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Systematic Review/Meta-analysis

Outcomes of Left Bundle Branch Area Pacing for Cardiac Resynchronization Therapy: An Updated Systematic Review and Meta-analysis

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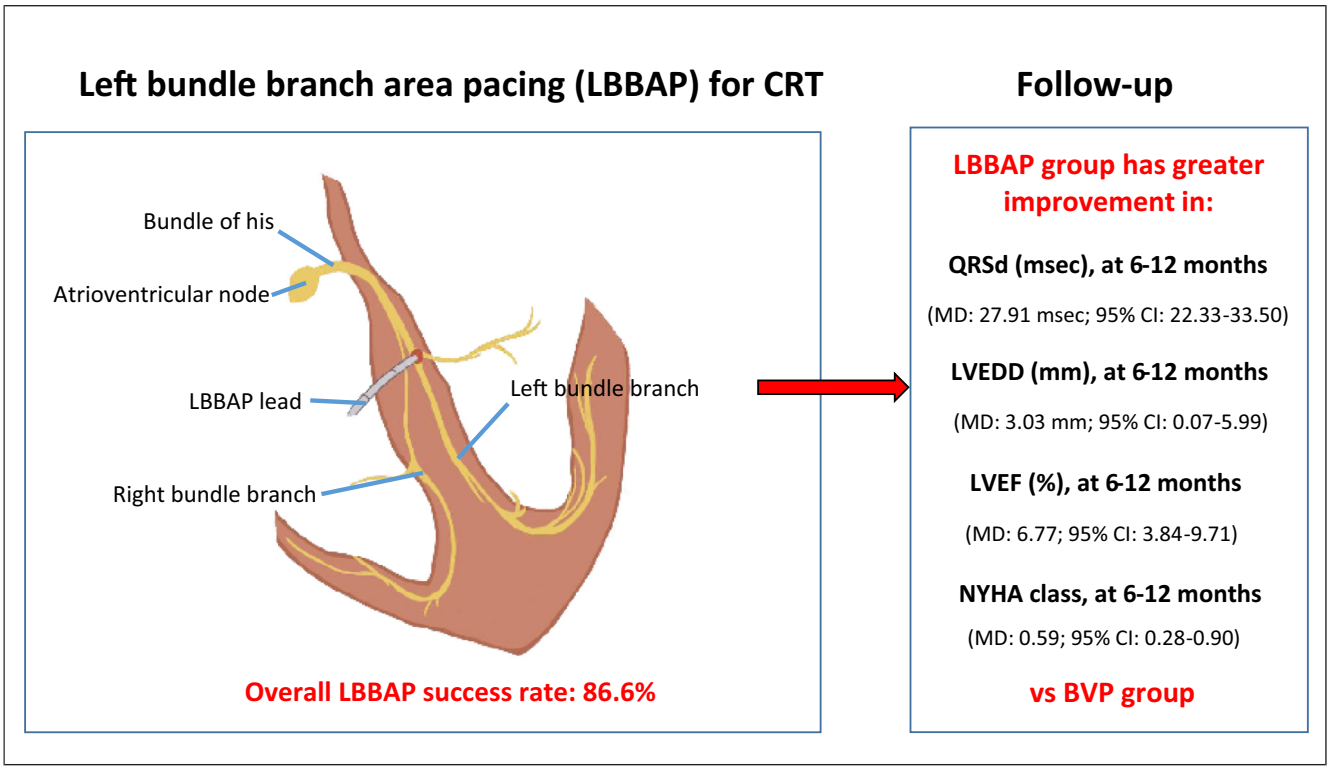

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Ethics Statement: The research reported above has adhered to the ethical guidelines from the authors' institutions.

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ABSTRACT

Background: Real-world data on the use of left bundle branch area pacing (LBBAP) as an alternative novel pacing strategy to biventricular pacing (BVP) for cardiac resynchronization therapy (CRT) remains scarce. We aimed to investigate the outcomes of LBBAP as an alternative to BVP as a method of CRT.

Methods: Electronic databases were searched for studies on the use of LBBAP as CRT and studies that compared LBBAP with BVP. The main outcomes examined were changes in New York Heart Association classification, left ventricular end-diastolic diameter, left ventricular ejection fraction, and paced QRS duration post CRT device implantation.

Results: Our meta-analysis included 8 nonrandomized studies with a total of 527 patients who underwent LBBAP as CRT. In studies with a BVP comparison group, patients with LBBAP had a greater reduction in paced QRS (mean difference [MD], 27.91 msec; 95% confidence interval [CI], 22.33-33.50), and a greater improvement in New York Heart Association class (MD, 0.59; 95% CI, 0.28-0.90) and left ventricular ejection fraction (MD, 6.77%; 95% CI, 3.84-9.71). Patients with underlying left bundle branch block appeared to benefit the most from LBBAP compared with patients without underlying left bundle branch block.

Conclusions: LBBAP might be a reasonable option for patients who meet indications for CRT, particularly in those who have limited anatomy or do not benefit from CRT. Randomized trials are needed to compare LBBAP with BVP for CRT and to identify which populations might benefit the most from LBBAP.

RÉSUMÉ

Contexte : On dispose de peu de données obtenues en contexte réel sur l'utilisation de la stimulation de la branche gauche (SBG) comme nouvelle stratégie remplaçant la stimulation biventriculaire (SBV) dans le cadre d'une thérapie de resynchronisation cardiaque (TRC). Nous avons voulu étudier les résultats de la SBG à titre de solution de rechange à la SBV comme méthode de TRC.

Méthodologie : Nous avons cherché dans les bases de données électroniques les études examinant l'utilisation de la SBG comme TRC, et les études comparant la SBG à la SBV. Les principaux résultats examinés étaient les changements dans les classes de la New York Heart Association (NYHA), le diamètre télédiastolique du ventricule gauche, la fraction d'éjection du ventricule gauche (FEVG) et la durée du QRS stimulé après l'implantation du dispositif de TRC.

Résultats : Notre méta-analyse portait sur huit études sans répartition aléatoire, portant sur un total de 527 patients ayant subi une SBG comme TRC. Dans les études comportant un groupe témoin ayant subi une SBV, les patients ayant subi une SBG présentaient une réduction plus importante du QRS stimulé (différence moyenne [DM] : 27,91 ms; intervalle de confiance [IC] à 95 % : 22,33-33,50), ainsi qu'une amélioration plus importante des classes de la NYHA (MD : 0,59; IC à 95 % : 0,28-0,90) et de la FEVG (MD : 6,77 %; IC à 95 % : 3,84-9,71). Les patients avec un bloc de la branche gauche (BBG) sous-jacent ont semblé bénéficier davantage de la SBG que les patients sans BBG sous-jacent.

Conclusions : La SBG peut être une option raisonnable pour les patients chez qui la TRC est indiquée, en particulier ceux qui ont des restrictions sur le plan de l'anatomie ou qui ne bénéficient pas de la TRC. Des essais randomisés sont nécessaires pour comparer la SBG à la SBV comme TRC, et pour déterminer les populations qui pourraient bénéficier le plus de la SBG.

Biventricular pacing (BVP) as a method of cardiac resynchronization therapy (CRT) has a well-established clinical record, with numerous clinical trials showing clinical benefits in improving functional capacity and quality of life, as well as reducing mortality and rehospitalizations in patients with heart failure with reduced ejection fraction (HFrEF) and a wide QRS complex, especially left bundle branch (LBB) block (LBBB).[1-3] BVP provides CRT via nonphysiological fusion of paced wave fronts. Therefore, BVP is not truly "physiologic" in that intrinsic conduction is not restored and thus, might not deliver the full potential of ventricular resynchronization. BVP is sometimes limited by implant failure due to unfavourable coronary venous anatomy.[4] Approximately one-third of the patients who received BVP might be classified as CRT nonresponders for a variety of reasons.[5]

His bundle pacing (HBP) was first reported by Deshmukh et al.[6] It aimed to restore physiological activation of the ventricles via the native His-Purkinje system. Although numerous studies have shown the clinical benefits of HBP in patients with HFrEF, concerns regarding high pacing threshold, lead instability, damage to the His bundle, and long-term performance and safety issues have limited its widespread use.[7,8] Hence, there has been increased interest to explore other physiological pacing techniques.

LBB area pacing (LBBAP) has recently emerged as an alternative novel method for delivering physiological ventricular pacing to capture the left-sided conduction system. Real-world data on the use of LBBAP as an alternative CRT to BVP remains scarce. One prospective study by Huang et al. showed that LBBAP could be an effective technique for CRT in patients with BVP indications.[9] Several other studies have shown that LBBAP provides an electrical and left ventricular (LV) mechanical synchrony comparable to HBP.[10,11] Hence, we conducted an updated systematic review and meta-analysis of the existing literature to evaluate the short-term clinical outcomes of LBBAP as CRT, and compared with BVP.[12]

Methods

A systematic literature search was planned and performed in accordance with the **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) guidelines for systematic review.[13] Methods of the systematic review and meta-analyses and the inclusion and exclusion criteria were prespecified and are documented in the protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42020213814).[14] The institutional review board review was exempt because of the nature of the study.

Search strategy

We searched for publications on LBBAP published from PubMed, EMBASE, and Cochrane Central Register of Controlled Trials between the database inception and December 31, 2020. After consulting with a clinical information specialist, we searched for articles using a combination of main search terms ("left bundle OR left bundle branch OR left

bundle branch area OR heart ventricles") AND ("pacing OR cardiac pacing") as either key words or medical subject heading terms. Additional searching for grey literature was conducted in the Web of Science and keyword searching was conducted in Google Scholar. No language or study type restriction was applied. Complete search strategies are available in Supplemental Appendix S1.

Eligibility criteria

Articles that reported LBBAP were reviewed. Studies that reported LBBAP implantation with CRT indication as stated in Table 1 were included in this meta-analysis. Studies that enrolled patients without CRT indications were excluded. Case reports, review articles, editorials, letters, and studies with fewer than 5 patients were excluded. Abstracts presented at conferences that were not published as full reports were also excluded.

Data extraction and appraisal

Rayyan QCRI, a Web-based and smartphone screening application developed by the Qatar Computing Research Institute (Doha, Qatar), was used to screen the articles after duplicates were removed using the Systematic Review Assistant DeDupe-UI software developed by the Bond University Institute for Evidence-Based Health Care. Two reviewers (J.L.

Table 1. Characteristics of included studies

					Treatment groups		
Reference	Design	Comparative type	Indication for CRT-D/CRT-P	N	LBBAP	BVP	Follow-up, months
Wang et al.[18]	Prospective, case-control, single-centre	LBBAP vs BVP	Sinus rhythm, LBBB defined by Strauss criteria, NYHA functional class II-IV with LVEF ≤ 35%	40	Primary LBBAP,* n = 10 Implant success, not reported	n = 30 Primary BVP, n = 30	6
Li et al.[17]	Prospective, observational, multicentre	LBBAP vs BVP	Symptomatic heart failure with LVEF ≤ 35 with LBBB, and had received ≥ 4 months GDMT for HFrEF	91	Primary LBBAP,* n = 25 Rescue LBBAP,† n = 12 Implant success, n = 30 (81.1%)	n = 54‡	6
Wu et al.[11]	Retrospective, single-centre	LBBAP vs BVP	LBBB defined according to Strauss criteria, symptomatic heart failure with LVEF ≤ 40%	86	Rescue LBBAP,§ n = 32 Implant success, not reported	Primary BVP, n = 39 Rescue BVP,§ n = 15	12
Guo et al.[21]	Prospective, observational, single-centre	LBBAP vs BVP	LBBB defined according to Strauss criteria, NYHA functional class II-IV with LVEF ≤ 35%	45	Primary LBBAP,* n = 24 Implant success, n = 21 (87.5%)	Primary BVP, n = 21	6
Li et al.[22]	Prospective, observational, single-centre	LBBAP only	NYHA functional class II-IV with LVEF < 50% (LBBB, n = 14; RBBB, n = 3; IVCD, n = 4; RVP, n = 4)	25	Primary LBBAP,* n = 20 Rescue LBBAP,† n = 5 Implant success, not reported	NA	Mean 9.1 ± 5.1
Vijayaraman et al.[20]	Retrospective, observational, multicentre	LBBAP only	NYHA functional class II-IV, baseline LVEFs ≤ 50%, and indications for ventricular pacing and/or CRT (LBBB, n = 126; RBBB, n = 54; IVCD, n = 49; RVP, n = 48, narrow, n = 48)	325	A mix of primary LBBAP* and rescue LBBAP†, and LBBAP§, n = 325 Implant success, n = 277 (85.2%)	NA	Mean 6 ± 5
Huang et al.[9]	Prospective, observational, multicentre	LBBAP only	Complete LBBB, nonischemic cardiomyopathy, symptomatic heart failure with LVEF < 50%	63	Rescue LBBAP,§ n = 63 Implant success, n = 61 (96.8%)	NA	Mean 18 (range, 15 to 20)
Zhang et al.[19]	Prospective, observational, single-centre	LBBAP only	Symptomatic heart failure with LVEF ≤ 40 with LBBB, and had received ≥ 3 months GDMT for HFrEF	11	Primary LBBAP*, n = 11 Implant success, not reported	NA	Mean 6.7 ± 3.3

BVP, biventricular pacing; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; GDMT, guideline directed medical therapy; HBP, His bundle pacing; HFrEF, heart failure with reduced ejection fraction; IVCD, intraventricular conduction delay; LBBAP, left bundle branch area pacing; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association; RBBB, right bundle branch block; RVP, right ventricular pacing.

*Procedure attempted as the first option in place of coronary sinus left ventricular lead.

†Procedure attempted because of failed coronary sinus left ventricular lead placement.

‡Primary or rescue biventricular pacing data were not reported.

§Procedure attempted because of failed HBP lead placement.

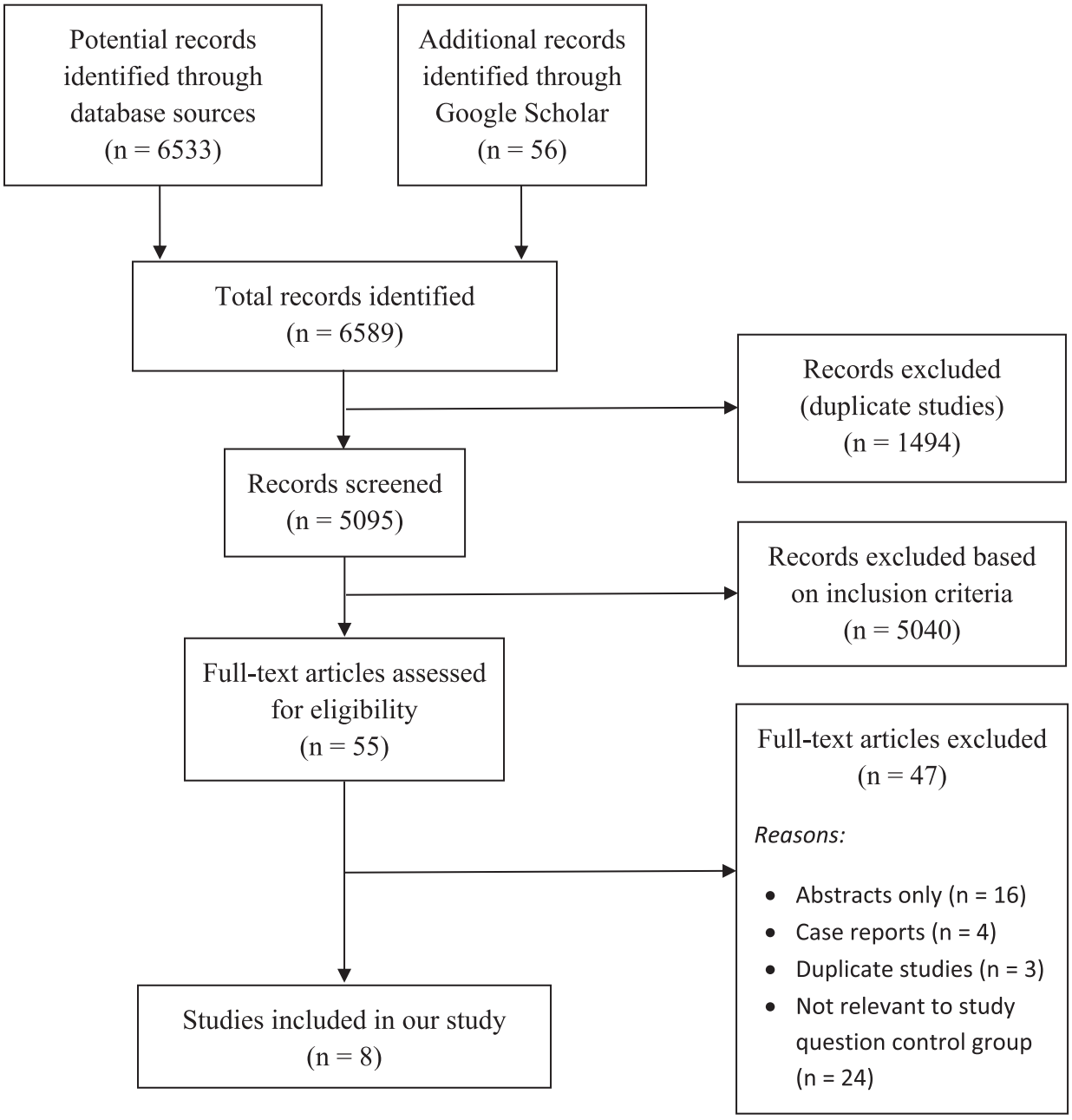

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of included and excluded studies in the network meta-analyses. Flow chart of identification of published articles retrieved from published data searches and from other sources. Reasons for exclusion of potentially eligible studies are shown.

T. and V.T.) independently reviewed all titles and abstracts. A third reviewer (A.M.R.) resolved any discrepancies. Full text of potential studies were manually searched and further analyzed to see if they met our eligibility criteria (Fig. 1). We systematically reviewed 8 original research papers, which included 686 patients across multiple centres in the United States, China, Spain, India, Brazil, and Poland. These studies reported outcomes of LBBAP as an alternative pacing modality for delivering CRT. We extracted characteristics of each study, including study name, sample size of the LBBAP group with underlying LBBB and non-LBBB, and BVP group, baseline patient characteristics (age, sex, race/ethnicity, and comorbidities), duration of follow-up, procedural characteristics (average procedural and fluoroscopic time), pacing parameters (paced QRS duration, capture threshold, R-wave amplitude, and impedance), and safety outcomes.

Outcomes

The primary outcomes of this study included changes in the following: (1) QRS duration post CRT device implantation; (2) LV end-diastolic diameter (LVEDD); (3) New York Heart Association (NYHA) classification; and (4) LV ejection fraction (LVEF). Other outcomes of interest included the

average procedural and fluoroscopic time, echocardiographic (LV end-systolic diameter, LV end-diastolic volume (LVEDV), LV end-systolic volume; LVESV) outcomes, pacing characteristics (capture threshold, R-wave amplitude, impedance), and acute procedural-related issues. We performed a separate analysis on the clinical outcomes of LBBAP for CRT in LBBB and non-LBBB patients.

Quality assessment

We used the Newcastle Ottawa Quality Assessment Scale to assess the risk of bias and quality of the studies with a control group.[15] Studies without a control group were assessed using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields.[16] Details of how these were performed are shown in Supplemental Tables S1 and S2. Two authors independently assessed the quality of the articles. A third reviewer resolved any disagreements.

Statistical analysis

Statistical analysis was performed using Review Manager (RevMan Version 5.4, The Cochrane Collaboration, 2020, Oxford, United Kingdom) and STATA software version 16 (StataCorp, College Station, TX). For the primary analysis, individual studies were treated as a random variable. Hence, random effect models were used to assess pooled effect size from aggregate data. For continuous outcomes, pooled effect estimates were calculated by comparing the change from baseline to study end for each group (LBBAP and BVP groups). The mean difference (MD) and 95% confidence interval (CI) for each outcome were calculated and graphically presented using Forest plots. The I^2 statistic was used to measure heterogeneity across the studies attributable to the difference between studies rather than chance. I^2 values of $< 25\%$, 25%-50%, and $> 50\%$ were considered low, moderate, and high amounts of heterogeneity, respectively. Funnel plots were used to visually estimate for potential publication bias. The baseline characteristics of the studies were tested for the proportions using the proportion calculator. All the tests were 2-sided and a P value < 0.05 was considered statistically significant.

Results

Patient population

Overall, 8 studies, with a total of 527 patients who underwent LBBAP for CRT and 159 patients who underwent BVP, fulfilled the inclusion criteria and were included in the meta-analysis. The PRISMA diagram is shown in Figure 1.

Table 1 shows a summary of the study characteristics of the 8 included studies.[9,11,17-22] Five of the studies were single-centre studies and the remaining of them were multicentre studies. Six were prospective studies and 2 were retrospective studies. Among the included studies, only 4 studies had comparative treatment groups, with 3 studies that compared LBBAP with BVP and 1 study that compared LBBAP with BVP and HBP.[11,17,18] Because there was only 1 study that compared the LBBAP group with the HBP group, the result of the HBP group was not included in our data analysis.[11] The remaining 4 studies without the comparative group investigated the outcomes of LBBAP in patients with CRT indications.[9,19,20,22] Of all of the included studies, the LBBAP procedure was attempted in 527 subjects and BVP was attempted in 159 subjects. As shown in Table 1, 7 studies specified the number of subjects who underwent primary LBBAP and rescue LBBAP procedures because of failed HBP lead or coronary sinus (CS) lead placement.[9,11,17-19,21,22]

Table 2 shows the overall baseline clinical characteristics of the total population with LBBAP.[9,11,17-22] The mean age was 68 years. On average, men accounted for 61% of the included subjects. Most of the subjects had nonischemic cardiomyopathy (69.2%). The mean QRS duration was 159.98 ± 29.12 msec and the mean LVEF was 31.84 ± 10.35%.

Table 3 shows the baseline clinical characteristics of the 4 studies that compared LBBAP with BVP.[11,17,18,21] Many of these characteristics were comparable between the LBBAP and BVP groups, including age, sex, and comorbidities. Most subjects had nonischemic cardiomyopathy in both groups (89.0% vs 86.8%; $P = 0.60$). Of note, the BVP group had significantly larger mean LVEDD (69.14 ± 6.05 vs 66.31 ± 7.68; $P = 0.01$) and LVESV (158.63 ± 58.37 vs 136.16 ± 50.90; $P = 0.04$) compared with the LBBAP group. Although not statistically significant, the BVP group had larger mean LVEDV (220.05 ± 69.89 vs 195.30 ± 58.42 mL; $P = 0.06$) and lower mean LVEF (28.34 ± 5.53 vs 29.71 ± 6.09%; $P = 0.06$) compared with the LBBAP group. Most of the subjects also received guideline-directed medical therapy with β-blockers, angiotensin−converting enzyme inhibitor/angiotensin II receptor blocker, and aldosterone antagonist for the treatment of HFrEF before the procedure, without differences between the LBBAP and BVP groups. There were significantly more subjects in the BVP group taking diuretics (99.4% vs 95.0%; $P = 0.02$) compared with the LBBAP group.

Implantation procedure

It is important to note that there was heterogeneity in the criteria used to confirm LBB capture. All 8 studies used paced right bundle branch block morphology in lead V_1 with

Table 2. Overall baseline characteristics of total population with LBBAP

Baseline characteristics	Overall LBBAP	n
Mean age ± SD, years	68.43 ± 12.43	524
Male sex, n (%)	318 (60.7)	524
Hypertension, n (%)	292 (61.1)	478
Diabetes mellitus, n (%)	155 (32.4)	478
AF, n (%)	219 (45.8)	478
ICM, n (%)	161 (34.9)	461
NICM, n (%)	363 (69.2)	524
Mean NYHA class ± SD	2.76 ± 0.68	518
Mean LVEF ± SD, (%)	31.84 ± 10.35	524
Mean LVEDD ± SD, mm	59.54 ± 10.07	486
Mean LVESV ± SD, mL	117.79 ± 65.61	373
Mean LVEDV ± SD, mL	173.70 ± 80.68	374
Mean LAD ± SD, mm	45.75 ± 6.83	104
Mean baseline QRSd ± SD, ms	159.98 ± 29.12	514

AF, atrial fibrillation; ICM, ischemic cardiomyopathy; LAD, left atrial diameter; LBBAP, left bundle branch area pacing; LVEDD, left ventricular end−diastolic diameter; LVEDV, left ventricular end−diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end−systolic volume; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; QRSd, QRS duration.

Table 3. Baseline characteristics of populations with comparison groups

Baseline characteristics	LBBAP*		BVP		$P^{\dagger}$
	Value	n	Value	n	
Mean age ± SD, years	62.88 ± 11.67	100	63.54 ± 10.07	159	0.63
Male, n (%)	54 (54.0)	79	94 (61.6)	159	0.26
Hypertension, n (%)	35 (38.9)	90	53 (41.1)	129	0.74
Diabetes mellitus, n (%)	26 (28.9)	90	34 (26.4)	129	0.68
AF, n (%)	17 (18.9)	90	23 (17.8)	129	0.83
ICM, n (%)	11 (11.0)	100	20 (12.6)	159	0.70
NICM, n (%)	89 (89.0)	100	139 (86.8)	159	0.60
Mean NYHA class ± SD	2.96 ± 0.65	100	2.95 ± 0.68	159	0.91
Mean QRSd ± SD, ms	172.08 ± 18.04	90	170.70 ± 24.03	159	0.64
Mean LVEF ± SD, %	29.71 ± 6.09	100	28.34 ± 5.53	159	0.06
Mean LVEDD ± SD, mm	66.31 ± 7.68	68	69.14 ± 6.05	105	0.01
Mean LVESV ± SD, mL	136.16 ± 50.90	40	158.63 ± 58.37	79	0.04
Mean LVEDV ± SD, mL	195.30 ± 58.42	40	220.05 ± 69.89	79	0.06
Mean LAD ± SD, mm	44.36 ± 5.99	47	46.13 ± 6.08	84	0.69
β−blocker, n (%)	92 (92.0)	100	149 (93.7)	159	0.60
ACEi/ARB, n (%)	93 (93.0)	100	148 (93.1)	159	0.98
Diuretics, n (%)	95 (95.0)	100	158 (99.4)	159	0.02
Aldosterone antagonist, n (%)	93 (93.0)	100	147 (92.3)	159	0.83
Digoxin, n (%)	37 (63.8)	58	49 (65.3)	75	0.86

ACEi, angiotensin−converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BVP, biventricular pacing; ICM, ischemic cardiomyopathy; LAD, left atrial diameter; LBBAP, left bundle branch area pacing; LVEDD, left ventricular end−diastolic diameter; LVEDV, left ventricular end−diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end−systolic volume; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; QRSd, QRS duration.

*LBBAP studies with comparison group.

†Analysis of patients from studies with a comparison group of LBBAP and BVP.

terminal R-wave and short stimulus to peak LV activation time in lead V_5 or V_6 as one of the criteria to confirm LBB capture.[9,11,17-22] In Wang et al., the final position of the lead tip under the subendocardium of the interventricular septum was included as one of the criteria for LBBAP.[18] Other studies included evidence for direct capture of LBB potential, and selective and nonselective LBBAP in their criteria for LBB capture.[9,11,17]

Procedure duration and success

Table 4 shows the overall procedure, echocardiographic, and pacing characteristics of studies with LBBAP (all patients).[9,11,17-19,21,22] The average procedural time was 105.70 ± 51.13 minutes. The mean LVEF at 6-12 months follow-up was 46.61 ± 11.32%. The mean capture threshold at implantation and follow-up were 0.60 ± 0.28 V and 0.67 ± 0.27 V, respectively.

Table 5 shows the procedure, echocardiographic, and pacing characteristics of studies that compared LBBAP with BVP.[11,17,18,20,21] Compared with BVP, the average fluoroscopic exposure time of the LBBAP procedure (27.04 ± 16.68 vs 12.48 ± 8.29 minutes; $P < 0.001$), and the average procedural time (122.7 ± 53.5 vs 98.4 ± 36.5 minutes; $P = 0.03$) were significantly shorter. The LBBAP group was associated with significantly lower capture threshold at implantation (0.59 ± 0.26 vs 1.07 ± 0.59 V; $P < 0.001$) and at 6-12 month follow-up (0.63 ± 0.23 vs 1.21 ± 0.66 V; $P < 0.001$) compared with the BVP group; although pulse widths varied at testing in the LBBAP group (0.4-0.5 ms).

Only 4 studies reported the procedural success rate of LBBAP implantation as shown in Table 1. Sixty of 449 subjects (13.4%) had unsuccessful LBBAP procedures. Thirty-three of them were because of an inability to capture the LBB system, 26 were because of failure to penetrate into the interventricular septal at the target site, and 1 had repeated recurrent ventricular tachycardia by pacing the LBB area during the pacing test. Nine of the subjects who had failed LBBAP attempts received BVP, 2 of the subjects received epicardial LV lead implantation, 1 of the subjects received a single-chamber implantable cardioverter defibrillator, and the remaining 48 subjects did not have end points specified.

Procedural complications

The procedural complications in patients with LBBAP included acute lead dislodgment (8 cases), transient complete heart block (5 cases), pneumothorax (3 cases), loss of left septal capture (2 cases), and device infection (2 cases). No other acute procedural complications (septal perforation, pericardial effusion, stroke, tricuspid regurgitation, or vascular injuries) were noted in these studies.

Follow-up: rehospitalization and mortality

During 6-12 months of follow-up, 17 of 467 patients (3.6%) who received LBBAP were hospitalized with acute heart failure and 11 of 467 patients (2.4%) died (all-cause mortality).[9,11,17-20] Four of 159 patients (2.5%) who received BVP experienced heart failure hospitalization, and 2 of 159

Table 4. Procedure and echocardiographic and pacing characteristics of LBBAP (all patients)

Variable	Overall LBBAP	n
Average procedural time, minutes	105.70 ± 51.13	370
Average fluoroscopic time, minutes	15.75 ± 13.78	418
NYHA class at 6- to 12-month follow-up	1.63 ± 0.63	458
LVEF at 6- to 12-month follow-up, %	46.61 ± 11.32	446
LVEDD at 6- to 12-month follow-up, mm	54.41 ± 8.90	417
LVESV at 6- to 12-month follow-up, mL	78.55 ± 49.53	373
LVEDV at 6- to 12-month follow-up, mL	139.90 ± 65.69	374
Paced QRSd post-implant, ms	129.76 ± 20.83	464
Capture threshold at implantation, V	0.60 ± 0.28	464
Capture threshold at follow-up, V	0.67 ± 0.27	443
R-wave amplitude post implantation, mV	10.81 ± 5.67	416
R-wave amplitude at follow-up, mV	12.60 ± 5.60	406
Impedance post implant, Ω	656.26 ± 187.39	411
Impedance at follow-up, Ω	529.38 ± 118.90	340

LBBAP, left bundle branch area pacing; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NHYA, New York Heart Association; QRSd, QRS duration.

Table 5. Procedure and echocardiographic and pacing characteristics of studies with comparison groups

	LBBAP*		BVP		
Baseline characteristics	Value	n	Value	n	$P^{\dagger}$
Average procedural time, minutes	98.4 ± 36.5	32	122.7 ± 53.5	54	0.03
Average fluoroscopic time, minutes	12.48 ± 8.29	80	27.04 ± 16.68	129	< 0.001
NYHA class at 6- to 12-month follow-up	1.38 ± 0.62	88	2.00 ± 0.79	154	< 0.001
LVEF at 6- to 12-month follow-up, %	49.47 ± 10.42	88	40.80 ± 13.31	154	< 0.001
LVEDD at 6- to 12-month follow-up, mm	57.03 ± 8.83	58	63.11 ± 9.59	105	< 0.001
LVESV at 6- to 12-month follow-up, mL	64.46 ± 39.26	40	100.97 ± 65.68	79	< 0.001
LVEDV at 6- to 12-month follow-up, mL	126.33 ± 50.47	40	167.05 ± 72.41	79	< 0.001
Paced QRSd post-implant, ms	117.62 ± 13.06	90	143.78 ± 22.31	159	< 0.001
Capture threshold at implantation, V	0.59 ± 0.26	90	1.07 ± 0.59	159	< 0.001
Capture threshold at follow-up, V	0.63 ± 0.23	69	1.21 ± 0.66	138	< 0.001
R-wave amplitude post implantation, mV	10.61 ± 5.11	42	14.1 ± 6.3	54	0.004
R-wave amplitude at follow-up, mV	12.5 ± 4.9	32	12.3 ± 4.9	54	0.86
Impedance post implant, Ω	644.33 ± 144.81	37	817.5 ± 222.1	54	< 0.001
Impedance at follow-up, Ω	563.9 ± 122.3	27	712.4 ± 189.2	54	< 0.001

BVP, biventricular pacing; LBBAP, left bundle branch area pacing; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NHYA, New York Heart Association; QRSd, QRS duration.

*LBBAP studies with comparison group.

†Analysis of patients from studies with a comparison group of LBBAP and BVP.

patients (1.3%) were classified as non-BVP responders. No deaths were reported in the BVP group.

Outcomes of LBBAP vs BVP groups

Effect on paced QRS duration. Pooled analysis from the 4 studies showed a significant difference in a mean reduction of paced QRS duration in the LBBAP group vs BVP group (MD, 27.91 msec; 95% CI, 22.33-33.50 msec; $P < 0.001$; $I^2 = 0\%$) as shown in Figure 2A.[11,17,18,21] Only 1 study compared the LBBAP group with the HBP group, and there was no significant difference in mean reduction of paced QRS duration between them (MD, −5.10 msec; 95% CI, −12.34 to 2.14; $P = 0.170$).[11]

Effect on LVEDD. Pooled analysis from the 3 studies showed a significant difference in a mean reduction of LVEDD in the LBBAP group vs BVP group (MD, 3.03 mm; 95% CI, 0.07-5.99; $P = 0.04$; $I^2 = 0\%$) as shown in Figure 2B.[17,18,21]

Effect on NYHA. Pooled analysis from the 4 studies showed that LBBAP was associated with a significantly greater improvement in NYHA classification compared with BVP at 6-12 months follow-up (MD, 0.59; 95% CI, 0.28-0.90; $P = < 0.001$; $I^2 = 40\%$; Fig. 2C).[11,17,18,21] There was no significant difference in mean improvement of NYHA classification at 12 months follow-up between the HBP and LBBAP groups in the 1 study in which this was evaluated (MD, −0.10; 95% CI, −0.45 to 0.25; $P = 0.58$).[11]

Effect on LVEF. Pooled analysis from the 4 studies showed that LBBAP was associated with a significantly greater improvement in LVEF compared with BVP at 6-12 months follow-up (MD, 6.77%, 95% CI, 3.84-9.71; $P < 0.001$; $I^2 = 0\%$; Fig. 2D).[11,17,18,21] There was no significant difference in mean improvement of LVEF between the HBP and LBBAP groups (24.0 ± 10.9% vs 23.9 ± 11.7%; $P = 0.977$) in the 1 study in which this was evaluated.[11]

Outcomes of LBBAP as CRT in the LBBB group

Figure 3 shows the clinical outcomes of LBBAP as CRT in patients with LBBB.[9,11,17-22] In patients with LBBB, pooled analysis showed that LBBAP significantly improved their QRS duration (MD, 50.04 msec; 95% CI, 42.25-57.83 msec; $P < 0.001$; $I^2 = 86\%$), NYHA class (MD, 1.47; 95% CI, 1.27-1.67; $P < 0.001$; $I^2 = 76\%$), and LVEF (MD, −22.05%, 95% CI, −22.05 to −15.41; $P < 0.001$; $I^2 = 78\%$) compared with baseline. Table 6 shows there was significant improvement in LVEDD, left ventricular end−systolic diameter, LVESV, and LVEDV compared with baseline in patients with underlying LBBB who received LBBAP as CRT.

Outcomes of LBBAP as CRT in LBBB vs Non-LBBB

Pooled analysis from 2 studies showed a borderline significant difference in mean reduction of paced QRS duration (MD, 20.77 msec; 95% CI, −0.40 to 41.93 msec; $P = 0.05$; $I^2 = 71\%$), and improvement in LVEF (MD, 6.00%; 95% CI, 0.15-11.84 %; $P = 0.04$; $I^2 = 44\%$) in patients with underlying LBBB vs patients with underlying non-LBBB (Fig. 4).[19,20]

Quality assessment and publication bias

Quality assessment of the individual studies determined that 8 of the included studies were of good quality with a low risk of bias. Details of the quality assessment of the studies are shown in Supplemental Tables S1 and S2. There was no publication bias according to visual assessment of the funnel plots for the selected outcomes of reduction in paced QRS duration, reduction in LVEDD, NYHA improvement, and LVEF improvement (Supplemental Fig. S1).

Discussion

The results of our meta-analysis showed that: (1) LBBAP was capable of delivering physiological pacing with a significantly narrower paced QRS duration in patients with LBBB and HFrEF

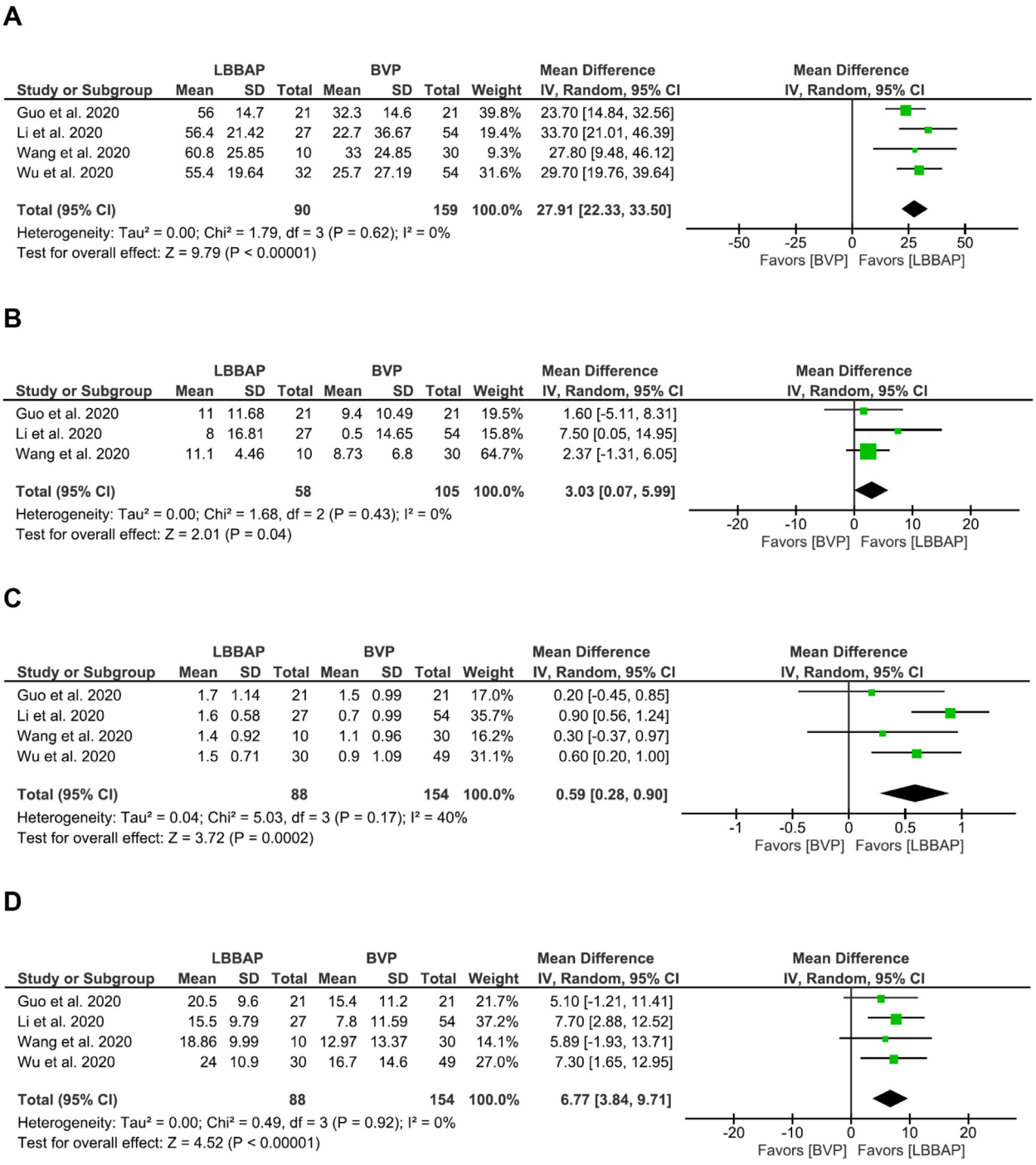

Figure 2. Forest plot of standardized mean difference in reduction in paced QRS duration, reduction in LVEDD, NYHA improvement, and LVEF improvement (LBBAP vs BVP groups). (**A**) Reduction in paced QRS duration. (**B**) Reduction in LVEDD. (**C**) NYHA improvement. (**D**) LVEF improvement. BVP, biventricular pacing; CI, confidence interval; LBBAP, left bundle branch area pacing; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NHYA, New York Heart Association.

compared with BVP; (2) LBBAP results in an improvement in the LVEDD, LVEF, and NYHA class compared with baseline, and might have at least a similar benefit to BVP in a nonrandomized group of patients studied; (3) LBBAP results in a greater mean reduction in paced QRS duration and mean improvement in LVEF in the LBBB group compared with the non-LBBB group; and (4) there was a low rate of device- or lead-related issues at the time of implantation and during short-term follow-up in small, nonrandomized studies.

To our knowledge, it was Zhong et al. who reported the first systematic review and meta-analysis of LBBAP for CRT.[12] The authors performed pooled analysis from 6

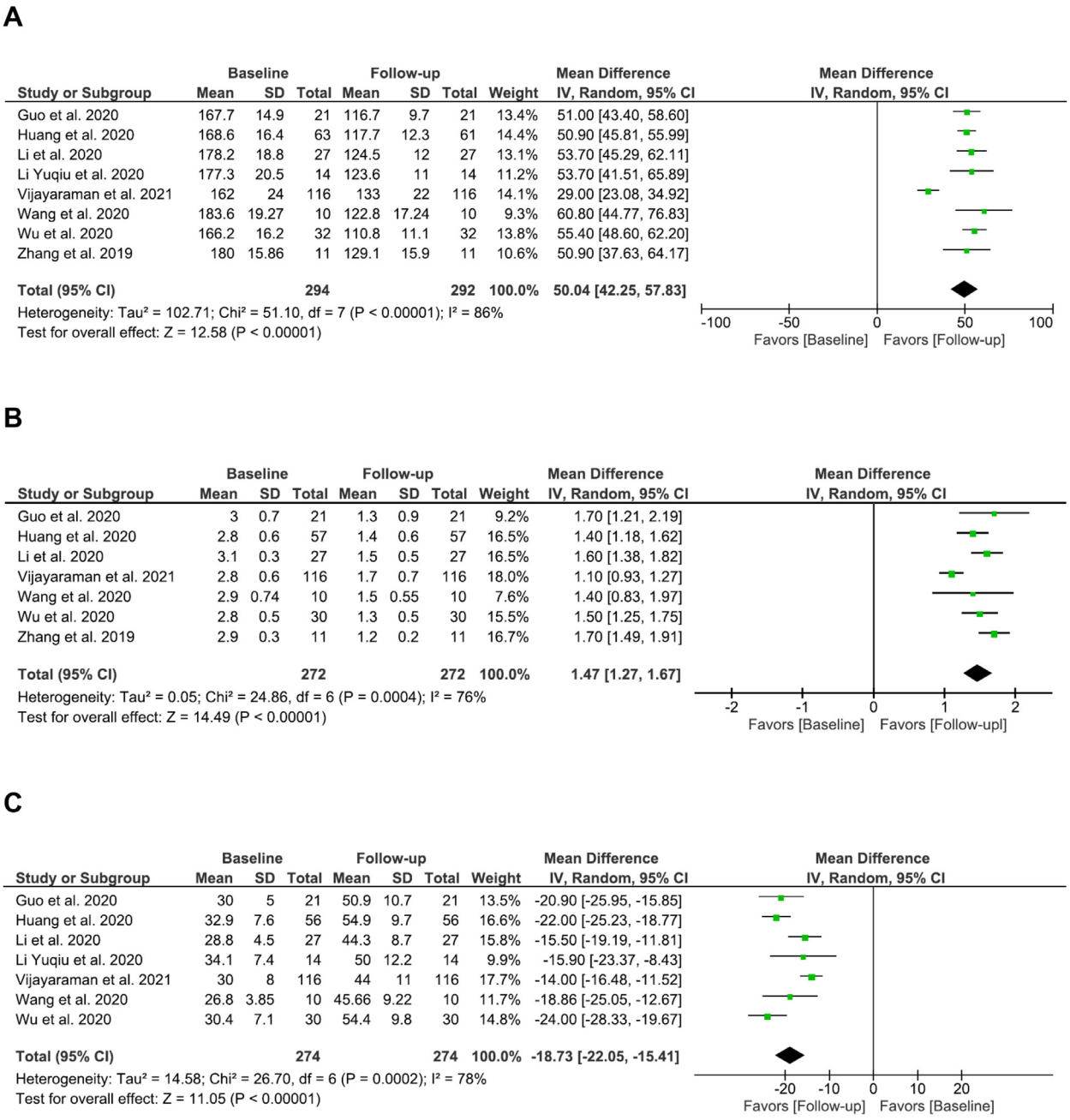

Figure 3. Forest plot of standardized mean difference in reduction in QRS duration, NYHA improvement, and LVEF improvement in patients with underlying LBBB. (**A**) Reduction in paced QRS duration. (**B**) NYHA improvement. (**C**) LVEF improvement. CI, confidence interval; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NHYA, New York Heart Association.

studies, which examined the clinical outcomes of LBBAP for CRT in 174 patients with LBBB and HFrEF. In our updated systematic review and meta-analysis of 8 nonrandomized studies, we examined the clinical outcomes of LBBAP from a pool of 527 patients with CRT indications.[9,11,17-22] In contrast to Zhong et al., in our study we reported a detailed analysis on the clinical outcomes of QRS duration, LVEDD, LVEF, and NYHA class from the 4 studies with comparison groups (between the LBBAP and BVP groups).[11,17,18,21] We also performed a pooled analysis from the 8 studies on the clinical outcomes of LBBAP for CRT in patients with LBBB. Furthermore, we also performed a pooled analysis from the 2 studies on the clinical outcomes of LBBAP for CRT in patients with non-LBBB.[19,20] To our knowledge, this is by far the single largest and most comprehensive meta-analysis on LBBAP for CRT to date.

Huang et al. first reported a successful direct LBBAP in a patient with HFrEF and LBBB in the literature as a rescue pacing modality after the failure of CS and His-lead placement.[23] The patient had a remarkable clinical improvement in LVEF by 30% and NYHA functional class from a baseline IV to I. Chen et al. further reported successful correction of

Table 6. Echocardiographic outcomes of LBBAP in patients with underlying LBBB

	Baseline		Follow-up		
Variable	Value	n	Value	n	*P**
LVEDD, mm	61.15 ± 9.09	255	54.61 ± 8.63	254	< 0.001
LVESD, mm	52.38 ± 9.24	88	38.73 ± 9.71	88	< 0.001
LVEDV, mL	183.80 ± 74.45	212	142.13 ± 68.82	212	< 0.001
LVESV, mL	125.59 ± 60.32	212	76.26 ± 49.90	212	< 0.001

Data are presented as mean ± SD, except where otherwise noted. Subgroup analysis of patients with underlying LBBB who had successfully underwent for LBBAP.

LBBAP, left bundle branch area pacing; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end−systolic diameter; LVESV, left ventricular end-systolic volume.

*Analysis of patients from studies with underlying LBBB at baseline and follow-up.

LBBB by LBB capture in 2 patients with dilated cardiomyopathy, in which 1 of the patients had a significant improvement in LVEF from 39% at baseline to 49% at 1-year follow-up.[24] In an electromechanistic study, Hou et al. reported that LBBAP generated comparable if not favourable electromechanical LV synchrony and hemodynamic effects compared with HBP.[10] These observations are hypothesis-generating and have important implications on the potential use of LBBAP in patients who meet the criteria for CRT. The results of this meta-analysis further support the use of LBBAP as an alternative rescue CRT in patients with failed CS-LV lead implantation or CRT nonresponders. However, large randomized controlled trials (RCTs) on the effect of LBBAP with BVP will be necessary to determine the long-term clinical benefits of LBBAP in this population.

Our pooled analysis showed an overall average LBBAP implantation success rate of 86.6% (389/449). As noted by Li et al.[17] and Huang et al.[9] the operators had significant experience in LBBAP implantation. Hence, the high procedural success rates might not translate to represent the real-world experience. Failure of LBBAP implantation in the pooled studies was mainly because of the inability to capture the LBB conduction system. Further advances and modifications in delivery sheaths and lead design might help to optimize LBBAP and improve the procedural success rate. In a study by Padala et al., the acute success rates of LBBAP implantation was reported at 87% during the first half of the experience.[25] As the operators gained more experience, the latter half of the LBBAP group had success rates of 91%.[25] There is a significant learning curve to mastering the LBBAP implantation technique. Overall, the implantation success rates of LBBAP remained high, which has been reported to be 89%-94% in the literature.[25-28]

In our pooled analysis, the LBBAP group had a significantly lower pacing threshold to achieve LBBB correction compared with the capture threshold in the BVP group (0.59 ± 0.26 V vs 1.07 ± 0.59 V; $P < 0.001$). The pacing thresholds of the LBBAP group remained relatively stable at 6-12 months follow-up. The data on pacing thresholds in the BVP group are consistent with previous CRT studies.[29,30] The relatively higher pacing thresholds in patients with BVP could be attributed to differences in local scar burden in the lateral LV wall or epicardial fat compared with the septal

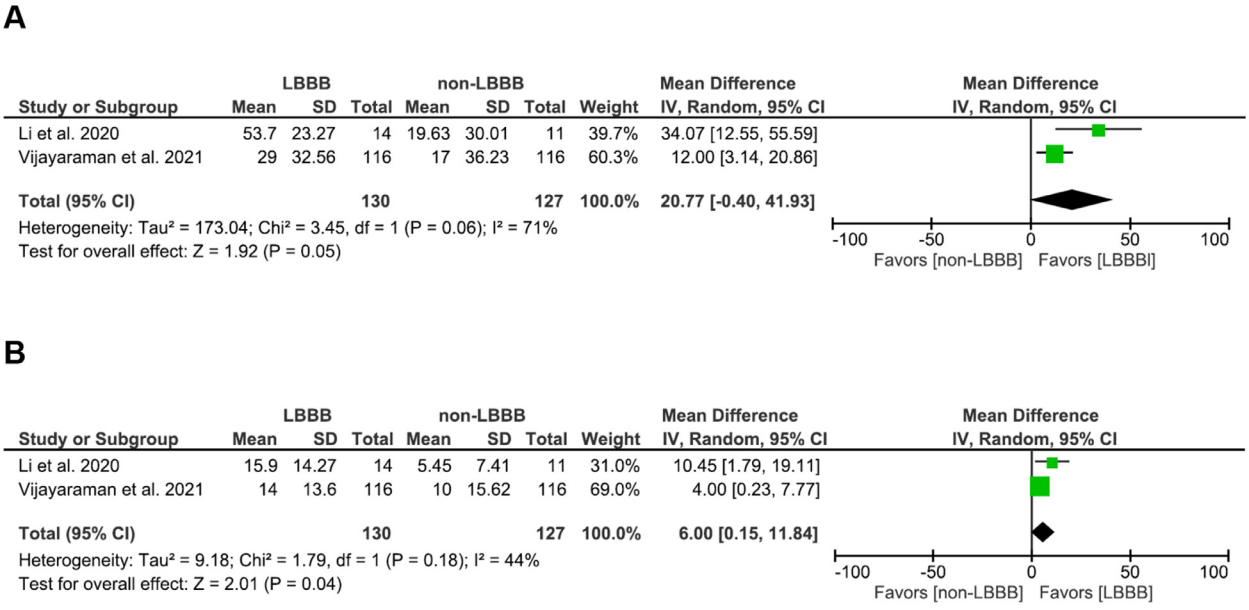

Figure 4. Forest plot of standardized mean difference in reduction in paced QRS duration and LVEF improvement in LBBB vs Non-LBBB groups. (**A**) Reduction in paced QRS duration. (**B**) LVEF improvement. CI, confidence interval; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

myocardium in patients who meet CRT indication. A lower pacing threshold could potentially translate into longer device longevity.

Of note, the average procedural and fluoroscopic times were significantly shorter for the LBBAP group compared with the BVP group. This is likely because of direct myocardial contact with an active fixation lead and less anatomical limitation to the CS vasculature. The anatomy of CS might be distorted in dilated hearts. Thus, this might account for the increase in time taken and the use of radiographs to place the CS lead into the target branch vessel.

Study limitations

The included studies are prospective and retrospective observational studies because, to our knowledge, there is no RCT to date on the effect of LBBAP in patients with CRT indications. It is important to note that in our meta-analysis we only examined the use of LBBAP in a limited CRT population. This CRT population might not be a standard cohort because it included a large proportion of nonischemic (62.9%) patients as shown in Table 2. So far, there are only 4 non-RCT studies available in the literature that have comparing the effect of LBBAP with BVP in patients with a CRT indication. Hence, generalization of the results remains difficult.

Known and unknown confounders affect observational studies. As noted in our data analysis (Table 3), the selection criteria for LBBAP and BVP are not uniform. Compared with the LBBAP group, the BVP group had a trend toward a lower baseline LVEF, and larger baseline LVEDD and LVESV. The BVP group were also more likely to receive diuretic therapy. Hence, the BVP group might have been "sicker" than the LBBAP group. Thus, RCTs with uniform patient selection criteria are required to reduce these confounders. Of note, the data included in our systematic review and meta-analysis are not patient-level data. Hence, we were unable to analyze any potential confounding factors and patient selection bias that could potentially affect the clinical outcomes between treatment groups.

Although the implantation success rates of LBBAP are close to 87%, experienced operators performed most of the LBBAP device implantations. Most of the included subjects had nonischemic cardiomyopathy. In addition, these studies did not assess hard clinical outcomes such as heart failure hospitalizations and long-term mortality. The short follow-up periods limit the ability to assess the long-term benefits of physiological pacing of the LBBAP device, the effects of LBBAP on right ventricular function, and potential long-term lead and/or device malfunction. Thus, adequately powered RCTs from multicentre studies are required to assess the long-term clinical benefits of LBBAP and to ensure the generalizability of the results around the globe.

Conclusion

The results of this meta-analysis show that LBBAP, as an alternative CRT, is safe, feasible, and appears effective in limited, small, nonrandomized studies. However, large prospective RCTs that compare LBBAP with BVP and have long-term follow-up are required to better characterize the use of this novel pacing strategy in a cardiomyopathy population with LBBB and HFrEF to investigate potential indications and populations that might benefit the most from LBBAP.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at doi:10.1016/j.cjco.2021.05.019.