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REVIEW ARTICLES

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Effectiveness of conduction system pacing for cardiac resynchronization therapy: A systematic review and network meta-analysis

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Abstract

Introduction: Cardiac resynchronization therapy (CRT) with biventricular pacing (BiV-CRT) is ineffective in approximately one-third of patients. CRT with Conduction system pacing (CSP-CRT) may achieve greater synchronization. We aimed to assess the effectiveness of CRT with His pacing (His-CRT) or left bundle branch pacing (LBB-CRT) in lieu of biventricular CRT.

Methods and Results: The PubMed, Embase, Web of Science, Scopus, and the Cochrane Library were systematically searched until August 19, 2023, for original studies including patients with reduced left ventricular ejection fraction (LVEF) who received His- or LBB-CRT, that reported either CSP-CRT success, LVEF, QRS duration (QRSd), or New York Heart Association (NYHA) classification. Effect measures were compared with frequentist network meta-analysis. Thirty-seven publications, including 20 comparative studies, were included. Success rates were 73.5% (95% CI: 61.2–83.0) for His-CRT and 91.5% (95% CI: 88.0–94.1) for LBB-CRT. Compared to BiV-CRT, greater improvements were observed for LVEF (mean difference [MD] for His-CRT +3.4%; 95% CI [1.0; 5.7], and LBB-CRT: +4.4%; [2.5; 6.2]), LV end-systolic volume (His-CRT:17.2mL [29.7; 4.8]; LBB-CRT:15.3mL [28.3; 2.2]), QRSd (His-CRT: −17.1ms [−25.0; −9.2]; LBB-CRT: −17.4ms [−23.2; −11.6]), and NYHA (Standardized MD [SMD]: His-CRT:0.4 [0.8; 0.1]; LBB-CRT:0.4 [−0.7; −0.2]). Pacing thresholds at baseline and follow-up were significantly lower with LBB-CRT versus both His-CRT and BiV-CRT. CSP-CRT was associated with reduced mortality (*R* = 0.75 [0.61–0.91]) and hospitalizations risk (RR = 0.63 [0.42–0.96]).

Conclusion: This study found that CSP-CRT is associated with greater improvements in QRSd, echocardiographic, and clinical response. LBB-CRT was associated with

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lower pacing thresholds. Future randomized trials are needed to determine CSP-CRT efficacy.

KEYWORDS

biventricular pacing, cardiac resynchronization therapy, conduction system pacing, His pacing, left bundle branch pacing, network meta-analysis

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) with biventricular pacing (BVP) is an important treatment for patients with wide QRS and heart failure; however, approximately one third of patients who receive biventricular CRT (BiV-CRT) do not demonstrate a favorable response.[1,2] New approaches to cardiac pacing which engage the native His-Purkinje system—conduction system pacing (CSP)—may help achieve resynchronization and improve clinical outcomes in candidates of CRT, since CRT with both His-pacing (His-CRT) and left bundle branch (LBB) pacing (LBB-CRT) can theoretically restore electromechanical synchrony.[3]

To date, studies investigating CRT via CSP (CSP-CRT) have been limited by the small sample sizes, and heterogeneity in their findings,[4–8] and the clinical evidence has lagged behind the enthusiasm for implementing these novel techniques for CRT. Herein, we report a systematic review and network meta-analysis of studies that report outcomes in patients undergoing CSP-CRT with either His-CRT or LBB-CRT. Since His-CRT and LBB-CRT are distinct approaches, a network meta-analysis is the optimal approach to compare outcomes between these novel approaches and against the conventional BiV-CRT control group.

2 | METHODS

2.1 | Design, search, and study selection

The review protocol is available on PROSPERO (CRD42022328042). The reporting conforms to the Preferred Reporting Items for Systematic Reviews (PRISMA).[9,10] Since this study used data from other publications, it was exempted from an additional institutional review board and ethics committee approval.

A systematic search was conducted in PubMed, Embase, Web of Science, Scopus, and the Cochrane Library from database inception until August 19, 2023. Details of search keywords are presented in Supporting Information: Supplemental Methods. Detection, screening, and removal of duplicate records, and then title/abstract screening was performed with the Rayyan web application (Rayyan Systems, Inc.).[11]

At each stage of review, original studies—randomized trials or observational—were selected if they had the following eligibility criteria: (1) focused on a population of patients with reduced left ventricular ejection fraction (LVEF) who had indications for CRT; (2) investigated the intervention of CSP in the form of his or LBB pacing, whether in comparison to BiV-CRT or as a single group; and (3) reported at least one outcome of interest in the CSP group, including CSP success rate, LVEF, QRS duration (QRSd), New York Heart Association (NYHA) classification, death, or hospitalization. Non-English publications were excluded.

2.2 | Review and data extraction

Two reviewers (HT and SK) independently evaluated the retrieved full texts for eligibility, extracted data, and assessed risk-of-bias. Discrepancies were resolved by discussion with a third author (AB). The study publication year, country, design, number, age, sex, reported study eligibility criteria, and study indications for CRT were recorded. Characteristics including baseline QRS morphology and rhythm, QRSd, LVEF, NYHA, left ventricular end-systolic volume (LVESV), pacing thresholds after implantation and at follow-up, clinical events, etiology of cardiomyopathy, and device type were extracted. For continuous data, the number, mean, and standard deviation for data at baseline and follow-up/post-implant (for QRSd, and NYHA classification, thresholds), or for changes from baseline (follow-up minus baseline or Δ, for LVEF and LVESV) were entered into data sheets. Extracted binary data included CSP success rate, clinical response (defined based on NYHA class), death, and hospitalization.

2.3 | Risk of bias

For randomized studies, the second version of the Cochrane risk-of-bias tool for randomized trials (RoB-2) was used, whereas the Methodological Index for Non-Randomized Studies (MINORS) was considered for observational studies.[12,13] The RoB-2 evaluates studies in five domains and grades each as "low risk," "some concerns," or "high risk." The MINORS includes 12 items graded as 0 (not reported), 1 (reported, but inadequately), or 2 (reported and adequate). Four items are specific to comparative studies; therefore, the maximum scores for comparative and non-comparative studies would be 24 and 16, respectively.

2.4 | Data synthesis

All analyses were conducted using R version 4.1.3, and the packages "meta," "metafor," and "netmeta." For continuous effect measures, the number of cases, mean, and standard deviations were extracted. For studies that did not report standard deviations for change from baseline (for ΔLVEF and ΔLVESV), these values were estimated using the methods from *Cochrane Handbook for Systematic Reviews of Interventions, version 6.3*.[14] The means were pooled in the CSP and BVP groups to acquire estimates for each outcome measure. Between-group mean difference (MD) was used to compare LVEF, LVESV, and QRSd between CSP and BVP. Hedges' *g* Standardized MD (SMD) was used for the comparison of pacing thresholds (due to differences in measurements and slightly variable pulse widths) and the NYHA classification (due to subjectivity of its assessment and expected variation in measurements). The proportions of successful CSP implantations were pooled using generalized linear mixed-effects model with logit transformations. For binary outcomes (Clinical response, death, and hospitalization), the relative benefit/relative risk were calculated and pooled using the Mantel–Haenszel method. The Higgins and Thompson's I^2-statistic and the between-study variance in random-effects models (τ^2) were used to measure statistical heterogeneity. To calculate the heterogeneity variance τ^2, the restricted maximum likelihood estimator and the Sidik-Jonkman estimator were used for continuous and binary effect sizes, respectively.[15,16] Since considerable between-study heterogeneity was anticipated, all analyses were conducted with a random-effects model. To compare the outcomes of His-CRT or LBB-CRT with the control group of BiV-CRT, the frequentist network meta-analysis was used with the *netmeta* function. Consistency in the networks was evaluated by node splitting, looking for agreement between direct and indirect evidence.[17] Comparison-adjusted network funnel plots were visually inspected for symmetry and the Egger's test was applied to investigate the risk of publication bias.

3 | RESULTS

3.1 | Search results and study characteristics

The systematic search identified 37 eligible publications,[4–8,18–49] including 20 comparative studies—among which four were randomized controlled trials—and 17 single-arm investigations reporting outcomes in patients undergoing CSP for CRT (details shown in Figure 1). The comparative studies enabled network meta-analyses of the three interventions—His-CRT, LBB-CRT, and BiV-CRT. The single-arm data were used to pool outcome measures in patients undergoing CSP. Eight studies presented patient-level data for outcomes.[25,26,29,32,40,45,47,48] Durations of follow-up ranged between 5 and 31 months, with most studies (25/37) following patients between 6 and 12 months. Notably, the most common etiology for cardiomyopathy was nonischemic (64.5% of study populations). Eleven studies mentioned the inclusion of cases undergoing device revisions or upgrades.[6,7,27,28,30,34–36,39,42,48] Study characteristics and risk-of-bias are shown in Table 1 and Supporting Information: Figures S1–S4. Baseline characteristics of included patients across studies are summarized in Table 2.

3.2 | Feasibility of conduction system pacing

The success rate of CSP implant was reported in 25 studies,[4–8,18,20,22–25,27,28,30,31,34–37,39,45–49] among 1629 patients who were candidates of either His- or LBB-CRT. The overall pooled result showed an 86.2% (95% CI: 80.7–90.4, $I^2 = 84\%$) success rate.

The main reasons for His-CRT failure were lack of His capture with inadequate QRS narrowing, and high pacing thresholds for LBBB correction. The top causes of LBB-CRT failure were no success in fixation of the pacing lead within interventricular septum, and non-capture of LBB or not fulfilling pre-defined LBBP criteria (Figure 2; Supporting Information: Table S1). Among patients undergoing His-CRT, the implantation success rate was 73.5% (95% CI: 61.2–83.0, $I^2 = 79\%$), whereas LBB-CRT was successfully implanted in 91.5% (95% CI: 88.0–94.1, $I^2 = 35\%$) of patients. Notably, the difference between His- and LBB-CRT subgroups was statistically significant, showing a higher success rate reported for LBB-CRT than His-CRT ($p < .001$; Figure 2).

Among the included studies, the success rates of BiV-CRT implantations were only reported in nine studies (820 procedures).[4,5,7,8,27,31,37,39,49] The pooled success rate for BiV-CRT was 89.9% (95% CI: 82.0–94.6, $I^2 = 83\%$; Figure 2).

3.3 | Left ventricular function and end-systolic volume

LVEF measurements before and after CSP were reported in 32 studies (2145 patients),[4–8,18–26,28–35,37–39,41,42,44,45,47–49] showing an overall mean LVEF improvement of +15.4% (95% CI: [13.3–17.5]; $I^2 = 95\%$; Supporting Information: Figure S5). LVEF changes were compared between CSP and BVP in 18 studies.[4,5,7,8,20–22,24,25,31,33,37–39,41,42,44,49] Among the comparative studies the pooled LVEF Improvement was +16.7% (95% CI: [13.8–19.6]; $I^2 = 96\%$) in the CSP groups (1563 patients) and +11.5% (95% CI: [9.5–13.5]; $I^2 = 89\%$) after BVP (1734 patients; Supporting Information: Figure S6).

The pooled improvement was +14.8 (95% CI: [9.9–19.6]; $I^2 = 97\%$) after His-CRT and +15.9 (95% CI: [13.4–18.3]; $I^2 = 91\%$) in the LBB-CRT subgroup. In the network meta-analysis, the mean difference of LVEF improvement was significantly higher with His-CRT (+3.4%; 95% CI: [1.0–5.7], $p = .005$) and LBB-CRT (+4.4%; 95% CI: [2.5–6.2]; $p < .001$) compared to BiV-CRT (Figure 3A). There was no significant difference in LVEF improvement for LBB-CRT compared to His-CRT in the network (+1.0%; 95% CI: [−1.8 to 3.8]; $p = .479$; Supporting Information: Figure S7).

Measurements of LVESV were reported in 14 studies[4–8,18,22–24,35,36,38,39,49] (601 patients), which reported an overall mean reduction in LVESV of −54.6 mL (95% CI: [−68.7 to −40.4]; $I^2 = 95\%$; Supporting Information: Figure S8). Reductions in LVESV with CSP were compared to BVP in nine studies.[4,5,7,8,22,24,38,39,49] Pooled LVESV reduction among comparative studies was −63.5 mL (95% CI: [−78.5 to −48.5]; $I^2 = 90\%$) in subjects

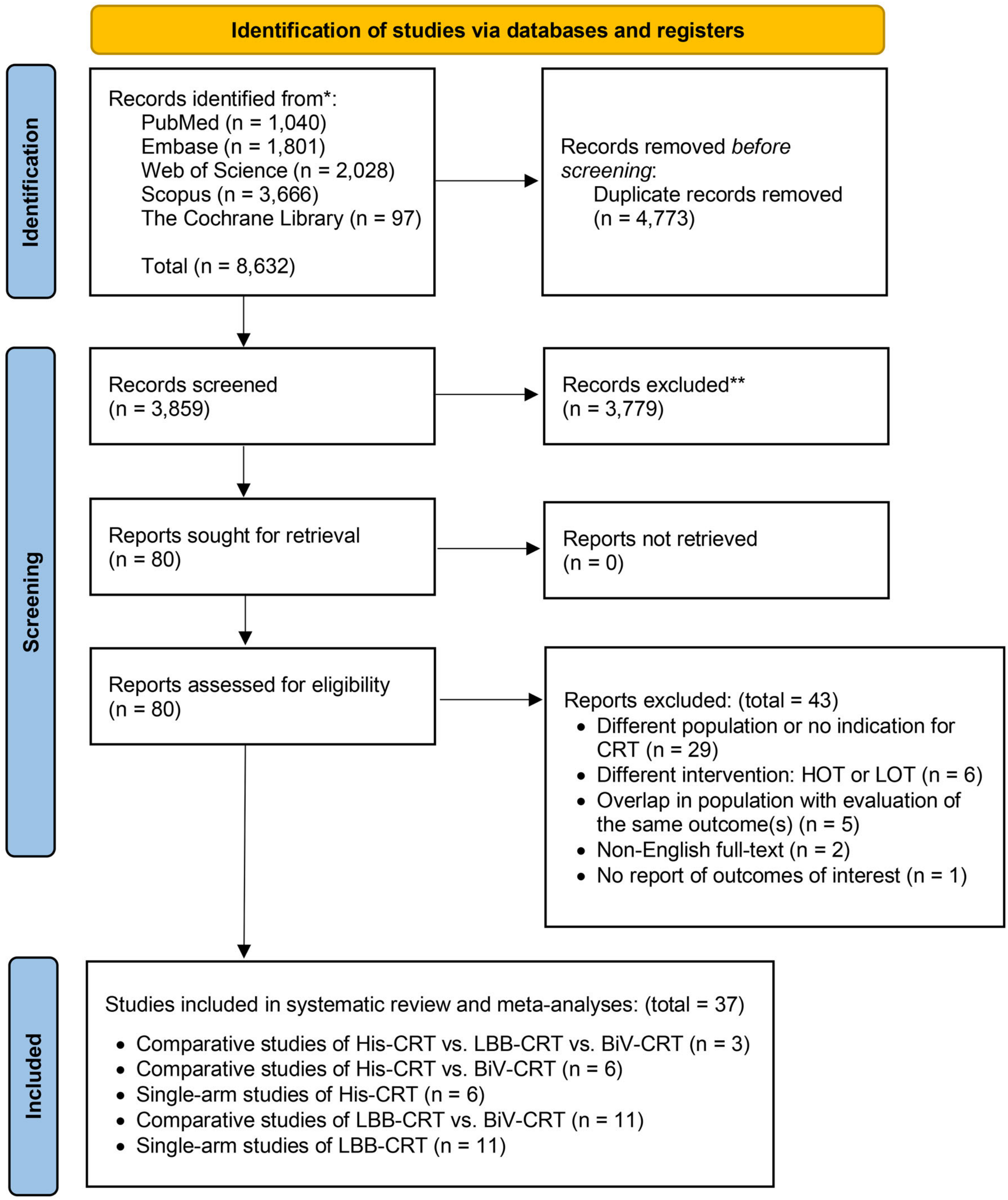

FIGURE 1 The PRISMA flow diagram.

undergoing CSP (267 patients) compared to −46.0 mL (95% CI: [−60.0 to −32.0]; $I^2 = 93\%$) in the BVP group (257 patients; Supporting Information: Figure S9).

Pooled reductions in LVESV were −56.0 mL (95% CI: [−82.9 to −29.0]; $I^2 = 92\%$) after His-CRT (123 patients) and −53.8 mL (95% CI: [−74.5 to −33.0]; $I^2 = 96\%$) after LBB-CRT (478 patients). The network meta-analysis showed greater reductions in LVESV after His-CRT (−17.2 mL; 95% CI: [−29.7 to −4.8]; $p = .007$), or LBB-CRT (−15.3 mL; 95% CI: [−28.3 to −2.2]; $p = .022$) versus BiV-CRT (Figure 3B). There was no significant difference between His-CRT and LBB-CRT (−1.9 mL 95% CI: [−19.0 to 15.1]; $p = .823$; Supporting Information: Figure S10).

3.4 | QRS and pacing thresholds

QRSd was reported in 35 studies (2378 patients).[4–8,18–26,28–42,44–49] The pooled mean native QRSd of 166.2 ms (95% CI: [162.5–169.9]; $I^2 = 96\%$) was reduced to 123.4 ms (95% CI: [119.2–127.8]; $I^2 = 98\%$) after CSP (Supporting Information: Figure S11).

TABLE 1 Study characteristics.

First author, year	Country	Design	Patients, *n*	Age, years	Males/ females	Follow-up duration	RoB
Comparative studies of His-CRT versus BiV CRT							
Huang et al., 2018[22]	China	Observational, Prospective	74	69.6 ± 9.2	43/31	12 months	12/24
Upadhyay et al., 2019[8]	USA	RCT, Prospective	40	64.6 ± 12.6	25/15	6 months	Some concerns
Vinther et al., 2021[4]	Denmark	RCT, Prospective	50	65.8 ± 9.1	32/18	6 months	Some concerns
Kato et al., 2022[24]	Japan	Observational, Prospective	14	70.9 ± 12	11/3	12 months	17/24
Sarkar et al., 2022[33]	India	Observational, Prospective	38	58.9 ± 18.6	19/19	6 months	16/24
Moriña-Vázquez et al, 2023[43]	Spain	Observational, Prospective	103	His-CRT: 64 (61–75) BiV-CRT: 68 (61–74)	68/35	12 months	13/24
Single-arm studies of His-CRT							
Barba-Pichardo et al., 2012[a47]	Spain	Observational, Retrospective	13	67.6 ± 5.8	9/4	6 months	9/16
Ajijola et al., 2017[a45]	USA	Observational, Retrospective	21	66.0 ± 14.4	15/6	12 months	8/16
Arnold et al., 2018[46]	UK	Observational, Prospective	17	67 ± 10	9/8	NA	9/16
Sharma et al., 2018[34]	USA	Observational, Retrospective	106	71 ± 12	74/32	8 months	8/16
Boczar et al., 2019[a48]	Poland	Observational, Prospective	14	67.4 ± 10	11/3	14 months	11/16
Sarkar et al., 2019[ab32]	India	Observational, Retrospective	7 (Total: 22)	65.8 ± 16.9	11/11	5 months	6/16
Comparative studies of LBB-CRT versus BiV CRT							
Guo et al., 2020[20]	China	Observational, Prospective	Case: 21 Control: 21	65.6 ± 8.6	9/12	6 months	21/24
Xiaofei Li et al., 2020[a25]	China	Observational, Prospective	Case: 30 Control: 54	56.8 ± 10.1	17/13	6 months	19/24
Wang et al., 2020[38]	China	Observational, Prospective	40	63.4 ± 9.6	32/8	6 months	21/24
Zu et al., 2021[41]	China	Observational, Retrospective	32	60.3 ± 8.7	23/9	12 months	17/24
Chen et al., 2022[49]	China	Observational, Prospective	100	65.7 ± 8.8	54/46	12 months	17/24
Hua et al., 2022[21]	China	Observational, Prospective	41	66.5 ± 9.4	30/11	24 months	21/24

TABLE 1 (Continued)

First author, year	Country	Design	Patients, *n*	Age, years	Males/ females	Follow-up duration	RoB
Liang et al., 2022[27]	China	Observational, Retrospective	491	65 (57-70)	331/160	31 months	18/24
Pujol-Lopez et al., 2022[7]	Spain	RCT, Prospective	70	66.9 ± 8.9	48/22	6 months	Some concerns
Rademakers et al., 2022[31]	The Netherlands	Observational, Prospective	80	69.5 ± 11.3	46/34	6 months	19/24
Wang et al., 2022[5]	China	RCT, Prospective	40	63.7 ± 10.9	20/20	6 months	Low risk
Vijayaraman et al., 2023[44]	7 European, 6 North American, and 3 Asian sites	Observational, Retrospective	1778	69 ± 12	1203/575	33 months	17/24
Single-arm studies of LBB-CRT							
Zhang et al., 2019[a40]	China	Observational, Prospective	11	67.4 ± 13.7	6/5	7 months	13/16
Huang et al., 2020[23]	China	Observational, Prospective	63	67.8 ± 11.1	33/30	18 months	12/16
Yuqiu Li et al., 2020[a26]	China	Observational, Retrospective	25	59.3 ± 12.5	13/12	9 months	9/16
Vijayaraman et al., 2020[b6]	USA; Spain; India; Brazil; Poland	Observational, Retrospective	116 (Total: 277)	71 ± 12	176/101	6 months	8/16
Ponnusamy et al., 2021[a29]	USA	Observational, Retrospective	13	63.2 ± 16.4	4/9	13 months	9/16
Ponnusamy et al., 2021[b28]	India	Observational, Prospective	41 (Total: 93)	62.6 ± 13	55/38	5 months	14/16
Grieco et al., 2022[18]	Italy	Observational, Prospective	55	72 ± 9	30/25	6 months	13/16
Gu et al., 2022[19]	China	Observational, Retrospective	34	65.6 ± 11.2	23/11	12 months	10/16
Qian et al., 2021[30]	China	Observational, Retrospective	13	75.8 ± 6.8	9/4	10 months	12/16
Vijayaraman et al., 2022[35]	5 American, 4 European, and 2 Asian sites	Observational, Retrospective	121	74 ± 12	91/30	9 months	11/16
Vijayaraman et al., 2022[36]	7 European, 6 North American, and 3 Asian sites	Observational, Retrospective	200	68 ± 11	129/71	12 months	9/16
Three-arm study of His-CRT versus LBB-CRT versus BiV-CRT							
Wu et al., 2021[39]	China	Observational, Prospective	135	68.1 ± 10.7	74/61	12 months	18/24

(Continues)

TABLE 1 (Continued)

First author, year	Country	Design	Patients, n	Age, years	Males/ females	Follow-up duration	RoB
Ezzeddine et al., 2023[42]	6 American, 1 Canadian, and 1 Spanish sites	Observational, Retrospective	238	69.9 ± 12.5	172/66	9 months	15/24
Studies of His- or LBB-CRT versus BiV-CRT							
Vijayaraman et al., 2022[37]	USA	Observational, Retrospective	477	72 ± 12	326/151	27 months	17/24

Abbreviations: CRT, cardiac resynchronization therapy; HOT-CRT, His optimized cardiac resynchronization therapy; LBB, left bundle branch; LOT-CRT, left bundle optimized cardiac resynchronization therapy; RCT, randomized controlled trial; RoB, risk of bias.

[a]Patient-level data available from study tables.

[b]Patients with indication of CRT are a subgroup of the total population, for whom outcomes of interest are reported.

The mean baseline and paced QRSd were 162.8 ms (95% CI: [153.7–172.3]) decreased to 120.9 ms (95% CI: [112.0–130.4]) for His-CRT, and 168.1 ms (95% CI: [164.5–171.8]) decreased to 124.4 ms (95% CI: [119.5–129.5]) for LBB-CRT. Comparison of QRSd between CSP-CRT and BiV-CRT were available in 18 studies (Supporting Information: Figure S12).[4,5,7,8,20–22,24,25,31,33,37–39,41,42,44,49] The network meta-analysis showed significantly higher levels of QRS narrowing with both His-CRT (MD: −17.1 ms; 95% CI: [−25.0 to −9.2]; $p < .001$) and LBB-CRT (MD: −17.4 ms; 95% CI: [−23.2 to −11.6]; $p < .001$) compared to BiV-CRT. The difference between His-CRT and LBB-CRT was not statistically significant ($p = .938$; Figure 3C; Supporting Information: Figure S13).

Pacing thresholds of the His, LBB, or left ventricular (LV) leads were recorded in 26 studies.[4,5,7,18–26,29,31,32,34–40,44,47–49] At the time of implant, the pooled pacing threshold was 1.4 V (95% CI: [1.0–2.1]; $I^2 = 89\%$) for His-CRT, 0.7 V (95% CI: [0.6–0.8]; $I^2 = 95\%$) for LBB-CRT, and 1.1 V (95% CI: [0.9–1.3]; $I^2 = 98\%$) for the LV lead in the BiV-CRT group (Supporting Information: Figures S14–S15). In the network meta-analysis of 11 comparative studies,[4,5,7,20,21,25,31,37,39,44,49] the pacing thresholds at baseline were significantly higher with His-CRT compared to LBB-CRT (SMD: 1.2; 95% CI: [0.6–1.8]; $p < .001$), and lower with LBB-CRT than the BiV-CRT LV-leads (SMD: −0.8; 95% CI: [−1.2 to −0.5]; $p < .001$). The higher pacing thresholds of His-CRT compared to BiV-CRT did not show statistical significance (SMD: 0.4; 95% CI: [−0.2 to 1.0]; $p = .209$; Figure 4A; Supporting Information: Figures S16).

Pooled pacing thresholds at the time of follow-up were 1.7 V (95% CI: [0.9–3.0]; $I^2 = 95\%$) for His-CRT, 0.7 V (95% CI: [0.7–0.8]; $I^2 = 82\%$) for LBB-CRT, and 1.3 V (95% CI: [1.2–1.4]; $I^2 = 84\%$) for BiV-CRT (Supporting Infomation: Figures S17-S18). Results from a network of 10 studies[4,5,7,21,25,31,37,39,44,49] were again in favor of lower pacing thresholds with LBB-CRT compared to both His-CRT ($p = .001$) and BiV-CRT ($p < .001$), while the difference between His-CRT and BiV-CRT was not significant ($p = .657$; Figure 4B; Supporting Infomation: Figure S19).

3.5 | Clinical response

Comparisons of NYHA functional class at baseline and after CRT were available from 13 studies.[4,5,7,20–22,24,25,31,33,38,39,44] Both CSP and BVP were associated with significant reductions in NYHA class. During follow-up, the mean NYHA classification improved to 1.4 (95% CI: [0.9–2.2]; $I^2 = 97\%$) in the His-CRT, 1.5 (95% CI: [1.3–1.7]; $I^2 = 93\%$) in the LBB-CRT, and 1.8 (95% CI: [1.5–2.1]; $I^2 = 93\%$) in the BiV-CRT groups (Supporting Infomation: Figure S20). The network meta-analysis for NYHA class at the time of follow-up showed an SMD of −0.4 (95% CI: [−0.8 to −0.1]; $p = .023$) for His-CRT, and −0.4 (95% CI: [−0.7 to −0.2]; $p < .001$) for LBB-CRT compared to BiV-CRT. There was no significant difference between His- and LBB-CRT ($p = .950$; Figure 4C; Supporting Infomation: Figure S21).

TABLE 2 Baseline characteristics of included patients.

First author, year	Indication for CRT	Baseline QRSd, ms	Baseline QRS morphology	Rhythm	LVEF, %	NYHA Class	Etiology	CRT-D/CRT-P
Comparative studies of His-CRT versus BiV CRT								
Huang et al., 2018[22]	NYHA: II–IV; Typical LBBB; QRSd > 130 ms; Indication for CRT or pacing Controls: failed CSP	CSP: 170 ± 19 BVP: 175 ± 12	LBBB	18/74: AF 12/74: AVB	CSP: 31 ± 5 BVP: 33 ± 7	CSP: 2.8 ± 0.7 BVP: 2.8 ± 0.6	Ischemic: 11 NICM: 63	NR
Upadhyay et al., 2019[8]	HF with class I/II indication for CRT based on ACCF/AHA/HRS guidelines	CSP: 174 ± 18 BVP: 165 ± 17	35/40: LBBB 2: RBBB 3: RVP	13/40: history of AF	CSP: 28 (23-34) BVP: 28 (24-31)	CSP: 3.0 (2.3-3.0) BVP: 2.8 (2.3-3.0)	NR	NR
Vinther et al., 2021[4]	LVEF ≤ 35%; NYHA: II–IV despite OMT Typical LBBB	CSP: 163 ± 14 BVP: 167 ± 15	LBBB	SR	CSP: 31 ± 6 BVP: 29 ± 8	CSP: 2.4 ± 0.4 BVP: 2.4 ± 0.4	Ischemic: 11 NICM: 39	32/18
Kato et al., 2022[24]	LVEF ≤ 35%; NYHA: II–IV despite OMT; typical complete LBBB; QRSd ≥ 120 ms; SR Controls: failed CSP	CSP: 169 ± 13 BVP: 186 ± 10	LBBB	SR	CSP: 21 ± 4 BVP: 18 ± 8	CSP: 2.7 ± 0.5 BVP: 2.6 ± 0.5	Ischemic: 4 NICM: 10	1/13
Sarkar et al., 2022[33]	LVEF ≤ 40% with HBP; Controls: PS-matched	CSP: 133 ± 31 BVP: 143 ± 22	NR	NR	CSP: 36 ± 9 BVP: 33 ± 6	CSP: 2.8 ± 0.1 BVP: 3.2 ± 0.3	NR	NR
Moriña-Vázquez et al, 2023[43]	NICM; LVEF < 35%; LBBB	CSP: 160 (150–160) BVP: 110 (110–120)	LBBB	19/103: AF	CSP: 30 (28–34) BVP: 30 (29–35)	NR	All NICM	NR
Single-arm studies of His-CRT								
Barba-Pichardo et al., 2012[47]	Dilated LV; LBBB; indicated for CRT and ICD; NYHA: III CRT not achievable via CS	166 ± 8	LBBB	6/16: AF 10/16: SR	29 ± 5	All Class III	Ischemic: 5 NICM: 8	13/0
Ajijola et al., 2017[45]	LVEF < 35%; NYHA: II–IV despite OMT BBB with QRSd > 120 ms	180 ± 23	17/21: LBBB 4/21: RBBB	1/21: Permanent AF	25 ± 8	II: 3/21 III: 14/21 IV: 4/21	Ischemic: 9 NICM: 12	19/2
Arnold et al., 2018[46]	LVEF < 35%; NYHA: II–IV; LBBB with QRSd > 130 ms; Standard clinical criteria for BiV-CRT	178 ± 30	LBBB	NR	26 ± 7	II: 12/17 III: 3/17 IV: 1/17	Ischemic: 6 NICM: 11	NR
Sharma et al., 2018[34]	LVEF ≤ 50%; NYHA: II–IV; Candidates of or failure of BiV-CRT	163 ± 22	36/106: LBBB 12/106: RBBB/IVCD	60/106: AF 7/106: AVB	30 ± 10	2.8 ± 0.5	Ischemic: 67	60/35

(Continues)

TABLE 2 (Continued)

First author, year	Indication for CRT	Baseline QRSd, ms	Baseline QRS morphology	Rhythm	LVEF, %	NYHA Class	Etiology	CRT-D/ CRT-P
			7/106: AVB 41/106: RVP	10/106: AVNA			NICM: 39	
Boczar et al., 2019[48]	LVEF ≤ 35% or <40 with indication for SP-ICD; NYHA: III–IV despite OMT; BBB with QRSd > 130 ms or QRS < 130 ms with expected high VP	159 ± 29	10/14: LBBB 4/14: RBBB	All had permanent AF with optimal medical rate control	24 ± 11	3.1 ± 0.3	Ischemic: 5 NICM: 9	14/0
Sarkar et al., 2019[32]	Patients who underwent HBP for CRT with BBB	127 ± 30	5/7: LBBB 2/7: RBBB	NR	38 ± 9	NR	NR	2/5
Comparative studies of LBB-CRT versus BiV CRT								
Guo et al., 2020[20]	LVEF ≤ 35%; NYHA: II–IV despite OMT; LBBB Controls: PS-matched	CSP: 168 ± 15 BVP: 164 ± 14	LBBB	3/21: AF	CSP: 30 ± 5 BVP: 30 ± 4	CSP: 3 ± 0.7 BVP: 3 ± 0.7	Ischemic: 19 NICM: 2	12/9
Xiaofei Li et al., 2020[25]	LVEF ≤ 35%; HF symptoms with at least 4 months of OMT; LBBB Controls: PS-matched	CSP: 178 ± 18 BVP: NR	LBBB	1/30: AF	CSP: 29 ± 5 BVP: NR	CSP: 3.1 ± 0.6 BVP: NR	Ischemic: 6 NICM: 24	22/8
Wang et al., 2020[38]	LVEF ≤ 35%; NYHA: II–IV; Complete LBBB; SR Controls: PS-matched	CSP: 184 ± 19 BVP: 175 ± 19	LBBB	SR	CSP: 27 ± 4 BVP: 26 ± 5	CSP: 2.9 ± 0.7 BVP: 3.1 ± 0.7	Ischemic: 4 NICM: 36	5/5 in cases
Zu et al., 2021[41]	DCM with CRT indication; LVEF < 35%; LBBB with QRSd > 150 ms; persistent symptoms despite OMT	CSP: 167 ± 28 BVP: 163 ± 22	LBBB	6/32: AF 6/32: AVB	CSP: 31 ± 7 BVP: 29 ± 5	NR	All NICM	0/32
Chen et al., 2022[49]	LVEF ≤ 35%; NYHA: II–IV despite OMT Typical LBBB	CSP: 180 ± 16 BVP: 176 ± 11	LBBB	SR	CSP: 29 ± 5 BVP: 28 ± 5	CSP: III–IV: 92% BVP: III–IV: 88%	Ischemic: 23 DCM: 77	70/30
Hua et al., 2022[21]	HF; NYHA: II–IV despite >3 months OMT; complete LBBB; QRSd > 150 ms	CSP: 178 ± 15 BVP: 178 ± 17	LBBB	9/41: AF	CSP: 30 ± 7 BVP: 31 ± 9	CSP: 3 ± 0.7 BVP: 3.1 ± 0.9	NR	13/28
Liang et al., 2022[27]	LVEF ≤ 35%; NYHA: II–IV despite OMT; QRSd ≥ 130 ms; Or LVEF < 40% + high/3rd AVB + high expected VP rate	CSP: 160 (150–180) BVP: 160 (150–180)	313/491: LBBB 28/491: RBBB 130/491: IVCD 20/491: RVP	116/491: AF 26/491: AVNA	CSP: 32 (28–37) BVP: 30 (25–36)	CSP: 2.6 ± 0.6 BVP: 2.6 ± 0.6	Ischemic: 61 NICM: 430	290/201
Pujol-Lopez et al., 2022[7]	LVEF ≤ 35%; symptomatic HF despite OMT; QRSd ≥ 130 ms LBBB or ≥150 ms non-LBBB; or indication for CRT due to AVB + cardiac dysfunction	CSP: 177 ± 21 BVP: 178 ± 22	43/70: LBBB 8/70: IVCD 19/70: RVP	15/70: permanent AF 6/70: AVB 6/70: AVNA	CSP: 27 ± 7 BVP: 28 ± 7	CSP: 2.4 ± 0.7 BVP: 2.4 ± 0.7	Ischemic: 22 NICM: 48	54/16

TABLE 2 (Continued)

First author, year	Indication for CRT	Baseline QRSd, ms	Baseline QRS morphology	Rhythm	LVEF, %	NYHA Class	Etiology	CRT-D/ CRT-P
Rademakers et al., 2022[31]	LVEF ≤ 35%; NYHA: II–IV; Complete LBBB Controls: Historical	CSP: 166 ± 15 BVP: 159 ± 16	LBBB	22/80: AF/AFL	CSP: 28 ± 8 BVP: 31 ± 6	CSP: 2.8 ± 0.5 BVP: 2.7 ± 0.6	Ischemic: 25 NICM: 55	Two thirds/ One third
Wang et al., 2022[5]	LVEF ≤ 40%; NYHA: II–IV despite OMT; LBBB; SR; NICM	CSP: 175 ± 14 BVP: 175 ± 14	LBBB	SR	CSP: 28 ± 5 BVP: 31 ± 6	CSP: 2.4 ± 0.5 BVP: 2.5 ± 0.5	All NICM	31/9
Vijayaraman et al., 2023[44]	LVEF ≤ 35%; NYHA: II–IV; indication for CRT or expected frequent ventricular pacing >40%	CSP: 160 ± 28 BVP: 160 ± 24	1073/1778: LBBB 173/1778: RBBB 153/1778: IVCD 248/1778: RVP 127/1778: Normal	650/1778: AF	CSP: 27 ± 6 BVP: 26 ± 6	CSP: 2.8 ± 0.6 BVP: 2.7 ± 0.6	Ischemic: 649 NICM: 1029 Mixed: 100	1362/416
Single-arm studies of LBB-CRT								
Zhang et al., 2019[40]	HFrEF; LBBB; indication for CRT	180 ± 16	LBBB	1/11: AF	32 ± 5	II: 2/11 III: 9/11	Ischemic: 2 NICM: 9	5/6
Huang et al., 2020[23]	Complete LBBB; LVEF < 50% with HF symptoms; NICM; Indication for CRT or VP; Failure of HBP	169 ± 16	LBBB	18/63: AF 5/63: 2nd/3rd AVB	33 ± 8	2.8 ± 0.6	All NICM	NR
Li et al., 2020[26]	LVEF < 50%; NYHA: II–IV; indication for CRT	164 ± 29	14/25: LBBB 3/25: RBBB 4/25: IVCD 2/25: RVP 2/25: Normal	7/25: AF 18/25: SR	35 ± 7	2.6 ± 0.6	Ischemic: 4 NICM: 19 PICM: 2	6/19
Vijayaraman et al., 2020[6]	LVEF ≤ 50%; NYHA: II–IV; LBBB; indication for CRT	162 ± 24	LBBB	NR	30 ± 8	2.8 ± 0.6	NR	NR
Ponnusamy et al., 2021a[29]	LBBB-induced CM; NYHA: II–IV; LBBB	168 ± 12	LBBB	SR	30 ± 7	3.1 ± 0.3	All had LBBB-induced CM	5/8
Ponnusamy et al., 2021b[28]	Dilated cardiomyopathy LVEF ≤ 35%; QRSd > 150 ms	158 ± 32	32/41: LBBB 5/41: RBBB	NR	34 ± 8	NR	NR	NR

(Continues)

TABLE 2 (Continued)

First author, year	Indication for CRT	Baseline QRSd, ms	Baseline QRS morphology	Rhythm	LVEF, %	NYHA Class	Etiology	CRT-D/ CRT-P
			4/41: PICM					
Grieco et al., 2022[18]	LVEF ≤ 35%; HF symptoms despite OMT; LBBB	167 ± 24	LBBB	19/55: AF	29 ± 5	NR	Ischemic: 23	47/8
							NICM: 32	
Gu et al., 2022[19]	LVEF < 50%; HF symptoms; LBBB	153 ± 2	LBBB	6/34: AF 2/34: AVB	35 ± 10	II: 4/34 III: 18/34 IV: 12/34	Ischemic: 7 NICM: 27	NR
Qian et al., 2021[30]	PICM (LVEF ≤ 50% with ≥10 decrease after RVP)	173 ± 18	All: RVP	6/13: AF with slow rate	40 ± 5	2.5 ± 0.5	All had PICM	NR
				7/13: AVB				
Vijayaraman et al., 2022[35]	LVEF ≤ 50%; NYHA: II–IV; QRSd > 120ms; RBBB; Indication for CRT or pacing	156 ± 20	RBBB	50/121: AF	35 ± 9	2.5 ± 0.8	Ischemic: 59	37/70
							NICM: 62	
Vijayaraman et al., 2022[36]	Rescue LBB-CRT after failure of BiV-CRT with lead failure or nonresponse	170 ± 28	109/200: LBBB	80/200: AF	29 ± 10	2.8 ± 0.6	Ischemic: 55	154/46
			10/200: RBBB					
			28/200: IVCD				NICM: 126	
			45/200: RVP				Mixed: 19	
			8/200: Normal					
Three-arm study of His-CRT versus LBB-CRT versus BiV-CRT								
Wu et al., 2021[39]	LVEF ≤ 40%; symptomatic HF; complete LBBB	LBB-CRT: 166 ± 16	LBBB	34/135: AF	LBB-CRT: 31 ± 7	LBB-CRT: 2.8 ± 0.5	Ischemic: 16	100/35
		His-CRT: 170 ± 19			His-CRT: 30 ± 6	His-CRT: 2.8 ± 0.7		
		BiV-CRT: 161 ± 18		4/135: AVB	BiV-CRT: 30 ± 6	BiV-CRT: 2.8 ± 0.6	NICM: 119	
Ezzeddine et al., 2023[42]	Controls: PS-matched	LBB-CRT: 159 ± 30	82/238: LBBB	115/238: AF	LBB-CRT: 31 ± 9	NR	Ischemic: 59	NR
		His-CRT: 145 ± 34	103/238: non-LBBB		His-CRT: 35 ± 10			
		BiV-CRT: 151 ± 33	53/238: RVP		BiV-CRT: 35 ± 12		NICM: 179	

TABLE 2 (Continued)

First author, year	Indication for CRT	Baseline QRSd, ms	Baseline QRS morphology	Rhythm	LVEF, %	NYHA Class	Etiology	CRT-D/ CRT-P
Studies of His- or LBB-CRT versus BiV-CRT								
Vijayaraman et al., 2022[37]	LVEF ≤ 35%; NYHA: II-IV; Class I or II indication for CRT	CSP: 151 ± 30 BVP: 161 ± 23	247/477: LBBB 44/477: RBBB 44/477: IVCD 93/477: RVP 49/477: Normal	247/477: AF	CSP: 26 ± 7 BVP: 26 ± 6	NR	Ischemic: 187 NICM: 258 Mixed: 32	421/56

Note: Continuous data are represented as mean ± standard deviation, or median (25th–75th percentile).

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AVB, atrioventricular block; AVNA, atrioventricular node ablation; BiV, biventricular; BVP, biventricular pacing; CM, cardiomyopathy; CRT, cardiac resynchronization therapy; CSP, conduction system pacing; DCM, dilated cardiomyopathy; HBP, his-bundle pacing; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IVCD, intra-ventricular conduction block; LBBB, left bundle branch block; NICM, nonischemic cardiomyopathy; NR, not reported; OMT, optimal medical therapy; PICM, pacemaker-induced cardiomyopathy; PS-matched, propensity score-matched; RBBB, right bundle branch block; RVP, right ventricular pacing; SP-ICD, secondary prevention implantable cardioverter defibrillator; SR, sinus rhythm; VP, ventricular pacing.

The proportion of patients who achieved clinical response after CRT was reported in eight comparative studies, albeit with slightly heterogeneous definitions for response—improvement of NYHA class ≥1,[4,8,20,25,44] improvement ≥1 class with no admission for heart failure,[31] or NYHA I–II at follow-up.[38,49] In the network meta-analysis, the relative benefit for clinical response with LBB-CRT compared to BiV-CRT was 1.17 (95% CI: [1.04–1.31]; $p = .007$; Supporting Infomation: Figures S22–S23). No significant difference was found when comparing His-CRT with BiV-CRT ($p = .370$), or His-CRT with LBB-CRT ($p = .782$).

The incidence of death and hospitalization were reported, and compared between CSP-CRT and BiV-CRT in 15 studies[4,5,7,8,21,22,27,31,37–39,42–44,49] and 12 studies,[4,5,7,21,27,31,37–39,42,44,49] respectively. The relative risk of death was 0.75 (95% CI: [0.61–0.91]; $p = .008$; $I^2 = 0\%$; Supporting Infomation: Figure S24). In addition, the risk of hospitalization was lower with CSP-CRT compared to conventional BiV-CRT (RR: 0.63; 95% CI: [0.42–0.96]; $p = .034$; $I^2 = 30\%$; Supporting Infomation: Figure S25).

3.6 | Network consistency

Node splitting analysis of the networks did not reveal evidence of statistical inconsistency (Supporting Infomation: Table S2), except for one comparison between LBB-CRT and BiV-CRT for QRSd ($p = .007$). This was caused by one three-arm study;[39] thus, the analysis of QRSd was repeated after its exclusion, which produced similar findings (His-CRT vs. BiV-CRT, MD: −13.9 ms [−23.4 to −4.3]; LBB-CRT vs. BiV-CRT, MD: −18.3 ms [−25.6 to −10.9]; His-CRT vs. LBB-CRT, MD: 4.4 ms [−7.6 to 16.4]).

3.7 | Evidence from randomized trials

Four randomized controlled trials were included.[4,5,7,8] The main limitations of these trials were small samples, and the high rate of cross-overs. Using the intention-to-treat data from these studies, we ran the analyses for each outcome, whenever such data was available. LVEF improvement was statistically higher (MD: +2.5% [0.1–5.0]; $p = .045$), and NYHA class was lower (SMD: −0.36 [−0.67 to −0.05]; $p = .025$) after CSP versus conventional BiV-CRT. Differences between CSP and BVP were not statistically or clinically significant for QRSd (MD: −4.4 [−9.0 to 0.2]; $p = .059$), and neither for LVESV reduction ($p = .118$), or baseline ($p = .648$) and follow-up thresholds ($p = .822$). Forest plots, including only randomized trials, are presented in Supporting Infomation: Figures S26–S30.

3.8 | Publication bias

We found evidence of publication bias for LVEF outcome (Egger's test $p = .002$). There was no evidence for publication bias for other

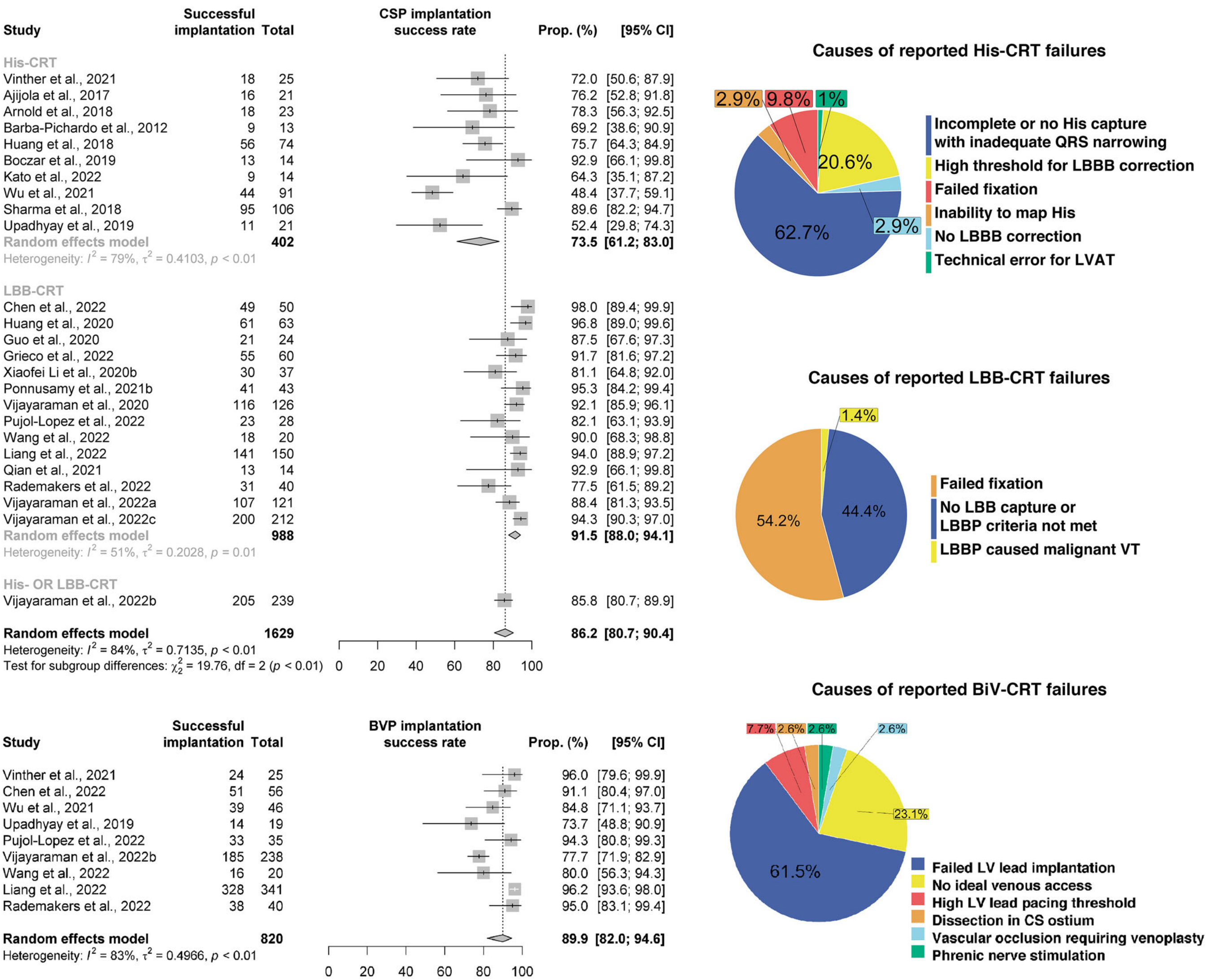

FIGURE 2 Forest plots for success rates of cardiac resynchronization therapy with His pacing (His-CRT), left bundle branch pacing (LBB-CRT), and biventricular pacing (BiV-CRT) with reported causes of failure.

outcomes after inspection of funnel plots and applying Egger's test (Supporting Infomation: Figures S31–S36).

4 | DISCUSSION

This study demonstrates that CSP-CRT can be implemented with a high success rate, and may achieve superior improvements in LV function and dimensions compared to conventional BiV-CRT. The degree of QRS narrowing, as a measure of electrical synchronization, was more favorable after CSP-CRT. Furthermore, patients undergoing CSP demonstrated better clinical response based on NYHA classification, and there was a signal for reduced hospitalizations in individuals receiving CSP-CRT compared to BiV-CRT. This systematic review has generated the largest data set to date for evaluating the effectiveness of CSP as a strategy of CRT. While clinical trials of CSP-CRT are awaited, this investigation highlights notable implications for clinical practice and future research.

The statistically significant benefit of improvement in LVEF and reduction in LVESV with both His-CRT and LBB-CRT should be interpreted with the magnitude of changes in mind. It can be argued that a difference in ΔLVEF of 5% or less compared to BiV-CRT may not be clinically meaningful; however, it should be noted that these improvements were observed with relatively short follow-ups, and the benefits may increase with time. Such a trend has been observed in CSP-CRT studies,[5,23,49] as well as in the seminal trials of BiV-CRT versus medical therapy,[50,51] where LVEF improvements became more prominent with longer follow-ups. Furthermore, observed reductions in LVESV indicate reverse LV remodeling, which supports the notion that electrical and mechanical resynchronization with CSP-CRT has been superior to BiV-CRT in these studies. Results of symptomatic improvements and clinical response, which were based

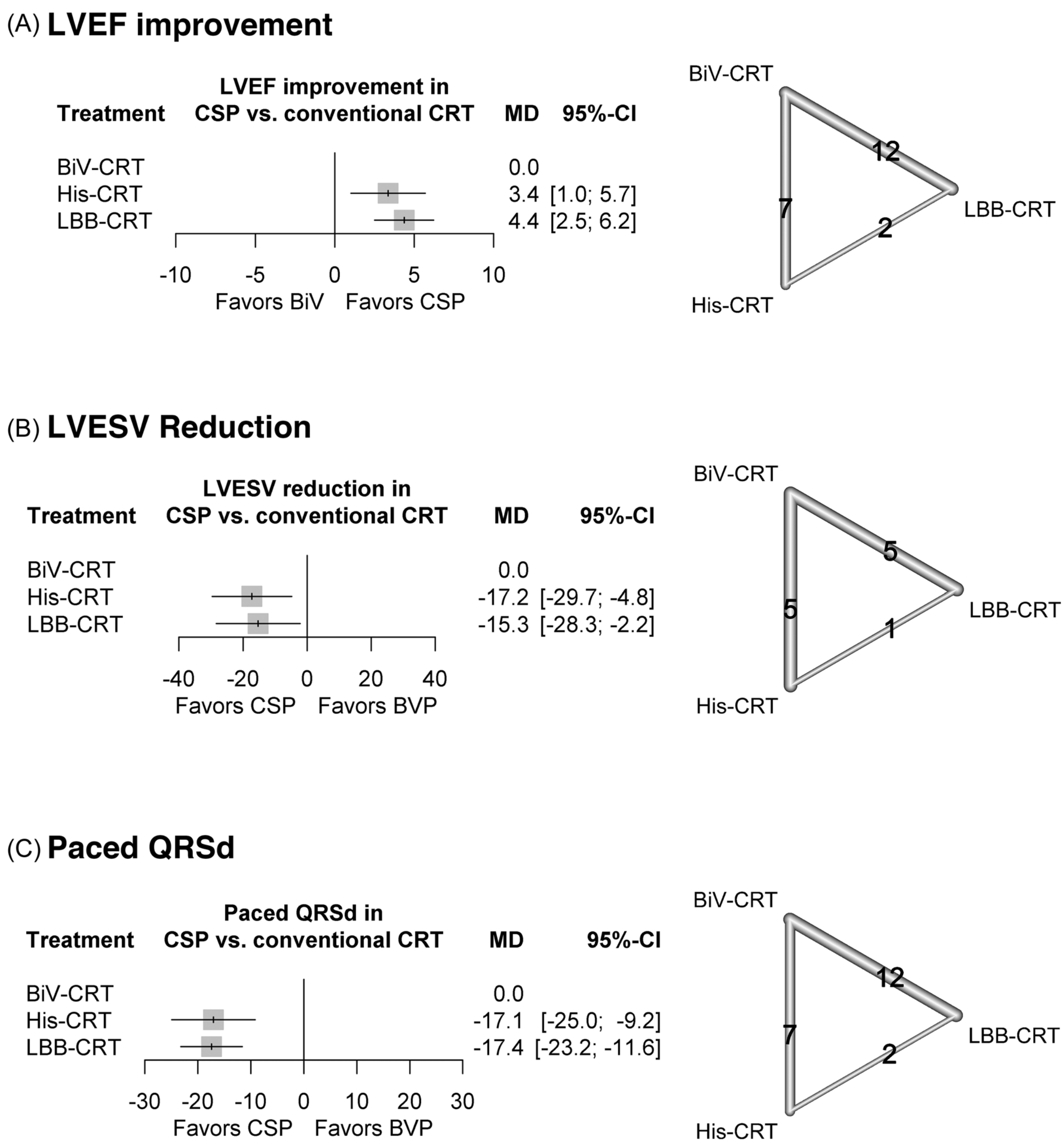

FIGURE 3 Pooled mean differences in network meta-analyses with corresponding network graphs for (A) left ventricular ejection fraction (LVEF), (B) left ventricular end-systolic volume (LVESV), and (C) paced QRS duration (QRSd).

on NYHA classification, should be interpreted with caution due to lack of blinding in studies, the subjective nature of such outcomes, and the ambiguity of the minimal clinically important difference of these subjective changes.[52] Reports of other more objective measures of symptomatic burden, such as the 6-min walk test, were infrequent among included studies. Despite some inherent limitations, evidence of significant improvements in LVEF and NYHA in meta-analysis of intention-to-treat results of included randomized trials, corroborates the hypothesis of higher efficacy with CSP-CRT in select cases.

The significantly greater QRS narrowing with CSP-CRT could have been crucial in achieving echocardiographic and clinical response, since QRSd, as a simple and routinely used measure of electrical resynchronization, determines both the indication and success of CRT. In other words, it may not be the conduction system capture itself, but rather narrow-paced QRS, whether it is achieved by CSP- or BiV-CRT, that results in improved LVEF and clinical outcomes.[53] It is crucial to consider that measurements of QRSd may be subjective and lack reliability and reproducibility. In addition, heterogeneity exists in the methods of measuring QRSd used by each study. Therefore, caution is advised in interpretation of QRSd results.

The reported procedural success rates of 91% for LBB-CRT and 73% for His-CRT are promising; nevertheless, the success rates showed significant heterogeneity among studies. Experience of the operators is perhaps an important determinant of implantation success, as CSP is shown to have a steep learning curve.[54,55]

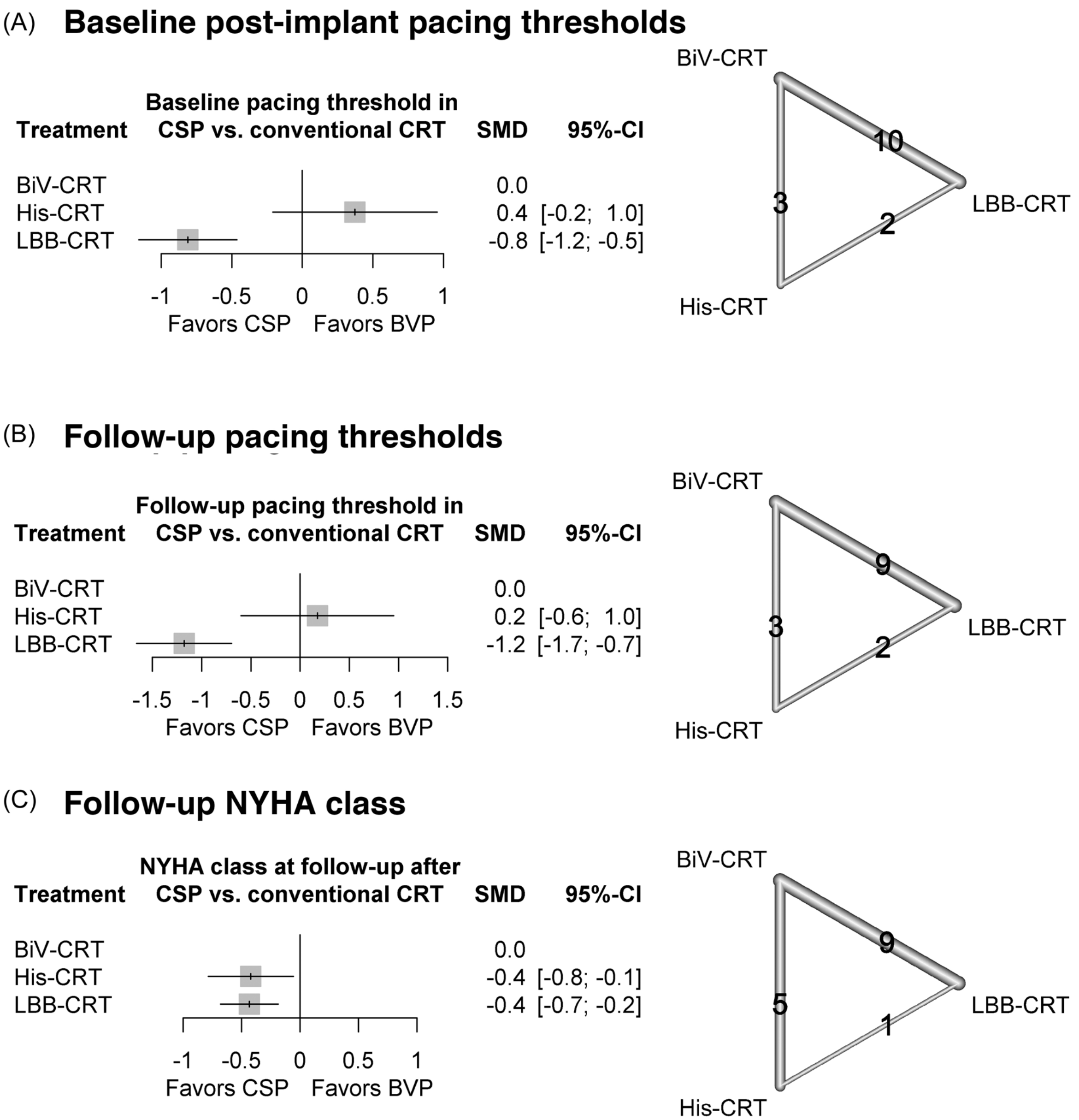

FIGURE 4 Pooled Hedges standardized mean differences in network meta-analyses with corresponding network graphs for (A) baseline post-implant pacing thresholds, (B) follow-up pacing thresholds, and (C) New York Heart Association (NYHA) class.

Registry data from European centers shows a success rate of 90% for left bundle branch area pacing; however, implantation for heart failure indications was associated with lower success rates of about 82%.[54] On the other hand, the implantation success of BiV-CRT in clinical trial setting has been about 95%.[50,51,56] In patients with heart failure, it is hypothesized that enlarged cardiac chambers or septal fibrosis may contribute to higher rates of LBB-CRT lead implantation failures.[54] The lower success rates with His-CRT may be attributable to higher proportion of unacceptable pacing thresholds. Moreover, the probability of success for His-CRT to correct left bundle branch block is significantly lower when the block is more distal, while His-CRT, and maybe even LBB-CRT, fail to achieve resynchronization in patients with conduction defects due to intraventricular or intramyocardial disease.[3] This latter group of conduction abnormalities may be more prevalent among patients with heart failure indicated for CRT. Notably, due to heterogenous reporting of studies, we could not investigate the rates of selective and nonselective His- or LBB-pacing. In several studies of LBB-CRT, left bundle branch area pacing or left septal pacing could be considered a success. While implantation success rates are acceptable, the question of CSP-CRT durability is still unresolved. In this study, the numerically higher pacing thresholds with His-CRT may result in lower generator longevity.

In addition to His- and LBB-CRT, His-optimized and LBB-optimized pacing, which use a combination of previous methods to optimize resynchronization, are also available as CRT options, albeit with lower number of studies.[57,58] Considering the diversity of clinical features in patients indicated for CRT, an ideal scenario would be to individualize CRT options in the future. Our study could not provide data about the effectiveness of CSP-CRT with regard to patients' characteristics. A meta-regression considering baseline LVEF, QRSd, and QRS morphology was considered but was not feasible due to the low number of studies that report outcomes in different subgroups. Notably, most participants in the CSP-CRT studies had nonischemic causes of heart failure. This may be due to a higher proportion of patients with ischemic cardiomyopathy having distal intramyocardial conduction disease, and would potentially derive more benefit from BiV-CRT rather than CSP-CRT. Another notable feature in our study was the higher number of publications investigating LBB-CRT compared to His-CRT, which marks a shift of interest towards the more novel LBB-CRT. Ongoing clinical trials of CSP-CRT will provide a better understanding of the efficacy, as well as tailored indications of these novel approaches.[59,60]

4.1 | Limitations

First, most of the included studies use observational designs, which increases the risk of selection bias and unmeasured confounding. Second, we observed a high level of heterogeneity in our meta-analyses, that could not be attributed to a heterogenous design in studies. Third, we could not report outcomes among different subgroups of patients since such data was not available from the included studies.

5 | CONCLUSION

The currently available evidence favors CSP-CRT as a feasible and effective treatment that achieves greater improvements in LV function, QRSd, and heart failure symptoms. Notably, LBB-CRT showed a higher clinical response rate and lower pacing thresholds than His-CRT. While this study has synthesized evidence supporting the effectiveness of CSP-CRT, the observational designs and relatively short follow-up durations of the included studies limit the robustness of conclusions. Future data from randomized controlled trials is needed to confirm or refute these findings.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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