Left bundle branch area pacing for heart failure patients requiring cardiac resynchronization therapy: a meta-analysis

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March 1, 2023

Abstract

Background: Left bundle area branch pacing (LBBP) is a novel conduction system pacing method to achieve effective physiological pacing and an alternative to cardiac resynchronization therapy (CRT) with biventricular pacing (BVP) for patients with heart failure and reduced ejection fraction (HFrEF). **Objective:** To review current data comparing BVP and LBBP in patients with HFrEF and indication CRT. **Methods:** We searched PubMed/Medline, Web of Science, and Cochrane Library from the inception of the database to November 2022. All studies that compared LBBP with BVP in patients with HFrEF and indications of CRT were included. Two reviewers performed the study selection, data abstraction, and risk of bias assessment. We calculated risk ratios with the Mantel-Haenszel method and mean difference with inverse variance using random effect models. We assessed heterogeneity using the I^2 index, with $I^2 > 50\%$ indicating significant heterogeneity. **Results:** Ten studies (9 observational studies and 1 randomized controlled trial; 616 patients; 15 centers) published between 2020 and 2022 were included. We observed a shorter fluoroscopy time [mean difference (MD) 9.68, 95% CI 4.49-14.87, I^2=95%, $P<0.01$, minutes] as well as a shorter procedure time (MD 33.68, 95% CI 17.80-49.55, I^2=73%, $P<0.01$, minutes) during implantation of LBBP CRT compared to conventional BVP CRT. LBBP was shown to have a greater reduction in QRSd (MD 25.13, 95%CI 20.06-30.20, I^2= 51%, $P<0.01$, milliseconds) a greater left ventricular ejection fraction (LVEF) improvement (MD 5.80, 95% CI 4.81-6.78, I^2=0%, $P<0.01$, percentage) and a greater ventricular end-diastolic diameter (LVEDD) reduction (MD 2.11, 95% CI 0.12-4.10, I^2=18%, P=0.04, millimeter). There was a greater improvement in New York Heart Association function (NYHA) class with LBBP (MD 0.37, 95% CI 0.05-0.68, I^2=61%, P=0.02).LBBP was also associated with a lower risk of a composite of heart failure hospitalizations and all-cause mortality [Risk ratio (RR) 0.48, 95% CI 0.25-0.90, I^2=0%, p=0.02] driven by reduced heart failure hospitalizations (RR 0.39, 95% CI 0.19-0.82, I^2=0%, p=0.01). However, all-cause mortality rates were low in both groups (1.52% vs. 1.13%) and similar (RR 0.98, 95%CI 0.21-4.68, I^2=0%, p=0.87). **Conclusion:** Compared to BVP, LBBP is associated with, a greater improvement in LV systolic function, and a lower rate of heart failure-related hospitalization. Dedicated randomized controlled trials and larger patient populations are needed to further elucidate the long-term safety and efficacy of LBBP CRT.

Introduction

Heart failure is a global health problem, with over 64 million patients worldwide and over one million hospitalizations annually in the United States alone[1, 2]. Heart failure with reduced ejection fraction (HFrEF) can be associated withleft and right ventricle desynchrony, which is hemodynamically disadvantageous and related to increased mortality[3]. Cardiac resynchronization therapy (CRT) is an established effective treatment for selected patients with HFrEF and , abnormal ventricular conduction resulting in wide QRS complex[4-8]. Conventionally, CRT is achieved by right ventricular and left ventricular pacing via coronary sinus (biventricular pacing, BVP). However, the success rate is highly related to coronary sinus anatomy (small caliber target vessels, tortuosity, and coronary sinus valves), and up to 30% of patients do not adequately respond to BVP CRT[5, 9, 10].

Conduction system pacing (CSP), including His bundle pacing (HBP) and left bundle branch area pacing (LBBP), was introduced in an attempt to mitigate these challenges by physiologically pacing the His-Purkinje system. His bundle pacing, however, requires a higher pacing threshold , and may not correct left bundle branch block (LBBB) below the level of His bundle[11-14]. LBBP was first introduced in 2017 in humans and has emerged as a feasible and safe alternative to BVP to achieve cardiac resynchronization with accumulating supporting data[15-18]. Hence, the objective of this study was to conduct a systematic review and meta-analysis of current studies to compare the efficacy of LBBP and BVP CRT in HFrEF patients.

Method

Search strategy

This systemic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[19].

A literature search of PubMed/Medline, Web of Science, and Cochrane Library were performed from the inception of the database to November 30, 2022, was performed. We also searched ongoing trials at clinical-trials.gov and controlled-trials.com.

Study and Patient Selection

Institutional Review Board review is not required for meta-analyses because only de-identified, publically-available data were used and no human subjects involvement[20]. We included all studies that: (1) reported permanent LBBP, (2) were in English, (3) included patients [?]18 years old, (4) had a previous diagnosis of HFrEF, (5) with an indication for CRT, (6)compared with BVP. Case reports, abstracts, editorials/letters, reviews, and studies with fewer than 5 patients were excluded. The study contained the most data included if multiple publications were generated from the same patient cohort. Two authors (C Jin and Q Dai) independently extracted data from the selected studies. A third reviewer was consulted (P Li) was consulted in the instance of a disagreement.

Meta-analysis

Heterogeneity was assessed using the I^2 index, with $I^2 > 50\%$ indicating significant heterogeneity[21]. Continuous variables of interest were described with means, standard deviations, and sample size to estimate confidence intervals (CIs). Dichotomous variables were described using numerators and denominators to estimate proportions and CIs. The random effects model was used to estimate summary statistics for variables of interest, where individual studies were treated as a random variable. To estimate the difference in variables of interest over time, only publications that contained both baseline and follow-up means and standard deviations were used. We calculated risk ratios using the Mantel-Haenszel method and the mean difference with inverse variance. All statistical analyses were performed using Review Manager 5.3 software (Cochrane).

Result

Main findings

A total of 1,604 publications were identified, and 1,225 were screened after excluding duplicates. Twenty full-text articles were assessed for eligibility after 1,205 were excluded with abstract and title screening. After the assessment of full-text articles, 10 publications were excluded for: no LBBP group data separately reported from HBP/CSP group, no human study, published study protocol without data, and no control group with BVP. Ten studies (9 observational studies and 1 randomized controlled trial) were included (Figure 1).

The included studies comprised 616 patients across 15 centers, enrolled from December 2012 to June 2021, with the median being 2019 (Table 1). Patient baseline characteristics were reported in all studies (Table 2).

Left ventricular ejection fraction (LVEF) improvement was reported in all 10 studies. Compared to BVP, LBBP was associated with greater improvement (MD 5.80, 95% CI 4.81-6.78, I^2=0%, P<0.01, percentage) at the end of follow-up period. Left ventricular end-diastolic diameter (LVEDD) reduction was also higher in the LBBP group (MD 2.11, 95% CI 0.12-4.10, I^2=18%, P=0.04, millimeter). There was a greater improvement in New York Heart Association function (NYHA) class with LBBP (MD 0.37, 95% CI 0.05-0.68, I^2=61%, P=0.02). Figure 2.

A composite outcome of heart failure-related hospitalization (HFH) and all-cause mortality was also lower with LBBP compared to BVP CRT [Risk ratio (RR) 0.48, 95% CI 0.25-0.90, I^2=0%, p=0.02] driven mainlyby heart failure hospitlizations (HFH) reduction (RR 0.39, 95% CI 0.19-0.82, I^2=0%, p=0.01). However, all-cause mortality rates were low in both groups (1.52% vs. 1.13%) and similar (RR 0.98, 95%CI 0.21-4.68, I^2=0%, p=0.87). Figure 3.

Pacing outcomes

LBBP was associated with a lower chronic pacing threshold (MD 0.56, 95% CI 0.47-0.64, I^2=39%, P<0.01, volts) and a lower impedance (MD 81.02, 95% CI 24.65-137.40, I^2=69%, P<0.01, ohm) on follow up.

All publications reported reduction of QRS duration (QRSd) with LBBP; however, 1 study did not report the data for BVP. LBBP was shown to have a greater reduction in QRSd (MD 25.13, 95%CI 20.06-30.20, I^2= 51%, P<0.01, milliseconds). Figure 4.

Procedure duration and fluororoscopy time

We observed a shorter fluoroscopy time [mean difference (MD) 9.68, 95% CI 4.49-14.87, I^2=95%, P<0.01, minutes] as well as a shorter procedure time (MD 33.68, 95% CI 17.80-49.55, I^2=73%, P<0.01, minutes) during implantation of LBBP CRT compared to BVP CRT. Figure 5.

Procedure success rate and complications

All studies exclusively used a fixed curve sheath (C315 HIS, Medtronic Inc., Minneapolis, MN, USA) and the Select Secure pacing lead (model 3830, Medtronic Inc., Minneapolis, MN, USA) except for Wu *et al.,*in whose study also used a deflectable delivery system (C304, Medtronic Inc., Minneapolis, MN, USA)[22]. The overall implant success rate was 88.3%, ranging from 77.5% to 98%. The most common reason for implant failure was difficulty/inability to penetrate the septum, representing 41.67% of all failures.

Eight studies reported procedure-related complications (Table 3). There were 15 complications observed in 245 patients. The most commonly reported complication was transient right bundle branch injury (14 total complications). The only other complication reported was one case of lead dislodgement.

Discussion

We systematically reviewed 10 original studies comparing LBBP and BVP CRT, which were comprised of patients from 15 centers around the world. This is the largest, most up-to-date systemic review and meta-analysis to demonstrate the effectiveness and safety of LBBP CRT to our knowledge. We found 1) performing LBBP compared to BVP is associated with shorter procedure and fluoroscopy time. 2) LBBP is associated with a greater reduction in QRSd and greater LVEF improvement. 3) A composite of HFH hospitalization and all-cause mortality had a greater reduction with LBBP as well as a greater improvement in overall function. However, the reported mortality was low and there was no difference in all-cause mortality alone. The overall implant success rate was approaching 90% and complication rates were low. Comparison of implant success rate of LBBP and BVP was not performed because most included studies only included historical cohor for BVP which only consist of successfully implanted cases.

Since the introduction of LBBP, multiple studies have explored the feasibility, safety, and clinical comparison of other existing pacing methods in various indications including heart failure requiring CRT[23-30]. A previous study had shown LBBP, if optimized AV delay, can achieve better interventricular synchrony compared to BVP in ex-vivo heart models[18]. A retrospective cohort of 34 patients who underwent LBBP CRT with a follow-up period of 12 months observed a significant decrease in QRSd, and improvement in LVEF, LVEDD, NYHA classification, brain natriuretic peptide (BNP) level, and 6-minute walk test (6MWT). The success rate of LBBP in the cohort was 100% with stable pacing capture threshold and R-wave amplitude at the end of 12 months follow-up[23]. Another study that compared CSP (87 HBP and 171 LBBP) and BVP also noted a significantly narrower QRSd, greater LVEF improvement, and lower composite of HFH and mortality[31].

Our findings were also consistent with recently published Left bundle branch area pacing outcomes: the multicenter European (MELOS) study and the Left Ventricular Activation Time Shortening With Conduction System Pacing vs Biventricular Resynchronization Therapy (LEVEL-AT) trial[32, 33]. The MELOS study was a registry-based observational study comprised of 2,533 patients attempted LBBP with 27.5% of whom had an indication from heart failure. The reported implant success rate in heart failure indication was 82.2%, which was similar to our finding. The overall complication rate of LBBP in the MELOS study was 11.68% mainly driven by lead complications including left ventricle perforation and dislodgement, which was much higher than our finding. The LEVEL-AT trial was a randomized controlled noninferiority trial that compared ventricular synchrony in CSP including HBP and LBBP with BVP in HFrEF patients with indications for CRT. Of the 35 CSP patients included, the majority of them were allocated to LBBP (80%). It showed ventricular synchronization achieved by CSP was non-inferior to BVP. There was a trend towards a greater QRSd reduction and a lower composite of HFH or mortality after a 6-month follow-up period but no difference in LVEF improvement. The implant success rate of LBBP was 82% which was similar to our finding. The high crossover rate (8/35 crossed over from CSP to BVP and 2/35 corssed over from CVP to CSP) and small sample size of the trial might limit further interpretation of results.

The improvement in interventricular synchrony by EKG findings (QRSd) and clinical outcomes we had observed may not be limited to HFrEF patients but to patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with midrange ejection fraction (HFmrEF), as one recent study suggests[27]. Echocardiographic parameters of interventricular synchrony assessment including interventricular mechanical delay (defined as difference between the pre-ejection intervals from QRS onset to the beginning of ventricular ejection at pulmonary and aortic valve level), the regional time intervals of left ventricular 12 segments between the onset of the QRS complex and the peak of systolic myocardial velocity during the ejection phase (Ts), standard deviation of Ts (Ts-SD) and peak strain dispersion had greater improvement with LBBP compared to BVP but they were only studied in two of included studies[34, 35].

Despite LBBP having greater hemodynamic improvement as well as lower HFH in our analysis, we did not observe a clear benefit in all-cause mortality compared to BVP CRT, which can be attributed to the short follow-up period by most studies included. This was evidenced by the lower-than-expected mortality rate. The short follow-up can also potentially preclude the delayed effect in mortality benefit by improved interventricular synchrony and hemodynamics.

In patients with failed BVP due to CS lead failure or nonresponsive to BVP, it has been demonstrated that LBBP can be a safe and viable alternative [36]. In the 2021 ESC Guidelines on Cardiac Pacing and CRT, there was no official recommendation for LBBP pending more evidence for long-term safety and efficacy from randomized trials[37].

With shorter procedural and fluoroscopy time and possible improved clinical outcomes, LBBP is a promising and emerging alternative to BVP. Further studies, especially randomized controlled trials are required to demonstrate the long-term safety and efficacy of LBBP, and further, elucidate the clinical benefit of LBBP CRT. ChiCTR200028726 is an ongoing single-center randomized controlled noninferiority trial aiming to recruit 180 patients with HFrEF and indication of CRT[38]. Patients will be randomized at a 1:1 ratio to LBBP or BVP CRT. The recruitment period concluded in December 2022. The completion of this trial and other ongoing trials can potentially better demonstrate the role of LBBP CRT.

Limitations

Our meta-analysis had several limitations: First, only one study included in our analysis was a randomized control trial and the other 9 were observational studies, which can potentially introduce confounding factors and compromise the interpretation of results. Second, all 10 studies had a relatively small sample size and short follow-up period, limiting the power to assess the long-term outcome and safety of LBBP. Third, the definition and classification of data reporting in different studies varies (e.g. definition of implant success, use of BNP versus N-terminal-pro BNP, etc.) thereby limiting further data extraction and analysis.

Conclusion

Compared to BVP, LBBP is associated with, a greater improvement in LV systolic function, and a lower rate of heart failure-related hospitalization from this meta-analysis. Dedicated large randomized controlled trials are needed to further elucidate the comparative long-term efficacy and safety of LBBP CRT vs. BIV CRT.

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Table 1. Included studies in the meta-analysis

Publication	Year	Study type	Center	Patient Number (enrollment) BVP	Patient Number (enrollment) LBBP	Patient Number (as treated) BVP	Patient Number (as treated) LBBP	Follow-up (months)	Re
Guo *et al.*	2020	Observational	Single	21	24	21	21	6	As
Li *et al.*	2020	Observational	Multiple	54	37	54	27	6	As
Wang *et al.*	2020	Observational	Single	30	10	30	10	6	As
Wu *et al.*	2020	Observational	Single	49	30	54	32	12	As

Liu *et al.*	2021	Observational	Multiple	28	34	35	27	6	As
Zu *et al.*	2021	Observational	Single	22	10	19	13	12	As
Chen *et al.*	2022	Observational	Multiple	56	50	51	49	12	As
Hua *et al.*	2022	Observational	Single	20	21	20	21	24	As
Rademakers *et al.*	2022	Observational	Single	40	40	38	31	6	Eu
Wang *et al.*	2022	Randomized controlled trial	Multiple	20	20	18	16	6	As

BVP, biventricular pacing with coronary sinus lead; LBBP, left bundle branch pacing.

Table2. Baseline Characteristics of LBBP Patients in Included Studies

Study	Inclusion criteria	Age (Years)	Gender (M
Guo *et al.*2020	LBBB, LVEF[?]35%, NYHA functional class II to IV	66.1 ± 9.7	42.9
Li *et al.* 2020	LBBB, LVEF [?] 35%, NYHA functional class II to IV	56.8 ± 10.1	59.5
Wang *et al.* 2020	Sinus rhythm, LBBB, LVEF[?]35%, NYHA functional class II to IV	64.80 ± 7.25	90
Wu *et al.* 2020	LBBB, LVEF[?]40%, NYHA functional class II to IV, failed HBP	67.2 ± 13	43.8
Liu *et al.* 2021	LBBB, LVEF[?]35%, NYHA functional class II to IV	65.5 ± 8.8	51.9
Zu *et al.* 2021	QRSd>150 ms, LBBB, LVEF<35%, NYHA functional class II to IV	61.77 ± 12.37	61.5
Chen *et al.* 2022	QRSd>150 ms, LBBB, LVEF<35%, NYHA functional class II to IV	67.14± 8.88	49.98
Hua *et al.* 2022	QRSd>150 ms, LBBB, LVEF<35%, NYHA functional class II to IV	65.50 ± 6.91	71.43
Rademakers *et al.* 2022	LBBB, LVEF[?]35%, NYHA functional class II to IV	68± 13	48
Wang *et al.* 2022	LBBB, LVEF[?]40%, NYHA functional class II to IV, NICM	62.3 ±11.2	35

LBBP, left bundle branch area pacing; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; ICM, ischemic cardiomyopathy; NICM, non- ischemic cardiomyopathy; HBP, His bundle pacing; N/A, not available.

Table 3. Complications related to LBBP procedure

Study	Right bundle branch injury	Lead/ device infection	Coronary artery injury	Phrenic nerve stimulation	Chronic capture threshold elevation	Lead dislodgement	Perforation	Embolism	Pn
Guo *et al.*2020	4 (All self-resolved within 24 hours)	0	0	0	0	0	0	0	0
Li *et al.* 2020	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/

Wang *et al.* 2020	0	0	0	0	0	0	0	0	0
Wu *et al.* 2020	0	0	0	0	0	0	0	0	0
Liu *et al.* 2021	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/
Zu *et al.* 2021	0	0	0	0	0	0	0	0	0
Chen *et al.* 2022	10 (9 cases recovered prior to discharge)	0	0	0	0	0	0	0	0
Hua *et al.* 2022	0	0	0	0	0	0	0	0	0
Rademakers *et al.* 2022	0	0	0	0	0	0	0	0	0
Wang *et al.* 2022	0	0	0	0	0	1	0	0	0

LBBP, left bundle branch area pacing.

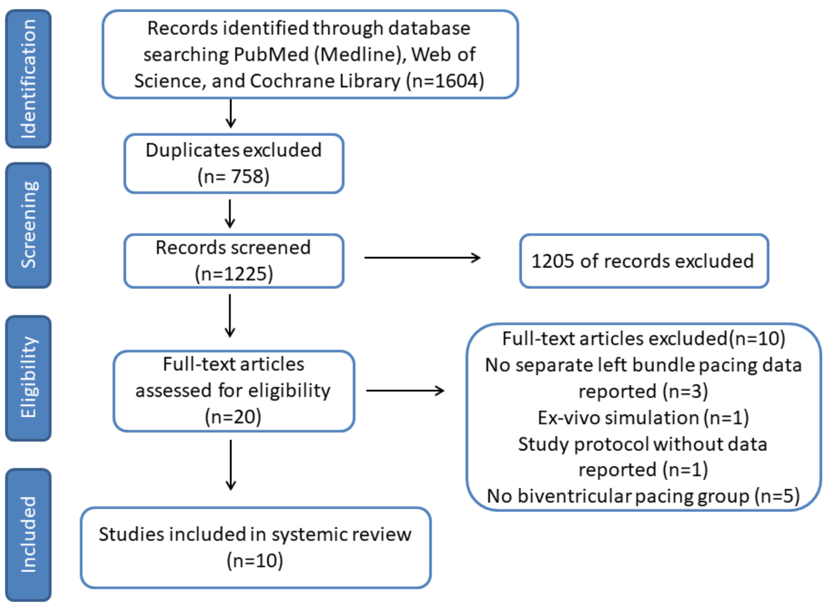


Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

Depiction of selection of studies.

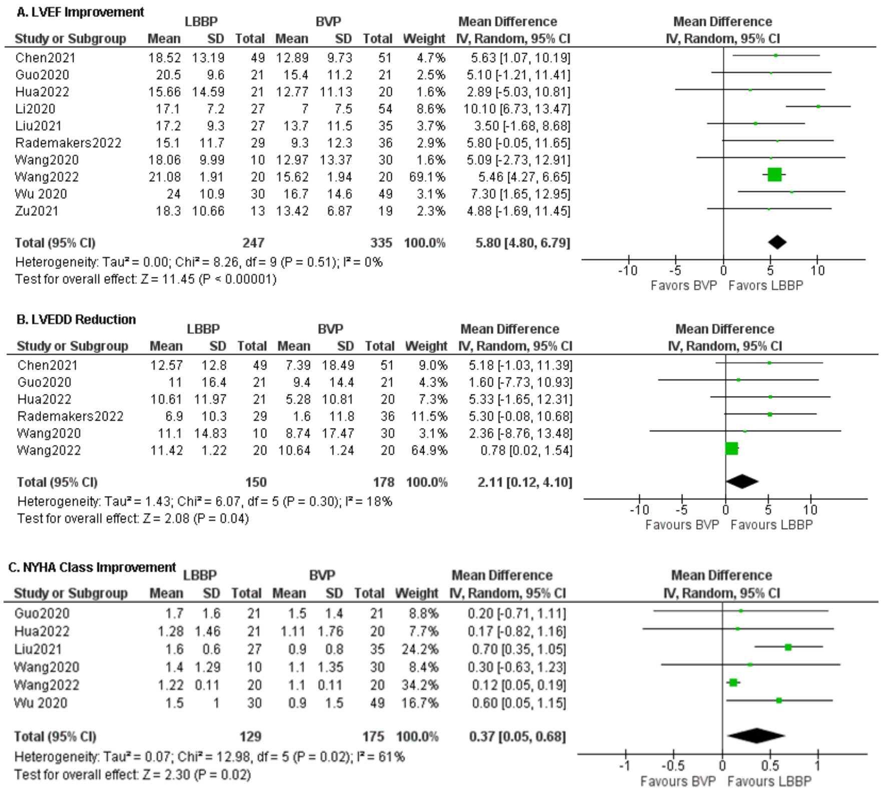


Figure 2: (A) Left ventricular ejection fraction improvement from baseline to longest follow-up, percent. (B) Left ventricular end-diastolic diameter reduction from baseline to longest follow-up, millimeter. (C) Improvement of NYHA function class. LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; SD, standard deviation; CI, confidence interval; LBBP, left bundle branch area pacing; BVP, biventricular pacing.

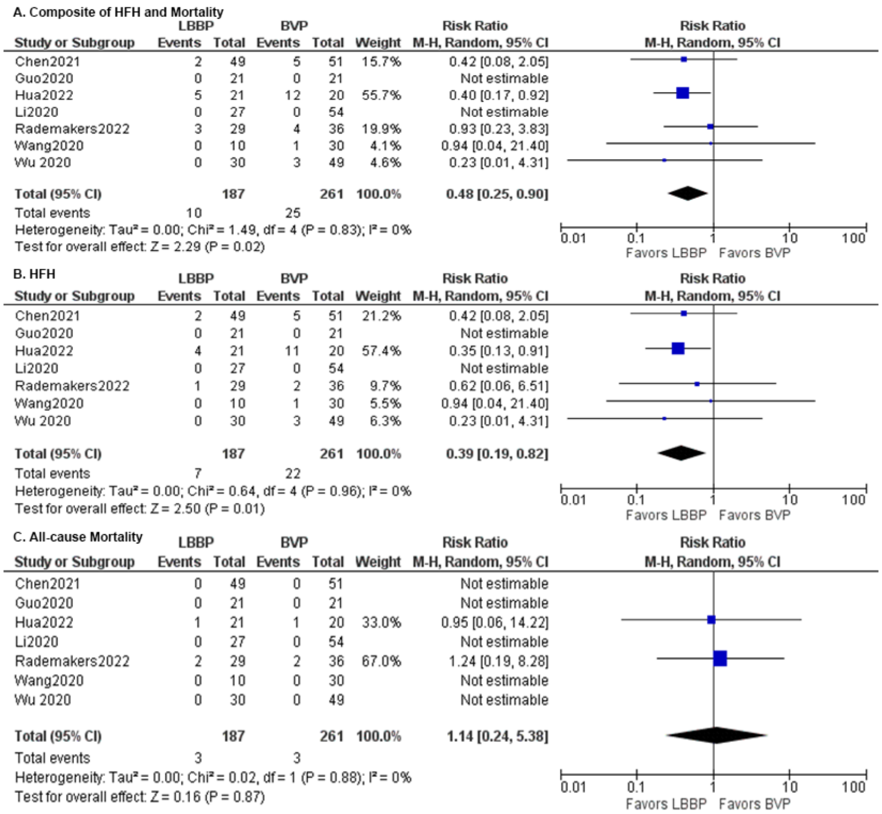


Figure 3: (A) Composite outcome of heart failure-related hospitalizations and all-cause mortality, number of event. (B) Heart failure-related hospitalizations, number of event. (C) All-cause mortality, number of event. HFH, heart failure-related hospitalizations; CI, confidence interval; LBBP, left bundle branch area pacing; BVP, biventricular pacing; M-H, Mantel-Haenszel method.

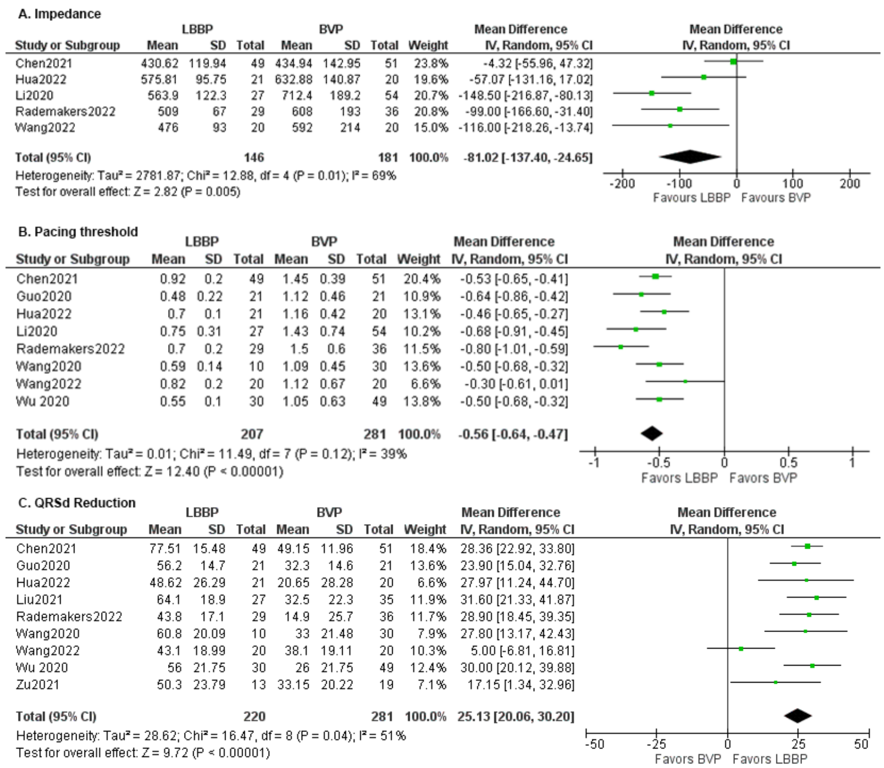


Figure 4: (A) Pacing impedance at longest follow-up, ohm. (B) Pacing threshold at longest follow-up, volts. (C) QRS duration reduction, millisecond. QRSd, QRS duration; CI, confidence interval; LBBP, left bundle branch area pacing; BVP, biventricular pacing; SD, standard deviation.

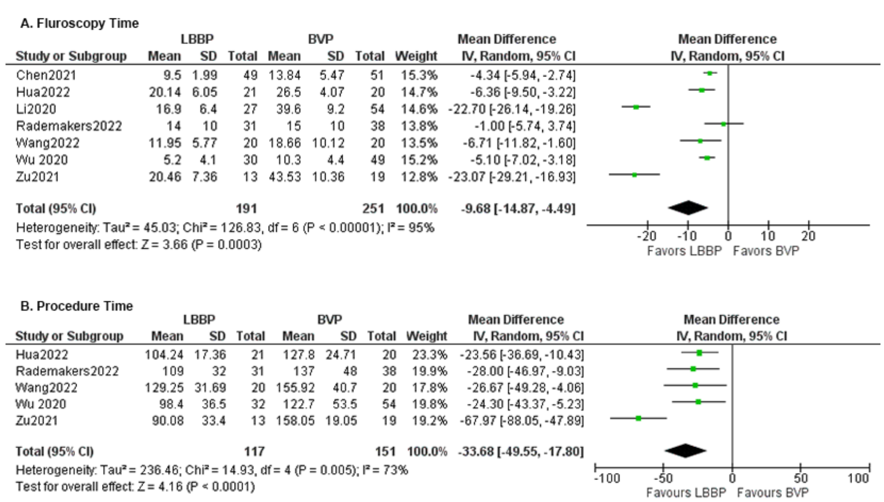
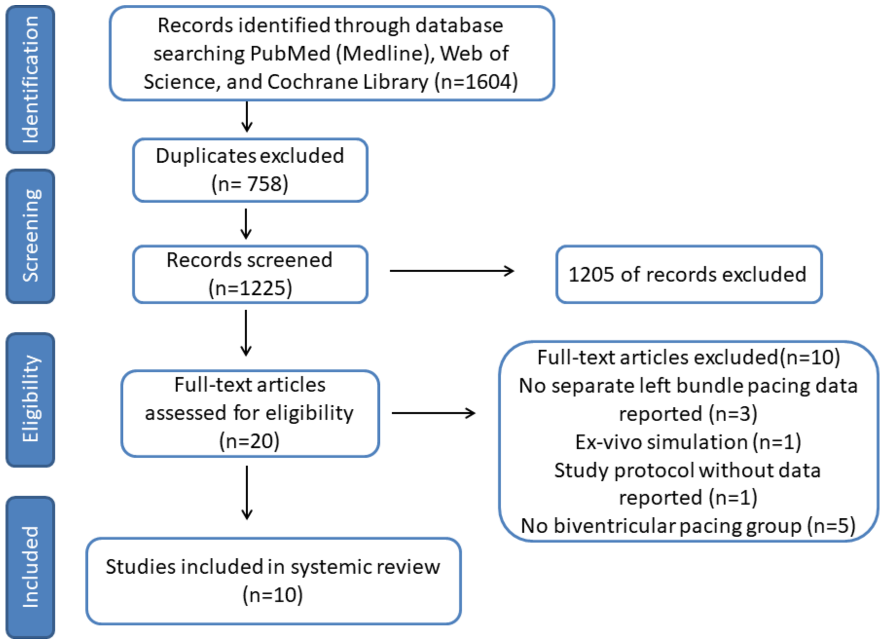


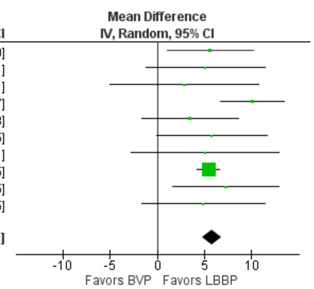
Figure 5: (A) Fluoroscopy time, minute. (B) Procedure time, minute. SD, standard deviation; CI, confidence interval; LBBP, left bundle branch area pacing; BVP, biventricular pacing.



A. LVEF Improvement

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BVP Mean	BVP SD	BVP Total	Weight	Mean Difference IV, Random, 95% CI
Chen2021	18.52	13.19	49	12.89	9.73	51	4.7%	5.63 [1.07, 10.19]
Guo2020	20.5	9.6	21	15.4	11.2	21	2.5%	5.10 [-1.21, 11.41]
Hua2022	15.66	14.59	21	12.77	11.13	20	1.6%	2.89 [-5.03, 10.81]
Li2020	17.1	7.2	27	7	7.5	54	8.6%	10.10 [6.73, 13.47]
Liu2021	17.2	9.3	27	13.7	11.5	35	3.7%	3.50 [-1.68, 8.68]
Rademakers2022	15.1	11.7	29	9.3	12.3	36	2.9%	5.80 [-0.05, 11.65]
Wang2020	18.06	9.99	10	12.97	13.37	30	1.6%	5.09 [-2.73, 12.91]
Wang2022	21.08	1.91	20	15.62	1.94	20	69.1%	5.46 [4.27, 6.65]
Wu 2020	24	10.9	30	16.7	14.6	49	3.1%	7.30 [1.65, 12.95]
Zu2021	18.3	10.66	13	13.42	6.87	19	2.3%	4.88 [-1.69, 11.45]
Total (95% CI)			**247**			**335**	**100.0%**	**5.80 [4.80, 6.79]**

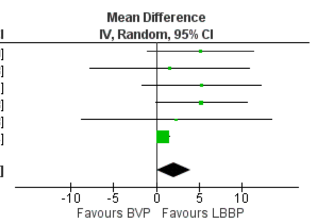
Heterogeneity: Tau² = 0.00; Chi² = 8.26, df = 9 (P = 0.51); I² = 0%
Test for overall effect: Z = 11.45 (P < 0.00001)



B. LVEDD Reduction

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BVP Mean	BVP SD	BVP Total	Weight	Mean Difference IV, Random, 95% CI
Chen2021	12.57	12.8	49	7.39	18.49	51	9.0%	5.18 [-1.03, 11.39]
Guo2020	11	16.4	21	9.4	14.4	21	4.3%	1.60 [-7.73, 10.93]
Hua2022	10.61	11.97	21	5.28	10.81	20	7.3%	5.33 [-1.65, 12.31]
Rademakers2022	6.9	10.3	29	1.6	11.8	36	11.5%	5.30 [-0.08, 10.68]
Wang2020	11.1	14.83	10	8.74	17.47	30	3.1%	2.36 [-8.76, 13.48]
Wang2022	11.42	1.22	20	10.64	1.24	20	64.9%	0.78 [0.02, 1.54]
Total (95% CI)			**150**			**178**	**100.0%**	**2.11 [0.12, 4.10]**

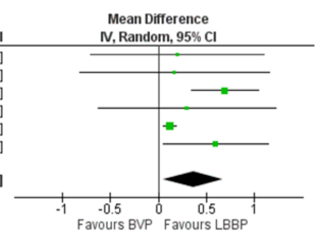
Heterogeneity: Tau² = 1.43; Chi² = 6.07, df = 5 (P = 0.30); I² = 18%
Test for overall effect: Z = 2.08 (P = 0.04)



C. NYHA Class Improvement

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BVP Mean	BVP SD	BVP Total	Weight	Mean Difference IV, Random, 95% CI
Guo2020	1.7	1.6	21	1.5	1.4	21	8.8%	0.20 [-0.71, 1.11]
Hua2022	1.28	1.46	21	1.11	1.76	20	7.7%	0.17 [-0.82, 1.16]
Liu2021	1.6	0.6	27	0.9	0.8	35	24.2%	0.70 [0.35, 1.05]
Wang2020	1.4	1.29	10	1.1	1.35	30	8.4%	0.30 [-0.63, 1.23]
Wang2022	1.22	0.11	20	1.1	0.11	20	34.2%	0.12 [0.05, 0.19]
Wu 2020	1.5	1	30	0.9	1.5	49	16.7%	0.60 [0.05, 1.15]
Total (95% CI)			**129**			**175**	**100.0%**	**0.37 [0.05, 0.68]**

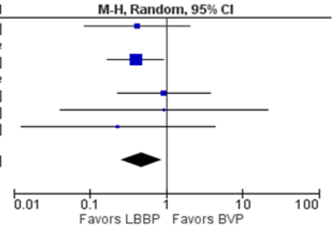
Heterogeneity: Tau² = 0.07; Chi² = 12.98, df = 5 (P = 0.02); I² = 61%
Test for overall effect: Z = 2.30 (P = 0.02)



A. Composite of HFH and Mortality

Study or Subgroup	LBBP Events	LBBP Total	BVP Events	BVP Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen2021	2	49	5	51	15.7%	0.42 [0.08, 2.05]
Guo2020	0	21	0	21		Not estimable
Hua2022	5	21	12	20	55.7%	0.40 [0.17, 0.92]
Li2020	0	27	0	54		Not estimable
Rademakers2022	3	29	4	36	19.9%	0.93 [0.23, 3.83]
Wang2020	0	10	1	30	4.1%	0.94 [0.04, 21.40]
Wu 2020	0	30	3	49	4.6%	0.23 [0.01, 4.31]
Total (95% CI)		**187**		**261**	**100.0%**	**0.48 [0.25, 0.90]**
Total events	10		25			

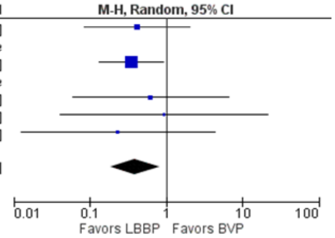
Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 4 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)



B. HFH

Study or Subgroup	LBBP Events	LBBP Total	BVP Events	BVP Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen2021	2	49	5	51	21.2%	0.42 [0.08, 2.05]
Guo2020	0	21	0	21		Not estimable
Hua2022	4	21	11	20	57.4%	0.35 [0.13, 0.91]
Li2020	0	27	0	54		Not estimable
Rademakers2022	1	29	2	36	9.7%	0.62 [0.06, 6.51]
Wang2020	0	10	1	30	5.5%	0.94 [0.04, 21.40]
Wu 2020	0	30	3	49	6.3%	0.23 [0.01, 4.31]
Total (95% CI)		**187**		**261**	**100.0%**	**0.39 [0.19, 0.82]**
Total events	7		22			

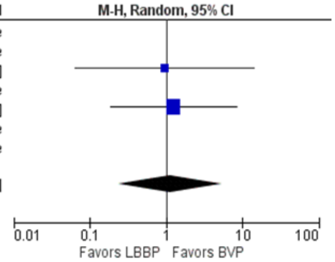
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 4 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)



C. All-cause Mortality

Study or Subgroup	LBBP Events	LBBP Total	BVP Events	BVP Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen2021	0	49	0	51		Not estimable
Guo2020	0	21	0	21		Not estimable
Hua2022	1	21	1	20	33.0%	0.95 [0.06, 14.22]
Li2020	0	27	0	54		Not estimable
Rademakers2022	2	29	2	36	67.0%	1.24 [0.19, 8.28]
Wang2020	0	10	0	30		Not estimable
Wu 2020	0	30	0	49		Not estimable
Total (95% CI)		**187**		**261**	**100.0%**	**1.14 [0.24, 5.38]**
Total events	3		3			

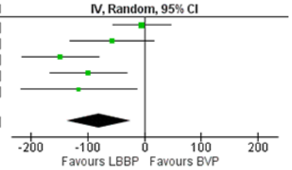
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



A. Impedance

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BVP Mean	BVP SD	BVP Total	Weight	Mean Difference IV, Random, 95% CI
Chen2021	430.62	119.94	49	434.94	142.95	51	23.8%	-4.32 [-55.96, 47.32]
Hua2022	575.81	95.75	21	632.88	140.87	20	19.6%	-57.07 [-131.16, 17.02]
Li2020	563.9	122.3	27	712.4	189.2	54	20.7%	-148.50 [-216.87, -80.13]
Rademakers2022	509	67	29	608	193	36	20.8%	-99.00 [-166.60, -31.40]
Wang2022	476	93	20	592	214	20	15.0%	-116.00 [-218.26, -13.74]
Total (95% CI)			**146**			**181**	**100.0%**	**-81.02 [-137.40, -24.65]**

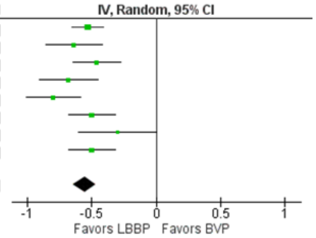
Heterogeneity: Tau² = 2781.87; Chi² = 12.88, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 2.82 (P = 0.005)



B. Pacing threshold

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BVP Mean	BVP SD	BVP Total	Weight	Mean Difference IV, Random, 95% CI
Chen2021	0.92	0.2	49	1.45	0.39	51	20.4%	-0.53 [-0.65, -0.41]
Guo2020	0.48	0.22	21	1.12	0.46	21	10.9%	-0.64 [-0.86, -0.42]
Hua2022	0.7	0.1	21	1.16	0.42	20	13.1%	-0.46 [-0.65, -0.27]
Li2020	0.75	0.31	27	1.43	0.74	54	10.2%	-0.68 [-0.91, -0.45]
Rademakers2022	0.7	0.2	29	1.5	0.6	36	11.5%	-0.80 [-1.01, -0.59]
Wang2020	0.59	0.14	10	1.09	0.45	30	13.6%	-0.50 [-0.68, -0.32]
Wang2022	0.82	0.2	20	1.12	0.67	20	6.6%	-0.30 [-0.61, 0.01]
Wu 2020	0.55	0.1	30	1.05	0.63	49	13.8%	-0.50 [-0.68, -0.32]
Total (95% CI)			**207**			**281**	**100.0%**	**-0.56 [-0.64, -0.47]**

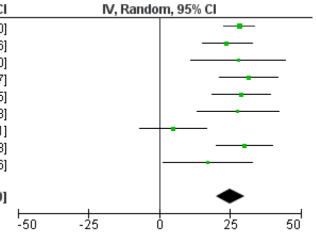
Heterogeneity: Tau² = 0.01; Chi² = 11.49, df = 7 (P = 0.12); I² = 39%
Test for overall effect: Z = 12.40 (P < 0.00001)

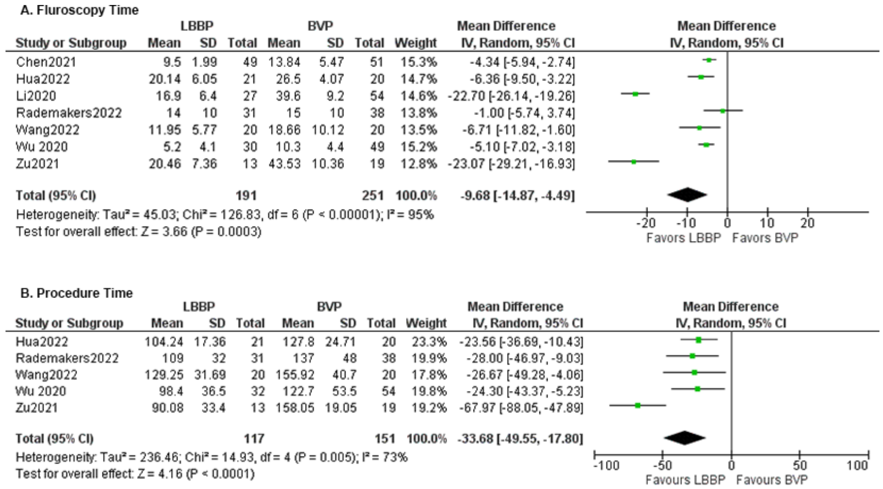


C. QRSd Reduction

Study or Subgroup	LBBP Mean	LBBP SD	LBBP Total	BVP Mean	BVP SD	BVP Total	Weight	Mean Difference IV, Random, 95% CI
Chen2021	77.51	15.48	49	49.15	11.96	51	18.4%	28.36 [22.92, 33.80]
Guo2020	56.2	14.7	21	32.3	14.6	21	13.6%	23.90 [15.04, 32.76]
Hua2022	48.62	26.29	21	20.65	28.28	20	6.6%	27.97 [11.24, 44.70]
Liu2021	64.1	18.9	27	32.5	22.3	35	11.9%	31.60 [21.33, 41.87]
Rademakers2022	43.8	17.1	29	14.9	25.7	36	11.7%	28.90 [18.45, 39.35]
Wang2020	60.8	20.09	10	33	21.48	30	7.9%	27.80 [13.17, 42.43]
Wang2022	43.1	18.99	20	38.1	19.11	20	10.3%	5.00 [-6.81, 16.81]
Wu 2020	56	21.75	30	26	21.75	49	12.4%	30.00 [20.12, 39.88]
Zu2021	50.3	23.79	13	33.15	20.22	19	7.1%	17.15 [1.34, 32.96]
Total (95% CI)			**220**			**281**	**100.0%**	**25.13 [20.06, 30.20]**

Heterogeneity: Tau² = 28.62; Chi² = 16.47, df = 8 (P = 0.04); I² = 51%
Test for overall effect: Z = 9.72 (P < 0.00001)





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