

Conduction System Pacing versus Biventricular Pacing in Heart Failure with Reduced Ejection Fraction: A Bayesian Meta-Analysis

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Abstract

Background

Conduction system pacing (CSP) has emerged as a physiological alternative to biventricular pacing (BiVP) for cardiac resynchronization therapy in patients with heart failure with reduced ejection fraction (HFrEF), although its comparative clinical effectiveness remains uncertain.

Objectives

To compare CSP with BiVP for cardiac resynchronization in patients with HFrEF.

Methods

We searched PubMed, Embase, Cochrane, and Clinicaltrials.gov for RCTs comparing CSP vs BiVP in patients with HFrEF. For binary outcomes, odds ratio (OR) with 95% CrI were estimated using a Bayesian binomial-normal hierarchical model. For continuous outcomes, mean differences (MD) with 95% credible intervals (CrIs) were estimated using a Bayesian random-effects model.

Results

Thirteen studies comprising 1,221 patients met the inclusion criteria. Compared with BiVP, CSP was associated with a lower odds of all-cause mortality (OR, 0.63; 95% CrI, 0.33–1.13), corresponding to a 94% posterior probability of benefit (OR < 1). Similarly, CSP was associated with a lower odds of heart failure hospitalization (OR, 0.75; 95% CrI, 0.41–1.36), with an 84% probability of benefit. The 95% prediction interval for mortality ranged from 0.28 to 1.45, indicating uncertainty regarding the treatment effect in future studies. CSP resulted in a high probability (> 98%) for improvement in surrogate clinical outcomes of QRS narrowing, left ventricular end-systolic volume, left ventricular end-diastolic volume, and left ventricular ejection fraction.

Conclusion

CSP offers advantages in surrogate outcomes over BiVP pacing in CRT selected patients; however, additional randomized trials are required before CSP can be recommended as the routine first-line CRT strategy to improve survival and reduce future hospitalizations.

1. Introduction

Cardiac resynchronization therapy (CRT) with biventricular pacing (BiVP) is an established treatment for selected patients with heart failure with reduced ejection fraction (HFrEF) and electrical dyssynchrony. [1, 2] Despite its proven efficacy, approximately one-third of patients fail to achieve a clinically meaningful response, prompting interest in alternative approaches that may provide more physiological ventricular activation. [3, 4]

Conduction system pacing (CSP), including His bundle pacing (HBP) and left bundle branch area pacing (LBAP), directly engages the native cardiac conduction system and may improve electrical resynchronization compared with conventional BiVP. [4–6] Early randomized trials and observational studies have reported favorable effects on electrical and echocardiographic measures, including QRS duration and left ventricular remodeling. However, uncertainty remains regarding whether these physiological advantages translate into improved clinical outcomes such as mortality and heart-failure hospitalization.

Previous meta-analyses have suggested potential benefits of CSP but were limited by relatively small numbers of randomized trials and patients. [7–9] Since publication of these reviews, several additional randomized trials have become available, substantially increasing the evidence base. [10–15] We, therefore, performed an updated systematic review and Bayesian meta-analysis of randomized trials comparing CSP with BiVP in patients with HFrEF. Our primary objective was to evaluate the probability of CSP benefit on mortality and heart-failure hospitalization. Secondary objectives were to assess the probability of improvements in the surrogate markers of cardiac resynchronization, ventricular remodeling, functional status, and procedural outcomes.

2. Methods

The Bayesian framework was used to estimate the probabilities and uncertainties of clinically relevant treatment effects. [16–18] This systematic review and Bayesian meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guideline. [20] The PRISMA checklist is provided in the Supplemental file 2. We conducted this systematic review and meta-analysis according to a prespecified protocol registered with PROSPERO

(CRD420261450587). Institutional review board approval and informed consent were not required because this study synthesized aggregate data from previously published trials and did not involve access to individual participant level data.

2.1. Data Sources and Search Strategy

We searched PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov from inception to July 2026, without restriction on language or publication status. The complete search strategy for each database is provided in eTable 1 in Supplementary file. Two authors (M.Q. and W.R.) independently screened titles and abstracts against prespecified eligibility criteria; discrepancies were resolved by consensus, with a third author (O.A.G.) adjudicating unresolved disagreements.

2.2. Eligibility Criteria

Studies were eligible for inclusion if they were (1) peer reviewed randomized clinical trials; (2) direct comparisons of conduction system pacing (CSP) with biventricular pacing (BiVP); (3) conducted in patients with heart failure with reduced ejection fraction (HFrEF) and a left ventricular ejection fraction (LVEF) of 40% or less; and (4) reported at least one outcome of interest.

Studies were excluded if they (1) enrolled children or adolescents; (2) used a nonrandomized design; (3) included a control group that received a resynchronization strategy other than BiVP; (4) enrolled patients with preserved ejection fraction; or (5) were conference abstracts without a corresponding peer-reviewed publication. Studies were included regardless of the length of follow-up

2.3. Outcomes of Interest

The prespecified primary outcomes were all-cause mortality and hospitalization for heart failure. Secondary outcomes included QRS narrowing, improvement in LVEF, reduction in left ventricular end-diastolic and end-systolic volumes, New York Heart Association (NYHA) functional class and procedural outcomes including procedure duration, fluoroscopy time, and periprocedural complications.

2.4. Bayesian Analysis

Random-effects meta-analyses were conducted within a Bayesian framework. [21, 22] For the primary binary outcomes (all-cause mortality and heart-failure hospitalization), we used a binomial-normal hierarchical model specifically developed for meta-analyses of rare events. [23] In this model, study-specific treatment effects were assumed to arise from a common distribution characterized by an overall treatment effect and a between-study heterogeneity parameter. Weakly informative priors were specified for treatment effects, centered on no difference between treatment groups. For between-study heterogeneity, we used empirically derived priors proposed by Turner et al. based on distributions observed across large collections of randomized clinical trials. [24] Detailed model specifications and prior distributions are provided in the Supplement.

Treatment effects for binary outcomes are reported as posterior median odds ratios (ORs) with 95% credible intervals (CrIs). Posterior probabilities of benefit were calculated directly from the posterior distributions. To facilitate clinical interpretation, pooled ORs were additionally converted to absolute risk differences using plausible baseline event risks; details of these calculations are provided in the Supplement. [25, 26] Continuous outcomes were analyzed using Bayesian random-effects meta-analysis implemented in the *bayesmeta* package. [27] Results are reported as mean differences (MDs) with corresponding 95% CrIs. Additional details regarding priors and model specifications are provided in the Supplement.

2.4.1. Between-Study Heterogeneity and Predictive Distribution

Because treatment effects may vary across studies, we estimated between-study heterogeneity using random-effects models and incorporated this uncertainty into posterior predictive distributions. These distributions provide the range of treatment effects that might reasonably be expected in a future study population by accounting for uncertainty in both the pooled treatment effect and between-study heterogeneity. [21, 28–31]

2.4.2. Sensitivity and Subgroup Analyses

Sensitivity analyses confirmed the robustness of results to alternative prior distributions for the treatment-effect and heterogeneity parameters. Additional details are provided in the Supplement. [32] We also performed leave-one-out analyses in which each study was sequentially excluded and the primary model refitted to assess the influence of individual studies on the pooled estimates. Prespecified subgroup analyses compared studies evaluating HBP and LBAP. Given the limited number of studies and the absence of direct randomized comparisons between pacing modalities potentially introducing an ecological bias, these analyses were considered exploratory.

2.4.3. Model Diagnostics and Code

Meta-analyses and posterior predictive analyses of the primary outcomes were conducted using Stan⁹ through the R packages brms and MetaStan. [33, 34] Four Markov chains were run, each with an initial warm-up phase of 2000 iterations followed by 4000 sampling iterations. Model convergence and adequate posterior sampling were confirmed against the When to Worry and How to Avoid the Misuse of Bayesian Statistics (WAMBS) checklist [35–37] and its subsequent extension. Reporting of the Bayesian analyses was further cross-checked against the more comprehensive Bayesian Analysis Reporting Guidelines (BARG), [38] as well as against methodological recommendations specific to Bayesian analyses of clinical and epidemiologic studies, [39, 40] to ensure that prior justification, convergence diagnostics, and posterior interpretation were reported with the

transparency these guidelines recommend. All analyses were conducted in R, version 4.4.3 (R Foundation for Statistical Computing). All code is available at (<https://github.com/omargill26/Electro-Physio-Bayesian-Meta-analysis>).

3. Results

3.1. Studies selection and characteristics

The initial search yielded 1779 results (eFigure 1). After removing duplicate records and screening ineligible studies based on title and abstract, 58 remained and were fully reviewed according to the inclusion criteria. A total of 13 studies were included [10–15, 41–50], comprising 11 randomized controlled trials and 2 crossover trials (Table 1). [47, 48] Two studies were reported in multiple publications. [41–45] Only data from the longest follow-up was considered with multiple publications. Across all included studies, the total sample size was 1221 participants (650 patients undergoing CSP and 571 patients undergoing BiV). CSP was predominantly performed through LBAP in recent studies. Additionally, the characteristics of included studies are given in Supplementary eTable 3.

Table 1
Baseline Characteristics of Included Studies

Study ID (Trial)	Population / Intervention	Age, y (CSP/BiV)	Male, n (%) (CSP/BiV)	Hypertension, n (%) (CSP/BiV)	Diabetes, n (%) (CSP/BiV)	Atrial Fibrillation, n (%) (CSP/BiV)	LVEF, % (CSP/BiV)	HF Etiology, n (CSP/BiV)	
								Ischemic	Non- ischemic
Lustgarten et al. 2015	HFrEF + LBBB/RBBB; Dual HBP/BiVP implantation with randomized 6-month crossover (patient-blinded)	71.3 (55.9–86.8) [†]	19 (65.5%) / NR	NR / NR	5 (17.2%) / NR	NR / NR	26.5 (21.0–32.0) [†] / NR	16	13
Upadhyay et al. (His-SYNC) 2019	HFrEF + LBBB/RBBB + AF; Central randomization to His-CRT or BiV-CRT	63.4 ± 13.3 / 65.5 ± 12.4	9 (56.3%) / 16 (66.7%)	NR / NR	8 (50.0%) / 11 (45.8%)	NR / NR	28.0 (23.0–34.0) [†] / 27.7 (23.6–30.7) [†]	27	14
Vinther et al. (His Alternative) 2021	HFrEF + LBBB; 1:1 randomization to BiV pacing or His pacing (CRT-P/CRT-D)	67.7 ± 9.0 / 63.8 ± 9.4	18 (72.0%) / 14 (56.0%)	12 (48.0%) / 22 (88.0%)	NR / NR	12 (48.0%) / 22 (88.0%)	30 ± 8 / 30 ± 6	6/5	19/20
Huang et al. (ALTERNATIVE AF) 2022	AF + AVNA + HFrEF; AVNA with randomized 9-month HBP/BVP crossover	63.7 ± 12.1 / 65.1 ± 8.2	19 (76.0%) / 17 (68.0%)	NR / NR	3 (6.0%) / 4 (8.0%)	NR / NR	31 ± 6 / 29 ± 8	2	48
Pujol-Lopez et al. (LEVEL AT) 2022	HFrEF + LBBB/RBBB; 1:1 randomization to BiVP or CSP	65.7 ± 9.0 / 68.1 ± 9.0	23 (69.7%) / 25 (71.4%)	15 (45.5%) / 12 (36.4%)	10 (30.3%) / 14 (42.4%)	15 (45.5%) / 12 (36.4%)	27 ± 7 / 28 ± 7	11/11	24/24
Wang Y et al. (LBBP-RESYNC) 2022	HFrEF + LBBB; Prospective randomized trial comparing LBBP and BiVP for CRT	62.3 ± 11.2 / 65.3 ± 10.6	7 (35.0%) / 13 (65.0%)	NR / NR	NR / NR	NR / NR	28.3 ± 5.3 / 31.1 ± 5.6	0	40
Vijayaraman et al. (HOT-CRT) 2023	HFrEF + LBBB + AF; CSP (HBP→LBBAP if needed) vs standard BiVP implantation	71.0 ± 13.4 / 68.9 ± 11.5	39 (78.0%) / 30 (60.0%)	NR / NR	26 (52.0%) / 23 (46.0%)	4 (25.0%) [‡] / 9 (37.5%) [‡]	30.1 ± 9.1 / 30.7 ± 9.3	20/19	30/31
Zimmerman et al. (Physio Sync HF) 2026	HFrEF + LBBB; 1:1 randomization to CSP (preferentially LBBAP) or BiVP	61 (55–67) [†] / 63 (57–70) [†]	42 (48.3%) / 45 (52.3%)	66.7% / 61.6%	40.2% / 34.9%	8.0% / 5.8%	26 (23–31) [†] / 27 (22–32) [†]	13/9	74/77
Cano Ó et al. (LEFT-BUNDLE-CRT) 2026	HFrEF + LBBB; Randomization to LBBAP-CRT or BiVP-CRT	67.3 ± 9.7 / 68.7 ± 12.0	61 (74.4%) / 56 (60.9%)	16 (19.5%) / 16 (17.4%)	56 (68.3%) / 47 (51.1%)	NR / NR	30 ± 7.5 / 29.3 ± 6.7	25/23	67/60
Pujol-López et al. (CONSYST-CRT (LEVEL AT)) 2025	HFrEF + LBBB; Randomization to BiVP or CSP	69 ± 9 / 69 ± 9	81 (60.4%)* / 50 (74.6%)	48 (71.6%) / 47 (70.1%)	27 (40.3%) / 26 (38.8%)	48 (71.6%) / 47 (70.1%)	28 ± 6 / 27 ± 7	23/23	44/44

Study ID (Trial)	Population / Intervention	Age, y (CSP/BiV)	Male, n (%) (CSP/BiV)	Hypertension, n (%) (CSP/BiV)	Diabetes, n (%) (CSP/BiV)	Atrial Fibrillation, n (%) (CSP/BiV)	LVEF, % (CSP/BiV)	HF Etiology, n (CSP/BiV)	
								Ischemic	Non- ischemic
Žižek et al. (CSP-SYNC) 2025	HFrEF + LBBB; 1:1 randomization to LBBAP or BiV	65 (59– 72) [†] / 70 (57–77) [†]	23 (74.2%) / 21 (67.7%)	NR / NR	NR / NR	NR / NR	30 ± 5 / 28 ± 6	11/9	20/22
Chen X et al. (Heart Sync LBBP) 2026	HFrEF + LBBB; 1:1 randomization to LBBP or BiVP	64.3 ± 9.5 / 65.3 ± 9.5	67 (67.0%) / 69 (69.0%)	26 (26.0%) / 28 (28.0%)	21 (21.0%) / 23 (23.0%)	NR / NR	28.3 ± 3.8 / 28.1 ± 5.0	84/81	16/19
Frandsen et al. 2026	HFrEF + LBBB; 1:1 randomization to His-CRT or BiV-CRT	67.4 ± 9.1 / 63.2 ± 9.2	18/14	No data§	No data§	No data§	No data§	2/9	23/16
Zhang et al. 2025	HFrEF + LBBB; 1:1 randomization to LOT-CRT or BiV-CRT	55.8 ± 10.0/ 56.5 ± 10.4	24/21	NR	8/6	NR	26.0 ± 4.3 / 26.8 ± 4.2	NR	NR

3.2. Primary Outcomes

3.2.1. All-cause Mortality

The average OR for all-cause mortality was 0.63 (95% credible interval [CrI], 0.33, 1.13; Fig. 1, eTable 4) with a posterior probability of any clinical benefit (OR < 1) of 94% and the probability of clinical meaningful association (OR < 0.9) of 88% (Fig. 2). Clinical decision making is better informed by absolute risk differences (RDs). For patients with HFrEF receiving CSP compared with BiVP, the risk difference for mortality was 3.2% (95% CrI, – 0.7% to 6.7%), with 87% probability of clinically meaningful benefit (RD > 1%), assuming the 10% baseline risk. Regarding the predictive distribution (Fig. 1), we found a 95% probability that the true OR of a future study would lie between 0.28 and 1.45 (Fig. 1), posterior probability of 87% for OR < 1.0 (eTable 4). Sensitivity analyses with sequential omission of individual studies resulted in OR values ranging from 0.39 to 0.72. The recent randomized controlled trial (Physio-Synch HF) exerted a disproportionate influence on the overall estimate. Excluding this trial shifted the posterior distribution toward a stronger treatment effect, with the 95% credible interval (0.20 to 0.78) no longer including the null value. (eFigure 07).

3.2.2. Heart Failure Hospitalization

For heart failure hospitalization, CSP was associated with a lower odds of hospitalization than BiVP (OR, 0.74; 95% CrI, 0.41–1.36) (Figs. 3, eTable 4). This corresponded to an 84% posterior probability of any clinical benefit (OR < 1) and a 75% posterior probability of a clinically meaningful benefit (OR < 0.9) (Fig. 4). On the absolute scale, the estimated risk difference was 3% (95% CrI, – 3.4% to 8.9%), corresponding to an 77% posterior probability of an absolute risk reduction greater than 1% (RD > 1%) (eTable 4). For the predictive distribution (Fig. 3), there is 95% probability that the treatment effect of a future study for this clinical endpoint would lie between 0.21 and 2.60, with 68% probability of any benefit. Leave-one-out sensitivity analysis showed the pooled estimates ranging from 0.61 [0.34; 1.09] (excluding Vijayaraman, 2023) to 1.01 [0.57; 1.68] (excluding Chen et al., 2026), compared with 0.74 [0.41; 1.36] overall. All leave-one-out estimates, including those with the largest point-estimate shifts, retained 95% credible intervals crossing the null value (OR = 1) (eFigure 10).

3.3. Secondary outcomes

The overall pooled mean difference for QRS duration was – 14.4 ms (95% CrI, – 22.5 to – 6), corresponding to a 99.9% posterior probability of benefit (MD < 0) (Table e4; eFigures 11 and 12). CSP was also associated with improvements in LVEF (eFigures 16 and 17) and reductions in LVESV (eFigures 18 and 19) and LVEDV (eFigures 20 and 21), and improvements in NYHA functional class (eFigures 22 and 23). Posterior marginal distributions and posterior probabilities of benefit for all secondary outcomes are presented in eTable 4.

3.4. Procedural outcomes

CSP was associated with longer procedural time (MD 7.3 minutes; 95% CrI – 0.1 to 14.7), and fluoroscopy time MD 0.33 minutes; 95% CrI – 3.7 to 4.5), with 2% and 43% posterior probabilities of any benefit (MD < 0), respectively (eTable 4; eFigures 24 and 25). However, there was no clear evidence of a difference in risk between CSP and BiVP for procedural complications (OR 0.68; 95% CrI 0.41–1.11), and lead displacement or revision (OR 1.01; 95% CrI 0.52–1.96) (eFigures 26 and 27).

3.5. Subgroup analysis

HBP was associated with greater QRS narrowing than LBAP (MD, - 24 ms [95% CrI, - 37 to - 12] vs - 10.4 ms [95% CrI, - 19 to -2]). The posterior probability of any benefit (MD < 0) was 99.9% for HBP and 98.9% for LBAP, respectively (eTable 5). The posterior probability of a subgroup difference was 96%. For the remaining secondary outcomes, LBAP had higher posterior probabilities of benefit than HBP, including LVEF improvement (97% vs 75%), LVESV reduction (99% vs 70%), LVEDV reduction (95% vs 74%), and NYHA functional class improvement (98% vs 68%) (eTable 5).

3.6. Sensitivity analysis

Sensitivity analyses for primary endpoint all-cause mortality showed that different priors did not substantially affect overall effect estimates (eFigure 8). On the other hand, posterior predictive distributions were dependent on the choice of prior for the between-study heterogeneity parameter (eFigure 9). However, these posterior predictive distributions did not vary substantially and suggested adequate model calibrations. Furthermore, sensitivity analysis for QRS interval shortening showed that different priors did not substantially affect subgroups (HBP and LBAP), and overall effect estimates (eFigures 13–15).

3.7. Risk of bias assessment

Among the 11 parallel-group randomized controlled trials assessed using the RoB 2 tool, 9 were judged as having **some concerns**, primarily because of deviations from intended interventions. Concerns related to the missing outcome data, and outcome measurement were generally low across most of the studies. The 2 randomized crossover trials, assessed using the RoB 2 extension for crossover trials, were also judged as having **some concerns**, predominantly because of potential bias arising from period and carryover effects in addition to deviations from intended interventions. No study was judged to be at high risk of bias or to have critical methodological limitations (eFigures 28 and 30, eTable 6).

3.8. Certainty of Evidence

The certainty of evidence was low for the primary clinical outcomes of all-cause mortality and heart failure hospitalization. The certainty was downgraded because of concerns regarding risk of bias, primarily related to the open-label design of the included trials and crossover between treatment groups, as well as imprecision due to the limited number of events. In contrast, the certainty of evidence was moderate for the secondary outcomes, including QRS duration, left ventricular ejection fraction, left ventricular end-systolic volume, and left ventricular end-diastolic volume, reflecting generally consistent findings despite some remaining concerns regarding risk of bias and imprecision. Detailed certainty assessments for each outcome are presented in Supplementary eTable 7.

4. Discussion

This systematic review and meta-analysis of randomized controlled trials provides the most up-to-date assessment of conduction system pacing (CSP) compared with biventricular pacing (BiVP) in patients with heart failure and reduced ejection fraction. Across surrogate outcomes, CSP demonstrated consistent improvements in ventricular electrical synchrony, left ventricular reverse remodeling, and systolic function, with high posterior probabilities supporting clinically meaningful benefit. In contrast, although the posterior distributions favored CSP for mortality and heart failure hospitalization, substantial uncertainty remained, with credible and prediction intervals encompassing no treatment effect or null. Similarly, estimates for periprocedural complications and lead displacement or revision were imprecise, with credible intervals spanning both benefit and harm, precluding definitive conclusions regarding differences in safety between the two pacing strategies.

Although the analyses of all-cause mortality and heart failure hospitalization did not provide conclusive evidence of benefit, the posterior median odds ratios consistently favored CSP, suggesting that a clinically meaningful treatment effect remains plausible.

However, these findings should be interpreted with caution because the 95% credible intervals encompassed both substantial benefit and no effect. Moreover, the wide prediction intervals indicate considerable uncertainty regarding the treatment effect that may be observed in future studies, reflecting the limited number of available randomized trials and the observed between-study heterogeneity. While the posterior probability favored CSP over BiVP, more stringent thresholds for clinically meaningful benefit were not consistently supported, indicating that the current evidence remains insufficient to establish definitive reductions in mortality or heart failure hospitalization. These findings are consistent with the variability observed across the individual randomized trials. Collectively, these findings suggest that the true treatment effect is likely more modest than the most optimistic estimates reported by individual studies. Therefore, rather than confirming or refuting a survival or hospitalization benefit, the current evidence indicates that any clinical advantage of CSP remains uncertain and requires confirmation in future high-quality randomized trials.

Several factors may have contributed to the observed between-study heterogeneity, including differences in patient selection, pacing phenotype, criteria used to confirm conduction system capture, operator experience, and the quality of the BiVP comparator. One potentially important source of variation is the inclusion of left ventricular septal pacing (LVSP) within the broader category of left bundle branch area pacing (LBBAP), despite true left bundle branch capture and septal myocardial pacing representing electrophysiologically distinct pacing strategies. [51, 52] Notably, nearly 30% of patients randomized to CSP in the PhysioSync-HF trial underwent LVSP rather than true left bundle branch pacing, a factor that may have attenuated the observed treatment effect. This interpretation is supported by Cano et al., who classified deep septal pacing as an unsuccessful CSP implant and reported a lower likelihood of clinical response, suggesting that failure to achieve true conduction system capture may reduce the effectiveness of cardiac resynchronization therapy. However, this explanation remains hypothesis-generating because patient-level data were unavailable, precluding definitive assessment of the contribution of pacing phenotype to the observed between-study heterogeneity.

Despite this heterogeneity, CSP consistently improved markers of electrical synchrony and reverse ventricular remodeling, reducing QRS duration by approximately 14 ms, increasing left ventricular ejection fraction by approximately 4 percentage points, reducing left ventricular end-systolic volume by approximately 6 mL, and reducing left ventricular end-diastolic volume by approximately 7 mL. These findings are biologically plausible, as CSP directly recruits the native His–Purkinje conduction system, resulting in more physiological ventricular activation than conventional BiVP. Restoration of near-normal ventricular activation reduces electrical dyssynchrony, improves mechanical coordination, and promotes reverse remodeling, providing a mechanistic explanation for the consistent improvements observed across echocardiographic outcomes. Our exploratory subgroup analyses suggested that His bundle pacing achieved greater QRS narrowing than left bundle branch area pacing, whereas left bundle branch area pacing was associated with larger improvements in ventricular remodeling and systolic function. These differences may reflect the distinct electrophysiological characteristics of the two pacing modalities. However, these subgroup findings should be interpreted cautiously because they were derived by combining within-trial and across-trial interaction estimates, an approach that is susceptible to ecological bias and therefore cannot establish definitive differences between pacing strategies. [53]

Several meta-analyses have compared conduction system pacing (CSP) with biventricular pacing (BiVP), but their conclusions regarding major clinical outcomes have been inconsistent. [7–9] The meta-analysis study by Ferreira Felix., including 7 RCTs assessed all-cause mortality and heart failure hospitalization, but reported no significant differences between CSP and BiVP, highlighting the uncertainty surrounding the comparative effectiveness of these pacing strategies for these clinical endpoints. [7] In contrast, another meta-analysis demonstrated that CSP was associated with a significant decrease in all-cause mortality and hospitalization for heart failure, however, its findings were derived predominantly from observational studies and were therefore more susceptible to residual confounding and selection bias.

Our findings are broadly consistent with previous meta-analyses demonstrating superior electrical resynchronization and improved ventricular function with CSP, while extending and sharpening the current evidence and its interpretation in several important ways. First, we included six additional [10–15] randomized trials compared with recent previous review. [7] The inclusion of these contemporary trials substantially increasing the evidence base and doubled the cumulative sample size, resulting in more precise effect estimates. Second, we applied a Bayesian framework in our study which generates posterior distributions and directly estimates the probability of treatment effects across a range of clinically relevant values. [54] Finally, the posterior predictive distributions enabled estimation of how CSP may perform in hypothetical future settings, helping to bridge the gap between clinical trial findings and real-world clinical decision-making.

4.1. Clinical implications and Future directions

Our findings support increasing consideration of CSP as an alternative to conventional BiVP in appropriately selected patients requiring cardiac resynchronization therapy, particularly when improvement in ventricular synchrony and reverse remodeling is the primary therapeutic objective. Nevertheless, the current evidence does not yet justify definitive conclusions regarding reductions in mortality or heart failure hospitalization. Therefore, treatment decisions should remain individualized, considering patient characteristics, the likelihood of successful conduction system capture, operator expertise, and the quality of the BiVP comparator, until further high-quality randomized controlled trials provide more conclusive evidence. In addition, evaluations of procedural complexity, resource utilization, and cost-effectiveness are needed to inform the broader implementation of CSP, particularly in low- and middle-income countries and centers with limited experience. Prespecified subgroup analyses based on heart failure etiology, conduction abnormalities, ventricular function, and pacing phenotype may help identify the patients most likely to benefit from each pacing strategy.

4.2. Limitations:

Our findings should be interpreted in the context of certain limitations that are predominantly inherent to the studies included. First, the primary clinical analyses were based on few events, and most individual trials were not designed or powered primarily for mortality or heart failure hospitalization. Second, follow-up duration and outcome definitions varied across studies, and pooled odds ratios do not account directly for differences in follow-up time or censoring. Third, the trials included heterogeneous populations and pacing strategies, with variable definitions of conduction system capture and potential differences in implantation success, crossover, device programming, and BiVP optimization. Moreover, most trials were open-label, and reporting of blinded outcome adjudication, attrition, and prespecified analysis plans was incomplete. Fourth, we could not perform several prespecified subgroup analyses on ischemic and non-ischemic populations due to the lack of granularity in reported data. Further, the lack of patient-level data does not allow analyses using more complex statistical models that incorporate multiple characteristics. [55] Finally, the available follow-up provides limited information regarding chronic capture thresholds, lead durability, battery longevity, and late device-related complications. Lastly, we could not include ongoing trials, the Canadian LEFT-HF trial, HIS-CRT, Left vs left, HIS Alternative II-UK Site, and RECOVER-HF in our study.

Despite these limitations, the present study has several important strengths. It represents the largest Bayesian synthesis of randomized evidence comparing CSP with BiVP, incorporates recently published trials, evaluates both relative and absolute treatment effects, examines clinically meaningful benefit using posterior probabilities, and explicitly quantifies predictive uncertainty through prediction intervals. The Bayesian updating analysis further illustrates how future randomized evidence could modify current estimates, providing a transparent framework for interpreting evolving evidence.

5. Conclusions

This systematic review and Bayesian meta-analysis demonstrates that, in patients with heart failure and reduced ejection fraction requiring cardiac resynchronization therapy, conduction system pacing is associated with consistent improvements in electrical synchrony, left ventricular reverse remodeling, and systolic function compared with biventricular pacing. Although the posterior probabilities favored CSP for reducing all-cause mortality and heart failure hospitalization, the available randomized evidence remains uncertain and does not permit definitive conclusions regarding clinically meaningful improvement in hard outcomes. These findings support CSP as a promising physiological alternative to conventional BiVP while emphasizing the need for further high-quality randomized controlled trials to determine whether its physiological advantages translate into meaningful long-term clinical benefits.

Abbreviations

AF, atrial fibrillation; AVNA, atrioventricular node ablation; BiV, biventricular; BiVP, biventricular pacing; CRT, cardiac resynchronization therapy; CRT-D, CRT with defibrillator; CRT-P, CRT with pacemaker; CSP, conduction system pacing; HBP, His bundle pacing; HFrEF, heart failure with reduced ejection fraction; LBBAP, left bundle branch area pacing; LBBB, left bundle branch block; LBBP, left bundle branch pacing; NR, not reported; RBBB, right bundle branch block; SD, standard deviation.

Declarations

CRedit Author Statement

OAG. contributed to conceptualization, methodology, formal analysis, writing – review and editing, writing – original draft, supervision, and project administration. **AZ.** was involved in conceptualization, investigation, and writing – review and editing. **AS.** participated in methodology, investigation, and writing – review and editing. **MF.** was responsible for data curation, visualization, and writing – original draft. **WR.** was responsible for data curation, visualization, and writing – original draft. **UAK.** participated in methodology, investigation, and writing – review and editing. **MUG** were responsible for methodology, formal analysis, data curation, and visualization. **MQ.** contributed to data curation and visualization and validation, and writing – review and editing. **AHEK.** contributed to data curation and visualization and validation, and writing – review and editing. **PP.** contributed to data curation and visualization and validation, and writing – review and editing. **Prof. JMB.** contributed to data curation and visualization and validation, code validation and writing – review and editing original manuscript.

Patient Consent Statement

Not Applicable

Conflict of interest

The authors declared no conflicts of interest.

Author Approval

All authors reviewed and approved the final version of the manuscript.

Disclosures

All authors declare no conflicts of interest and take full responsibility for the integrity and interpretation of data.

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Figures

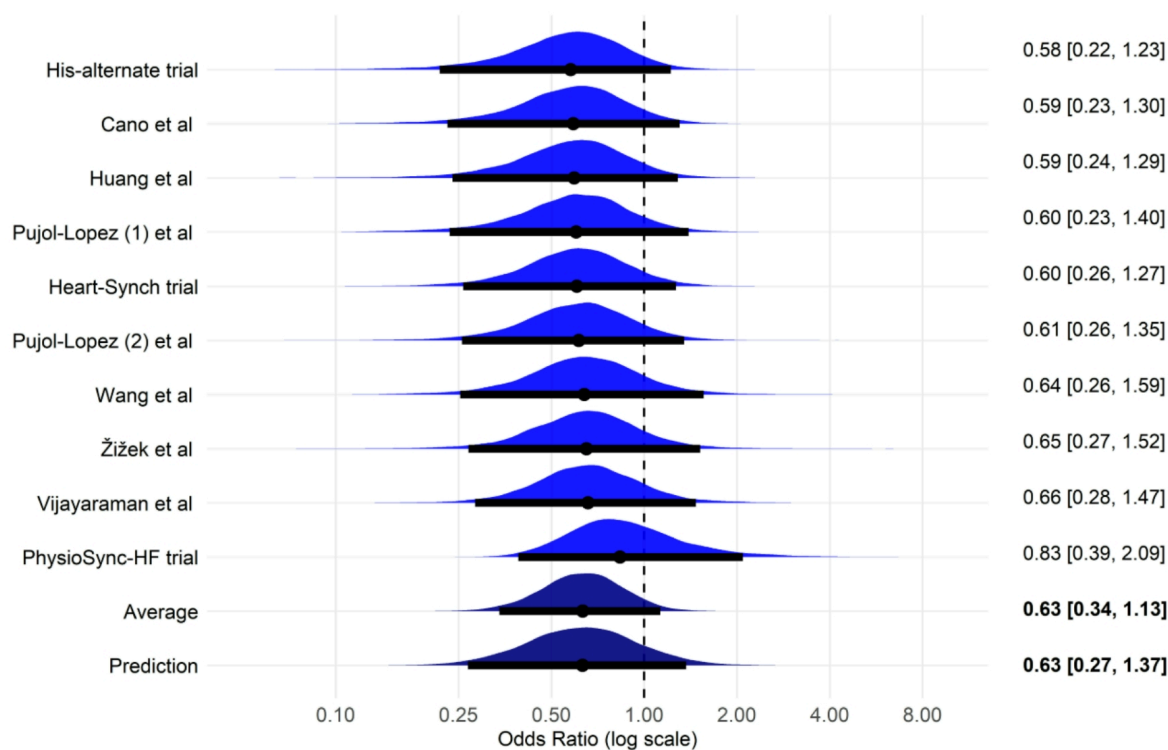


Figure 1

Plot of all-cause mortality performed using a Bayesian hierarchical binomial random-effects model. Weakly informative priors were specified as $\theta \sim \text{Normal}(0, 0.82^2)$ for the primary overall treatment effect on the log-odds ratio scale and informative prior $\tau \sim \text{lognormal}(-1.75, 0.63^2)$ for the between-study heterogeneity, based on the empirical priors proposed by Turner et al. Pooled posterior odds ratios (ORs) with corresponding 95% credible intervals (CrIs) are presented.

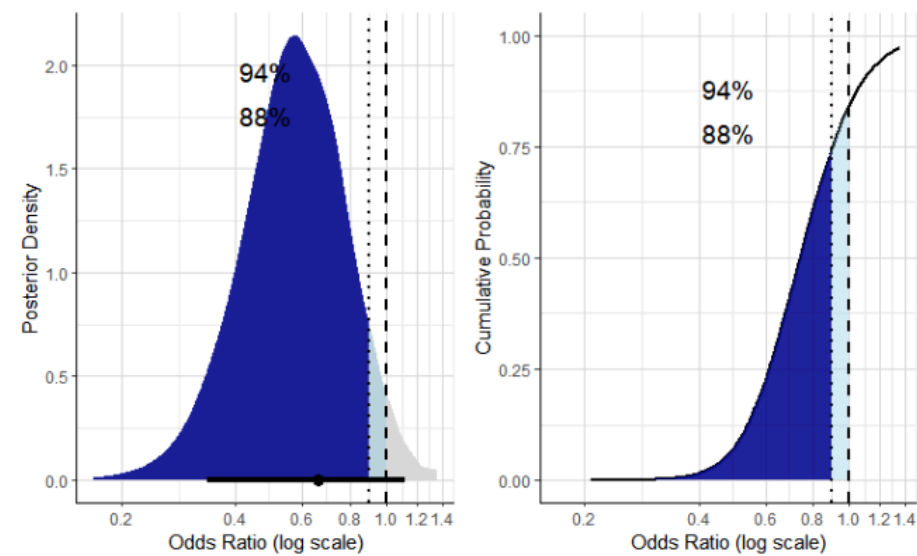


Figure 2

Posterior distribution and cumulative posterior probability for the pooled odds ratio of all-cause mortality. The left panel shows the posterior probability density of the pooled odds ratio (OR) comparing conduction system pacing (CSP) with biventricular pacing (BiVP). The right panel displays the corresponding cumulative posterior probability distribution. The dashed vertical line denotes the null effect (OR = 1), and the dotted vertical line denotes a prespecified threshold for clinically meaningful benefit (OR = 0.9). The shaded areas represent the posterior probabilities that the true treatment effect favors CSP (OR < 1) and that CSP achieves a clinically meaningful reduction in all-cause mortality (OR < 0.9), corresponding to posterior probabilities of 94% and 88%, respectively.

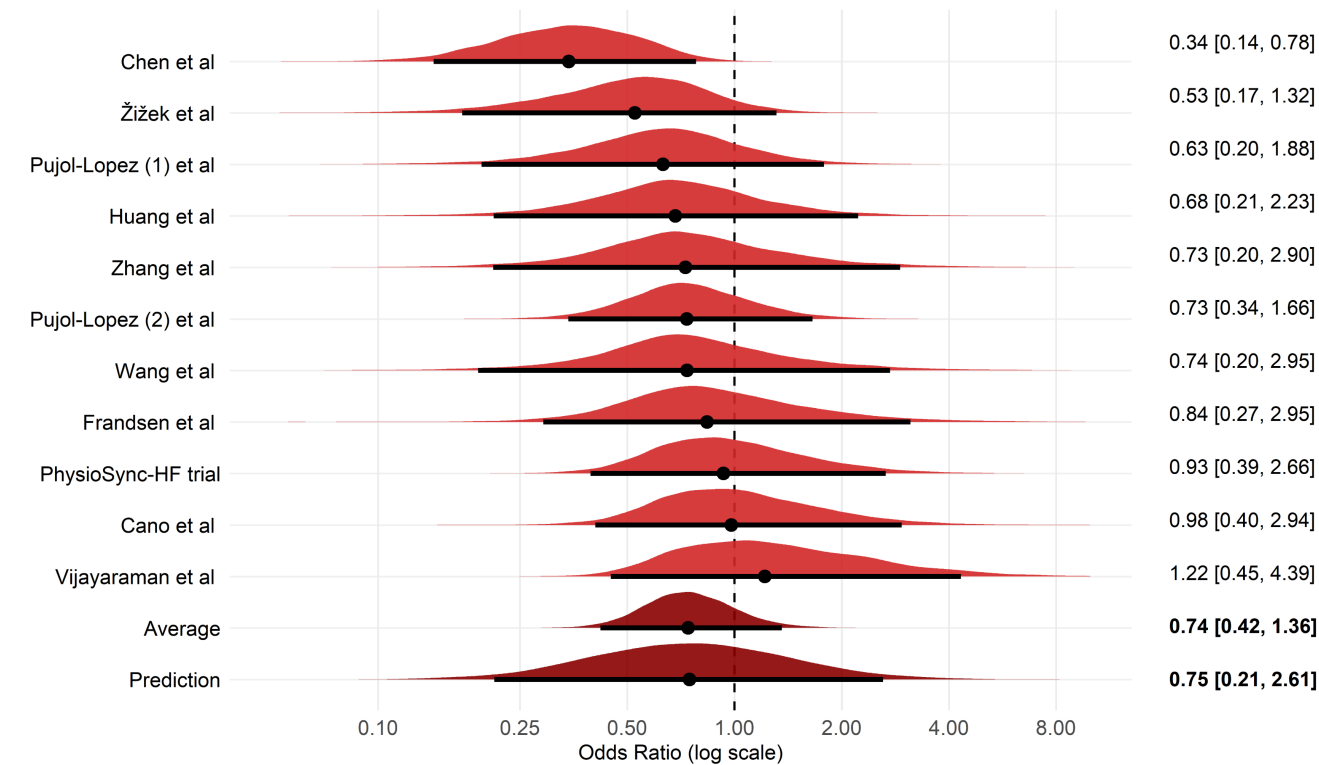


Figure 3

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Plot of heart failure hospitalization performed using a Bayesian hierarchical binomial random-effects model. Weakly informative priors were specified as $\theta \sim \text{Normal}(0, 0.82^2)$ for the overall treatment effect on the log-odds ratio scale and informative prior $\tau \sim \text{Log-Normal}(-1.635, 0.84^2)$ for the between-study heterogeneity, based on the empirical priors proposed by Turner et al. Pooled posterior odds ratios (ORs) with corresponding 95% credible intervals (CrIs) are presented.

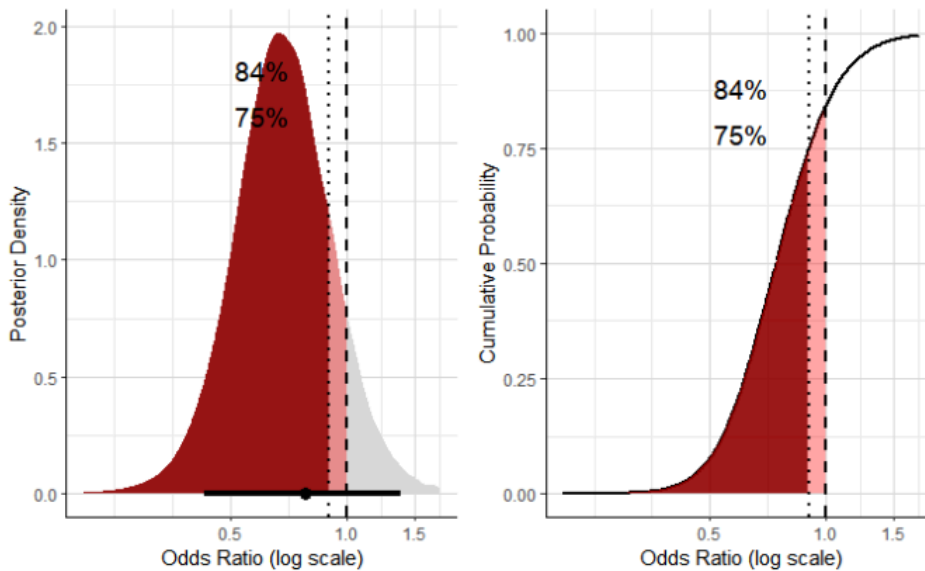


Figure 4

Posterior distribution and cumulative posterior probability for the pooled odds ratio of HF hospitalization. The left panel shows the posterior probability density of the pooled odds ratio (OR) comparing conduction system pacing (CSP) with biventricular pacing (BiVP). The right panel displays the corresponding cumulative posterior probability distribution. The dashed vertical line denotes the null effect (OR = 1), and the dotted vertical line denotes a prespecified threshold for clinically meaningful benefit (OR = 0.9). The shaded areas represent the posterior probabilities that the true treatment effect favors CSP (OR < 1) and that CSP achieves a clinically meaningful reduction in hospitalization (OR < 0.9), corresponding to posterior probabilities of 84% and 75%, respectively.

Supplementary Files

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