

Clinical Outcomes After Ablation of the AV Junction in Patients With Atrial Fibrillation: Impact of Cardiac Resynchronization Therapy

Suneet Mittal, MD; Dan L. Musat, MD; Michael H. Hoskins, MD; Julie B. Prillinger, PhD; Gregory J. Roberts, BS; Yelena Nabutovsky, MS; Faisal M. Merchant, MD

Background—Patients with atrial fibrillation (AF) often undergo AV junction ablation (AVJA) and pacemaker implantation. Right ventricular (RV) pacing contributes to increased risk of heart failure (HF), which may be mitigated by biventricular pacing. We sought to determine the impact of AVJA concurrent with RV versus biventricular pacemaker implantation on AF and HF hospitalizations.

Methods and Results—The MarketScan Commercial and Medicare Supplemental claims database was used to select 18- to 100-year-old patients with AF with pacemaker implantation. Patients were divided into those with an RV and a biventricular pacemaker and further into those who did (AVJA⁺) or did not undergo concurrent ablation. Separately, the AVJA⁺ group was divided into those receiving RV versus biventricular pacemakers. AF and HF hospitalization rates were compared between groups after matching on demographics, comorbidities, and baseline hospitalization rates. The study included 24 361 patients, with RV (n=23 377) or biventricular (n=984) pacemakers; 1611 patients underwent AVJA. AVJA⁺ was associated with reduced AF hospitalization risk (RV hazard ratio [HR], 0.31; $P<0.001$; biventricular HR, 0.20; $P=0.003$) compared with no AVJA. However, HF hospitalization risk was increased for RV (HR, 1.63; $P=0.001$), but not biventricular (HR, 0.98; $P=0.942$), pacemakers. In AVJA⁺ patients, biventricular pacing was associated with reduced risk of HF hospitalization versus RV pacing (HR, 0.62; $P=0.017$).

Conclusions—In a large cohort of patients with AF, AVJA⁺ significantly reduced AF hospitalizations, irrespective of whether an RV or a biventricular pacemaker was implanted. However, AVJA was associated with a marked HF hospitalization increase in patients with an RV pacemaker, which was ameliorated with biventricular pacing. (*J Am Heart Assoc.* 2017;6:e007270. DOI: 10.1161/JAHA.117.007270.)

Key Words: ablation • atrial fibrillation • biventricular pacing • heart failure • pacemaker

In patients with atrial fibrillation (AF), hospitalizations to manage symptoms of AF or those related to development of heart failure (HF) are common. AV junction ablation (AVJA) is sometimes necessary to achieve ventricular rate control and to mitigate the need for recurrent AF- or HF-related hospitalizations.^{1,2} By nature of the ablation procedure, patients require pacemaker implantation to maintain an adequate heart rate. Although right ventricular (RV) pacing has been most commonly used, concerns have been raised about the deleterious impact of RV pacing on clinical

outcomes; in some patients, clinical deterioration can occur within months of pacemaker implantation.³ Thus, several investigators have explored the role of biventricular pacing in this patient population.^{4–8} However, these studies have produced conflicting results, likely in part because of the relatively few patients enrolled and variability in follow-up duration. Therefore, in this large retrospective study using real-world data from a cohort of patients with AF who were undergoing pacemaker implantation, we sought to determine the following: (1) the impact of AVJA at pacemaker implantation on subsequent AF- and HF-related hospitalizations and associated costs and (2) whether these differed in patients implanted with an RV versus a biventricular pacemaker after AVJA.

Methods

Data Source

This retrospective, observational, cohort study used data from inpatient hospital encounters and outpatient physician office

From the Valley Health System of NY and NJ, Paramus, NJ (S.M., D.L.M.); Emory University School of Medicine, Atlanta, GA (M.H.H., F.M.M.); and Abbott, Sylmar, CA (J.B.P., G.J.R., Y.N.).

Correspondence to: Suneet Mittal, MD, 200 W 57th St, Ste 610, New York, NY 10019. E-mail: mittsu@valleyhealth.com

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Clinical Perspective

What Is New?

- We analyzed a large database of patients with atrial fibrillation who underwent ablation of the AV junction, followed by either right ventricular or biventricular pacemaker implantation, and found that AV junction ablation was associated with a reduced likelihood and rate of atrial fibrillation–related hospitalization, irrespective of pacemaker type implanted.
- Right ventricular pacing was associated with a greater likelihood and rate of heart failure hospitalizations, whereas this was not observed in patients with a biventricular pacemaker.
- Implantation of a biventricular pacemaker was associated with a 38% reduction in heart failure hospitalizations, and this translated into a 27% reduction in annual payments.

What Are the Clinical Implications?

- In a large national cohort of patients with atrial fibrillation undergoing AV junction ablation, a marked increase in heart failure hospitalizations was observed in patients implanted with a right ventricular pacemaker, whereas this was not observed with biventricular pacing.
- Thus, studies comparing a selective conduction system with biventricular pacing in this patient population are needed to define the optimal post–AV junction ablation pacing strategy.

visits collected in the Truven Health MarketScan Commercial Claims and Medicare Supplemental databases. The databases capture paid and adjudicated claims for privately insured and Medicare Advantage (supplemental) patients throughout the United States, and include records from >170 million enrollees since 1995.⁹ A monthly enrollment indicator is used to determine when a patient is followed up in MarketScan. Health outcomes research using MarketScan data has been widely published in peer-reviewed journals, including studies of patients undergoing cardiac procedures and receiving implantable electronic devices.^{10–12} This study was a retrospective analysis of a deidentified database and, thus, the research was exempt from institutional review board review under 45 CFR 46.101(b)(4). All codes used to identify implants, baseline characteristics, and events are listed in Table 1.

Study Population

Patients implanted with a de novo single-chamber, dual-chamber, or biventricular pacemaker from any manufacturer between April 1, 2008, and March 31, 2014, were included. De novo implants were identified as patients with a

pacemaker without a prior device implant and without a remote or in-office pacemaker follow-up visit in the 1 year before implantation. Patients were required to have at least 1 year of continuous enrollment in the MarketScan database before and after pacemaker implant, to be ≥ 18 and ≤ 100 years old at the implantation, and to have a diagnosis of AF (*International Classification of Diseases, Ninth Revision [ICD-9]* code 427.31) within 1 year before pacemaker implantation.

To evaluate the impact of AVJA (*Current Procedural Terminology* code 93650) on clinical outcomes, patients with AF were dichotomized into those with an AVJA (AVJA⁺) versus those without an AVJA (AVJA⁻) at pacemaker implantation. Patients with an AVJA occurring on a day other than the day of pacemaker implantation were excluded from the analysis. To compare the effect of AVJA on patients with biventricular versus RV-only pacing, patients implanted with biventricular pacemakers were evaluated separately from those implanted with single- or dual-chamber pacemakers.

Patient demographics included age, sex, US region, year of pacemaker implantation, and number of pacing leads (patients with an RV pacemaker only). In addition, 20 baseline comorbidities (based on the Charlson comorbidity index) were determined using diagnosis and procedure codes collected across all available fields in the MarketScan inpatient and outpatient encounters in the 1 year before pacemaker implantation (Table 1), as previously validated.^{13,14} US regions included Northeast, North Central, South, and West. Propensity scores for undergoing an AVJA were calculated for every patient in the study cohort on the basis of a multivariable logistic regression model, including all covariates used in the patient characterization and cumulative AF and HF hospitalization rates in the 1 year before pacemaker implantation. Patients were propensity score matched using greedy matching without replacement. A match ratio of 1:1 was used for patients implanted with biventricular pacemakers. For those implanted with RV pacemakers, a 4:1 match ratio was used because of the large proportion of AVJA⁻ patients.

Outcomes

Primary outcomes included AF and HF hospitalizations occurring in the 3 years after pacemaker implantation. AF and HF hospitalizations were identified by any inpatient encounter for which the primary diagnosis was AF or HF related, respectively. A 1-week postimplantation blanking window was used to exclude complications associated with pacemaker implantation or AVJA. The secondary outcome was annualized total payments associated with AF or HF hospitalizations, evaluated over the 3 years after pacemaker implantation.

Table 1. ICD-9, CPT, and HCPCS Codes Used for Clinical Diagnoses, AVJA, Pacemaker Implantation, and Pacemaker Follow-Up

Codes used for patient characterization and outcomes	
Atrial fibrillation	427.31
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
VT/VF	427.1, 427.4x
Coronary artery disease	410.x-414.x, 429.2, V45.81
Hypertension	401.x-405.x, 437.2
Cerebrovascular disease	362.34, 430.x-438.x
Diabetes mellitus	250.x
Valve disease	394.x-397.x, 424.x, 746.x, V42.2, V43.3
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
Chronic pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Chronic kidney disease	403.1, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586, 588.0, V42.0, V56.x
Rheumatic disease	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x
Peptic ulcer disease	531.x-534.x
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0-456.1, 570.x, 571.x, 572.2-572.8, 573.3, 573.4, 573.8, 573.9, V42.7
Hypothyroidism	240.9, 243.x, 244.x, 246.1, 246.8
Cancer	140.x-172.x, 174.x-194.x, 195.0-195.8, 196.x, 197.0-197.8, 198.0-198.8x, 1990-1992, 200.x-208.x, 238.6
Dementia	290.x, 331.0, 331.2
Depression	300.4, 309.x, 311
AIDS/HIV	042
Hemiplegia/paraplegia	334.1, 342.00-342.92, 343.x, 344.1, 344.2, 344.5, 344.9
Obesity	278.00
Codes used for AVJA, pacemaker implantation, and follow-up	
AVJA	93650
Dual-chamber RV pacemaker	33208, C1785, C2619
Single-chamber RV pacemaker	33206, 33207, C1786, C2620, 3781, 3782
Biventricular pacemaker	33224, 33225, 0050, 0052, C2621, C1900
Pacemaker follow-up	93279-93281, 93286, 93288, 93293, 93294, 93296, 93724, 93731-93736, 89.45-89.48, E0610

AVJA indicates AV junction ablation; CPT, *Current Procedural Terminology*; HCPCS, healthcare common procedure coding system; ICD-9, *International Classification of Diseases, Ninth Revision*; RV, right ventricular; and VT/VF, ventricular tachycardia/ventricular fibrillation.

AVJA⁺ Subanalysis

To directly compare the impact of biventricular versus RV-only pacing on HF hospitalizations after AVJA, a subanalysis was performed in only AVJA⁺ patients. Propensity scores for receiving an RV versus a biventricular pacemaker were computed, as described previously. Patients with RV and biventricular pacemakers were 1:1 propensity score matched using greedy matching without replacement. HF hospitalizations and associated payments were compared between the matched RV and biventricular pacemaker cohorts.

Statistical Analyses

For the primary analysis, baseline characteristics were compared between matched AVJA⁻ and AVJA⁺ patients within the RV and biventricular pacemaker cohorts. For the AVJA⁺ subanalysis, baseline characteristics were compared for patients implanted with RV versus biventricular pacemakers. Continuous variables, including follow-up duration and age, were compared using a Student *t* test or Mann-Whitney test if the distribution was not normal. Categorical variables, such as sex and baseline comorbidities, were compared using a χ^2

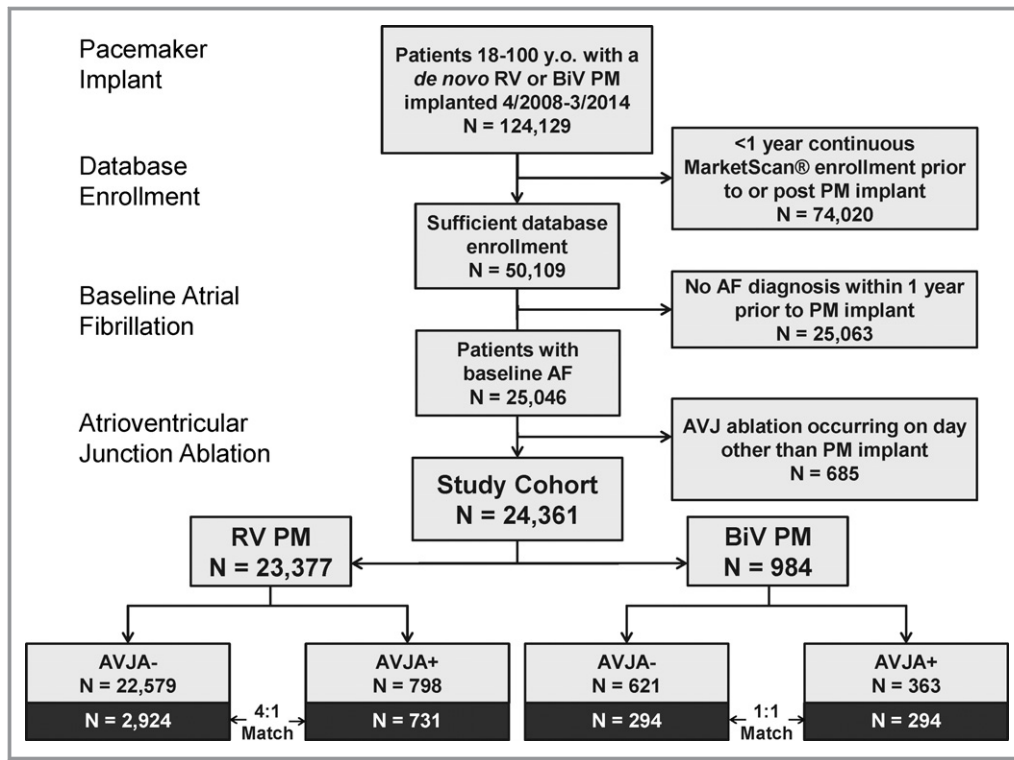


Figure 1. Cohort diagram. Schematic of patients included in the study cohort, including those with and without AV junction ablation (AVJA⁺ and AVJA⁻, respectively) on the same day as pacemaker implantation. AF indicates atrial fibrillation; and RV, right ventricular (single or dual chamber). BiV indicates biventricular; PM, pacemaker.

test. In addition, the standardized mean differences were computed for all variables. Standardized mean difference values >0.1 are considered meaningful. Standardized mean differences were computed with the `tableone` package in R, using previously described methods.¹⁵

Cumulative rates of AF and HF hospitalizations (events per 100 patient-years) were compared between matched groups using a Poisson regression. Event-free survival was measured by the Kaplan-Meier method, and differences between matched cohorts were compared using a univariate marginal Cox proportional hazards model to account for possible correlation or clustering in matched groups. The proportional hazards assumption was tested using Schoenfeld residuals and was met for all comparisons. Patients were censored at hospitalization, at the end of MarketScan enrollment, or at an administrative censoring date set at 3 years after pacemaker implantation. In addition, patients implanted with RV pacemakers were censored at biventricular upgrade. For multivariate analysis on the prematched cohorts, a Cox regression was performed with the propensity score as the covariate. Statistical significance was determined using $\alpha=0.05$.

For the secondary outcome of costs associated with AF or HF hospitalizations, a 2-part model was used to compare inpatient hospitalization payments between matched cohorts.

The 2-part model is a well-established econometric modeling technique that accounts for samples with a large proportion of 0 measurements, common to healthcare data in which healthy participants incur no medical costs. In part 1, a logistic regression was used to model the likelihood of incurring non-0 payments after pacemaker implantation, adjusting for therapy group, follow-up duration, and the computed propensity score. Using this model, the numeric probability of incurring non-0 payments at 1 year after implantation was then estimated for each patient. In part 2, using only those patients who had non-0 hospitalization payments in the 3 years after pacemaker implantation, a linear regression with γ distribution and log link was used to model the total hospitalization costs, adjusting for therapy group, follow-up duration, and the computed propensity score. The total payments at 1 year after implantation were then predicted for all patients using results from the linear regression model. The final adjusted cost for each patient was computed as the product of the probability from part 1 and the predicted payments from part 2. A Mann-Whitney test was used to compare the median adjusted costs between groups.

All analyses were performed on Revolution Analytics Revolution R Enterprise with Open Source R version 3.1.1.

Table 2. Baseline Characteristics for Matched Patients: AVJA⁺ and AVJA⁻ Groups

Characteristics	Matched RV Pacemaker				Matched Biventricular Pacemaker			
	AVJA ⁻ (N=2924)	AVJA ⁺ (N=731)	SMD	P Value	AVJA ⁻ (N=294)	AVJA ⁺ (N=294)	SMD	P Value
Demographics								
Follow-up, y	2.20 (1.54–3.25)	2.16 (1.57–3.10)	0.033	0.422	2.13 (1.51–3.05)	1.95 (1.47–3.06)	0.063	0.442
Male sex	900 (31)	244 (33)	0.056	0.190	146 (50)	151 (51)	0.034	0.741
Age, y	76.2±10.8	76.8±9.8	0.056	0.163	75.2±11.6	75.1±10.8	0.012	0.888
Device type								
Dual chamber	1708 (58)	425 (58)	0.006	0.926	NA	NA	NA	NA
Implant year								
2009	548 (19)	132 (18)	0.131	0.043	38 (13)	30 (10)	0.231	0.102
2010	769 (26)	167 (23)			70 (24)	81 (28)		
2011	717 (25)	192 (26)			94 (32)	72 (24)		
2012	703 (24)	205 (28)			77 (26)	99 (34)		
2013	187 (6)	35 (5)			15 (5)	12 (4)		
US region								
Northeast	546 (19)	101 (14)	0.179	0.002	41 (14)	43 (15)	0.052	0.942
North Central	1006 (34)	283 (39)			120 (41)	113 (38)		
South	910 (31)	254 (35)			92 (31)	97 (33)		
West	459 (16)	93 (13)			41 (14)	41 (14)		
Unknown	3 (0.1)	0 (0)			0 (0)	0 (0)		
Comorbidities								
Heart failure	887 (30)	239 (33)	0.051	0.234	116 (40)	138 (47)	0.151	0.080
VT/VF	233 (8)	70 (10)	0.057	0.182	33 (11)	32 (11)	0.011	1.000
Coronary artery disease	1539 (53)	376 (51)	0.024	0.590	151 (51)	155 (53)	0.027	0.804
Hypertension	2406 (82)	588 (80)	0.047	0.268	239 (81)	236 (80)	0.026	0.834
Cerebrovascular disease	600 (21)	171 (23)	0.069	0.099	69 (24)	62 (21)	0.057	0.552
Diabetes mellitus	909 (31)	218 (30)	0.027	0.537	95 (32)	87 (30)	0.059	0.532
Valve disease	1353 (46)	334 (46)	0.012	0.810	156 (53)	134 (46)	0.15	0.083
Peripheral vascular disease	573 (20)	138 (19)	0.018	0.699	62 (21)	58 (20)	0.034	0.759
Chronic pulmonary disease	1122 (38)	284 (39)	0.01	0.845	107 (36)	121 (41)	0.098	0.271
Chronic kidney disease	444 (15)	107 (15)	0.015	0.755	48 (16)	50 (17)	0.018	0.912
Rheumatic disease	114 (4)	40 (6)	0.074	0.073	11 (4)	8 (3)	0.058	0.641
Peptic ulcer disease	55 (2)	13 (2)	0.008	0.976	7 (2)	7 (2)	0.000	1.000
Liver disease	109 (4)	43 (6)	0.101	0.012	11 (4)	14 (5)	0.051	0.683
Hypothyroidism	622 (21)	157 (22)	0.005	0.944	52 (18)	56 (19)	0.035	0.749
Cancer	423 (15)	114 (16)	0.032	0.476	45 (15)	36 (12)	0.089	0.338
Dementia	61 (2)	19 (3)	0.034	0.480	10 (3)	7 (2)	0.061	0.623
Depression	225 (8)	74 (10)	0.085	0.039	28 (10)	31 (11)	0.034	0.784
AIDS/HIV	3 (<0.1)	0 (0)	0.045	0.885	1 (<1)	0 (0)	0.083	1.000
Hemiplegia/paraplegia	27 (1)	10 (1)	0.042	0.386	2 (1)	3 (1)	0.037	1.000
Obesity	193 (7)	53 (7)	0.026	0.586	21 (7)	24 (8)	0.038	0.756

Values are reported as median (quartile 1–quartile 3), mean±SD, or count (percentage). + indicates did undergo AVJA; –, did not undergo AVJA; AVJA, AV junction ablation; NA, not applicable; RV, right ventricular (single or dual chamber); SMD, standardized mean difference; and VT/VF, ventricular tachycardia/ventricular fibrillation.

Table 3. Cumulative Hospitalization Rates and Annualized Adjusted Payments for Matched Patients: AVJA⁺ and AVJA⁻ Groups

Variables	Matched RV Pacemaker			Matched Biventricular Pacemaker		
	AVJA ⁻ (N=2924)	AVJA ⁺ (N=731)	P Value	AVJA ⁻ (N=294)	AVJA ⁺ (N=294)	P Value
Atrial fibrillation hospitalizations						
Preimplantation event rate (per 100 patient-years)	27.6 (25.7–29.6)	31.1 (27.2–35.4)	0.117	24.2 (18.9–30.5)	25.2 (19.8–31.6)	0.803
Postimplantation event rate (per 100 patient-years)	3.9 (3.4–4.4)	1.3 (0.8–1.9)	<0.001	3.2 (1.9–4.9)	0.6 (0.2–1.7)	0.004
Annualized adjusted payments (\$/y)	866 (828–953)	241 (231–267)	<0.001	1488 (1175–1929)	294 (231–386)	<0.001
Heart failure hospitalizations						
Preimplantation event rate (per 100 patient-years)	6.6 (5.7–7.6)	7.4 (5.6–9.6)	0.485	11.9 (8.3–16.6)	11.2 (7.7–15.8)	0.808
Postimplantation event rate (per 100 patient-years)	6.4 (5.8–7.0)	9.4 (7.9–11.0)	<0.001	8.4 (6.3–10.9)	7.5 (5.5–10.0)	0.572
Annualized adjusted payments (\$/y)	1801 (1690–2062)	2404 (2263–2733)	<0.001	4157 (3572–4922)	3152 (2709–3733)	<0.001

Values are reported as median (quartile 1–quartile 3). Preimplantation events analyzed during the 1 year before pacemaker implantation; postimplantation events analyzed over the 3 years after pacemaker implantation. + indicates did undergo AVJA; –, did not undergo AVJA; AVJA, AV junction ablation; and RV, right ventricular (single or dual chamber).

Matching was performed in SAS version 9.3 using the OneToManyMTCH macro.

Results

Study Population

The study cohort included 24 361 patients with a pacemaker followed up for a median of 2.20 (quartile 1–quartile 3, 1.55–3.21) years. Overall, 1611 patients (4.8%) underwent a pacemaker implantation and same-day AVJA. Of these patients, 798 were implanted with an RV and 363 were implanted with a biventricular pacemaker (Figure 1). Matched cohorts in the RV pacemaker arm included 2924 AVJA⁻ and 731 AVJA⁺ patients (age, 76.3±10.6 years; 31% men). Biventricular pacemaker matched cohorts included 294 AVJA⁻ and 294 AVJA⁺ patients (age, 75.2±11.2 years; 51% men). Baseline characteristics after propensity score matching are presented in Table 2. The groups were well matched in terms of baseline characteristics (Table 2) and cumulative AF and HF hospitalization rates (Table 3) in the 1 year before pacemaker implantation.

AF Hospitalizations and Payments After Pacemaker Implantation

In the 3 years after pacemaker implantation, AVJA⁺ patients were associated with a significantly reduced risk for AF hospitalization compared with matched AVJA⁻ patients, whether they were implanted with an RV (hazard ratio [HR], 0.31; 95% confidence interval [CI], 0.18–0.53; *P*<0.001) or a biventricular (HR, 0.20; 95% CI, 0.07–0.59; *P*=0.003;

Figure 2A) pacemaker. Likewise, the cumulative rate of AF hospitalizations after pacemaker implantation was significantly lower for AVJA⁺ patients compared with matched AVJA⁻ patients in both RV and biventricular pacemaker cohorts (Table 3). These rate reductions translated to significantly lower adjusted healthcare payments associated with AF hospitalizations, regardless of device type. Patients implanted with an RV pacemaker at AVJA were associated with a 72.2% reduction in annualized inpatient AF payments compared with matched patients with an RV pacemaker without an AVJA (Table 3). Those implanted with a biventricular pacemaker at AVJA were associated with an even greater reduction of 80.2% in annualized inpatient AF payments (Table 3).

HF Hospitalizations and Payments After Pacemaker Implantation

Although the risk of HF hospitalization was significantly increased for AVJA⁺ compared with matched AVJA⁻ patients implanted with RV pacemakers (HR, 1.63; 95% CI, 1.21–2.19; *P*=0.001), this was not the case for those implanted with biventricular pacemakers (HR, 0.98; 95% CI, 0.63–1.54; *P*=0.942; Figure 2B). After RV pacemaker implantation, the cumulative rate of HF hospitalizations was significantly higher for AVJA⁺ patients compared with the matched AVJA⁻ cohort (Table 3). This translated to a 33.5% increase in annualized payments related to HF hospitalizations for AVJA⁺ versus AVJA⁻ patients with an RV pacemaker (Table 3). In contrast, the cumulative rate of HF hospitalizations was similar between matched AVJA⁺ and AVJA⁻ patients implanted with biventricular pacemakers (Table 3). For those

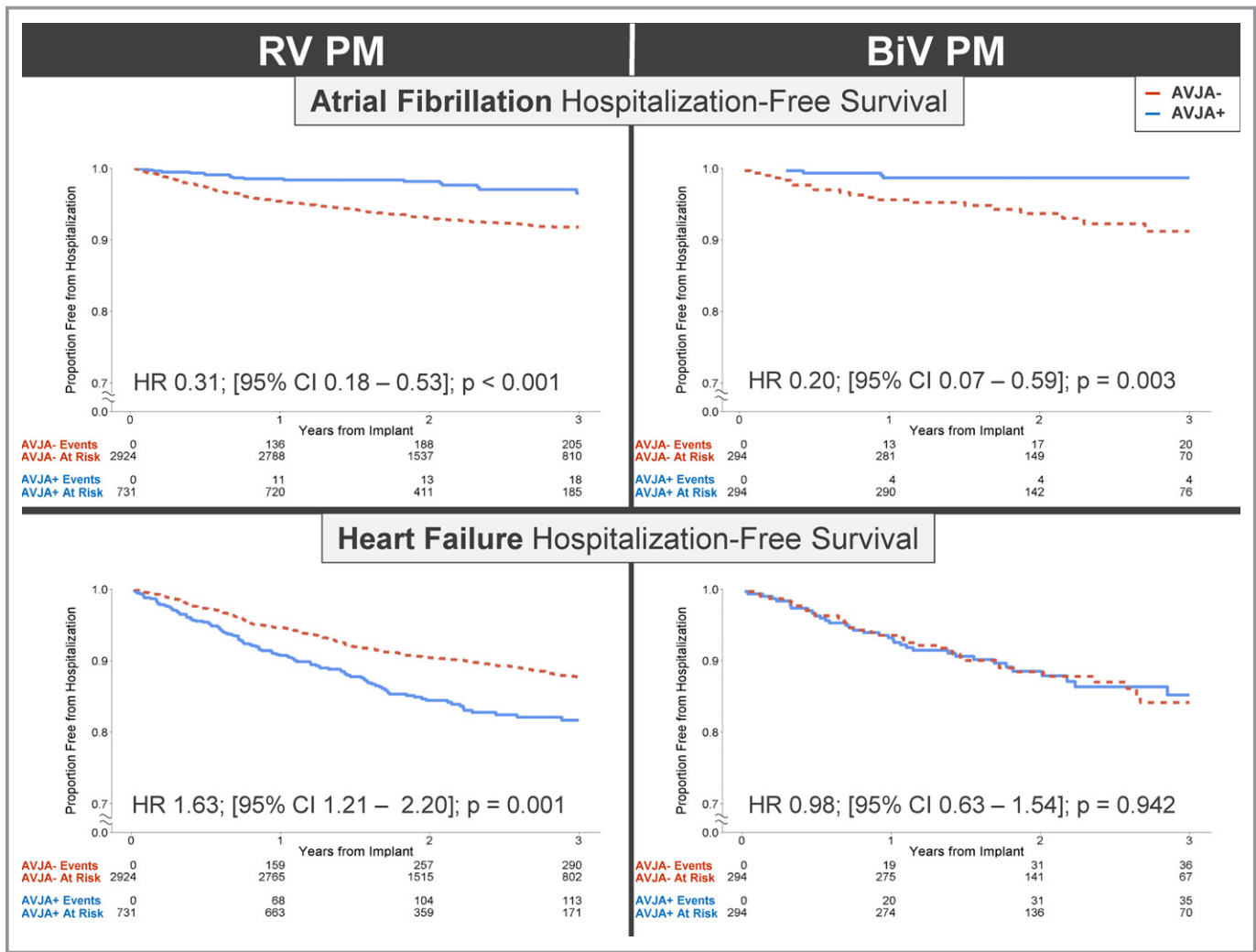


Figure 2. Risk of hospitalization after pacemaker implantation. Kaplan-Meier survival curves for risk of atrial fibrillation (A) or heart failure hospitalization (B) in matched patients with vs without AV junction ablation (AVJA⁺ and AVJA⁻, respectively) at pacemaker implantation. CI indicates confidence interval; HR, hazard ratio; and RV, right ventricular (single or dual chamber). BiV indicates biventricular; PM, pacemaker.

implanted with biventricular pacemakers, AVJA⁺ patients were associated with 24.2% lower annualized HF hospitalization payments compared with matched AVJA⁻ patients (Table 3).

AVJA⁺ Subanalysis

From the 798 patients with an RV and 363 patients with a biventricular pacemaker in the study cohort with an AVJA, propensity score matching yielded 357 patients with an RV and 357 patients with a biventricular pacemaker. The matched cohorts did not differ in baseline characteristics (Table 4) or cumulative AF and HF hospitalization rates in the 1 year before implantation (Table 5). Compared with patients implanted with RV pacemakers after AVJA, those implanted with biventricular pacemakers were associated with a significantly reduced risk of HF hospitalization (HR, 0.62; 95% CI,

0.41–0.92; $P=0.017$) in the 3 years after implantation (Figure 3). Minimal heterogeneity was observed within subgroups on the basis of patient age, sex, and baseline comorbidities, with all stratifications showing either a non-significant or a reduced risk for HF hospitalizations associated with biventricular versus RV pacemaker implantation after AVJA (Figure 4). The cumulative rate of HF hospitalizations was significantly lower for AVJA⁺ patients implanted with biventricular pacemakers compared with matched patients implanted with RV pacemakers (Table 5). These results correlated with a 27.2% reduction in annualized HF hospitalization payments for AVJA⁺ patients implanted with biventricular versus RV pacemakers (Table 5).

During a median of 2.08 (quartile 1–quartile 3, 1.51–2.95) years after AVJA, 60 patients (16.8%) with an RV pacemaker and 38 patients (10.6%) with a biventricular pacemaker were hospitalized for HF ($P=0.022$). In both device groups, most

Table 4. Baseline Characteristics for Matched AVJA⁺ Patients Implanted With RV and Biventricular Pacemakers

Characteristics	Matched AVJA ⁺ Patients			SMD	P Value
	RV Pacemaker (N=357)	Biventricular Pacemaker (N=357)			
Demographics					
Follow-up, y	2.14 (1.55–2.89)	2.01 (1.47–3.06)		0.005	0.952
Male sex	150 (42)	164 (46)		0.079	0.327
Age, y	74.7±10.2	74.3±11.2		0.038	0.616
Year of implant					
2009	41 (11)	37 (10)		0.110	0.709
2010	85 (24)	98 (27)			
2011	105 (29)	92 (26)			
2012	113 (32)	115 (32)			
2013	13 (4)	15 (4)			
US region					
Northeast	48 (13)	50 (14)		0.053	0.919
North Central	137 (38)	143 (40)			
South	127 (36)	124 (35)			
West	45 (13)	40 (11)			
Unknown	0 (0)	0 (0)			
Comorbidities					
Heart failure	169 (47)	160 (45)		0.051	0.548
VT/VF	46 (13)	45 (13)		0.008	1.000
Coronary artery disease	190 (53)	178 (50)		0.067	0.410
Hypertension	282 (79)	293 (82)		0.078	0.345
Cerebrovascular disease	85 (24)	69 (19)		0.109	0.172
Diabetes mellitus	108 (30)	104 (29)		0.025	0.806
Valve disease	151 (42)	163 (46)		0.068	0.407
Peripheral vascular disease	72 (20)	67 (19)		0.035	0.705
Chronic pulmonary disease	142 (40)	151 (42)		0.051	0.543
Chronic kidney disease	48 (13)	58 (16)		0.079	0.343
Rheumatic disease	22 (6)	14 (4)		0.103	0.231
Peptic ulcer disease	8 (2)	7 (2)		0.02	1.000
Liver disease	26 (7)	17 (5)		0.106	0.208
Hypothyroidism	88 (25)	78 (22)		0.066	0.425
Cancer	44 (12)	47 (13)		0.025	0.822
Dementia	10 (3)	7 (2)		0.055	0.623
Depression	39 (11)	36 (10)		0.027	0.807
AIDS/HIV	0 (0)	0 (0)		0.000	1.000
Hemiplegia/paraplegia	4 (1)	2 (1)		0.061	0.682
Obesity	37 (10)	46 (13)		0.079	0.350

Values are reported as median (quartile 1–quartile 3), mean±SD, and count (percentage). + indicates did undergo AVJA; AVJA, AV junction ablation; RV, right ventricular (single or dual chamber); SMD, standardized mean difference; and VT/VF, ventricular tachycardia/ventricular fibrillation.

Table 5. Cumulative HF Hospitalization Rates and Annualized Adjusted Payments for Matched AVJA⁺ Patients Implanted With RV and Biventricular Pacemakers

Variables	RV Pacemaker Group (N=357)	Biventricular Pacemaker Group (N=357)	P Value
Preimplantation event rate (per 100 patient-years)	7.8 (5.2–11.3)	10.1 (7.1–14.0)	0.319
Postimplantation event rate (per 100 patient-years)	10.2 (8.1–12.8)	6.5 (4.8–8.6)	0.013
Adjusted annualized payments (\$/y)	3513 (2472–4699)	2556 (1800–3417)	<0.001

Values are reported as median (quartile 1–quartile 3). Preimplantation events analyzed during the 1 year before pacemaker implantation; postimplantation events analyzed over the 3 years after pacemaker implantation. + indicates did undergo AVJA; AVJA, AV junction ablation; HF, heart failure; and RV, right ventricular (single or dual chamber).

hospitalized patients incurred only 1 or 2 HF hospitalizations during the follow-up, with only 5 patients incurring between 3 and 5 total hospitalizations (Figure 5). These results suggest that the observed difference in HF hospitalization rates may be attributed to the higher proportion of patients with an RV pacemaker hospitalized, rather than an accumulation of hospitalizations in either group.

Discussion

This retrospective investigation using data from the Truven Health MarketScan Commercial Claims and Medicare Supplemental databases represents the largest analysis to date of patients undergoing AVJA and concomitant RV or biventricular pacemaker implantation. In addition, the 3-year follow-up represents the longest reported follow-up in an AVJA patient cohort. The principal findings of this study are as follows: (1)

AVJA was associated with a significantly reduced likelihood and rate of AF-related hospitalization, irrespective of whether an RV or a biventricular pacemaker was implanted; (2) RV pacing was associated with a significantly greater likelihood and rate of HF hospitalizations after AVJA, whereas this was not observed in patients with a biventricular pacemaker; (3) after AVJA, implantation of a biventricular pacemaker was associated with a 38% reduction in HF hospitalizations compared with patients with an RV pacemaker; and (4) this translated into a 27% reduction in annual payments related to HF hospitalizations.

Although a single-center retrospective study suggested that AVJA, followed by RV pacing, was not associated with an adverse impact on left ventricular (LV) ejection fraction,¹⁶ this was not confirmed by a randomized clinical trial, especially in patients with underlying LV dysfunction or symptomatic HF.⁴ Furthermore, the deleterious effect of RV pacing was mitigated by the use of biventricular pacing. Around the same time, Brignole et al randomized 56 patients with permanent AF who were undergoing AVJA and implantation of a biventricular pacing system to undergo either RV- or LV-only pacing.⁶ Three months later, the patients were crossed over to the other arm. Subsequently, the patients were randomized to RV or biventricular pacing and then crossed over 1 final time 3 months later. The primary end points were quality of life and exercise capacity at the end of each 3-month period. Much of the observed benefit was a direct result of the AVJA itself; LV or biventricular pacing provided, at best, only modest additional benefit.

These conflicting results led several investigators to conduct randomized clinical trials. Orlov et al randomized 108 patients in a 4:1 manner to biventricular versus RV pacing after AVJA.⁸ Six months after AVJA, RV pacing was associated with a significantly greater increase in left atrial volume, LV end-systolic volume, and LV mass compared with biventricular pacing. To assess hard clinical outcomes, Brignole et al reported on 186 patients with permanent AF who underwent AVJA and were then randomized to receive

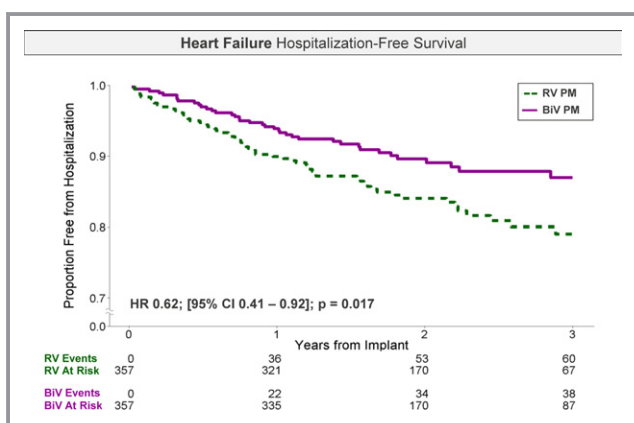


Figure 3. Risk of heart failure hospitalization after AV junction ablation (AVJA). Kaplan-Meier survival curve for risk of heart failure hospitalization in matched patients implanted with a biventricular vs a right ventricular (RV; single or dual chamber) pacemaker at AVJA. CI indicates confidence interval; and HR, hazard ratio.

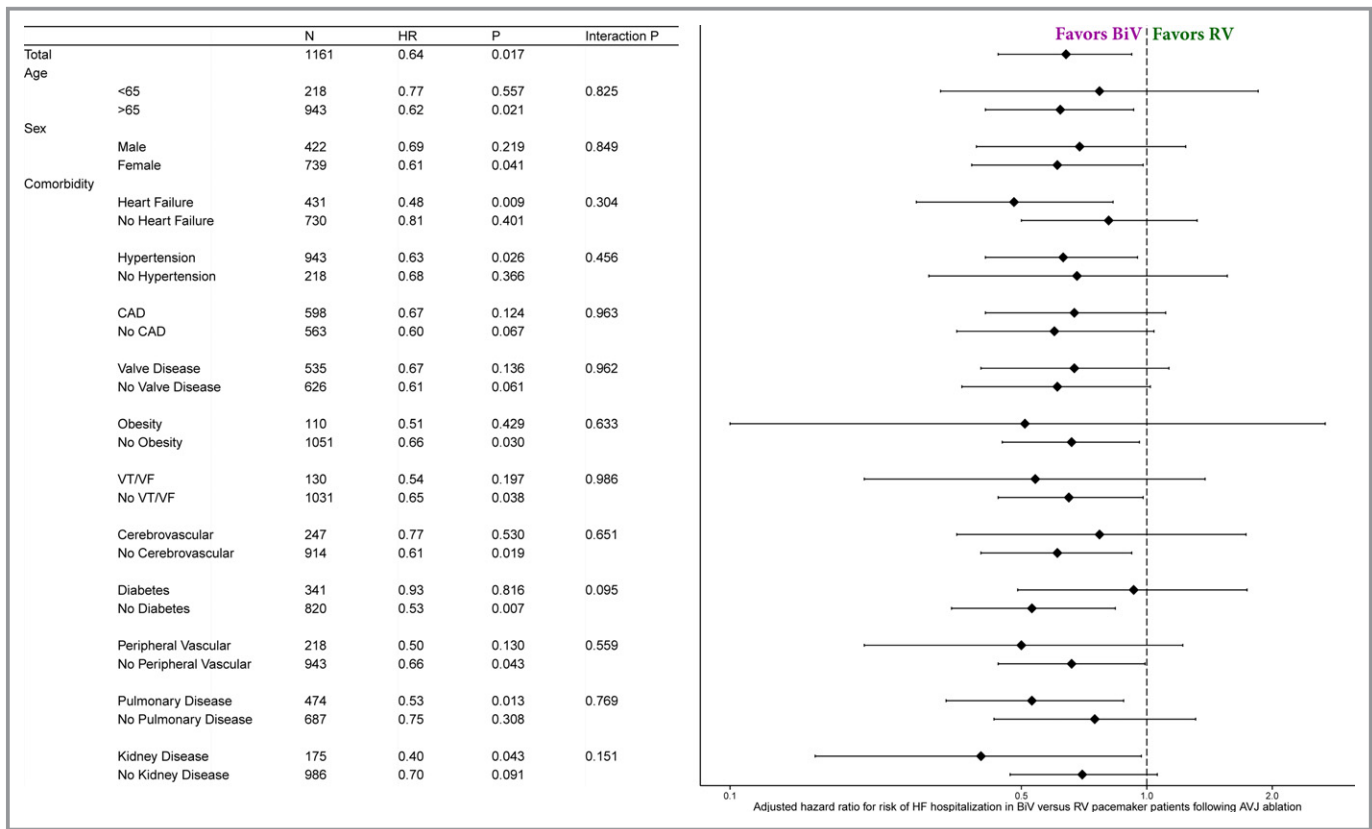


Figure 4. Forest plot showing adjusted risk of heart failure (HF) hospitalization after AV junction ablation (AVJA). Propensity score–adjusted risk of HF hospitalization in patients implanted with a biventricular vs a right ventricular (RV; single or dual chamber) pacemaker at AVJA. CAD indicates coronary artery disease; HR, hazard ratio; and VT/VF, ventricular tachycardia/ventricular fibrillation. BiV indicates biventricular; PM, pacemaker.

either biventricular or RV-only pacing.⁵ The primary end point was a composite of death from HF, hospitalization attributable to HF, and worsened HF, with a median follow-up of 20 months. The biventricular group had a 63% reduction in the composite outcome, which was driven by a 73% reduced likelihood of worsening HF and an 80% reduced likelihood of HF hospitalization. The benefit of biventricular was observed in both patients with and without LV dysfunction.

These prior studies have been limited by small sample size, the disparate timing between pacemaker implantation and AVJA, short duration of follow-up (most commonly just 6 months), and lack of comparison to a group of patients who did not undergo AVJA. In contrast, our study has several important advantages. First, this is the largest study reported to date of patients undergoing AVJA. Second, we have a matched population of patients who did not undergo AVJA. In addition, for the first time ever, we have event rate data on these patients for 1 year before pacemaker implantation. This allowed us to make a more meaningful comparison of outcomes between patients with AF who did or did not undergo AVJA, stratified by whether they received an RV or a

biventricular pacemaker. Before pacemaker implantation, the RV and biventricular pacemaker cohorts had a similar number of AF- and HF-related hospitalizations. Subsequently, hospitalization attributable to AF was less common in patients who underwent AVJA, irrespective of whether they received an RV or a biventricular pacemaker. In contrast, HF hospitalizations increased dramatically in patients who underwent AVJA followed by RV pacing. This adverse effect was not observed in patients who received a biventricular pacemaker. In an analysis of a matched cohort, biventricular pacing was associated with a 38% reduction in HF hospitalization, consistent with data reported from a prior meta-analysis.¹⁷ Third, payments in patients receiving a biventricular pacemaker after an AVJA were \$957 per year lower than in those receiving an RV pacemaker, a decrease of 27.2% in HF hospitalization–related costs. Previous analyses of MarketScan data found total annual medical expenditures to be \$11 528 in patients with AF¹⁸ and \$11 394 in patients with HF,¹⁹ so \$957 accounts for ≈8% of the annual payments in patients with these conditions. These savings pertain solely to avoidance of HF hospitalizations and are likely underestimates of total savings associated with reducing HF hospitalizations,

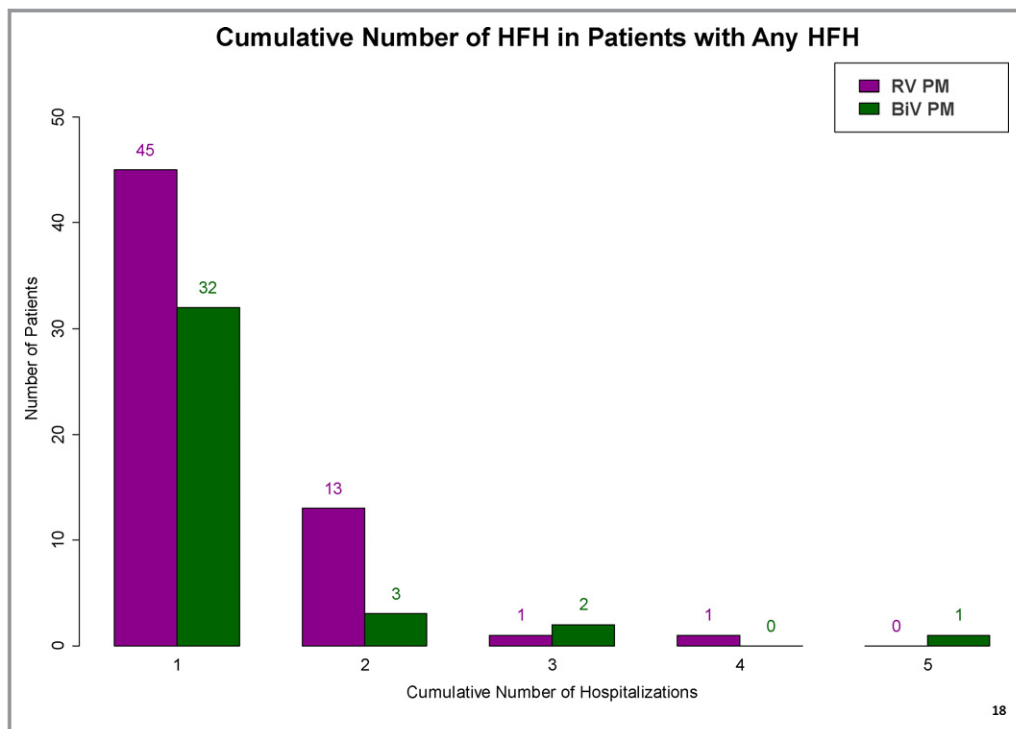


Figure 5. Bar plot showing the distribution of cumulative heart failure hospitalizations (HFHs) during a median 2.08 years of follow-up after AV junction ablation (AVJA). After AVJA, the cumulative number of HFHs in matched biventricular and right ventricular (RV; single or dual chamber) pacemaker cohorts. BiV indicates biventricular; PM, pacemaker.

because they do not account for other expenses incurred by patients experiencing HF, such as increase in medication, home care, and loss of productivity. Total medical expenditures in patients with congestive HF can range between \$33 000 and \$40 000.^{19,20} In the RV group, when patients required an HF hospitalization, most experienced 1 or 2 hospitalizations; this was enough to result in the increased expenditure in this patient population.

Limitations

The limitations of this type of analysis have been reported previously.² We have no information about LV ejection fraction and, thus, cannot distinguish between HF with preserved versus reduced ejection fraction. Similarly, because we used *ICD-9* codes to diagnose AF, we cannot distinguish paroxysmal from persistent and permanent forms of AF, and there is no way to assess the success of AF management. We also cannot reliably determine the pacemaker implantation indication. Lack of information on ejection fraction, pacemaker indication, and AF may introduce confounding. Finally, mortality data are not available in the data set used for this analysis. When MarketScan enrollment ends for a particular patient, we cannot determine whether this was because of death or other reasons,

such as cancellation in health insurance coverage or transfer to Medicare. However, because the primary end point of an inpatient or outpatient HF diagnosis is likely to precede an HF-related mortality event, it is expected that our analysis reflects the real-world incidence of new-onset HF after pacemaker implantation.²

Conclusions

In a large national cohort of patients with AF, those who underwent AVJA had a significantly lower likelihood of hospitalization for AF, irrespective of whether an RV or a biventricular pacemaker was implanted. However, AVJA was associated with a marked increase in HF hospitalizations in patients implanted with an RV pacemaker, whereas this was not observed with biventricular pacing. Similarly, a recent study found that His-bundle pacing after AVJA significantly improved echocardiographic measurements, New York Heart Association symptom class, and requirement for diuretics in patients with AF with a narrow QRS, irrespective of whether the LV ejection fraction was preserved or reduced.²¹ Thus, we await the results of ongoing studies (eg, NCT02805465²²) that compare selective conduction system pacing with biventricular pacing in this patient population to define the optimal post-AVJA pacing strategy.

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