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Comparison of Left Bundle Branch Area Pacing and Biventricular Pacing in Candidates for Resynchronization Therapy

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ABSTRACT

BACKGROUND Cardiac resynchronization therapy (CRT) with biventricular pacing (BVP) is a well established therapy in patients with reduced left ventricular ejection fraction (LVEF), heart failure, and wide QRS or expected frequent ventricular pacing. Left bundle branch area pacing (LBBAP) has recently been shown to be a safe alternative to BVP.

OBJECTIVES The aim of this study was to compare the clinical outcomes between BVP and LBBAP among patients undergoing CRT.

METHODS This observational study included patients with LVEF ≤35% who underwent BVP or LBBAP for the first time for Class I or II indications for CRT from January 2018 to June 2022 at 15 international centers. The primary outcome was the composite endpoint of time to death or heart failure hospitalization (HFH). Secondary outcomes included endpoints of death, HFH, and echocardiographic changes.

RESULTS A total of 1,778 patients met inclusion criteria: 981 BVP, 797 LBBAP. The mean age was 69 ± 12 years, 32% were female, 48% had coronary artery disease, and mean LVEF was 27% ± 6%. Paced QRS duration in LBBAP was significantly narrower than baseline (128 ± 19 ms vs 161 ± 28 ms; $P < 0.001$) and significantly narrower compared to BVP (144 ± 23 ms; $P < 0.001$). Following CRT, LVEF improved from 27% ± 6% to 41% ± 13% ($P < 0.001$) with LBBAP compared with an increase from 27% ± 7% to 37% ± 12% ($P < 0.001$) with BVP, with significantly greater change from baseline with LBBAP (13% ± 12% vs 10% ± 12%; $P < 0.001$). On multivariable regression analysis, the primary outcome was significantly reduced with LBBAP compared with BVP (20.8% vs 28%; HR: 1.495; 95% CI: 1.213-1.842; $P < 0.001$).

CONCLUSIONS LBBAP improved clinical outcomes compared with BVP in patients with CRT indications and may be a reasonable alternative to BVP. (J Am Coll Cardiol 2023;82:228-241) © 2023 by the American College of Cardiology Foundation.

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Cardiac resynchronization therapy (CRT) with biventricular pacing (BVP) is an established therapy for patients with reduced left ventricular ejection fraction (LVEF), heart failure, and left bundle branch block (LBBB) or expected frequent ventricular pacing.[1,2] CRT with the use of BVP has been proven to reduce heart failure hospitalization (HFH) and all-cause mortality compared with guideline-directed medical therapy.[3] However, a significant number of patients treated with BVP may not derive clinical or echocardiographic benefits, and some may worsen.[4] Despite impressive results in clinical trials, some of the limitations of BVP may be due to anatomic constraints, phrenic nerve stimulation, and incomplete resynchronization. The feasibility and efficacy of conduction system pacing (CSP) with the use of His bundle pacing (HBP) was demonstrated in a few small randomized studies in patients requiring CRT but was limited by higher pacing thresholds, lower success, and significant crossover rates.[5-7] Recently, left bundle branch area pacing (LBBAP) was shown to be an effective alternative to HBP, with higher success and lower pacing thresholds.[8-14] The primary aim of the present study was to evaluate the clinical outcome differences between LBBAP and BVP in a large cohort of patients requiring CRT.

SEE PAGE 242

METHODS

STUDY DESIGN. This was a retrospective, multicenter, observational, case-control study designed to evaluate the real-world differences in the clinical outcomes of BVP and LBBAP. The study population included patients in whom successful CRT was achieved with the use of LBBAP or BVP at 15 international centers (6 in North America, 2 in Asia, and 7 in Europe) from January 2018 to June 2022. All patients had NYHA functional class II to IV heart failure symptoms, baseline LVEF ≤35%, and indication for CRT or expected frequent ventricular pacing >40%. Patients were excluded if they were aged <18 years or had a pre-existing CRT device, CRT was unsuccessful, or the did not complete a 6-month follow-up. Every patient provided written informed consent for the procedures, which included a discussion that LBBAP is a nonstandard approach to achieve cardiac resynchronization. All patients underwent an attempt at BVP or LBBAP based on operator preference and the clinical practice at that institution. Among the 15 centers, BVP was the first choice for all operators in 6 centers, LBBAP was the first choice all operators in 5 centers, and in 4 centers the choice varied among the operators. The Institutional Review Boards at each site approved the retrospective observational study and data analysis. The research reported in this paper adhered to Helsinki Declaration guidelines (as revised in 2013). The study data are available from the corresponding author on reasonable request.

PROCEDURE. Left bundle branch area pacing. LBBAP was performed using the Select Secure (model 3830; Medtronic) pacing lead delivered through a fixed curve or a deflectable sheath (C315HIS and C304His; Medtronic) as previously described.[15] The lead was inserted into the muscular interventricular septum by means of rapid clockwise rotations, and the final position was accepted based on previously published criteria.[8-10,15] If acceptable left bundle branch (LBB) area capture could not be initially achieved, the lead was repositioned at a slightly distal site. LBBAP was considered to be successful if the unipolar paced QRS morphology demonstrated a Qr or qR pattern along with any of the following: 1) recording of LBB potential; 2) demonstration of transition from nonselective to selective LBB/left ventricular (LV) septal capture during threshold testing; or 3) R-wave peak time in leads V_5-V_6 <90 ms. In some patients, an LV lead was also implanted in a coronary sinus branch at the operator's discretion to achieve LBBAP-optimized CRT (LOT-CRT) or to be available as a back-up lead.[12]

Biventricular pacing. LV leads were implanted in a standard fashion targeting the basal posterolateral LV, using quadripolar LV leads whenever feasible.

FOLLOW-UP. Baseline patient demographics, medical history, current medications, and electrocardiographic and echocardiographic findings were collected. LBBAP and LV capture thresholds were obtained at implantation and during device follow-up. Patients were followed in the device clinic at

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
BVP = biventricular pacing
CRT = cardiac resynchronization therapy
CS = coronary sinus
CSP = conduction system pacing
EF = ejection fraction
HBP = His bundle pacing
HFH = heart failure hospitalization
LBBAP = left bundle branch area pacing
LBBB = left bundle branch block
LOT-CRT = left bundle branch area pacing-optimized cardiac resynchronization therapy
LV = left ventricle
LVEF = left ventricular ejection fraction

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics

	All Patients (N = 1,778)				LBBB (n = 1,073)		
	All Patients	BVP (n = 981)	LBBAP (n = 797)	*P* Value	BVP (n = 626)	LBBAP (n = 447)	*P* Value
Age, y	69 ± 12	68 ± 12	69 ± 12	0.33	68 ± 12	67 ± 12	0.73
Female	575 (32)	294 (30)	281 (36)	0.02	204 (32)	178 (40)	0.02
Hypertension	1,145 (64)	614 (63)	529 (66)	0.12	373 (60)	281 (63)	0.32
Diabetes	698 (39)	381 (39)	317 (40)	0.69	242 (39)	165 (37)	0.56
Coronary artery disease	858 (48)	480 (49)	378 (47)	0.488	284 (46)	175 (39)	0.04
Atrial fibrillation	650 (37)	364 (37)	286 (36)	0.14	201 (32)	103 (23)	<0.01
BMI, kg/m^2	28 ± 6	28.8 ± 6.8	27.5 ± 6	<0.01	29 ± 6.8	28 ± 6	<0.01
Type of cardiomyopathy				<0.01			<0.01
Ischemic	649 (36)	386 (39)	263 (33)		234 (37)	123 (28)	
Nonischemic	1,029 (58)	550 (56)	479 (60)		370 (59)	297 (66)	
Mixed	100 (6)	45 (5)	55 (7)		22 (4)	27 (6)	
NYHA functional class	2.7 ± 0.6	2.7 ± 0.6	2.8 ± 0.6	<0.01	2.7 ± 0.6	2.8 ± 0.6	<0.01
LVEF, %	27 ± 6	26 ± 6	27 ± 6	<0.01	25.9 ± 7	26 ± 6	<0.01
LVEDD, mm	61 ± 9	62 ± 9	60 ± 9	<0.01	63 ± 9	60 ± 9	< 0.01
Baseline QRS, ms	160 ± 26	160 ± 24	160 ± 28	0.63	163 ± 19	168 ± 20	<0.01
QRS morphology				<0.01			
LBBB	1,073 (61)	626 (64)	447 (56)				
RBBB	173 (10)	96 (10)	77 (10)				
IVCD	153 (9)	76 (8)	77 (10)				
Normal	127 (7)	57 (6)	70 (9)				
RV pacing	248 (14)	126 (13)	126 (16)				
Medications							
Beta-blocker	1,587 (89)	871 (89)	716 (90)	0.48	570 (91)	412 (92)	0.52
ACEI/ARB	737 (42)	412 (42)	325 (41)	0.6	255 (41)	169 (38)	0.33
ARNI	683 (38)	384 (39)	299 (38)	0.47	262 (42)	194 (44)	0.64
Aldosterone antagonist	966 (54)	537 (55)	429 (54)	0.7	358 (57)	248 (56)	0.58
Diuretic	1,325 (74)	706 (72)	619 (78)	<0.01	488 (71)	349 (78)	0.02
Amiodarone	279 (15)	173 (18)	106 (13)	0.01	109 (17)	45 (10)	<0.01

Values are mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor blocker and neprilysin inhibitor; BVP = biventricular pacing; BMI = body mass index; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LBBAP = left bundle branch area pacing; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; RV = right ventricular.

regular intervals and via remote monitoring. Among patients with LBBB, atrioventricular (AV) delay optimization algorithms were used whenever possible to allow fusion with native right bundle branch conduction in both groups. Devices were programmed to optimize for the narrowest paced QRS duration. In cases with LBBAP, LV-right ventricle (RV) offset was maximized (80-100 ms) or programmed to LV-only pacing to allow for LBBAP only. In BVP cases, LV-RV offset was adjusted appropriately to allow for the narrowest paced QRS duration, including the use of "adaptive" LV-only pacing or similar algorithms. In some patients receiving LBBAP and LV leads, LBBAP-LV timing was optimized to achieve the narrowest QRS (LOT-CRT) in patients with intraventricular conduction delay or incomplete electrical resynchronization. In some of these patients, an LV lead was used as back-up (LBBAP-LV offset programmed to 80-100 ms or LV lead turned off). BVP percentage was routinely documented in all patients. Procedure and lead-related complications and device infections were documented.

Echocardiographic examination was performed with the use of a commercially available ultrasound system. The LVEF and LV volumes were calculated by means of Simpson's biplane method. Echocardiographic response was defined as a ≥5% increase in LVEF. Hyper-responder status was defined as an absolute improvement in LVEF by ≥20% or improvement of LVEF to >50%.

The primary outcome measured was the combined endpoint of time to death from any cause or the first episode of HFH. HFH was defined as an unplanned or emergency department visit or an inpatient hospitalization in which the patient presented with signs and symptoms consistent with heart failure requiring

TABLE 2 Procedural Characteristics

	All Patients (N = 1,778)			LBBB (n = 1,073)		
	BVP (n = 981)	LBBAP (n = 797)	*P* Value	BVP (n = 626)	LBBAP (n = 447)	*P* Value
Procedural duration, min	124 ± 48	142 ± 55	<0.001	121 ± 47	140 ± 58	<0.001
Fluoroscopy duration, min	16 ± 12	17 ± 15	0.63	16.3 ± 12.4	18.1 ± 16.8	0.33
Type of device						
Pacemaker	149 (15.0)	267 (33.0)	<0.001	86 (14.0)	157 (35.0)	<0.001
ICD	832 (85.0)	530 (67.0)	<0.001	540 (86.0)	290 (65.0)	<0.001
Dual chamber	-	237 (30.0)	<0.001	-	146 (33.0)	<0.001
CRT	981 (100.0)	537 (67.0)	<0.001	626 (100.0)	294 (66.0)	<0.001
Pacing threshold (LV-CS/LBBAP)						
Implant, V	1.15 ± 0.7	0.72 ± 0.4	<0.001	1.1 ± 0.6	0.8 ± 0.3	<0.001
Follow-up, V	1.31 ± 0.7	0.74 ± 0.3	<0.001	1.3 ± 0.7	0.7 ± 0.3	<0.001
Threshold increase ≥1 V	72 (7.3)	13 (1.6)	<0.001	44 (7.0)	10 (2.2)	<0.001
Baseline QRS duration, ms	160 ± 25	161 ± 28	0.63	163 ± 19	168 ± 20	<0.001
Paced QRS duration, ms	144 ± 23	128 ± 19	<0.001	143 ± 22	126 ± 18	<0.001
Ventricular pacing	96.0	95.2	0.17	96.5	97.2	0.07
Lead revision	48 (4.9)	29 (3.6)	0.20	28 (4.5)	18 (4)	0.72
Procedural complications	74 (7.5)	30 (3.8)	<0.001	44 (7.0)	19 (4.3)	0.06
Pericardial effusion	10 (1.0)	4 (0.5)		4 (0.6)	3 (0.7)	
Pneumothorax	5 (0.5)	3 (0.4)		3 (0.5)	1 (0.2)	
Acute lead dislodgement	34 (3.5)	13 (1.6)		23 (3.7)	10 (2.2)	
Infection	21 (2.1)	6 (0.8)		12 (1.9)	3 (0.7)	
Other	4 (0.4)	4 (0.5)		2 (0.3)	2 (0.4)	

Values are mean ± SD, n (%), or %.

CRT = cardiac resynchronization therapy; CS = coronary sinus; ICD = implantable cardioverter defibrillator; LV = left ventricular; V = volts; other abbreviations as in Table 1.

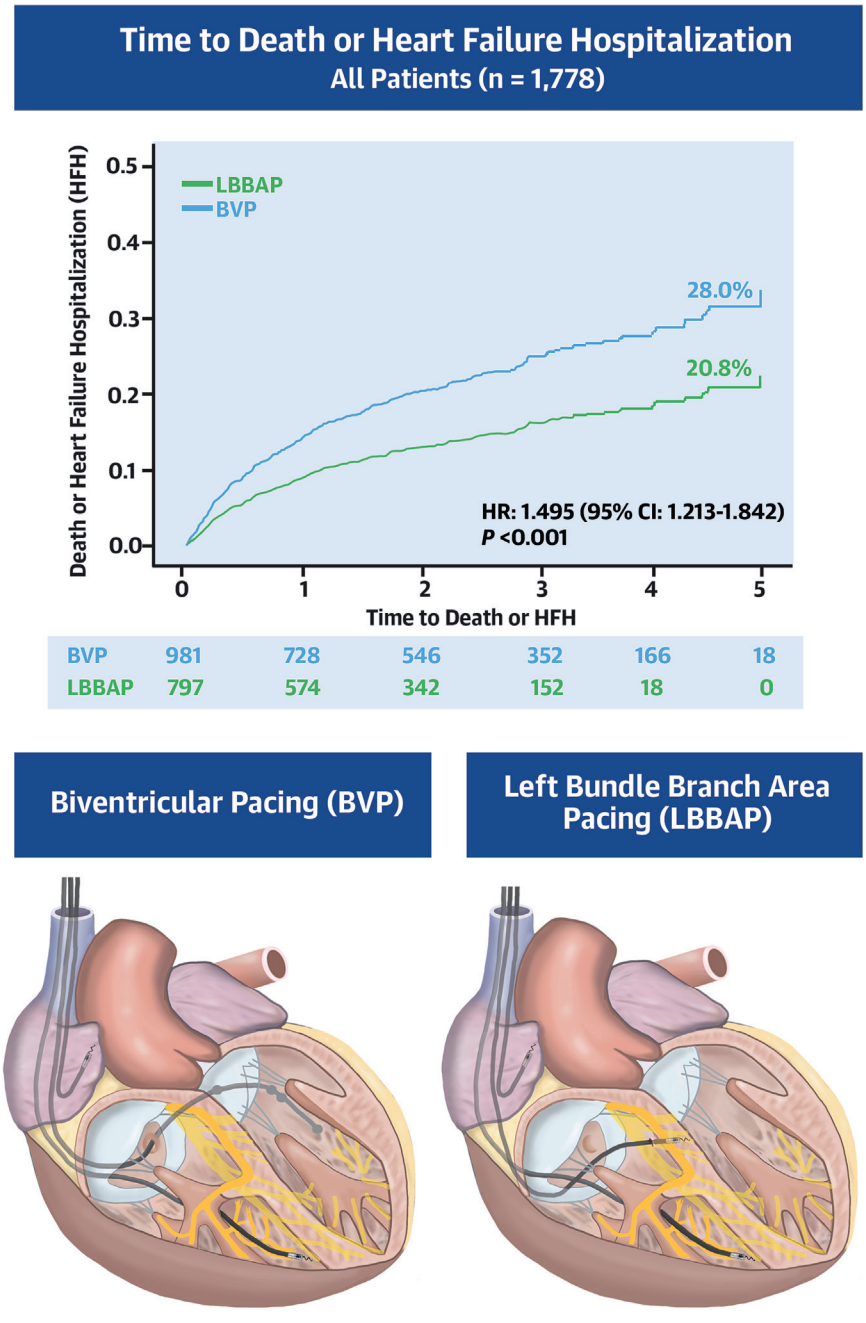
intravenous diuretic therapy. Information regarding mortality was obtained from the hospital records. Secondary endpoints included individual outcomes of death, HFH, and echocardiographic response/super-response. We also performed subgroup analysis in patients with LBBB.

STATISTICAL ANALYSIS. All data were summarized as frequencies and percentages for categoric data and mean ± SD or median (IQR) for continuous data (distribution-dependent). Descriptive statistics were reported for the full sample and stratified by LBBAP and BVP groups. Comparison between the groups was accomplished with the use of the chi-square or Fisher exact test and independent-sample Student's *t*-test or Mann-Whitney *U*-test, as appropriate. Within-group comparisons were performed by means of 2-tailed paired Student's *t*-test. Univariate and multivariable Cox proportional hazard models were used to estimate survival probability for the composite primary outcome and secondary outcomes for the CSP and BVP groups. Initially, univariate analysis was carried out using variables previously determined to be clinically significant. Univariate predictors with *P* values <0.10 were entered into multivariate Cox proportional hazard models to determine significant independent predictors. For secondary outcomes of mortality, HFH, echocardiographic outcomes, and subgroup analysis in patients with LBBB, univariate and multivariate regression models were performed as previously described. Competing risk analysis for HFH with mortality as a competing risk was performed to estimate the marginal probability of a certain event as a function of its cause-specific probability and overall survival probability. Patients' last follow-up dates were determined by the last time they were seen in the health care system or until the time of death. All data and follow-up dates were censored after December 31, 2022. For the survival analyses, time censoring was determined by time to event or time to last follow-up in the health care system, whichever came first. Statistical analysis was performed with the use of SPSS software version 27 (IBM). Competing risk analysis was performed with the use of R version 4.3 (R Core Team). A *P* value of <0.05 was considered to be significant.

RESULTS

BASELINE CHARACTERISTICS. A total of 1,778 patients underwent successful CRT during the study period, met final inclusion criteria, and were included

CENTRAL ILLUSTRATION **Death or Heart Failure Hospitalization**



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Cox survival curve and analysis demonstrate a statistically significant reduction in the primary composite outcome of all-cause mortality or heart failure hospitalization (HFH) with left bundle branch area pacing (LBBAP) compared with biventricular pacing (BVP).

in the analysis. The mean age of the cohort was 69 ± 12 years, and 32% were women. A history of hypertension was present in 64% of patients, diabetes in 39%, and coronary artery disease in 48%, and atrial fibrillation was noted in 37% of patients. At baseline, the mean LVEF of the entire cohort was 27% ± 6%, and the mean QRS duration was 160 ± 26 ms. The etiology of cardiomyopathy was ischemic in 36% and

TABLE 3 Comparison of Primary and Secondary Outcomes (All-Cause Mortality and HFH) Between BVP and LBBAP

				Univariate Analysis		Multivariate Analysis	
	BVP	LBBAP	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All patients (N = 1,778)	981	797					
Mortality or HFH	275 (28)	166 (21)	<0.001	1.621 (1.271-2.069)	<0.001	1.495 (1.213-1.842)	<0.001
Mortality	168 (17)	99 (12)	0.006	1.519 (1.108-2.083)	0.009	1.144 (0.881-1.485)	0.313
HFH	188 (19)	93 (12)	<0.001	1.528 (1.142-2.045)	0.004	1.494 (1.159-1.927)	0.002
Competing risk analysis for HFH (mortality as competing risk)				1.56 (1.11-1.83)	*P* < 0.01	1.49 (1.21-1.93)	<0.01
LBBB (n = 1,073)	626	447					
Mortality or HFH	161 (26)	74 (17)	<0.001	1.523 (1.080-2.147)	0.016	1.543 (1.150-2.071)	0.004
Mortality	89 (14)	44 (10)	0.032	1.210 (0.792-1.897)	0.406		
HFH	119 (19)	41 (9)	<0.001	1.953 (1.277-2.986)	0.002	2.158 (1.487-3.132)	<0.001
Competing risk analysis for HFH (mortality as competing risk)				2.23 (1.42-3.31)	*P* < 0.01	2.19 (1.35-3.17)	<0.01

Values are n or n (%), unless otherwise indicated.
HFH = heart failure hospitalization; other abbreviations as in Table 1.

nonischemic in 58%. Mixed cardiomyopathy out of proportion to the underlying coronary artery disease was noted in 6%. LBBB as defined by Strauss's criteria was present in 61% of the study population. The mean follow-up duration for the entire cohort was 33 ± 16 months. Table 1 presents baseline patient characteristics, preimplantation medical history, LVEF, and QRS duration. LBBAP was successfully performed in a total of 797 patients, and 981 patients underwent successful BVP. Among patients with LBBAP, prior attempts at BVP had failed in 59 (7.5%), and in 55 (5.6%) of the BVP patients prior attempts at CSP had failed. Among patients with LBBAP, 144 (18%) received a coronary sinus (CS) lead in addition to LBBAP, 69 (8.6%) LOT-CRT, and 75 (9.4%) an LV lead as back-up. Overall, both groups were well matched, except for a higher prevalence of ischemic cardiomyopathy and LBBB in the BVP group. Among patients with LBBB (n = 1,073; 626 BVP, 447 LBBAP), the 2 groups were well matched except for a slightly higher prevalence of men, atrial fibrillation, ischemic cardiomyopathy, and amiodarone use in the BVP group (Table 1).

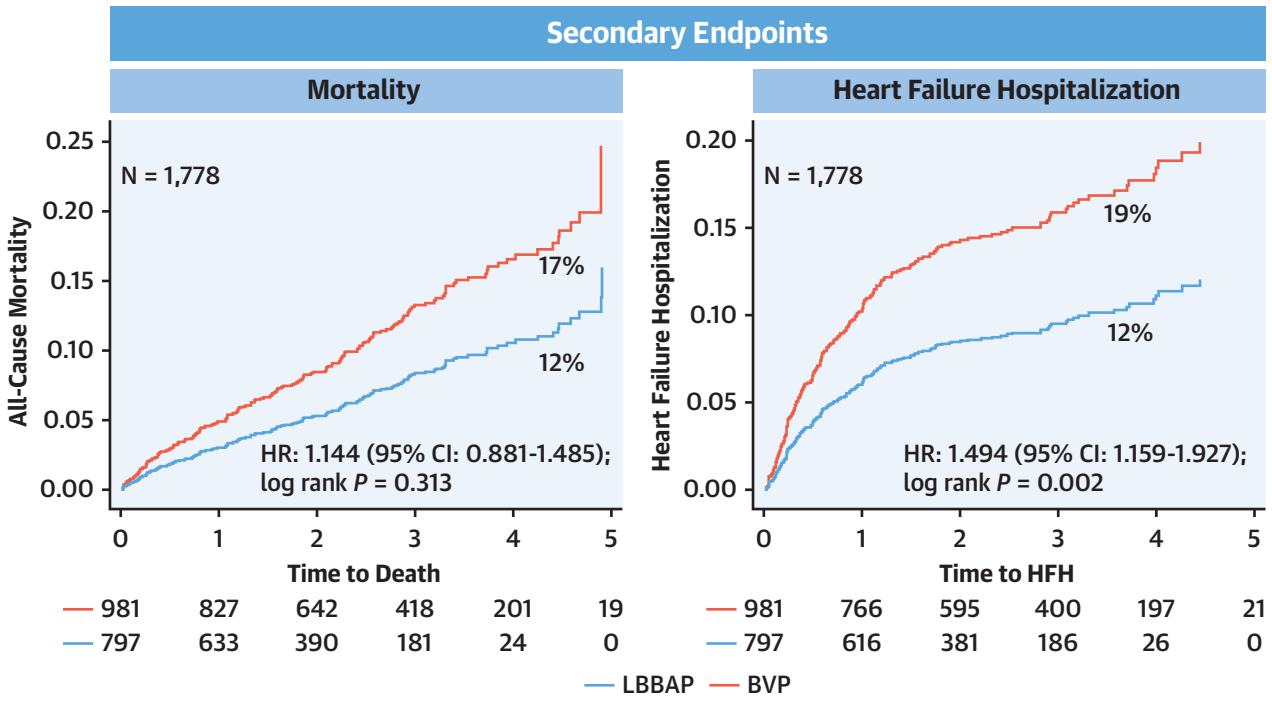
PROCEDURAL OUTCOMES. A total of 1,362 patients (77%) received implantable cardioverter-defibrillators and 416 patients (23%) underwent pacemaker implantation (Table 2). The number of patients receiving pacemakers for CRT was higher in the LBBAP group, and more patients in the BVP group received defibrillators ($P < 0.001$). The mean procedure duration was longer in the LBBAP group compared with the BVP group (142 ± 55 min vs 124 ± 48 min, respectively; $P < 0.001$), although there was no difference in the fluoroscopy duration (17 ± 15 min vs 16 ± 12 min, respectively; $P = 0.20$). Paced QRS duration was significantly shorter in the LBBAP group than in the BVP group (128 ± 19 ms vs 144 ± 23 ms, respectively; $P < 0.001$). LV capture thresholds were significantly higher than the LBBAP thresholds at implantation (1.15 ± 0.7 V at 0.5 ± 0.2 ms vs 0.72 ± 0.4 V at 0.5 ± 0.1 ms; $P < 0.001$). Overall, capture thresholds increased slightly during the follow-up period but remained stable. Pacing threshold increase of at least 1 V was noted in 72 patients (7.3%) in the BVP group compared with 13 (1.6%) in the LBBAP group ($P < 0.001$). In the BVP group, lead revision was required in 48 patients (4.9%) (LV-CS lead: n = 25;

TABLE 4 Predictors of Death or Heart Failure Hospitalization in All Patients

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
BVP vs LBBAP	1.621 (1.271-2.069)	<0.001	1.495 (1.213-1.842)	<0.001
Age	1.000 (0.989-1.010)	0.974		
Sex	0.679 (0.525-0.880)	0.003	0.658 (0.522-0.828)	<0.001
Hypertension	0.869 (0.684-1.104)	0.249		
Diabetes	0.616 (0.491-0.774)	<0.001	0.627 (0.516-0.763)	<0.001
Coronary artery disease	0.873 (0.632-1.206)	0.410		
Atrial fibrillation	0.775 (0.601-0.949)	0.016	0.751 (0.614-0.919)	0.005
Ischemic vs nonischemic	0.899 (0.652-1.239)	0.514		
LBBB	1.279 (1.017-1.607)	0.035	1.313 (1.072-1.606)	0.008
Baseline LVEF	0.982 (0.966-0.999)	0.037		
Baseline QRS duration	0.995 (0.991-0.999)	0.019		
Beta-blocker	1.125 (0.814-1.555)	0.476		
ACEI/ARB	1.852 (1.427-2.403)	<0.001	1.814 (1.445-2.278)	<0.001
ARNI	1.772 (1.329-2.364)	<0.001	1.917 (1.499-2.450)	<0.001
Diuretic	0.539 (0.399-0.728)	<0.001	0.546 (0.415-0.718)	<0.001
Aldosterone antagonist	0.932 (0.736-1.181)	0.561		
Amiodarone	1.489 (1.243-1.785)	<0.001	0.648 (0.513-0.818)	<0.001

Abbreviations as in Table 1.

FIGURE 1 Secondary Outcomes in All Patients



(Left) Mortality: Cox proportional hazard survival curves and analysis did not show a significant difference in all-cause mortality. **(Right)** Heart failure hospitalization: figure and analysis show a statistically significant reduction in heart failure hospitalization with left bundle branch area pacing (LBBAP) compared with biventricular pacing (BVP) among all patients.

2.5%) compared with 29 patients (3.6%; $P = 0.20$) in the LBBAP group (LBBAP lead: n = 10; 1.3%). Procedural complications occurred in 74 (7.5%) in the BVP group and 30 (3.8%) in the LBBAP group ($P < 0.001$). Procedural characteristics, including complications, are presented in detail in Table 2.

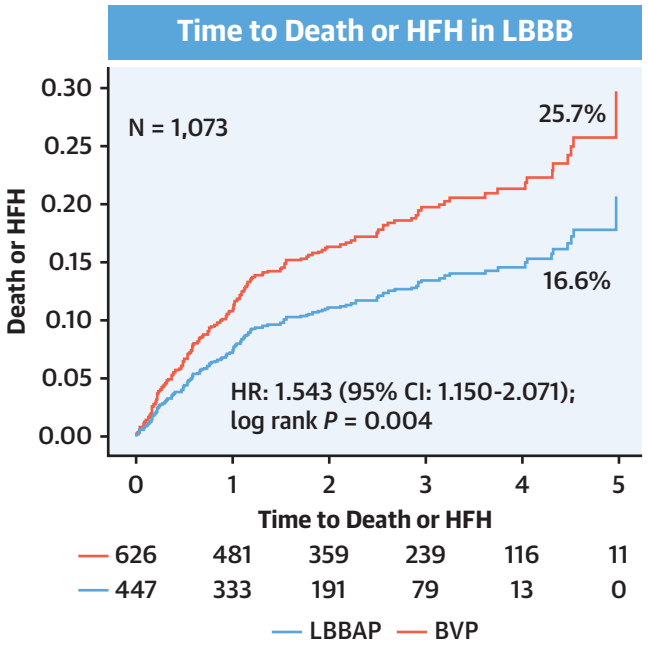
CLINICAL OUTCOMES. The primary outcome (combined endpoint of death from any cause or HFH) occurred in 28% of patients (275 of 981) in the BVP group vs 21% of patients (166 of 797) in the LBBAP group (HR: 1.495; 95% CI: 1.213-1.842; $P < 0.001$) (Central Illustration, Table 3). Univariate and multivariable analyses of the predictors of the primary outcome are presented in Table 4. During the study period, there were fewer deaths in the LBBAP group (99 of 797; 12%) than in the BVP group (168 of 981; 17%) but this did not reach statistical significance on multivariable analysis (HR: 1.144; 95% CI: 0.881-1.485; $P = 0.303$) (Figure 1A). There was a significant decrease in HFH in patients with LBBAP (93 of 797; 12%) compared with those with BVP (188 of 981; 19%) (HR: 1.494; 95% CI: 1.159-1.927; $P = 0.002$) (Figure 1B). Competing risk analysis for HFH with mortality as a competing risk was performed and confirmed the significant reduction in HFH associated with LBBAP compared with BVP in all patients (HR: 1.49; $P < 0.01$). Among patients with LBBB, the combined endpoint of death from any cause or heart failure occurred in 26% of patients (161 of 626) in the BVP group vs 17% of patients (74 of 447) in the LBBAP group (HR: 1.543; 95% CI: 1.150-2.071; $P = 0.004$) (Figure 2, Table 3). Table 5 presents univariate and multivariate analyses of the predictors of primary outcome in patients with LBBB. The incidence of HFH was significantly reduced in patients with LBBAP (41 of 447; 9%) compared with BVP (119 of 626; 19%) (HR: 2.158; 95% CI: 1.487-3.132; $P < 0.001$) (Figure 3, right). There was no significant difference in all-cause mortality between the 2 groups (10% vs 14%; $P = 0.41$) (Figure 3, left). NYHA functional class improved from 2.82 ± 0.7 to 2.01 ± 0.7 in the LBBAP group ($P < 0.001$) and from 2.69 ± 0.6 to 2.19 ± 0.8 in the BVP group ($P < 0.001$) (Figure 4). Clinical response as defined by improvement by at least 1 NYHA functional class was observed in 47% of the BVP group vs 64% of the LBBAP group ($P < 0.001$).

The LBBAP group included 144 patients with LBBAP and a CS lead. When the 69 patients with LOT-

CRT were excluded from the analysis, the primary or secondary outcomes did not change.

ECHOCARDIOGRAPHIC OUTCOMES. Echocardiographic follow-up was available for 1,424 patients (80%). LV end-diastolic diameter decreased (BVP: from 63 ± 9 mm to 57 ± 11 mm; $P < 0.001$; LBBAP: from 60 ± 9 mm to 55 ± 9 mm; $P < 0.001$). Change in LV end-diastolic diameter was 5.2 ± 8.6 mm in the BVP group vs 4.6 ± 7.8 mm in the LBBAP group ($P = 0.22$), significantly decreased in both groups compared with baseline. LVEF improved to a greater degree in the LBBAP group (from 27.5% ± 6.2% to 40.4% ± 13.3%; $P < 0.001$ vs baseline) than in the BVP group (from 26.6% ± 6.4% to 36.6% ± 12.5%; $P < 0.001$ vs baseline) (Figure 5). Change in LVEF was greater in the LBBAP group than in the BVP group (13% ± 12% vs 10% ± 12%; $P < 0.001$). In patients with LBBB, LVEF improved from 26.1% ± 5.7% to 41.4% ± 12.1% ($P < 0.001$) in the LBBAP group and from 26.4% ± 6.6% to 37.3% ± 12.8% ($P < 0.001$) in the BVP group. Change in LVEF was greater in the LBBAP group than in the BVP group (15.3% ± 12.0% vs 10.8% ± 12.0%; $P < 0.001$) among patients with LBBB. LBBAP resulted in significantly greater echocardiographic response rates (ΔLVEF ≥5%) compared with BVP in multivariate regression analysis (73.9% vs 65.4%; OR: 1.604; 95% CI: 1.247-2.063; $P < 0.001$). This difference in echocardiographic response rate was even greater among patients with LBBB (81.7% vs 68.2%; OR: 1.932; 95% CI: 1.352-2.760; $P < 0.001$). Echocardiographic hyper-response with a change in EF by 20% or more or normalization of LVEF to 50% or more was observed in a significantly greater percentage of patients with LBBAP compared with BVP (33.9% vs 25.1%; HR: 1.678; 95% CI: 1.291-2.181; $P < 0.001$). Similarly, among patients with LBBB, echocardiographic hyper-response was observed in a significantly higher percentage of patients (42.1% vs 28.5%; HR: 1.771; 95% CI: 1.305-2.402; $P < 0.001$) in the LBBAP group compared with the BVP group (Table 6). In multivariable analysis, female sex, LBBB, and nonischemic cardiomyopathy were predictors of echocardiographic response.

FIGURE 2 Subgroup Analysis of Primary Outcome in Patients With Left Bundle Branch Block



Cox proportional hazard survival curve and analysis demonstrates a statistically significant reduction in the primary composite outcome of all-cause mortality or heart failure hospitalization (HFH) with left bundle branch area pacing (LBBAP) compared with biventricular pacing (BVP) in patients with left bundle branch block (LBBB).

DISCUSSION

The main findings from this large, multicenter, international, observational, retrospective comparative study were as follows: 1) LBBAP was associated with a significant reduction in the primary composite endpoint of all-cause mortality or HFH compared with BVP in patients undergoing CRT; 2) LBBAP was associated with a significant reduction in HFH compared with BVP; 3) in patients with LBBB, LBBAP was associated with a greater reduction in clinical outcomes of death or HFH compared with BVP; 4) LBBAP resulted in a greater narrowing of QRS duration compared with BVP; and 5) echocardiographic response and hyper-response rates were significantly higher in the LBBAP group compared with the BVP group in all patients and in those with LBBB.

CRT using BVP has been the mainstay of therapy for patients with LVEF <35%, heart failure, and wide QRS or ventricular pacing. Despite its established mortality benefit, the rate of suboptimal response is about 30% with BVP, possibly owing to the non-physiologic electrical resynchronization between an epicardial wavefront from the CS lead and the RV endocardium, suboptimal lead position, presence of LV scar, and latency due to localized conduction delay.[16] In addition, CS lead implantation may be unsuccessful in 5% to 7% of patients owing to anatomic challenges, high pacing thresholds, or phrenic nerve stimulation despite the availability of multipolar leads.[17] CSP using LBBAP has recently been shown to achieve excellent electrical resynchronization, QRS narrowing, and improvements in

TABLE 5 Predictors of Death or Heart Failure Hospitalization in LBBB

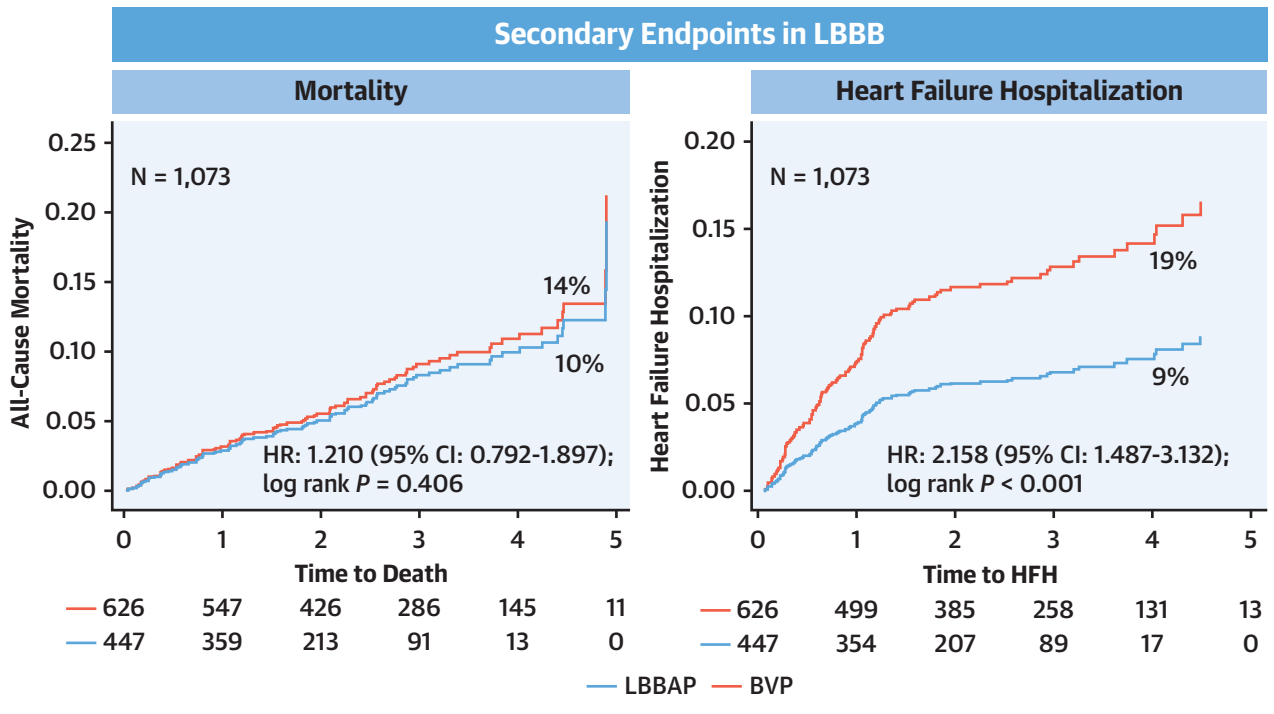
	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
BVP vs LBBAP	1.523 (1.080-2.147)	0.016	1.543 (1.150-2.071)	0.004
Age	0.993 (0.978-1.007)	0.333		
Sex	0.657 (0.468-0.921)	0.015	0.641 (0.470-0.873)	0.005
Hypertension	0.846 (0.615-1.163)	0.303		
Diabetes	0.571 (0.419-0.777)	<0.001	0.672 (0.481-0.823)	<0.001
Coronary artery disease	0.656 (0.416-1.034)	0.069	0.672 (0.509-0.886)	0.005
Atrial fibrillation	0.702 (0.515-0.957)	0.023	0.760 (0.575-1.003)	0.053
Ischemic vs nonischemic	1.050 (0.661-1.667)	0.836		
Baseline LVEF	0.989 (0.967-1.010)	0.300		
Baseline NYHA class	1.489 (1.243-1.785)	<0.001	1.508 (1.202-1.893)	<0.001
Baseline QRS duration	0.991 (0.984-0.999)	0.024	0.993 (0.986-1.001)	0.051
Beta-blocker	1.478 (0.954-2.290)	0.080	1.707 (1.159-2.515)	0.007
ACEI/ARB	2.053 (1.450-2.907)	<0.001	1.963 (1.443-2.670)	<0.001
ARNI	2.205 (1.496-3.271)	<0.001	02.232 (1.601-3.111)	<0.001
Diuretic	0.380 (0.238-0.606)	<0.001	0.385 (0.252-0.588)	<0.001
Aldosterone antagonist	0.986 (0.718-1.355)	0.931		
Amiodarone	0.693 (0.494-0.973)	0.034	0.690 (0.503-0.945)	0.021

Abbreviations as in Table 1.

LVEF in observational studies.[9-11] Small randomized trials have also demonstrated similar or greater improvement in LVEF with LBBAP compared with BVP.[13-14] LBBAP is increasingly being used as an alternative to BVP to achieve CRT both in patients with LBBB and in those with wide QRS or RV pacing.[11]

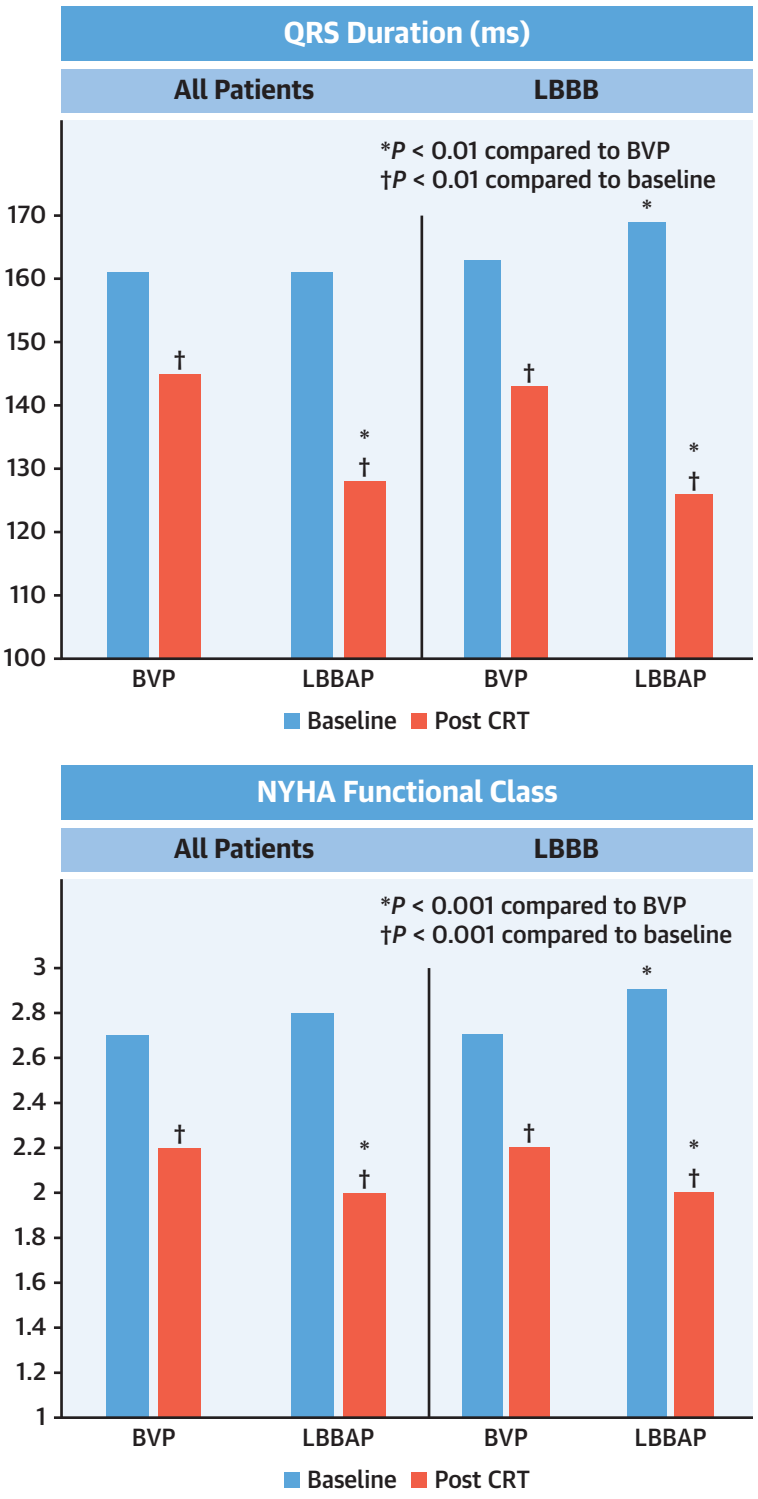
In the present study comparing LBBAP and BVP in patients undergoing CRT, we observed a greater reduction in QRS duration with LBBAP. Although the procedure duration was longer in the LBBAP group, the fluoroscopy duration was similar. It is likely that with improvements in dedicated lead and delivery systems, further procedural efficiency can be achieved. AV optimization with fusion LV/BVP has been shown to result in a greater reduction in QRS duration compared with traditional BVP with short AV delays.[18-19] AV optimization algorithms were routinely used in our study, with BVP resulting in a significant reduction in QRS duration compared with baseline. Nonetheless, LBBAP resulted in greater narrowing of QRS duration.

FIGURE 3 Secondary Outcomes in Patients With LBBB



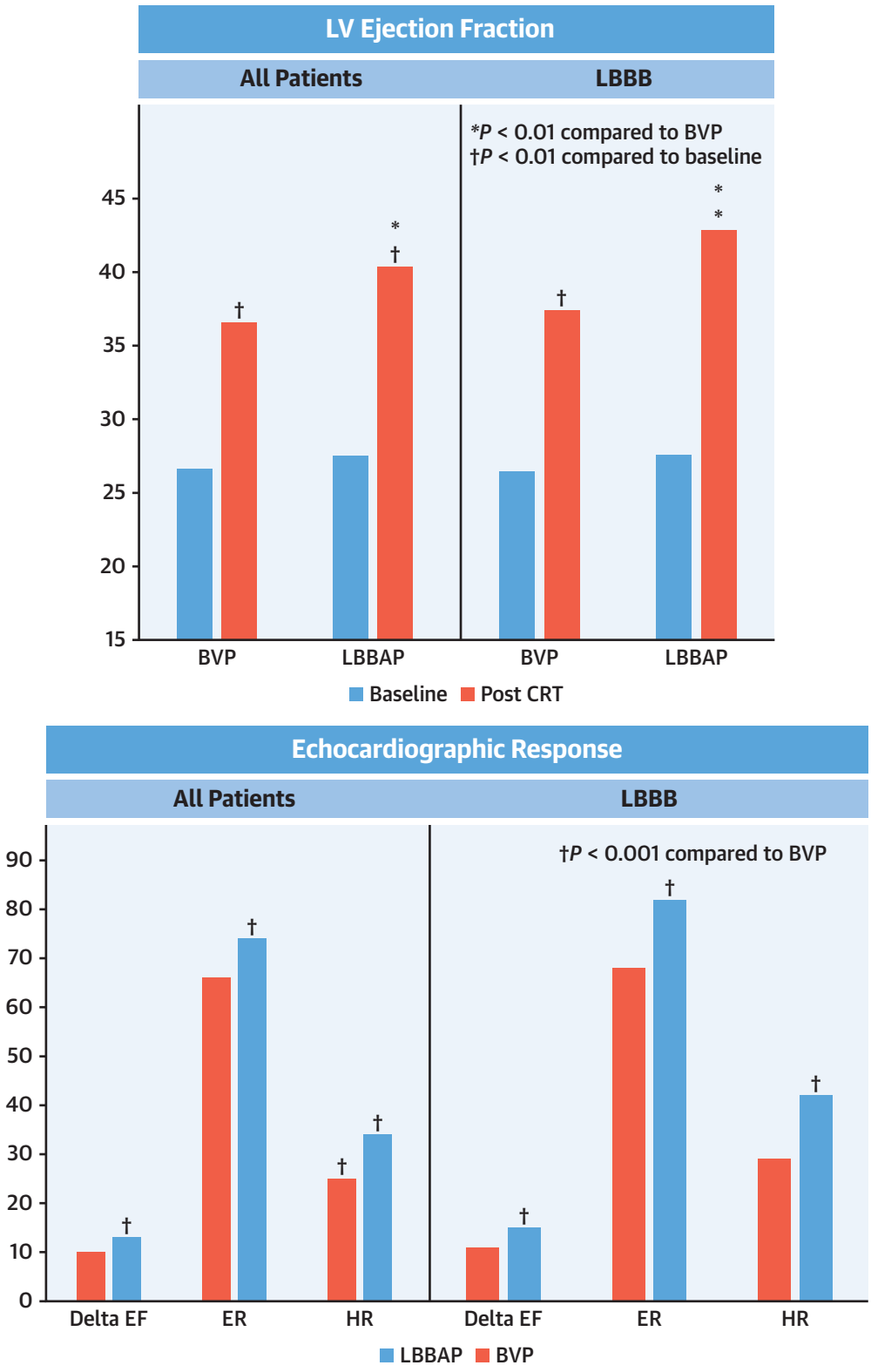
(Left) Mortality: Cox proportional hazard survival curves and analysis did not show a significant difference in all-cause mortality among patients with left bundle-branch block (LBBB). **(Right)** Heart failure hospitalization: Figure and analysis show a statistically significant reduction in heart failure hospitalization with LBBAP compared with BVP in patients with LBBB. Abbreviations as in Figure 2.

FIGURE 4 **QRS Duration and NYHA Functional Class**



LBBAP was associated with greater reduction in QRS duration and improvements in NYHA functional class compared with BVP. Abbreviations as in Figure 2.

FIGURE 5 Echocardiographic Outcomes



Left ventricular (LV) ejection fraction improved in both groups compared with baseline. Change in LV ejection fraction compared with baseline (ΔEF), echocardiographic response (ER), and hyper-response (HR) rates were greater with LBBAP compared with BVP. Abbreviations as in Figure 2.

TABLE 6 Comparison of Echocardiographic Response and Hyper-Response Between BVP and LBBAP

				Univariate Analysis		Multivariate Analysis	
	BVP	LBBAP	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
All patients (N = 1,424)	757	667					
Echocardiographic response	495 (65.4)	492 (73.9)	<0.001	1.727 (1.306-2.285)	<0.001	1.604 (1.247-2.063)	<0.001
Hyper-response	190 (25.1)	226 (33.9)	<0.001	1.638 (1.248-2.149)	<0.001	1.678 (1.291-2.181)	<0.001
LBBB (n = 874)	492	382					
Echocardiographic response	335 (68.2)	312 (81.7)	<0.001	2.197 (1.487-3.248)	<0.001	1.932 (1.352-2.760)	<0.001
Hyper-response	140 (28.5)	161 (42.1)	<0.001	1.619 (1.156-2.267)	0.005	1.771 (1.305-2.402)	<0.001

Values are n or n (%), unless otherwise indicated. On regression analysis, echocardiographic response and hyper-response rates were significantly higher in patients with LBBAP in all patients and in those with LBBB.

Abbreviations as in Table 1.

In an on-treatment analysis of CSP compared with BVP in a predominantly nonischemic cardiomyopathy population with LBBB, Wu et al[20] demonstrated greater improvements in LVEF and higher rates of normalization of EF with CSP. In a randomized study by Wang et al[14] of LBB pacing vs BVP in 40 patients with nonischemic cardiomyopathy, LBBB, and LVEF <40%, the intention-to-treat analysis showed significantly higher LVEF improvement at 6 months after LBB pacing than after BVP (mean difference: 5.6%; 95% CI: 0.3-10.9; $P = 0.039$).[14] In randomized clinical trials of BVP, LVEF improvements of 6.9% to 8.0% were observed at 12 to 18 months compared with control groups without BVP.[1,21] These changes in LVEF resulted in a remarkable reduction in mortality during long-term follow-up. In our study, the ΔLVEF was significantly higher in the LBBAP group compared with the BVP group in patients with LBBB (15.3% ± 12.0% vs 10.8% ± 12.0%; $P < 0.001$). In the randomized study by Wang et al,[14] similar rates of echocardiographic response of LVEF improvement by 5% were observed (90.0% vs 89.5%), while higher hyper-response rates (65.0% vs 42.1%) were observed with LBBAP compared with BVP. In the present study, echocardiographic response (≥5% change in LVEF: 81.7% vs 68.2%; $P < 0.001$) and hyper-response rates (LVEF ≥50% or ΔLVEF ≥20%: 42.1% vs 28.5%; $P < 0.001$) were observed in a significantly higher percentage of patients with LBBAP compared with BVP in patients (ischemic and nonischemic) with underlying LBBB. These observations may further support the hypothesis that greater electrical resynchronization may lead to better echocardiographic outcomes.

In a randomized study of BVP vs CSP (predominantly LBBAP) of 70 patients, the treatment-received analysis demonstrated the superiority of CSP for the combined endpoint of HFH or mortality at 6 months (0.0% vs 12.5%; $P = 0.048$).[13] Although that was a pilot study, our data support the idea that greater electrical resynchronization with the use of LBBAP has the potential to further improve the hard endpoints of death or HFH in patients requiring CRT. In a 2-center observational registry of 477 patients with severely reduced LVEF requiring CRT, greater improvements in QRS duration and LVEF was achieved with CSP (HBP/LBBAP) and was associated with further reduction in the combined endpoint of death or HFH compared with BVP.[22] In a retrospective multicenter study of CSP for CRT (119 patients with LVEF ≤50%), propensity matched with BVP (119 patients), CSP was associated with greater echocardiographic response rates (74% vs 60%; $P = 0.042$) but without significant difference in death or HFH.[23] In the randomized trials of CRT,[1,21] the incidence of the primary outcome of death or HFH ranged from 17.2% in the CRT-defibrillator arm of the MADIT-CRT trial (mean follow-up of 2.4 years, 90% NYHA functional class II) to 39% in the CRT-pacemaker arm of the CARE-HF trial (mean follow-up of 29.4 months). These outcomes are similar to the event rates of 28% in the BVP group during a mean follow-up of 33 months in the present study. Our findings of a significant reduction in death or HFH among patients with LBBAP compared with BVP in a larger series of 1,778 patients requiring CRT and in the subgroup of 1,073 patients with LBBB further support the value of more physiologic electrical resynchronization. These results should be considered only hypothesis generating and not as proof of the clinical superiority of LBBAP. The results from these studies provide great confidence for conducting large randomized controlled trials to compare LBBAP and traditional BVP to achieve CRT.

STUDY LIMITATIONS. This was a retrospective observational study from 15 different international centers and thereby has inherent limitations. Patients underwent LBBAP or BVP based on operator/institutional preference and were not randomized to either

strategy. This was an on-treatment analysis, and the true success rates of each approach were not analyzed in this study. Owing to its nonrandomized nature, this study does not ensure homogeneity between the study groups, with the possibility for selection bias and potential confounders from differences in population between centers, and the results should be interpreted with caution. Echocardiographic evaluations were not blinded or performed in a core laboratory. Large prospective randomized trials with longer follow-up comparing BVP and LBBAP are needed to confirm the outcome differences noted in this study.

CONCLUSIONS

In this large multicenter cohort of patients with reduced LVEF requiring CRT, LBBAP was associated with significant reduction in the composite outcome of all-cause mortality or HFH compared with traditional BVP.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Vijayaraman has received honoraria and consultancy, research, and fellowship support from Medtronic; has served as a consultant for Abbott and Eaglepoint; has received honoraria from Boston Scientific and Biotronik; and has a patent for a His bundle pacing delivery tool. Dr Sharma has received honoraria from Medtronic; and has served as a consultant for Medtronic, Abbott, and Biotronik. Dr Cano has received honoraria from and served as a consultant for Medtronic, Biotronik, and Boston Scientific. Dr Ponnusamy has received honoraria from Medtronic. Dr Herweg has served as a speaker and consultant for Abbott; and has received speaking and fellowship support from Medtronic. Dr Jastrzebski has received honoraria from and served as a consultant for Medtronic and Abbott. Dr Zou has received honoraria from Abbott, Biotronik, Boston Scientific, Medtronic, and Microport. Dr Chelu has received research support from Patient-Centered Outcomes Research Institute, National Institutes of Health, Abbott, and Impulse Dynamics; and has received honorarium from Impulse Dynamics. Dr Vernooy has served as a consultant for Biosense Webster, Philips, Medtronic, Abbott, and Boston Scientific; and has received research and educational grants to his institution from Philips, Abbott, Medtronic, and Biosense Webster. Dr Whinnett has received honoraria from Medtronic and Boston Scientific; and has served as a consultant for Medtronic and Abbott. Dr Nair has received grants-in-aid from Biosense Webster, Medtronic, Canadian Institutes of Health Research, and Heart and Stroke Foundation of Canada; and has received honoraria and consulting fees from Medtronic, Biosense Webster, and Boston Scientific. Dr Curila has served as a consultant for and received honoraria from Medtronic, Biotronik, and Abbott. Dr Ellenbogen has served as a consultant for Medtronic, Boston Scientific, Abbott, and Biotronik; and has received honoraria from Medtronic, Boston Scientific, and Biotronik. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with BVP in patients requiring cardiac resynchronization therapy, LBBAP is associated with a lower incidence of death or hospitalization for heart failure.

TRANSLATIONAL OUTLOOK: Randomized clinical trials with long-term follow-up are necessary to confirm the clinical benefits of permanent LBBAP compared with BVP in candidates for cardiac resynchronization therapy.

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KEY WORDS **biventricular pacing, cardiac resynchronization therapy, heart failure hospitalization, left bundle branch area pacing, mortality**