsequent device interrogation including remote device interrogation were collected. For the end point of new-onset AF, the subjects were censored at the time of last available follow-up or death, in the absence of new-onset AF. For the end point of progression of AF among those patients with a known history of AF, data collection was censored once patients underwent an AF or atrioventricular nodal ablation or were initiated on antiarrhythmic drug (AAD) therapy or at the time of last available follow-up or death. Reversible causes of AF, such as critical illness AF was not considered to meet the end point for new-onset AF. Baseline and 12-month follow-up transthoracic echocardiogram variables[10] when available were also collected. For the primary analysis of patients with no prior history of AF, data regarding AF episodes were not collected during a lead stabilization period of 4 weeks after device implantation.

Study End Points and Hypothesis

The primary end points were (1) new-onset AF among patients without a known history of AF and (2) progression of AF defined as an absolute increase in average daily AF burden by ≥10% from the AF burden at initial device follow-up. The secondary end point was outcomes of new-onset AF and progression of AF among patients with ≥20% RVP or HBP burden, stratified based on pacing percentage. We hypothesized that in patients with dual-chamber pacemakers, HBP is

associated with a lower risk of new-onset AF and lower risk of AF progression than conventional RV pacing.

Statistical Analysis

The χ^2 test was used to assess the association between categorical variables, whereas an independent samples t-test was performed to compare continuous variables between pacing sites. The Mann-Whitney test was used for comparing variables with nonnormal distribution. To determine significant predictors, univariate predictors with a *P* value <0.10 were entered in a multivariate Cox's proportional hazard model. Cox's proportional hazard model was used to estimate the hazard ratio of the first occurrence of new-onset AF and progression of AF according to different pacing site (HBP or RVP), adjusted for various potential confounders identified between left ventricular ejection fraction (LVEF), left atrial indexed volume, percentage of atrial and ventricular pacing, age, sex, diabetes mellitus, hypertension, coronary disease, QRS morphology, bundle branch block, use of antiarrhythmic drugs (propafenone, flecainide, dofetilide, sotalol, dronedarone, and amiodarone).[4,11] A 2-tailed *P* value of <0.05 was considered statistically significant. SPSS software, version 21 (IBM Corp., Armonk, NY) was used in all statistical analyses.

RESULTS

There were 360 permanent pacemaker implantations performed at our institution between January 1, 2016, and June 30, 2019. After exclusion criteria were applied, 225 patients were included in the analysis (Figure 1). There were 120 patients in the RVP group

Table 1. Baseline Characteristics of All Patients Included in the Study

Characteristic	HBP Group (n=105)	RVP Group (n=120)	*P* Value
Age, y	72.65±11.04	76.54±9.87	*P*=0.006
Sex, n (%)			*P*=0.422
Female	53 (50.5)	67 (55.8)	
Male	52 (49.5)	53 (44.2)	
Race/Ethnicity, n (%)			*P*=0.407
Black	32 (31.4	50 (42)	
White	53 (52)	54 (45.4)	
Hispanic	11 (10.8)	12 (10.1)	
Asian	3 (2.9)	1 (0.8)	
Other (including Native American or if race/ethnicity was unknown)	3 (2.9)	2 (1.7)	
Body mass index, kg/m^2	30.30±6.99	29.1±6.46	*P*=0.184
Hypertension, n (%)	87 (82.9)	105 (87.5)	*P*=0.326
Diabetes mellitus, n (%)	31 (29.5)	40 (33.3)	*P*=0.540
Coronary artery disease, n (%)	31 (29.5)	30 (25)	*P*=0.446
Heart failure, n (%)	15 (14.3)	21 (17.5)	*P*=0.512
History of AF at implant, n (%)	33 (31.4)	44 (36.7)	*P*=0.409
Indication for implant, n (%)			*P*=0.244
Sinus node dysfunction, n (%)	54 (51.4)	71 (59.2)	
Atrioventricular block, n (%)	51 (48.6)	49 (40.8)	
Native QRS morphology			*P*=0.159
Narrow, %	62.4	74.8	
LBBB, %	13.9	6.7	
RBBB, %	19.8	15.1	
IVCD, %	4	3.4	
Native QRS duration, ms	113.7±32.2	105.5±25.3	*P*=0.299
ACEi or ARB use, n (%)	50 (47.6)	54 (45)	*P*=0.694
AAD at implant, n (%)	14 (13.3)	11 (9.2)	*P*=0.332
LVEF baseline, %	59.84±8.06	61.00±7.19	*P*=0.262
LVEF at follow-up, %	56.67±9.29	57.85±7.80	*P*=0.466

AAD indicates antiarrhythmic drug; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; HBP, His bundle pacing; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; and RVP, right ventricular pacing.

Table 2. Baseline Characteristics of Patients With No Prior History of Atrial Fibrillation

Characteristic	HBP Group (n=72)	RVP Group (n=76)	*P* Value
Age, y	72.33±11.58	75.71±10.19	*P*=0.061
Sex, n (%)			*P*=0.612
Female	33 (45.8)	38 (50)	
Male	39 (54.2)	38 (50)	
Race/Ethnicity, n (%)			*P*=0.955
Black	25 (35.7)	31 (41.3)	
White	32 (45.7)	32 ((42.7)	
Hispanic	9 (12.9)	9 (12)	
Asian	1 (1.4)	1 (1.3)	
Other (including Native American or if race/ethnicity was unknown)	3 (4.3)	2 (2.7)	
Body mass index, kg/m^2	30.44±7.26	28.79±6.39	*P*=0.144
Hypertension, n (%)	60 (83.3)	62 (81.6)	*P*=0.779
Diabetes mellitus, n (%)	25 (34.7)	25 (32.9)	*P*=0.814
Coronary artery disease, n (%)	24 (33.3)	21 (27.6)	*P*=0.451
Heart failure, n (%)	9 (12.5)	12 (15.8)	*P*=0.566
Indication for implant, n (%)			*P*=0.298
Sinus node dysfunction	28 (38.9)	36 (47.4)	
Atrioventricular block	44 (61.1)	40 (52.6)	
Native QRS morphology, %			*P*=0.458
Narrow	61.8	64	
LBBB	7.4	9.3	
RBBB	23.5	22.7	
IVCD	2.9%	4	
Native QRS duration, ms	114.24±31.85	113.07±26.50	*P*=0.884
ACEi or ARB use, n (%)	35 (48.6)	33 (43.4)	*P*=0.527
LVEF baseline, %	60.2±8.3	61.24±7.58	*P*=0.439
LVEF at follow-up, %	57.03±9.6	56.34±8.9	*P*=0.890

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; HBP, His bundle pacing; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; and RVP, right ventricular pacing.

and 105 patients in the HBP group. Baseline characteristics are shown in Table 1. Age was significantly lower in the HBP group compared with the RVP group by about 4 years (*P*=0.006). Hypertension was the most common comorbidity seen in 84% of the patients included. LVEF was predominantly preserved,

Table 3. Outcomes of the Patients Included in the Study Based on Prior History of AF

(A) Patients With No Prior History of AF			
Characteristic	**HBP Group (n=72), n (%)**	**RVP Group (n=76), n (%)**	***P* Value**
His or RV pacing burden ≥20%	53 (73.6)	45 (59.2)	0.064
New diagnosis of AF	15 (20.8)	31 (40.8)	0.009
New diagnosis of AHRE ≥6 min	14 (19.4)	28 (36.8)	0.019
(B) Patients With Prior History of AF			
Characteristic	**HBP Group (n=33), n (%)**	**RVP Group (n=44), n (%)**	***P* Value**
His or RV pacing burden ≥20%	21 (63.6)	22 (50)	0.233
AAD at implant	13 (39.4)	10 (23.3)	0.129
Intervention performed*	9 (27.3)	8 (18.2)	0.341
AF burden increase by ≥25%	6 (18.2)	10 (22.7)	0.627
AF burden increase by ≥10%	7 (21.2)	12 (27.3)	0.542
AF burden increase by ≥5%	9 (27.3)	13 (29.5)	0.827

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AHRE, atrial high-rate episode; HBP, His bundle pacing; and RVP, right ventricular pacing
*Interventions included AF ablation, atrioventricular nodal ablation, and initiation or up-titration of antiarrhythmic medication.

with a mean LVEF of 60% in the HBP group and 61% in the RVP group (*P*=0.262). There was no significant difference in the 2 groups in the rest of the baseline characteristics (Table 1). Among the 105 patients in the HBP group, 5 patients (4.8%) required HBP lead revision during follow-up. Among them, 3 were performed for high His bundle capture threshold, and 2 were performed for loss of His bundle capture.

New-Onset AF

There were 72 patients in the HBP group and 76 patients in the RVP group without prior history of AF (Table 2). The mean follow-up duration was 1.95±0.9 years. A new diagnosis of AF was noted in 15 (20.8%) patients in the HBP group and 31 (40.8%) patients in the RVP group (*P*=0.009) (Table 3). A new diagnosis of AHRE ≥6 minutes was seen in 14 (19.4%) of patients in the HBP group and 28 (36.8%) of the patients in the RVP group (*P*=0.019). The type of device (ie, HBP/RVP) was the only statistically significant univariate predictor of new-onset AF (Table 4). Cox regression analysis demonstrated that there was a lower risk of a new diagnosis of AF in the HBP group when compared with RVP (hazard ratio [HR], 0.50; 95% CI, 0.27–0.94; *P*=0.029). When adjusted for the confounder (Table S1) of age, the risk of new-onset AF was still lower in HBP (HR, 0.53; 95% CI, 0.28–0.99; *P*=0.046) (Figure 2). A significantly lower burden of new-onset AF was observed in HBP across all pacing burden groups (Figure 3). Results of stratified Cox regression analysis for secondary outcomes based on His or RV pacing burden is shown in Figure 4. The benefit of HBP was primarily driven by His or ventricular pacing burden ≥20%. Adjusted risk of new diagnosis of AF was significantly lower in patients with HBP compared with RVP in the subgroups with His or RV pacing burdens ≥20 % (HR, 0.29; 95% CI, 0.13–0.64; *P*=0.002), ≥40% (HR, 0.31; 95% CI, 0.13–0.72; *P*=0.007), ≥60% (HR, 0.35; 95% CI, 0.15–0.81; *P*=0.015) and ≥80% (HR, 0.40; 95% CI, 0.17–0.95; *P*=0.038). In the patients with His or RV pacing burden <20%, there was no difference between the 2 groups (*P*=0.404). HBP also demonstrated a lower risk of a new diagnosis of AHRE ≥6 minutes in patients with His or RV pacing burden ≥20% (HR, 0.36; 95% CI, 0.16–0.83; *P*=0.016).

Table 4. Univariate Predictors of New-Onset AF in Patients With No Prior History of AF

Characteristic	New Diagnosis of AF (46)	No New Diagnosis of AF (n=102)	*P* Value
Age, y	76.22±11.55	73.10±10.63	0.110
Sex, n (%)			0.740
Male	23 (50)	54 (52.9)	
Female	23 (50)	48 (47.1)	
Body mass index, kg/m^2	30.03±6.43	29.39±7.05	0.599
Diabetes mellitus, n (%)	14 (31.8)	35(35.4)	0.681
Hypertension, n (%)	36 (81.8)	84 (84.8)	0.649
Heart failure	4 (8.7)	17 (16.7)	0.151
Indication for implant			0.969
Sinus node dysfunction, n (%)	20 (43.5)	44 (43.1)	
Atrioventricular block, n (%)	26 (56.5)	58 (56.9)	
Type of device			0.009*
HBP, n (%)	15 (32.6)	57 (55.9)	
RVP, n (%)	31 (67.4)	45 (44.1)	
LVEF, %	58.59±6.17	56.98±8.34	0.282
Pacing % burden ≥20%, n (%)	31 (67.4)	67 (65.7)	0.839
Atrial pacing burden	47.46±30.01	41.00±32.80	0.247
Native QRS duration, ms	116±26	113±30	0.502

AF indicates atrial fibrillation; HBP, His bundle pacing; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.
*Statistically significant univariate predictor.

AF Disease Progression

There were 33 patients in the HBP group and 44 patients in the RVP group who had a prior history of AF (Table 5). The mean follow-up duration was 1.97±0.8 years. AAD use at implant was not different between the 2 groups (*P*=0.129). There was no difference between the 2 groups in the history of AF ablation, atrioventricular nodal ablation, or AAD initiation (*P*=0.341). Progression of AF as defined by an increase in AF burden by ≥10% (AF10%) was seen in 7 (21.2%) patients in the HBP group and 12 (27.3%) patients in the RVP group with no statistically significant difference between the 2 pacing sites (*P*=0.542) (Table 3). There were no univariate predictors for AF disease progression (Table 6). There was no difference in diagnosis of AF 10% between HBP and RVP (HR, 0.84; 95% CI, 0.33–2.13; *P*=0.715) (Figure 5). There was no difference between the 2 groups in AF burden increase of ≥25% (*P*=0.627) and ≥5% (*P*=0.827). On adjusting for confounders (Table S2) of age, hypertension, and native QRS duration, there was no difference between the 2 groups (HR, 0.94; 95% 0.32–2.79; *P*=0.910) (Figure 5). Results of further analysis of secondary outcomes based on His or RV pacing percentage are shown in Figure 6. There was no statistically significant difference in adjusted risk of incidence of AF 10% between HBP and RVP, in patients with His or RV pacing ≥20% (HR, 0.44; 95% CI, 0.11–1.74; *P*=0.243), ≥40% (HR, 0.19; 95% CI, 0.03–1.16; *P*=0.072), ≥60% (HR, 0.30; 95% CI, 0.051.79] *P*=0.188), and ≥80% (HR, 0.32; 95% CI, 0.02–4.79; *P*=0.410). However, separation of the curves between HBP and RVP suggested a potential clinical difference between the 2 groups in patients with His or RV pacing burden ≥40%, which did not reach statistical significance (Figure 6B).

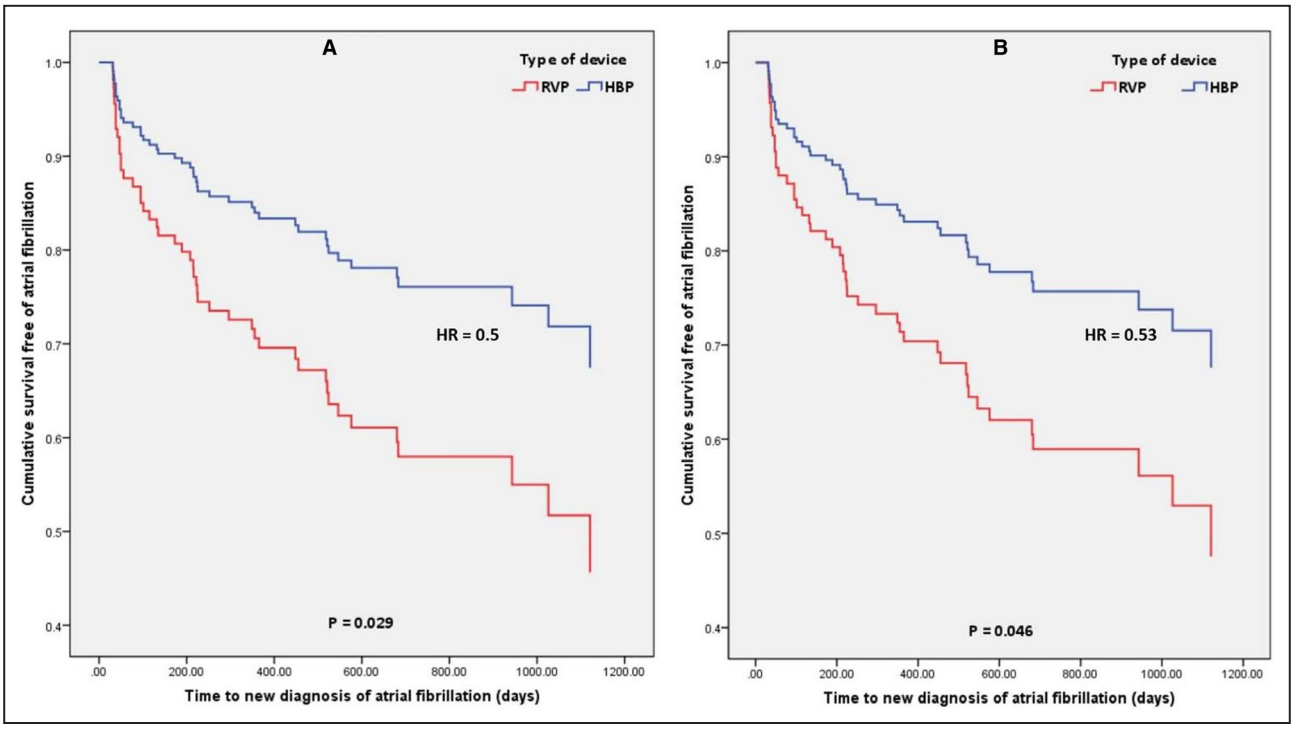

Figure 2. Cumulative proportion of patients free of a new diagnosis of AF based on the type of device (HBP vs RVP).
A, Unadjusted for confounders; (**B**) adjusted for confounders. The representations are derived from Cox model survival function. The *P* values are from Cox proportional hazards model. HBP indicates His bundle pacing; HR, hazard ratio; and RVP, right ventricular pacing.

DISCUSSION

Some important observations can be made from this study. First, in patients without a prior diagnosis of AF, HBP is associated with a lower incidence of a new-onset AF when compared with RVP. Second, the lower risk of new-onset AF with HBP compared with RVP was primarily driven by patients with a higher pacing burden,

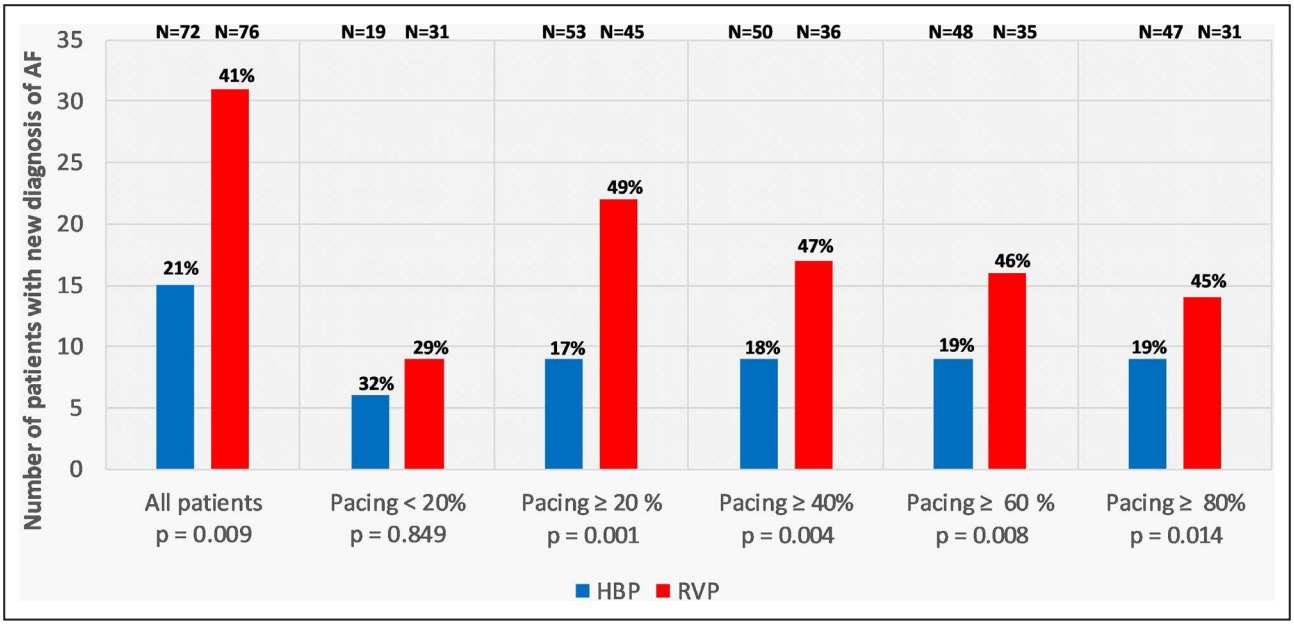

Figure 3. Comparison of new-onset AF by percentage between HBP and RVP in all patients and the subgroups based on ventricular pacing burden.
AF indicates atrial fibrillation; HBP, His bundle pacing; and RVP, right ventricular pacing.

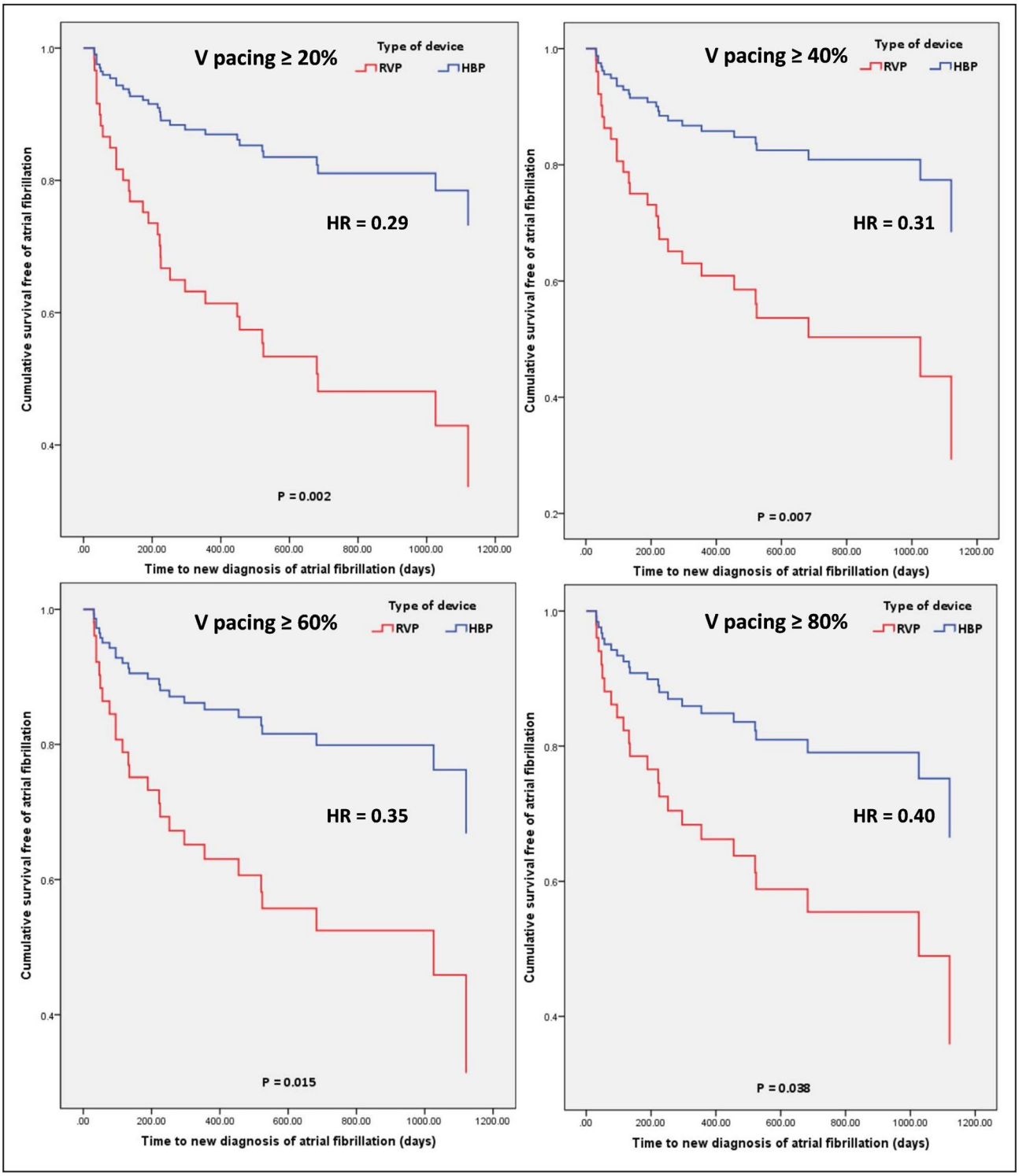

Figure 4. Cumulative proportion of patients free of a new diagnosis of AF based on the type of device (HBP vs RVP) and percentage of ventricular pacing adjusted for confounders.
(**A**) Ventricular pacing (VP) ≥ 20%; (**B**) VP ≥40%; (**C**) VP ≥60%; (**D**) ≥80%. The representations are derived from stratified Cox model survival function. The *P* values are from Cox proportional hazards model. HBP indicates His bundle pacing; HR, hazard ratio; and RVP, right ventricular pacing.

providing further evidence of a true relationship. In patients with a prior diagnosis of AF, HBP and RV pacing did not demonstrate a statistically significant difference in AF disease progression; however, there was a trend toward lower risk of progression of AF with HBP in the patients with His or RV pacing burden ≥40%.

Table 5. Baseline Characteristics of Patients With History of Atrial Fibrillation

Characteristic	HBP Group (n=33)	RVP Group (n=44)	*P* Value
Age, y	73.33±9.9	77.98±9.23	*P*=0.037
Sex, n (%)			*P*=0.632
Female	20 (60.6)	29 (65.9)	
Male	3 (39.4)	15 (34.1)	
Race/Ethnicity, n (%)			*P*=0.111
Black	7 (21.9)	19 (43.2)	
White	21 (65.6)	22 (50)	
Hispanic	2 (6.3)	3 (6.8)	
Asian	2 (6.3)	0	
Body mass index, kg/m^2	30±6.45	29.65±6.62	*P*=0.818
Hypertension, n (%)	27 (81.8)	43 (97.7)	*P*=0.016
Diabetes mellitus, n (%)	6 (18.2)	15 (34.1)	*P*=0.121
Coronary artery disease, n (%)	7 (21.2)	9 (20.5)	*P*=0.935
Heart failure, n (%)	6 (18.2)	9 (20.5)	*P*=0.803
Indication for implant, n (%)			*P*=0.935
Sinus node dysfunction	26 (78.8)	35 (79.5)	
Atrioventricular block	7 (21.2)	9 (20.5)	
Native QRS morphology, n (%)			*P*=0.458
Narrow	63.6	93.2	
LBBB	18.2	2.3	
RBBB	12.1	2.4	
IVCD	6.1	2.3	
Native QRS duration, ms	112.64±33.53	92.59±16.81	*P*=0.003
ACEi or ARB use, n (%)	15 (45.5)	21 (47.7)	*P*=0.843
AAD at implant, n (%)	13 (39.4)	10 (22.7)	*P*= 0.114
LVEF baseline, %	59.06±7.58	60.61±6.60	*P*=0.341
LVEF at follow up, %	56.06±8.93	58.56±5.94	*P*=0.265

AAD indicates antiarrhythmic drug; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HBP, His bundle pacing; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; and RVP, right ventricular pacing.

Table 6. Univariate Predictors of Progression of AF in Patients With Prior History of AF

Characteristic	Progression of AF 10% (n=19)	No Progression of AF (n=58)	*P* Value
Age, y	76.63±9.59	75.78±9.86	0.742
Sex, n (%)			
Male	6 (31.6)	22 (37.9)	0.617
Female	13 (68.4)	36 (62.1)	
Body mass index, kg/m^2	30.28±7.79	29.64±6.10	0.710
Diabetes mellitus, n (%)	5 (26.3)	16 (27.6)	0.914
Hypertension, n (%)	18 (94.7)	52 (89.7)	0.504
Heart failure, n (%)	3 (15.8)	12 (20.7)	0.461
Indication for implant, n (%)			0.204
Sinus node dysfunction	17 (89.5)	44 (75.9)	
Atrioventricular block, n (%)	2 (10.5%)	14 (24.1%)	
Type of device			0.542
HBP, n (%)	7 (36.8	26 (44.8)	
RVP, n (%)	12 (63.2)	32 (55.2	
LVEF, %	56.94±6.22	57.02±7.43	0.970
Pacing burden ≥20%, n (%)	13 (68.4)	30 (51.7)	0.203
Native QRS duration, ms	107.33±29.51	106.31±31.77	0.931
AAD at implant, n (%)	5 (26.3)	18 (31)	0.697

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; HBP, His bundle pacing; LVEF, left ventricular ejection fraction; and RVP, right ventricular pacing.

We demonstrated that HBP was associated with a 50% relative risk reduction and 20% absolute risk reduction of new-onset AF, compared with RVP. These results are consistent with the study by Pastore et al,[5] which showed the risk of progression to persistent or permanent AF in those without a history of AF was lower with HBP. The mechanism by which ventricular pacing induces AF is unclear, but the left atrial dysfunction induced by left ventricular dyssynchrony is a probable culprit.[5,12,13] HBP generates physiological electromechanical activation of the left ventricle without dyssynchrony when compared with RVP, potentially leading to the clinical benefit of the lower incidence of AF.[5,13] Prior studies on RVP have demonstrated that a higher ventricular pacing burden is associated with a higher risk of AF.[14] In our study, HBP was associated with a 71% relative risk reduction and 30% absolute risk reduction when compared with RVP in patients with His or ventricular pacing burdens ≥20%. This benefit was primarily driven by patients with a higher ventricular pacing burden. Our results add to the previously reported benefits of physiological pacing with HBP when compared with RVP in improving LVEF, quality of life, and New York Heart Association functional class.[15] Current guidelines recommend the use of physiological conduction system pacing implants like HBP in patients with LVEF <50% who are anticipated to require frequent pacing (>40%), to reduce the risk of pacing cardiomyopathy.[6] Our observations suggest that patients with normal LVEF who may require frequent pacing might also benefit from HBP by decreasing the risk of incident AF. This must be weighed against the concern for a higher pacing threshold with HBP compared with RVP, potentially resulting in reduced battery longevity and the requirement for HBP lead revision.[4] Further randomized studies are required to validate these observations.

We were unable to demonstrate a statistically significant difference in the progression of AF between

the 2 groups. These results are consistent with the study by Pastore et al,[5] which demonstrated that in a subgroup of patients with prior history of AF, HBP was not associated with a statistically significant difference in progression to persistent or permanent AF compared with RVP. This could be attributable to our sample size and follow-up duration, which might have underpowered our study to detect any difference in the progression of AF (type II error). Although we did not demonstrate a statistically significant difference, there was a trend toward a reduced risk of AF progression among patients with HBP, especially with pacing burden ≥40% as evident by a separation of the survival curves from about 6 months after device implantation in favor of HBP (Figure 6B). A sufficiently sized study may identify a significant difference in AF progression.

In the study by Pastore et al,[5] HBP was associated with a lower risk of progression to persistent or permanent AF in the subgroup analysis of patients with no prior history of AF, and in the subgroup of patients with a prior history of AF, there was no difference between the HBP and RVP groups. However, our definition for the end point of a new diagnosis of AF and progression of AF is different from that of Pastore et al. In addition, Pastore et al did not evaluate the impact of pacing modality on the occurrence of new-onset paroxysmal AF as demonstrated in our study, which makes our results unique. The mean left ventricular systolic function was preserved in both studies. Further studies in patients with reduced ejection fraction are needed to evaluate the potential beneficial effects of HBP compared with traditional biventricular pacing in terms of AF occurrence and progression.

The incidence of a new diagnosis of AF in our study was 21% in the HBP group and 41% in the RVP group. In the analysis of patients from the study by Sweeney et al, the incidence of a new diagnosis of AF based on ECG confirmation only ranged from 21% to 24 % based on the pacing mode, during a follow-up duration of 6 years.[1] In the same study, the risk of AF increased by 1% for each 1% increase in ventricular pacing burden in patients with DDDR mode.[1] Although the incidence of a new diagnosis of AF in our study was higher when compared with older data using only ECG diagnosis, it is consistent with the recent studies that used implantable device detection of AF to establish the diagnosis. In the study by Reiffel et al evaluating patients with risk factors ($CHADS_2$ ≥2) who underwent implantable loop recorders the incidence of a new diagnosis of AF was 29.3% at 18 months and 40% at 30 months.[16] A pooled analysis of 3 studies involving 6850 patients with cardiac implanted electronic devices showed the incidence of new AF ≥5 minutes was 34% during a follow-up period of 2.4 years.[17]

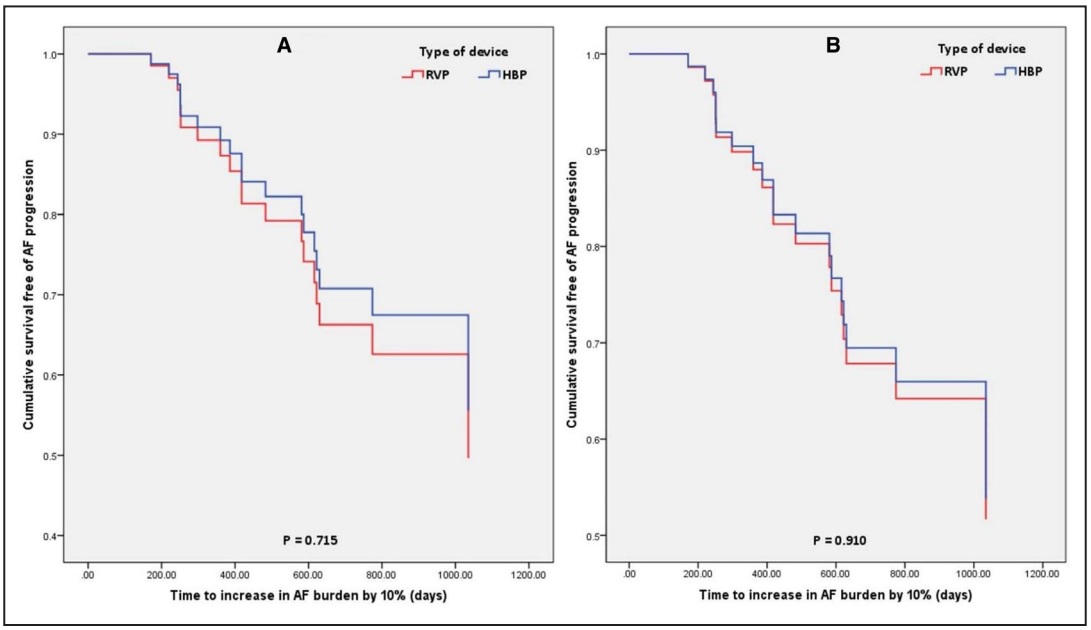

Figure 5. Cumulative proportion of patients free of progression of AF burden by 10%, based on the type of device (HBP vs RVP).
A, Unadjusted for confounders; (**B**) adjusted for confounders. The representations are derived from Cox model survival function. The *P* values are from Cox proportional hazards model. AF indicates atrial fibrillation; HBP, His bundle pacing; and RVP, right ventricular pacing.

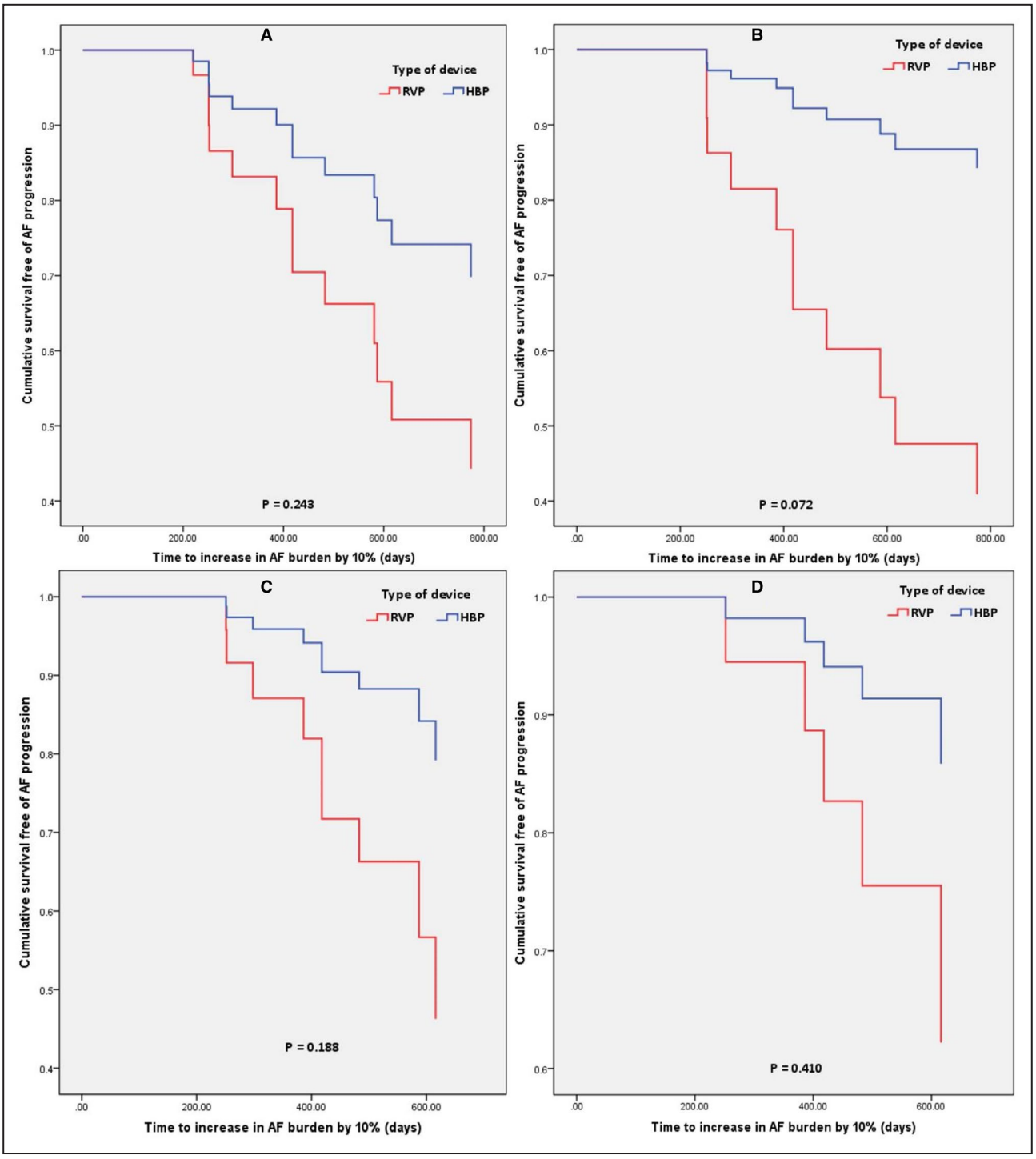

Figure 6. Cumulative proportion of patients free of progression of AF burden by 10%, based on the type of device (HBP vs RVP) and His or ventricular pacing percentage adjusted for confounders.
A, Ventricular pacing (VP) ≥20%; (**B**) VP ≥40%; (**C**) VP ≥60%; (**D**) ≥80%. The representations are derived from stratified Cox model survival function. The *P* values are from Cox proportional hazards model. AF indicates atrial fibrillation; HBP, His bundle pacing and RVP, right ventricular pacing.

Limitations

There are several limitations to our study. This was a retrospective, observational study that has inherent limitations. We used the Cox proportional hazards model to help minimize the effect of confounders as much as possible. Our study may have been underpowered to detect the outcomes of the progression of AF. In patients with a prior history of AF, a

minority of patients were on AAD therapy, which may be a potential bias; however, the subgroup analysis excluding patients on AAD yielded similar results to the primary analysis. Also, variation in the time between device checks may have affected the AF burden calculation, which may, in turn, bias our results. Our end point for AF progression based on the device detected change in AF burden by 10% was chosen to demonstrate the effect of pacing modality and identify patients at risk of persistent or permanent AF earlier, but the clinical significance of this end point is unclear. Hence, our results regarding the progression of AF must be interpreted with caution. Multiplicity adjustment was not performed. The CI of the hazard ratio for the new diagnosis of AF is broad, especially when stratified on the basis of pacing percentage, which needs to be noted when interpreting these results. The difference in manufacturers of the pacemakers used in the HBP and RVP groups might have confounded the results. The variation in follow-up duration between the HBP and RVP groups might have also confounded the results.

CONCLUSIONS

HBP was associated with a lower risk of new-onset AF compared with conventional RVP. Patients with a higher burden of ventricular pacing are more likely to benefit from HBP over RVP. HBP was associated with a trend toward reduced risk of AF progression. These findings should be further evaluated in randomized studies with a larger sample size.

ARTICLE INFORMATION

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Dr Trohman reports serving as an advisor to Boston Scientific/Guidant; receiving research grants from Boston Scientific/Guidant, Medtronic Inc., and St. Jude Medical (Abbott); serving as a consultant for St. Jude Medical (Abbott); and receiving speaker's fees or honoraria from Boston Scientific/Guidant CRM, Medtronic Inc., and St. Jude Medical (Abbott). Dr Huang reports serving as a consultant for Cardiofocus and receiving research grants from Medtronic. Dr Krishnan serves as a consultant to Abbott/St. Jude Medical, Cardiva, and Zoll and research funding from Abbott/St. Jude Medical. Dr Sharma has been a speaker for Medtronic and has been a consultant for Abbott, Boston Scientific, and Biotronik. Dr Vijayaraman has been a consultant to Abbott, Biotronik, Boston Scientific, and Medtronic; he also has a patent pending for a His delivery tool. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Confounders for new-onset atrial fibrillation in different pacing burden subgroups.

Characteristic	HBP	RVP	P-value
All patients			
Age (years)	72.33 ± 11.58	75.71 ± 10.19	0.061
Ventricular pacing ≥ 20%			
Age (years)	71.55 ± 12.27	76.76 ± 9.71	0.024
Ventricular pacing ≥ 40%			
Age (years)	71.24 ± 12.51	76.42 ± 9.42	0.040
BMI (kg/m2)	30.78 ± 7.63	28.34 ± 5.58	0.090
Ventricular pacing ≥ 60%			
Age (years)	71.40 ± 12.75	76.51 ± 9.53	0.049
Ventricular pacing ≥ 80%			
Age (years)	71.15 ± 12.77	76.81 ± 8.75	0.034

HBP, His bundle pacing; RVP, right ventricular pacing; BMI, body mass index

Table S2. Confounders of progression of atrial fibrillation burden by 10% in different pacing burden subgroups.

Characteristic	HBP (n =33)	RVP (n =44)	P-value
All patients			
Hypertension n (%)	27 (81.8%)	43 (97.7%)	0.016
Age (years)	73.33 ± 9.90	77.98 ± 9.23	0.037
Native QRS (ms)	112.64 ± 33.53	92.59 ± 16.81	0.003
Ventricular pacing burden ≥ 20%			
Age (years)	75.62 ± 9.59	80.09 ± 6.60	0.081
Native QRS (ms)	121.52 ± 37.24	98.64 ± 18.68	0.017
Ventricular pacing burden ≥ 40%			
Native QRS (ms)	125.65 ± 39.18	99.90 ± 19.12	0.022
Ventricular pacing burden ≥ 60%			
Age (years)	76.14 ± 9.55	81.33 ± 6.20	0.092
Native QRS (ms)	131.14 ± 40.00	100.53 ± 19.12	0.018
Ventricular pacing burden ≥ 80%			
Age (years)	75.33 ± 9.38	81.73 ± 5.90	0.067
Native QRS (ms)	131.33 ± 37.89	101.27 ±21.40	0.030

HBP, His bundle pacing; RVP, right ventricular pacing;