Left bundle branch area pacing vs biventricular pacing for cardiac resynchronization: A systematic review and meta-analysis

Amman Yousaf, MD,*[1] Soban Ahmad, MD,†[1] Joshua Peltz, MD,†
Muhammad Junaid Ahsan, MD,‡ Kirellos Said Abbas, MBBCh,§
Shoaib Muhammad, MBBS,|| Christopher Watson, MD,† Zain Ul Abideen Asad, MD, MS,¶
Michael H. Kim, MD, MMM, FHRS**

*From the *Department of Medicine, McLaren Flint-Michigan State University, Flint, Michigan, †Department of Medicine, East Carolina University, Greenville, North Carolina, ‡Division of Cardiology, Iowa Heart Center, Des Moines, Iowa, §Department of Medicine, Alexandria University, Alexandria, Egypt, ||Department of Medicine, Gulab Devi Hospital, Lahore, Pakistan, ¶Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, and **Department of Medicine, Creighton University and CHI Health, Omaha, Nebraska.*

BACKGROUND Left bundle branch area pacing (LBBAP) may offer greater physiological benefits than traditional biventricular pacing (BiVP). However, there are limited data comparing the efficacy of LBBAP vs BiVP in patients with systolic heart failure (HF).

OBJECTIVE The purpose of this meta-analysis was to compare the feasibility and electromechanical and clinical outcomes of both LBBAP and BiVP.

METHODS We conducted a systematic review of studies retrieved from various databases including PubMed, Embase, Google Scholar, Scopus, and Cochrane Central Register of Control Trials (CENTRAL) published up to May 22, 2023. The risk ratio (RR) and standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) were calculated for dichotomous and continuous outcomes, respectively.

RESULTS We included 12 studies with a total of 3004 patients (LBBAP = 1242, BiVP = 1762). Pooled results showed that LBBAP resulted in a significant increase in left ventricular ejection fraction (SMD 0.40, 95% CI 0.25, 0.54, $P < .00001$), echocardiographic response (RR 1.19, 95% CI 1.10 to 1.29, $P < .0001$), improvement in New York Heart Association functional class (SMD –0.44, 95% CI –0.65 to –0.23, $P < .0001$), QRS duration reduction (SMD –0.90, 95% CI –1.14 to –0.66, $P < .00001$), left ventricular end-diastolic diameter reduction (SMD –0.31, 95% CI –0.57 to –0.05, $P = .02$), fewer HF hospitalizations (RR 0.72, 95% CI 0.62, 0.85, $P < .0001$), and improved survival (RR 0.73, 95% CI 0.58, 0.92, $P = .007$). In addition, LBBAP was associated with shorter fluoroscopy time (SMD –0.94, 95% CI –1.42 to –0.47, $P < .0001$) and lower pacing threshold at implantation (SMD –1.03, 95% CI –1.32 to –0.74, $P < .00001$) and at 6 months (SMD –1.44, 95% CI –2.11 to –0.77, $P < .0001$) as compared with BiVP.

CONCLUSION Compared with BiVP, LBBAP was associated with better electromechanical and clinical outcomes, including left ventricular ejection fraction, QRS duration, echocardiographic response, New York Heart Association functional class, HF hospitalization, and all-cause mortality in patients with systolic HF.

KEYWORDS Left bundle branch block area pacing; LBBAP; Biventricular pacing; BiVP; Cardiac resynchronization therapy; CRT; Heart failure; Hospitalization

(Heart Rhythm O2 2023;4:671–680)

Introduction

Almost one-third of patients with left ventricular systolic heart failure (HF) have concomitant left bundle branch block (LBBB) and interventricular dyssynchrony, resulting in adverse cardiac remodeling and poor outcomes.[1] Cardiac resynchronization therapy (CRT), specifically biventricular pacing (BiVP), is a well-established treatment for interventricular dyssynchrony with proven efficacy in improving symptoms, reversing cardiac remodeling, and reducing mortality and hospitalizations. Current HF guidelines recommend CRT for HF with a reduced left ventricular ejection fraction (LVEF) ≤35%, QRS duration (QRSd) >120 to

[1]The first two authors contributed equally to this article. **Address reprint requests and correspondence**: Dr Soban Ahmad, Department of Internal Medicine, East Carolina University Medical Center, 2100 Stantonsburg Road, Greenville, NC 27834. E-mail address: ravian.soban@gmail.com; Twitter: @SobanAhmadMD

2666-5018/
https://doi.org/10.1016/j.hroo.2023.06.011

KEY FINDINGS

- Patients receiving left bundle branch area pacing (LBBAP) for cardiac resynchronization therapy experienced a greater reduction in mortality and heart failure hospitalizations.
- LBBAP demonstrated a significant improvement in left ventricular ejection fraction and New York Heart Association functional class compared with traditional biventricular pacing.
- LBBAP resulted in improved echocardiographic response and a greater reduction in QRS duration in patients with systolic heart failure compared with biventricular pacing patients.

130 ms in normal sinus rhythm, and moderate-to-severe HF symptoms despite treatment with maximally tolerated guideline-directed medical therapy.[2] However, up to 30% of patients may not respond to BiVP due to various reasons, including structural anomalies and technical challenges with leads placement.[3] BiVP is also a less physiologic form of pacing because it results in the fusion of the intrinsic wavefront of the atrioventricular node and the extrinsic wavefront of the implanted pacemaker leads. In theory, this may limit the effect of BiVP when compared with left bundle branch area pacing (LBBAP), which is a more physiologic form of pacing, as it uses intrinsic cardiac conduction pathways.

Since its initial description in 2017, LBBAP has evolved into a safe and feasible technique for CRT.[4] However, there is a paucity of outcome data comparing LBBAP with BiVP in patients with systolic HF. Hence, we have conducted this updated systematic review and meta-analysis with aims to compare various clinical, echocardiographic, and procedural outcomes between LBBAP and BiVP in patients with systolic HF.

Methods

Study registration

The protocol for this systematic review and meta-analysis was registered and published on PROSPERO (CRD42 023373647).

Data sources and search strategy

We conducted a comprehensive literature search using PubMed (MEDLINE), Embase, Google Scholar, Scopus, and Cochrane Central Register of Control Trials (CENTRAL) to identify relevant studies published up to May 22, 2023. The following search terms were used: ["cardiac resynchronization therapy" OR "CRT" OR "biventricular pacing" OR "left bundle branch pacing" OR "LBBP"] AND ["heart failure" OR "HF" OR "cardiac failure"]. We also manually searched the reference lists of the included studies to identify any additional relevant articles.

Study selection and eligibility criteria

Eligibility criteria were defined as (1) studies involving adult patients (18 years of age and older) comparing LBBAP and BiVP in HF and (2) studies reporting echocardiographic, procedural, and clinical outcomes. Only randomized controlled trials (RCTs) and observational cohort studies were included. Conference abstracts, case reports, single-arm studies, and animal studies were excluded.

Two reviewers (A.Y. and S.A.) independently screened the titles and abstracts for studies meeting the previously mentioned criteria. The full texts of potentially eligible studies were then reviewed by the same 2 reviewers to determine final inclusion. Any disagreements between the reviewers were resolved through discussion with a third reviewer (M.J.A.).

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines while reporting this literature review.[5]

Outcomes of interest

We collected data on the following clinical, echocardiographic, and procedural variables from the included studies: (1) improvement in LVEF; (2) reduction in New York Heart Association (NYHA) functional class; (3) QRSd reduction; (4) left ventricular end-diastolic diameter (LVEDD) reduction; (5) echocardiographic response (LVEF improvement of at least 5% after the procedure); (6) hospitalization due to HF; (7) all-cause mortality; (8) procedural characteristics including procedural duration, fluoroscopy time; and (9) pacing threshold at implantation and 6 months.

Statistical analysis

We used Review Manager (RevMan), version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) to perform all analyses. The random-effects Mantel-Haenszel method was used to calculate the pooled risk ratio (RR) for dichotomous variables and the standardized mean difference (SMD) for continuous variables, along with their 95% confidence intervals (CIs). Heterogeneity was calculated using Higgins' and Thompson's I^2 statistics, with an I^2 value of $\geq$50% deemed to suggest significant heterogeneity. Sensitivity analyses by excluding a single study at a time were performed for outcomes with significant heterogeneity. Publication bias was visually assessed using funnel plots. $P \leq .05$ was deemed to confer statistical significance. The Newcastle-Ottawa Scale and Cochrane Risk of Bias tool were used to assess the quality of the included cohort and randomized studies, respectively.

Results

Systematic review and study selection

The literature search yielded 1658 articles. An additional 29 studies were identified by checking the reference lists

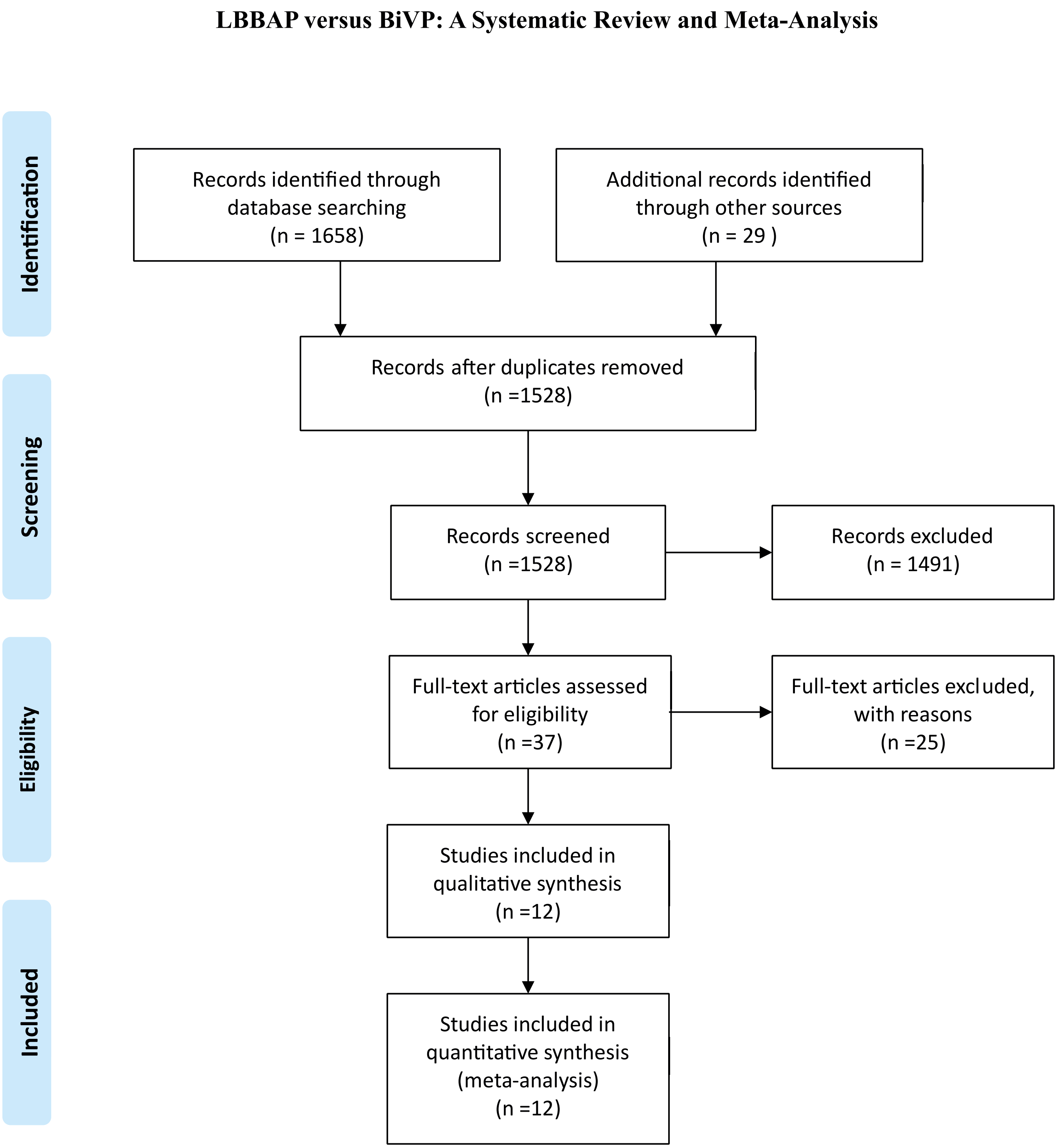


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart depicting the study selection process.

of initially selected articles. After duplicates and studies not meeting the inclusion criteria were excluded, a total of 12 studies (8 prospective, 3 retrospective, and 1 RCT) comparing LBBAP with BiVP in patients with HF were selected for result synthesis (Figure 1).[6–17] The mean follow-up duration varied between 6 and 33 months across the included studies. Table 1 shows other characteristics of the studies included in this meta-analysis.

Baseline characteristics

This meta-analysis included 3004 patients (LBBAP = 1242; BiVP = 1762). The mean age was 65 years in both the LBBAP and BiVP groups. There were no significant differences in the presence of nonischemic cardiomyopathy (RR 1.00, 95% CI 0.96 to 1.04, P = .98, I^2 = 14%), baseline LVEF (SMD 0.07, 95% CI –0.04 to 0.17, P = .20, I^2 = 14%) between the 2 groups (Supplemental Figure 1A and

Table 1 Study characteristics

First author, year	Study design	Country of origin	Total cohort	LBBAP	BiVP	Mean follow-up duration (mo)	CRT criteria used	NOS score
Guo et al, 2020[6]	Prospective	China	42	21	21	14.3	QRSd ≥150 ms, typical LBBB	8
Li et al, 2020[7]	Prospective	China	81	27	54	6	LBBB (QRSd N/A)	7
Wang et al, 2020[8]	Prospective	China	40	10	30	6	QRSd >140 ms (men) and >130 ms (women), typical LBBB	7
Wu et al, 2021[9]	Prospective	China	86	32	54	12	Typical LBBB (QRSd N/A)	8
Liu et al, 2021[15]	Prospective	China	62	27	35	6	QRSd ≥150 ms, typical LBBB	7
Chen et al, 2022[10]	Prospective	China	100	49	51	12	QRSd ≥150 ms, typical LBBB	8
Hua et al, 2022[11]	Prospective	China	41	21	20	23.71	QRSd ≥150 ms, typical LBBB	8
Wang et al, 2022[12]	RCT	China	40	20	20	6	QRSd >140 ms (men) and >130 ms (women), typical LBBB	N/A
Liang et al, 2022[13]	Retrospective	China	491	154	337	31	QRSd ≥130 ms	8
Rademakers et al, 2023[14]	Prospective	The Netherlands	80	40	40	6	QRSd ≥150 ms, typical LBBB	7
Ezzeddine et al, 2023[16]	Retrospective	United States, Spain, Canada	169	50	119	8 (LBBAP) and 10 (BiVP)	QRSd ≥120 ms	8
Vijayaraman et al, 2023[17]	Retrospective	North America, Asia, Europe	1778	797	981	33	NYHA II-IV, LVEF ≤35%, and indication for CRT or expected V-pacing >40%	8

BiVP = biventricular pacing; CRT = cardiac resynchronization therapy; LBBAP = left bundle branch area pacing; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; N/A = not available/not reported; NOS = Newcastle-Ottawa Scale; NYHA = New York Heart Association; QRSd = QRS duration; RCT = randomized controlled trial.

1B). However, the LBBAP cohort had slightly higher pooled baseline NYHA functional class scores (SMD 0.14, 95% CI 0.06 to 0.23, P = .007, I^2 = 0%) and longer QRSd (SMD 0.11, 95% CI 0.01 to 0.22, P = .04, I^2 = 19%) as compared with the BiVP group (Supplemental Figure 1C and 1D). Other baseline characteristics are listed in Table 2.

Improvement in LVEF, echocardiographic response, and NYHA functional class

Data regarding LVEF were reported by 11 of 12 studies. Pooled results showed a significant improvement in LVEF among patients undergoing LBBAP as compared with BiVP (SMD 0.40, 95% CI 0.25 to 0.54, P < .00001, I^2 = 28%). Echocardiographic response rate was higher in patients who underwent LBBAP (RR 1.19, 95% CI 1.10 to 1.29, P < .0001, I^2 = 39%). Similarly, a greater improvement in NYHA functional class was observed in patients with LBBAP than in those with BiVP (SMD –0.44, 95% CI –0.65 to –0.23, P < .0001, I^2 = 45%) (Figure 2A–2C).

Reduction in QRSd and LVEDD

QRSd reduction following pacemaker implantation was reported in 11 of 12 studies. A greater reduction in the QRSd was observed in LBBAP than in BiVP (SMD –0.90, 95% CI –1.14 to –0.66, P < .00001, I^2 = 72%). Postpacemaker change in LVEDD was reported in 8 of 12 studies, with a significantly higher reduction in LVEDD in the LBBAP group (SMD –0.31, 95% CI –0.57 to –0.05, P = .02, I^2 = 67%) (Figure 3A and 3B).

Hospitalization for HF exacerbation and all-cause mortality

Hospitalization due to HF exacerbation following CRT implantation was reported in 10 of 12 studies. Overall, despite a low incidence of HF hospitalizations among included studies, LBBAP group experienced fewer HF hospitalizations than BiVP (RR 0.72, 95% CI 0.62, 0.85, P < .0001, I^2 = 0%). Similarly, all-cause mortality was reported by 6 of 12 studies and was lower in the LBBAP group (RR 0.73, 95% CI 0.58, 0.92, P = .007, I^2 = 0%) (Figure 3C and 3D).

Procedural outcomes and pacing threshold at implantation and at 6 months

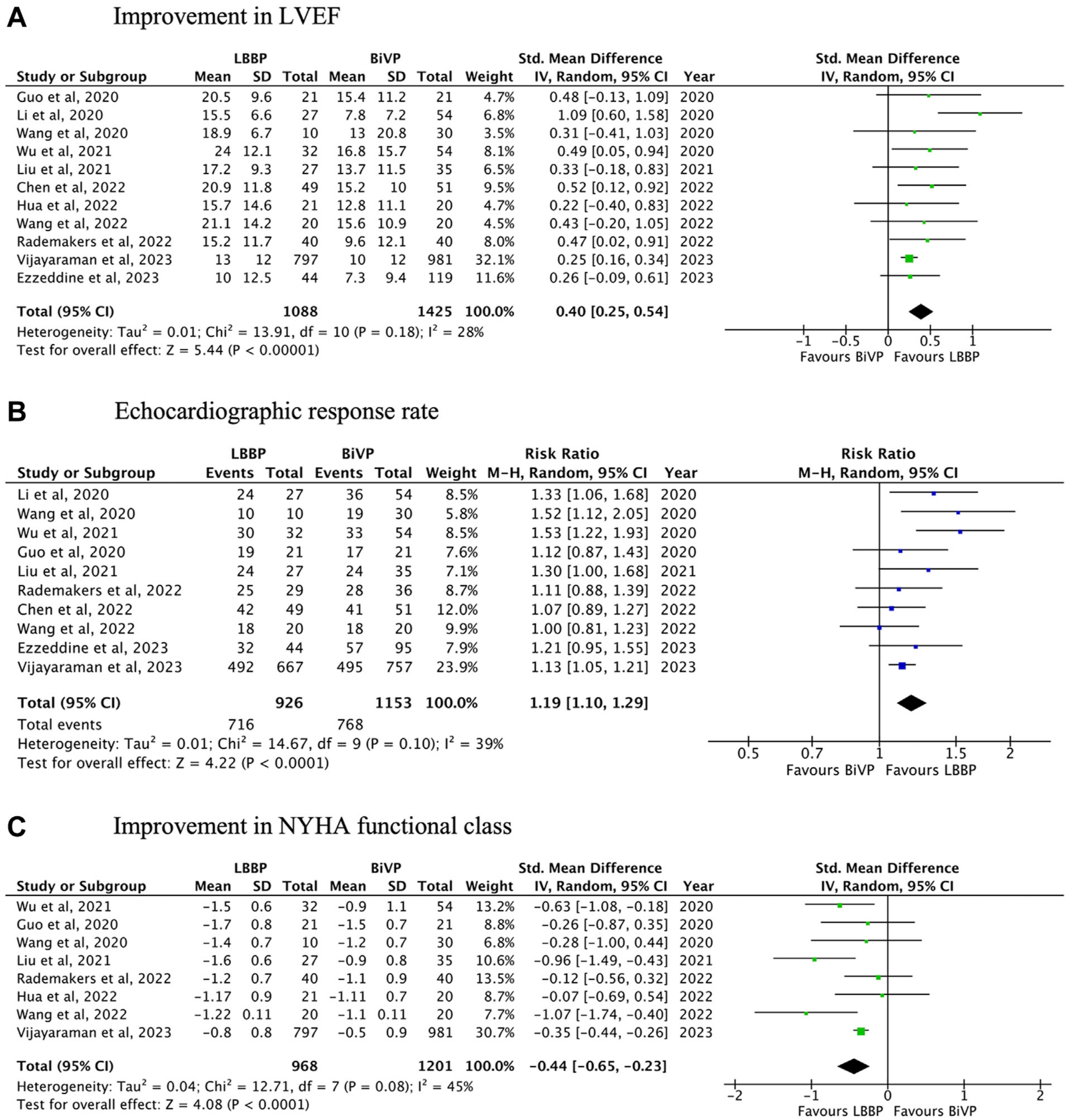
Procedure duration and fluoroscopy time were reported by 6 of 12 and 9 of 12 studies, respectively. Placement of the LBBAP ventricular lead required shorter fluoroscopy time (SMD –0.94, 95% CI –1.42 to –0.47, P < .0001, I^2 = 94%) than that of BiVP leads. However, the procedure time was comparable (SMD –0.46, 95% CI –0.95, 0.02, P < .06, I^2 = 95%). The pacing threshold at device implantation was significantly lower in patients undergoing LBBAP (SMD –1.03, 95% CI –1.32 to –0.74, P < .00001, I^2 = 70%). Furthermore, the pacing threshold at 6 months was also lower in the LBBAP cohort as compared with BiVP patients (SMD –1.44, 95% CI –2.11 to –0.77, P < .0001, I^2 = 83%) (Figure 4A–4D).

Table 2 Baseline patient and procedural characteristics

First Author, Year	Female (%)	Intervention	Age (y)	HTN	DM	AF	NICM	LVEF (%)	LVEDD (mm)	NYHA functional class	ACE inhibitor	BB	QRSd (ms)	Procedure time (min)	Fluoroscopy time (min)	Implant success	Reported Complications)
Guo et al, 2020[6]	24 (57)	LBBAP	66.1 ± 9.7	9 (43)	8 (38)	3 (14)	19 (90)	30.0 ± 5.0	64.9 ± 7.2	3.0 ± 0.7	19 (90)	20 (95)	167.7 ± 14.9	N/A	17.9 ± 7.1	21 (87)	Transient third-degree AVB 4 (19)
		BiVP	65.1 ± 7.5	7 (33)	1 (5)	1 (5)	19 (90)	29.8 ± 4.1	66.7 ± 5.4	3.0 ± 0.7	19 (90)	21 (100)	163.6 ± 13.8	N/A	37.8 ± 14.2	N/A	Transient third-degree AVB 1 (5)
Li et al, 2020[7]	34 (42)	LBBAP	57.5 ± 9.8	7 (28)	4 (16)	5 (20)	23 (85)	28.8 ± 4.5	66.5 ± 8.0	3.1 ± 0.7	27 (100)	25 (93)	178.2 ± 18.8	N/A	16.9 ± 6.4	30 (81)	N/A
		BiVP	58.5 ± 8.5	3 (25)	2 (17)	2 (17)	46 (87)	27.2 ± 4.9	69.4 ± 5.1	3.0 ± 0.7	54 (100)	53 (98)	180.9 ± 29.7	N/A	39.6 ± 9.2	N/A	N/A
Wang et al, 2020[8]	8 (20)	LBBAP	64.80 ± 7.25	N/A	N/A	N/A	9 (90)	26.80 ± 3.85	68.60 ± 7.15	2.90 ± 0.74	8 (80)	10 (100)	183.6 ± 19.27	N/A	N/A	N/A	N/A
		BiVP	62.93 ± 10.33	N/A	N/A	N/A	27 (90)	26.38 ± 5.27	70.37 ± 7.59	3.07 ± 0.74	26.1 (87)	27 (90)	174.6 ± 19.48	N/A	N/A	N/A	N/A
Wu et al, 2021[9]	43 (50)	LBBAP	67.2 ± 13	16 (50)	12 (37)	7 (22)	31 (97)	30.9 ± 7.3	N/A	2.8 ± 0.5	29 (91)	27 (84)	166.2 ± 16.2	98.4 ± 36.5	5.2 ± 4.1	N/A	N/A
		BiVP	68.3 ± 10	27 (50)	16 (30)	11 (20)	47 (87)	30.0 ± 6.2	N/A	2.8 ± 0.6	49 (91)	48 (89)	161.1 ± 18.2	122.7 ± 53.5	10.3 ± 4.4	N/A	N/A
Liu et al, 2021[15]	28 (45)	LBBAP	65.5 ± 8.8	11 (41)	9 (33)	3 (11)	20 (74)	29.9 ± 4.8	67.9 ± 6.6	3.0 ± 0.5	24 (89)	24 (89)	177.1 ± 16.7	N/A	N/A	27 (79)	N/A
		BiVP	64.3 ± 8.4	16 (46)	8 (23)	4 (11)	27 (87)	29.5 ± 4.9	N/A	2.8 ± 0.6	33 (94)	32 (91)	168.8 ± 16.8	N/A	N/A	N/A	N/A
Chen et al, 2022[10]	46 (46)	LBBAP	67.14 ± 8.88	14 (29)	12 (24)	N/A	36 (73)	29.05 ± 5.09	67.07 ± 6.67	N/A	48 (98)	48 (98)	180.12 ± 15.79	129.2 ± 31.7	11.9 ± 5.8	N/A	RBB injury 10 (20)
		BiVP	64.37 ± 8.74	16 (31)	10 (20)	N/A	41 (80)	28.36 ± 5.30	68.38 ± 7.81	N/A	50 (98)	51 (100)	175.70 ± 11.29	155.9 ± 40.7	18.7 ± 10.1	N/A	LV lead dislodgement 1 (2)
Hua et al, 2022[11]	11 (27)	LBBAP	65.50 ± 6.91	6 (28.57)	7 (33.33)	5 (23.81)	20 (95.24)	30.05 ± 7.03	68.05 ± 10.30	3.00 ± 0.71	18 (85.71)	18 (86)	177.91 ± 14.67	104.2 ± 7.4	9.5 ± 2.0	N/A	N/A
		BiVP	67.50 ± 11.69	11 (55)	5 (25)	4 (20)	17 (85)	31.40 ± 9.30	66.60 ± 11.50	3.05 ± 0.89	18 (90)	17 (85)	177.50 ± 16.99	127.8 ± 24.7	13.8 ± 5.5	N/A	N/A
Wang et al, 2022[12]	20 (50)	LBBAP	62.3 ± 11.2	N/A	N/A	N/A	20 (100)	28.3 ± 5.3	66.4 ± 8.1	2.40 ± 0.50	18 (90)	19 (95)	174.6 ± 14.3	129.2 ± 31.7	11.9 ± 5.8	18 (90)	Lead dislodgement 1 (5)
		BiVP	65.3 ± 10.6	N/A	N/A	N/A	20 (100)	31.1 ± 5.6	66.4 ± 9.8	2.45 ± 0.51	19 (95)	19 (95)	174.7 ± 14.1	155.9 ± 40.1	18.7 ± 10.1	16 (80)	Pneumothorax 1 (5)
Liang et al, 2022[13]	160 (33)	LBBAP	67 (61–73)	67 (44)	34 (22)	46 (30)	126 (82)	32 (28–37)	66 (60–73)	N/A	142 (92)	120 (78)	160 (150–180)	110.5 ± 35.7	14.6 ± 6.8	141 (94)	N/A
		BiVP	63 (55–69)	130 (39)	79 (23)	70 (21)	304 (90)	30 (25–36)	68 (61–75)	N/A	293 (87)	258 (77)	160 (150–180)	123.5 ± 42.6	19.3 ± 16.5	N/A	N/A
Rademakers et al, 2023[14]	34 (42)	LBBAP	68 ± 13	34 (85)	8 (20)	9 (23)	29 (72)	28 ± 8	60 ± 10	2.8 ± 0.5	38 (95)	37 (93)	166 ± 15	109 ± 32	14 ± 10	31 (78)	None
		BiVP	71 ± 9	32 (80)	9 (23)	13 (33)	26 (65)	31 ± 6	61 ± 9	2.7 ± 0.6	37 (93)	38 (95)	159 ± 16	137 ± 48	15 ± 10	N/A	N/A
Ezzeddine et al, 2023[16]	66 (28)	LBBAP	N/A	N/A	N/A	N/A	N/A	31.4 ± 8.9	59.3 ± 7.9	N/A	N/A	N/A	150.5 ± 34	N/A	N/A	N/A	Lead revision 1 (2.1)
		BiVP	70.6 ± 11.9	89 (75)	46 (39)	58 (49)	87 (73)	34.6 ± 12	58.2 ± 8.8	N/A	64 (54)	94 (79)	150.5 ± 34	N/A	N/A	N/A	Lead revision 11 (9.2)
Vijayaraman et al, 2023[17]	575 (32)	LBBAP	69 ± 12	529 (66)	317 (40)	286 (36)	479 (60)	27.5 ± 6.2	60 ± 9	2.8 ± 0.6	325 (41)	716 (90)	160 ± 28	142 ± 55	17 ± 15	N/A	Pericardial effusion 4 (0.5), pneumothorax 3 (0.4), lead dislodgement 13 (1.6), infection 6 (0.8)
		BiVP	68 ± 12	614 (63)	381 (39)	364 (37)	550 (56)	26.6 ± 6.4	63 ± 9	2.7 ± 0.6	412 (42)	871 (89)	160 ± 24	124 ± 48	16 ± 12	N/A	Pericardial effusion 10 (1), pneumothorax 5 (0.5), lead dislodgement 34 (3.5), infection 21 (2.1)

Values are as n (%), means ± SD, or median (interquartile range).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AVB = atrioventricular block; BB = beta-blocker; BiVP = biventricular pacing; DM = diabetes mellitus; HTN = hypertension; LBBAP = left bundle branch area pacing; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; N/A = not available/not reported; NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; QRSd = QRS duration.



A Improvement in LVEF

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BiVP Mean	BiVP SD	BiVP Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Guo et al, 2020	20.5	9.6	21	15.4	11.2	21	4.7%	0.48 [−0.13, 1.09]	2020
Li et al, 2020	15.5	6.6	27	7.8	7.2	54	6.8%	1.09 [0.60, 1.58]	2020
Wang et al, 2020	18.9	6.7	10	13	20.8	30	3.5%	0.31 [−0.41, 1.03]	2020
Wu et al, 2021	24	12.1	32	16.8	15.7	54	8.1%	0.49 [0.05, 0.94]	2020
Liu et al, 2021	17.2	9.3	27	13.7	11.5	35	6.5%	0.33 [−0.18, 0.83]	2021
Chen et al, 2022	20.9	11.8	49	15.2	10	51	9.5%	0.52 [0.12, 0.92]	2022
Hua et al, 2022	15.7	14.6	21	12.8	11.1	20	4.7%	0.22 [−0.40, 0.83]	2022
Wang et al, 2022	21.1	14.2	20	15.6	10.9	20	4.5%	0.43 [−0.20, 1.05]	2022
Rademakers et al, 2022	15.2	11.7	40	9.6	12.1	40	8.0%	0.47 [0.02, 0.91]	2022
Vijayaraman et al, 2023	13	12	797	10	12	981	32.1%	0.25 [0.16, 0.34]	2023
Ezzeddine et al, 2023	10	12.5	44	7.3	9.4	119	11.6%	0.26 [−0.09, 0.61]	2023
Total (95% CI)			**1088**			**1425**	**100.0%**	**0.40 [0.25, 0.54]**	

Heterogeneity: Tau² = 0.01; Chi² = 13.91, df = 10 (P = 0.18); I² = 28%
Test for overall effect: Z = 5.44 (P < 0.00001)

B Echocardiographic response rate

Study or Subgroup	LBBP Events	LBBP Total	BiVP Events	BiVP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Li et al, 2020	24	27	36	54	8.5%	1.33 [1.06, 1.68]	2020
Wang et al, 2020	10	10	19	30	5.8%	1.52 [1.12, 2.05]	2020
Wu et al, 2021	30	32	33	54	8.5%	1.53 [1.22, 1.93]	2020
Guo et al, 2020	19	21	17	21	7.6%	1.12 [0.87, 1.43]	2020
Liu et al, 2021	24	27	24	35	7.1%	1.30 [1.00, 1.68]	2021
Rademakers et al, 2022	25	29	28	36	8.7%	1.11 [0.88, 1.39]	2022
Chen et al, 2022	42	49	41	51	12.0%	1.07 [0.89, 1.27]	2022
Wang et al, 2022	18	20	18	20	9.9%	1.00 [0.81, 1.23]	2022
Ezzeddine et al, 2023	32	44	57	95	7.9%	1.21 [0.95, 1.55]	2023
Vijayaraman et al, 2023	492	667	495	757	23.9%	1.13 [1.05, 1.21]	2023
Total (95% CI)		**926**		**1153**	**100.0%**	**1.19 [1.10, 1.29]**	
Total events	716		768				

Heterogeneity: Tau² = 0.01; Chi² = 14.67, df = 9 (P = 0.10); I² = 39%
Test for overall effect: Z = 4.22 (P < 0.0001)

C Improvement in NYHA functional class

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BiVP Mean	BiVP SD	BiVP Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Wu et al, 2021	−1.5	0.6	32	−0.9	1.1	54	13.2%	−0.63 [−1.08, −0.18]	2020
Guo et al, 2020	−1.7	0.8	21	−1.5	0.7	21	8.8%	−0.26 [−0.87, 0.35]	2020
Wang et al, 2020	−1.4	0.7	10	−1.2	0.7	30	6.8%	−0.28 [−1.00, 0.44]	2020
Liu et al, 2021	−1.6	0.6	27	−0.9	0.8	35	10.6%	−0.96 [−1.49, −0.43]	2021
Rademakers et al, 2022	−1.2	0.7	40	−1.1	0.9	40	13.5%	−0.12 [−0.56, 0.32]	2022
Hua et al, 2022	−1.17	0.9	21	−1.11	0.7	20	8.7%	−0.07 [−0.69, 0.54]	2022
Wang et al, 2022	−1.22	0.11	20	−1.1	0.11	20	7.7%	−1.07 [−1.74, −0.40]	2022
Vijayaraman et al, 2023	−0.8	0.8	797	−0.5	0.9	981	30.7%	−0.35 [−0.44, −0.26]	2023
Total (95% CI)			**968**			**1201**	**100.0%**	**−0.44 [−0.65, −0.23]**	

Heterogeneity: Tau² = 0.04; Chi² = 12.71, df = 7 (P = 0.08); I² = 45%
Test for overall effect: Z = 4.08 (P < 0.0001)

Figure 2 **A:** Improvement in left ventricular ejection fraction (LVEF). **B:** Echocardiographic response rate. **C:** Improvement in New York Heart Association (NYHA) functional class. BiVP = biventricular pacing; CI = confidence interval; IV = inverse variance; LBBP = left bundle branch pacing; M-H = Mantel-Haenszel.

Sensitivity analysis

We observed that the heterogeneity in the pooled results for QRSd reduction, LVEDD reduction, and fluoroscopy time was lowest by omitting Vijayaraman and colleagues,[17] with no significant impact on the pooled effect sizes (I^2 = 33%, I^2 = 0%, and I^2 = 90%, respectively) (Supplemental Figure 2A–2C). Similarly, after excluding Vijayaraman and colleagues, we observed that the pooled procedural duration exhibited the lowest heterogeneity and became significantly shorter for LBBAP (SMD –0.58, 95% CI –0.80 to –0.35, $P < .00001$, I^2 = 40%) (Supplemental Figure 2D). Heterogeneity was lowest for the pacing threshold at implantation and at 6 months by omitting Chen and colleagues (I^2 = 35% and I^2 = 56%, respectively) (Supplemental Figure 2E and 2F).[10]

Lastly, we performed sensitivity analysis by removing the only RCT included in our meta-analysis, Wang and colleagues,[12] without significantly affecting pooled outcomes (Supplemental Figure 3A–3I).

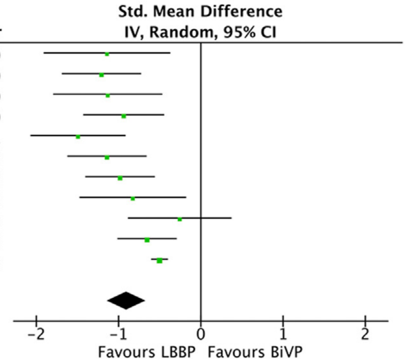
Quality assessment and publication bias

The Newcastle-Ottawa Scale was used to assess the quality of included observational cohort studies and the Cochrane Risk of Bias tool was used for the RCT (Supplemental Figure 4A

A Reduction in QRS duration

Study or Subgroup	LBBBP Mean	LBBBP SD	LBBBP Total	BiVP Mean	BiVP SD	BiVP Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Wang et al, 2020	−60.8	21.4	10	−33	24.6	30	6.0%	−1.14 [−1.90, −0.38]	2020
Wu et al, 2021	−55.4	19.7	32	−25.3	27.2	54	9.4%	−1.21 [−1.68, −0.73]	2020
Guo et al, 2020	−56	19.3	21	−33.5	19.7	21	7.1%	−1.13 [−1.79, −0.48]	2020
Li et al, 2020	−53.7	22.3	27	−22.2	37.5	54	9.3%	−0.94 [−1.42, −0.45]	2020
Liu et al, 2021	−64.1	18.9	27	−32.5	22.3	35	8.1%	−1.49 [−2.06, −0.92]	2021
Rademakers et al, 2022	−43	21.9	40	−13	29.6	40	9.4%	−1.14 [−1.62, −0.67]	2022
Chen et al, 2022	−50.1	20.3	49	−31	18.3	51	10.3%	−0.98 [−1.40, −0.57]	2022
Hua et al, 2022	−48.6	34.7	21	−20.7	31.3	20	7.2%	−0.83 [−1.47, −0.19]	2022
Wang et al, 2022	−43.1	19	20	−38.1	19.2	20	7.4%	−0.26 [−0.88, 0.37]	2022
Ezzeddine et al, 2023	−26.1	32.6	44	6.8	55.1	119	11.3%	−0.65 [−1.01, −0.30]	2023
Vijayaraman et al, 2023	−33	33.9	797	−16	33.8	981	14.5%	−0.50 [−0.60, −0.41]	2023
Total (95% CI)			**1088**			**1425**	**100.0%**	**−0.90 [−1.14, −0.66]**	

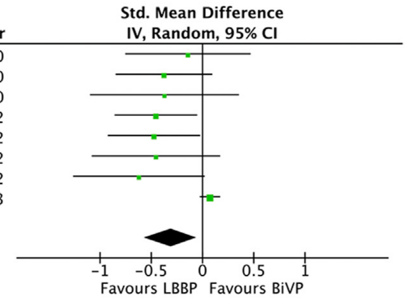
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 35.88$, df = 10 ($P < 0.0001$); $I^2 = 72\%$
Test for overall effect: Z = 7.37 ($P < 0.00001$)



B Reduction in LVEDD

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BiVP Mean	BiVP SD	BiVP Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Guo et al, 2020	−11	11.6	21	−9.4	10.4	21	10.0%	−0.14 [−0.75, 0.46]	2020
Li et al, 2020	−7.2	11.7	27	−3.2	9.9	54	12.9%	−0.38 [−0.84, 0.09]	2020
Wang et al, 2020	−11.1	4.5	10	−8.7	6.8	30	8.2%	−0.37 [−1.09, 0.35]	2020
Chen et al, 2022	−12.6	9	49	−7.4	13.2	51	14.6%	−0.46 [−0.85, −0.06]	2022
Rademakers et al, 2022	−6.9	10.3	40	−1.6	11.8	40	13.4%	−0.47 [−0.92, −0.03]	2022
Hua et al, 2022	−10.6	12	21	−5.3	10.8	20	9.8%	−0.45 [−1.08, 0.17]	2022
Wang et al, 2022	−11.4	1.2	20	−10.64	1.2	20	9.5%	−0.62 [−1.26, 0.02]	2022
Vijayaraman et al, 2023	−4.6	7.8	797	−5.2	8.6	981	21.5%	0.07 [−0.02, 0.17]	2023
Total (95% CI)			**985**			**1217**	**100.0%**	**−0.31 [−0.57, −0.05]**	

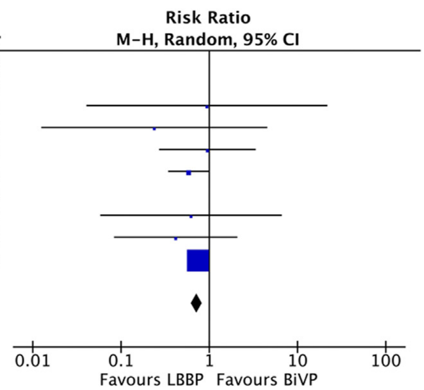
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 21.01$, df = 7 ($P = 0.004$); $I^2 = 67\%$
Test for overall effect: Z = 2.35 ($P = 0.02$)



C Hospitalization for heart failure exacerbation

Study or Subgroup	LBBP Events	LBBP Total	BiVP Events	BiVP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Guo et al, 2020	0	21	0	21		Not estimable	2020
Li et al, 2020	0	27	0	54		Not estimable	2020
Wang et al, 2020	0	10	1	30	0.3%	0.94 [0.04, 21.40]	2020
Wu et al, 2021	0	32	3	54	0.3%	0.24 [0.01, 4.47]	2020
Hua et al, 2022	4	21	4	20	1.6%	0.95 [0.27, 3.30]	2022
Liang et al, 2022	16	154	60	337	9.2%	0.58 [0.35, 0.98]	2022
Wang et al, 2022	0	20	0	20		Not estimable	2022
Rademakers et al, 2022	1	29	2	36	0.4%	0.62 [0.06, 6.51]	2022
Chen et al, 2022	2	49	5	51	1.0%	0.42 [0.08, 2.05]	2022
Vijayaraman et al, 2023	166	797	275	981	87.2%	0.74 [0.63, 0.88]	2023
Total (95% CI)		**1160**		**1604**	**100.0%**	**0.72 [0.62, 0.85]**	
Total events	189		350				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.02$, df = 6 ($P = 0.92$); $I^2 = 0\%$
Test for overall effect: Z = 4.04 ($P < 0.0001$)



D All-cause mortality

Study or Subgroup	LBBP Events	LBBP Total	BiVP Events	BiVP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Wang et al, 2020	0	10	0	30		Not estimable	2020
Hua et al, 2022	1	21	1	20	0.7%	0.95 [0.06, 14.22]	2022
Rademakers et al, 2022	2	40	2	40	1.4%	1.00 [0.15, 6.76]	2022
Wang et al, 2022	0	20	0	20		Not estimable	2022
Chen et al, 2022	0	49	0	51		Not estimable	2022
Vijayaraman et al, 2023	99	797	168	981	97.9%	0.73 [0.58, 0.91]	2023
Total (95% CI)		**937**		**1142**	**100.0%**	**0.73 [0.58, 0.92]**	
Total events	102		171				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 2 ($P = 0.93$); $I^2 = 0\%$
Test for overall effect: Z = 2.71 ($P = 0.007$)

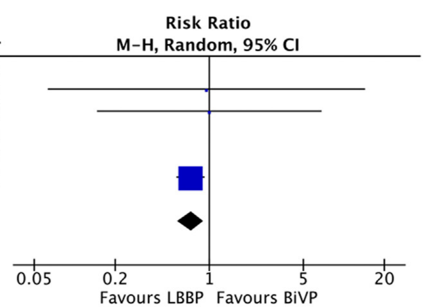


Figure 3 **A:** Reduction in QRS duration. **B:** Reduction in left ventricular end-diastolic diameter (LVEDD). **C:** Hospitalization for heart failure exacerbation. **D:** All-cause mortality. BiVP = biventricular pacing; CI = confidence interval; IV = inverse variance; LBBP = left bundle branch pacing; M-H = Mantel-Haenszel.

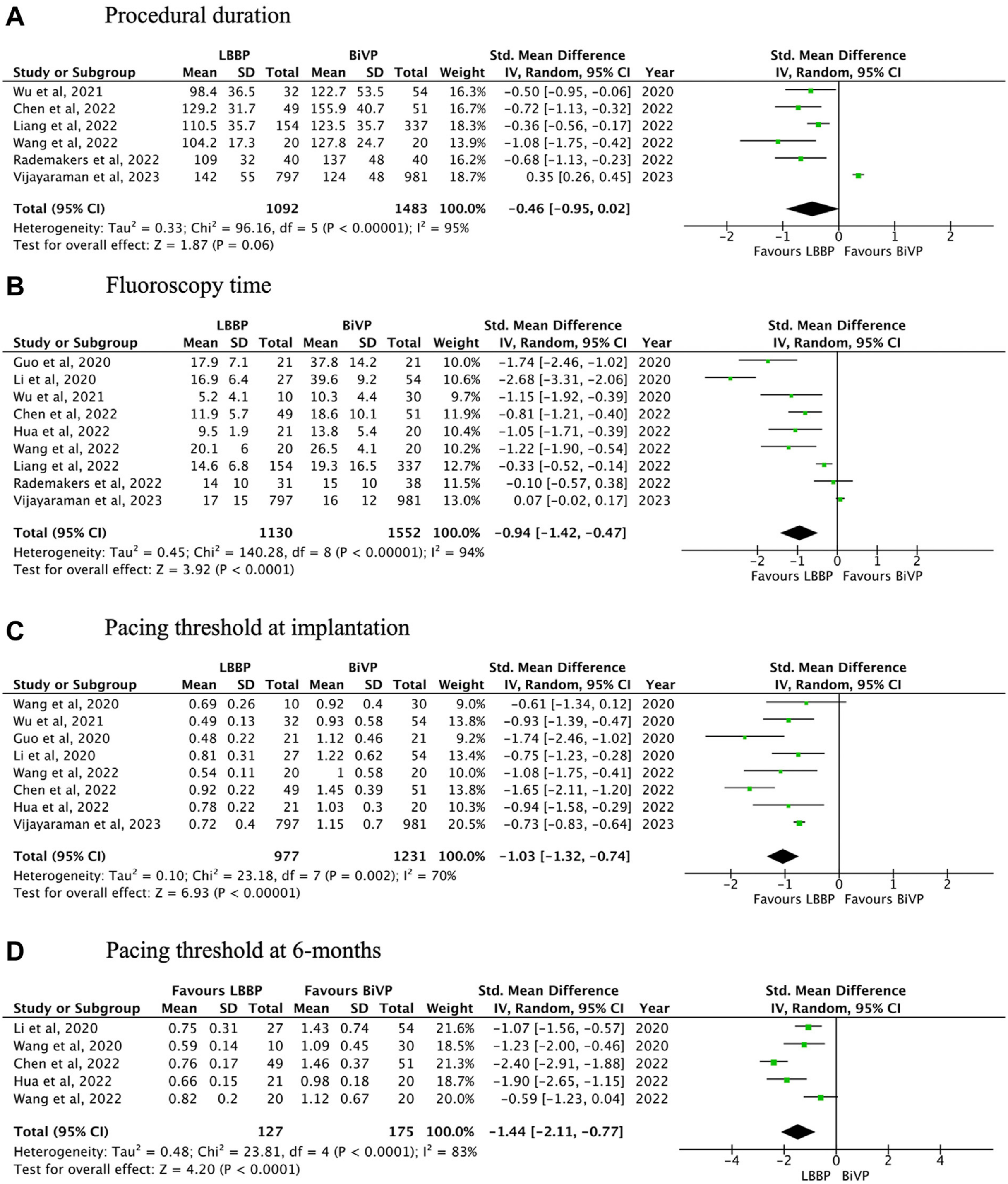


Figure 4 **A:** Procedural duration. **B:** Fluoroscopy time. **C:** Pacing threshold at implantation. **D:** Pacing threshold at 6 months. BiVP = biventricular pacing; CI = confidence interval; IV = inverse variance; LBBP = left bundle branch pacing; M-H = Mantel-Haenszel.

and 4B). Regarding publication bias, visual inspection of the funnel plots for different outcomes did not reveal any significant asymmetry, indicating an overall low risk of publication bias (Supplemental Figure 5A–5E).

Discussion

This meta-analysis compared the efficacy of LBBAP and BiVP in patients with left ventricular systolic failure who met the criteria for CRT. All included studies, except 4, had class I indication for CRT. The remaining 4 studies also included patients with class IIa and IIb indications for CRT.[8,12,13,16] Our analysis identified improvements in both electrical and mechanical functions, as demonstrated by QRSd shortening, increase in LVEF, echocardiographic response, reduction in LVEDD, improvement in NYHA functional class, fewer hospitalizations due to HF exacerbations, and improved survival in patients receiving LBBAP as compared with BiVP. This meta-analysis is an updated analysis that includes 12 studies (3004 patients) and provides more robust evidence than previous meta-analyses that included fewer studies.[18–20] Notably, this is the first meta-analysis to report a mortality benefit with LBBAP over BiVP in patients with systolic HF.

Limited data exist regarding HF hospitalizations and all-cause mortality in patients undergoing LBBAP. Contrary to the individual studies included in our analysis and prior meta-analysis by Tan and colleagues,[21] none of which showed improved HF hospitalization with LBBAP, our comprehensive analysis reveals a clear benefit of LBBAP in reducing HF hospitalizations. These findings align with a recent meta-analysis that also demonstrated a favorable effect of LBBAP over BiVP in reducing HF hospitalizations.[20] Similarly, our meta-analysis demonstrated improved survival in patients undergoing LBBAP as compared with BiVP. Our results are in contrast with the 2 of the included studies that did not find any mortality benefit with LBBAP use.[11,14] This reduction in mortality can be explained by a greater improvement in LVEF and reduction in QRSd with LBBAP. Kalogeropoulos and colleagues[22] reported that recovery of LVEF to ≥40% in patients with systolic HF was associated with an approximately 30% reduction in long-term mortality in patients with systolic HF. Additionally, a reduction in QRSd and QRS area following device therapy has been shown to improve cardiovascular outcomes including ventricular arrhythmias, HF hospitalization, and death.[23]

Longer QRSd is associated with worse prognosis in patients with systolic left ventricular failure.[24] Similarly, the degree of QRSd shortening after CRT signifies a favorable prognosis.[25] Our analysis showed that LBBAP resulted in a greater reduction in QRSd and improvement in LVEF as compared with BiVP. This difference could be explained by the difference in physiologic mechanisms of both techniques. BiVP simultaneously activates both left and right ventricular myocardium and propagates the signal directly through cardiac myocytes, a path 5 to 10 times slower than the His-Purkinje system.[26] In contrast, LBBAP relies on the quicker intrinsic specialized conduction pathways (ie, the left bundle branch of the His-Purkinje system to propagate electric impulse across the left ventricular myocardium). This may result in a shorter QRS complex as pacing signal propagates quickly through intrinsic conduction system. In addition, study by Upadhyay and colleagues[27] reported that up to 64% of LBBBs are situated at the proximal left bundle branch or bundle of His. This means that an LBBAP lead placed distal to site of conduction block could restore normal physiologic QRSd in a majority of patients. In addition, the longer baseline QRSd observed in the LBBAP group that is known to exhibit a favorable electrocardiographic response to CRT may also serve as another potential mechanism for greater reduction of QRSd following LBBAP.[28] The shorter, more physiologic QRSd and left ventricular activation time observed in LBBAP result in a more synchronous and efficient left ventricular contraction, resulting in improvement of LVEF, as seen in our analysis.

Our meta-analysis also demonstrated that LBBAP was associated with a lower pacing threshold at implantation and at 6-month follow-up. Thus, LBBAP required less energy for pacing compared with BiVP, which can help with increased battery life, decreased need for battery replacements, and potential reduction in battery size in future.[29] Additionally, LBBAP required less fluoroscopy during the procedure, as it requires placement of single ventricular lead, resulting in reduced radiation exposure for both patients and staff and decreased use of contrast and thus lower risk of contrast-induced nephropathy, particularly in HF patients who may already have baseline renal dysfunction.[30] Procedural success for LBBAP was 78% to 94% among included studies, which is comparable to the lead implantation success rate of 82% to 92% reported by the MELOS (Multicenter European Left Bundle Branch Area Pacing Outcomes Study) registry.[31]

We acknowledge following potential limitations of this meta-analysis. First, all included studies except 1 had nonrandomized design that could introduce selection bias. Second, few outcomes had high heterogeneity; however, multiple sensitivity analyses were performed. Third, the majority of patients included in the LBBAP group had longer baseline QRSd, and most of the studies involved an Asian population. Historically, both these cohorts respond better to CRT. This might limit the generalizability of our results. Fourth, LBBAP is a newer technique. Limited data were reported regarding cost, complications, and resources implications. Implementing LBBAP as a standard of care may require additional healthcare resources utilization, such as specialized equipment, training sessions for operators, and further studies to establish rigorous patient selection criteria.

Future perspectives

Further investigations are needed to better understand the implications of LBBAP as an alternative to traditional BiVP in left ventricular systolic failure. Ongoing trials such as the Conduction System Pacing Versus Biventricular Resynchronization in Patients With Chronic Heart Failure (PhysioSync-HF) trial (NCT05572736) will provide additional insights regarding LBBAP for HF.

Conclusion

Compared with BiVP, LBBAP was associated with better echocardiographic parameters and NYHA functional status, shorter QRSd, fewer HF hospitalizations, and a lower mortality. Additionally, LBBAP cohort had lower pacing thresholds both at implantation and during follow-up.

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: Michael H. Kim has a consultancy role at Sanofi Aventis. The other authors declare no financial or nonfinancial potential conflict of interest pertaining to this research.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement: This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2023.06.011.

References

1. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. Circulation 2003;108:2596–25603.
2. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895–e1032.
3. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol 2006;21:20–26.
4. Huang W, Su L, Wu S, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. Can J Cardiol 2017;33:1736.e1–1736.e3.
5. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
6. Guo J, Li L, Xiao G, et al. Remarkable response to cardiac resynchronization therapy via left bundle branch pacing in patients with true left bundle branch block. Clin Cardiol 2020;43:1460–1468.
7. Li X, Qiu C, Xie R, et al. Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing. ESC Heart Fail 2020;7:1711–1722.
8. Wang Y, Gu K, Qian Z, et al. The efficacy of left bundle branch area pacing compared with biventricular pacing in patients with heart failure: a matched case-control study. J Cardiovasc Electrophysiol 2020;31:2068–2077.
9. Wu S, Su L, Vijayaraman P, et al. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with his bundle pacing and biventricular pacing. Can J Cardiol 2021;37:319–328.
10. Chen X, Ye Y, Wang Z, et al. Cardiac resynchronization therapy via left bundle branch pacing vs. optimized biventricular pacing with adaptive algorithm in heart failure with left bundle branch block: a prospective, multicenter, observational study. Europace 2022;24:807–816.
11. Hua J, Chen Y, Yu J, et al. Long-term outcomes of left bundle branch area pacing versus biventricular pacing in patients with heart failure and complete left bundle branch block. Heart Vessels 2022;37:1162–1174.
12. Wang Y, Zhu H, Hou X, et al. Randomized trial of left bundle branch vs biventricular pacing for cardiac resynchronization therapy. J Am Coll Cardiol 2022; 80:1205–1216.
13. Liang Y, Xiao Z, Liu X, et al. Left bundle branch area pacing versus biventricular pacing for cardiac resynchronization therapy on morbidity and mortality. 2022. [E-pub ahead of print Dec 2]. Cardiovasc Drugs Ther 2022.
14. Rademakers LM, van den Broek JLPM, Bracke FA. Left bundle branch pacing as an alternative to biventricular pacing for cardiac resynchronisation therapy. Neth Heart J 2023;31:140–149.
15. Liu W, Hu C, Wang Y, et al. Mechanical synchrony and myocardial work in heart failure patients with left bundle branch area pacing and comparison with biventricular pacing. Front Cardiovasc Med 2021;8:727611.
16. Ezzeddine FM, Pistiolis SM, Pujol-Lopez M, et al. Outcomes of conduction system pacing for cardiac resynchronization therapy in patients with heart failure: a multicenter experience. Heart Rhythm 2023;20:863–871.
17. Vijayaraman P, Sharma PS, Cano Ó, et al. Comparison of left bundle-branch area pacing to biventricular pacing in candidates for resynchronization therapy. J Am Coll Cardiol 2023;82:228–241.
18. Liu J, Sun F, Wang Z, et al. Left bundle branch area pacing vs. biventricular pacing for cardiac resynchronization therapy: a meta-analysis. Front Cardiovasc Med 2021;8:669301.
19. Hua J, Wang C, Kong Q, et al. Comparative effects of left bundle branch area pacing, His bundle pacing, biventricular pacing in patients requiring cardiac resynchronization therapy: a network meta-analysis. Clin Cardiol 2022;45:214–2123.
20. Parlavecchio A, Vetta G, Caminiti R, et al. Left bundle branch pacing versus biventricular pacing for cardiac resynchronization therapy: a systematic review and meta-analysis. Pacing Clin Electrophysiol 2023;46:432–439.
21. Tan JL, Lee JZ, Terrigno V, et al. Outcomes of left bundle branch area pacing for cardiac resynchronization therapy: an updated systematic review and meta-analysis. CJC Open 2021;3:1282–1293.
22. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. JAMA Cardiol 2016;1:510–518.
23. Okafor O, Zegard A, van Dam P, et al. Changes in QRS area and QRS duration after cardiac resynchronization therapy predict cardiac mortality, heart failure hospitalizations, and ventricular arrhythmias. J Am Heart Assoc 2019;8:e013539.
24. Holmström L, Haukilahti A, Vähätalo J, et al. Electrocardiographic associations with myocardial fibrosis among sudden cardiac death victims. Heart 2020; 106:1001–1006.
25. Jastrzebski M, Baranchuk A, Fijorek K, et al. Cardiac resynchronization therapy-induced acute shortening of QRS duration predicts long-term mortality only in patients with left bundle branch block. Europace 2019;21:281–289.
26. Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation 1970;41:899–912.
27. Upadhyay GA, Cherian T, Shatz DY, et al. Intracardiac delineation of septal conduction in left bundle-branch block patterns. Circulation 2019;139:1876–1888.
28. Poole JE, Singh JP, Birgersdotter-Green U. QRS duration or QRS morphology: what really matters in cardiac resynchronization therapy? J Am Coll Cardiol 2016;67:1104–1117.
29. Lau CP, Siu CW. Pacing technology: advances in pacing threshold management. J Zhejiang Univ Sci B 2010;11:634–638.
30. Tester GA, Noheria A, Carrico HL, et al. Impact of radiocontrast use during left ventricular pacemaker lead implantation for cardiac resynchronization therapy. Europace 2012;14:243–248.
31. Jastrzębski M, Kiełbasa G, Cano O, et al. Left bundle branch area pacing outcomes: the multicentre European MELOS study. Eur Heart J 2022; 43:4161–4173.