

Systematic Review/Meta-analysis

Conduction System Pacing vs Right Ventricular Pacing in Preserved or Mildly Reduced Ejection Fraction: A Meta-Analysis of Randomised Trials

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See editorial by Kavanagh, pages 1936-1938 of this issue.

ABSTRACT

Background: Evidence, largely observational, has been mixed on whether conduction system pacing (CSP) improves outcomes over conventional right ventricular pacing (RVP). This meta-analysis compared the efficacy and safety of CSP vs RVP in randomised controlled trials (RCTs) of patients with preserved or mildly reduced left ventricular ejection fraction (LVEF) who require permanent pacing.

Methods: We analysed RCTs comparing different CSP modalities with RVP. Databases were searched through February 24, 2026. Outcomes were pooled using random-effects models for risk ratios (RRs) and mean differences (MDs).

RÉSUMÉ

Contexte : Les données probantes recueillies à ce jour proviennent largement d'études observationnelles et sont contradictoires sur la question de savoir si la stimulation du système de conduction (SSC) améliore le pronostic comparativement à la stimulation ventriculaire droite (SVD) classique. Cette étude visait à comparer l'efficacité et l'innocuité de la SSC par rapport à la SVD dans le cadre d'essais contrôlés randomisés (ECR) menés chez des patients présentant une fraction d'éjection ventriculaire gauche (FEVG) préservée ou légèrement réduite nécessitant une stimulation permanente.

Keywords: conduction system pacing; heart failure hospitalisation; pacing-induced cardiomyopathy; permanent pacemaker; right ventricular pacing

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See page 2108 for disclosure information.

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Cardiac pacing remains the cornerstone therapy for symptomatic bradyarrhythmias and conduction system disease. Most recipients have preserved or only mildly reduced left ventricular ejection fraction (LVEF > 40%), where the primary clinical goal is to maintain ventricular synchrony and systolic function while avoiding iatrogenic decline. Conventional right ventricular pacing (RVP), however, produces nonphysiologic activation by bypassing the native His-Purkinje system. This results in QRS widening, electrical

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Results: Fifteen RCTs ($n = 1466$; mean baseline left ventricular ejection fraction (LVEF) = $59.4 \pm 7.0\%$) showed lower pacing-induced cardiomyopathy (PICM) with CSP vs RVP (4.6% vs 16.2%; RR 0.34, 95% CI 0.19-0.60) and lower heart failure hospitalisation (HFH) (3.3% vs 9.1%; RR 0.34, 95% CI 0.17-0.70), with no difference in all-cause mortality. CSP shortened paced QRS duration (MD -30.10 ms, 95% CI -35.46 to -24.74 ms) and improved LVEF (MD $+2.96\%$, 95% CI 1.18%-4.73%), but had lower pacing success (93.6% vs 99.5%; RR 0.95, 95% CI 0.91-0.99) and worse procedural metrics (procedure time MD $+32.44$ min, 95% CI 21.22-43.67 min; fluoroscopy time MD $+5.27$ min, 95% CI 3.89-6.65 min; radiation dose MD $+24.91$ mGy, 95% CI 10.27-39.55 mGy).

Conclusions: In RCTs of predominantly preserved or mildly reduced LVEF requiring permanent pacing, CSP reduced PICM and HFH and preserved left ventricular function more effectively than RVP, but with longer procedural and fluoroscopy times. CSP is a reasonable preventive strategy when substantial ventricular pacing is anticipated in this population.

Méthodologie : Nous avons réalisé une méta-analyse à l'aide d'ECR comparant différentes modalités de SSC à la SVD. Nous avons effectué des recherches dans diverses bases de données jusqu'au 24 février 2026. Nous avons combiné les résultats de nos recherches à l'aide de modèles à effets aléatoires pour calculer les rapports de risque (RR) et les différences moyennes (DM).

Résultats : Dans quinze ECR ($n = 1466$; FEVG moyenne au départ : $59,4 \pm 7,0 \%$), la cardiomyopathie induite par la stimulation a été moins fréquente avec la SSC qu'avec la SVD (4,6 % vs 16,2 %; RR : 0,34; intervalle de confiance [IC] à 95 % : 0,19 à 0,60), tout comme l'hospitalisation pour insuffisance cardiaque (3,3 % vs 9,1 %; RR : 0,34; IC à 95 % : 0,17 à 0,70). Aucune différence n'a été notée au niveau de la mortalité toutes causes confondues. La SSC a réduit la durée du QRS stimulé (DM : $-30,10$ ms; IC à 95 % : $-35,46$ à $-24,74$) et a amélioré la FEVG (DM : $+2,96 \%$; IC à 95 % : 1,18 à 4,73), mais le taux de réussite de la stimulation a été plus faible (93,6 % vs 99,5 %; RR : 0,95; IC à 95 % : 0,91 à 0,99) et les paramètres procéduraux moins bons (durée de la procédure : DM : $+32,44$ min; IC à 95 % : 21,22 à 43,67; temps de fluoroscopie : DM : $+5,27$ min; IC à 95 % : 3,89 à 6,65; dose de rayonnement : DM : $+24,91$ milligray [mGy]; IC à 95 % : 10,27 à 39,55).

Conclusions : Dans les ECR dans le cadre desquelles la plupart des patients présentaient une FEVG préservée ou légèrement réduite et nécessitaient une stimulation permanente, la SSC a réduit la cardiomyopathie induite par la stimulation et la fréquence des hospitalisations pour insuffisance cardiaque tout en préservant la fonction ventriculaire gauche plus efficacement que la SVD, mais avec des temps de procédure et de fluoroscopie plus longs. La SSC est une stratégie de prévention raisonnable lorsqu'une stimulation ventriculaire importante est prévue dans cette population.

and mechanical dyssynchrony, and an increased risk of pacing-induced cardiomyopathy (PICM) and heart failure hospitalisation (HFH), particularly when ventricular pacing burden exceeds 20%-40%.^{1,2,3} Long-term apical RVP also promotes left atrial remodelling and increases the incidence of atrial fibrillation,⁴ both of which contribute to heart failure and the broader burden of pacing-related complications.

These limitations have driven a shift toward physiologic pacing strategies that engage the native conduction system. Conduction system pacing (CSP)—encompassing His bundle pacing (HBP), left bundle branch area pacing (LBBAP), and para-right bundle pacing—restores near-normal physiologic ventricular activation, thereby improving LVEF stability, reducing adverse remodelling, and enhancing synchrony compared with RVP.^{5,6,7}

The 2023 Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) guideline on cardiac physiologic pacing assigns CSP a class 2a recommendation for patients with LVEF 36%-50% and substantial anticipated ventricular pacing, and a class 2b recommendation for those with normal LVEF, to reduce the risk of PICM; however, the CSP-specific support for both recommendations remains derived mainly from observational evidence rather than randomised trials.⁸ Recent 2025 updates (American College of Cardiology/American Heart Association appropriate use criteria and European Heart Rhythm Association/European Society of Cardiology consensus) further position CSP as “appropriate”

or a “reasonable alternative” in preserved LVEF with high pacing burden.^{9,10}

Despite guideline support, randomised evidence quantifying the preventive benefit of CSP in this predominant real-world population with preserved or mildly reduced LVEF remains limited, and evidence has been derived largely from observational studies.^{11,12} The STAY and PACE-HF trials demonstrated superior LVEF preservation and fewer HFH events with CSP vs RVP,^{13,14} whereas the Phys-TAVI pilot trial found similar LVEF changes between LBBAP and RVP.¹⁵ The CSPACE randomized controlled trial (RCT) reported no difference in HFH, although CSP improved the composite end point of PICM and LVEF decline.¹⁶ These inconsistencies, together with evolving guideline nuances, underscore the need for a contemporary synthesis of high-quality randomised evidence. Although previous meta-analyses have addressed CSP vs RVP, most incorporated predominantly observational data, limiting causal inference.^{11,12} We therefore conducted a meta-analysis of RCTs comparing CSP (including HBP and LBBAP) with conventional RVP in adults requiring permanent pacing, with a focus on patients with preserved or mildly reduced LVEF. Our primary objective was to evaluate whether CSP provides superior preservation of LV systolic function, reduction in PICM and HFH, and favourable procedural/electrophysiologic outcomes compared with RVP in this population.

The principal findings of this study are summarised in the **Central Illustration**.

Methods

Protocol registration

This systematic review and meta-analysis was conducted in accordance with PRISMA 2020 guidelines¹⁷ and the Cochrane Handbook for Systematic Reviews of Interventions.¹⁸ The protocol was prospectively registered in the PROSPERO database (CRD420261303553).

Data sources and search

We systematically searched PubMed, Embase (via Ovid), Scopus, and Web of Science for studies published up to February 24, 2026, without restrictions based on geographic region or publication status. Only English-language articles were included.

The search strategy combined free-text keywords and MeSH terms for pacing modalities: ("conduction system pacing" OR "His bundle pacing" OR "left bundle branch pacing" OR "LBBP" OR "para-RBB pacing" OR "right ventricular pacing")—AND study design ("clinical trial" OR "controlled trial" OR randomis* OR randomiz* OR randomly OR random OR RCT OR blind*). Reference lists of included articles and relevant reviews were manually screened for additional eligible studies.

Eligibility criteria

We included RCTs comparing CSP (His bundle pacing, LBBAP, or para-right bundle pacing) with conventional RVP (septal or apical) in adults (≥ 18 years) requiring permanent pacing for bradyarrhythmias or conduction disease.

Inclusion criteria (PICOS framework):

- Population: Adults (≥ 18 y old) with preserved or mildly reduced ejection fraction requiring permanent pacing.
- Intervention: CSP as defined above.
- Comparator: Conventional RVP.
- Outcomes: Prespecified clinical, electrocardiographic, and procedural outcomes (see below).
- Study design: RCTs.

Exclusion criteria: nonrandomised designs (observational studies, case reports and series, protocols), nonhuman studies, paediatric populations, studies without extractable data, and non-English language publications.

Study selection

Eight reviewers (A.A., A.M., M.H., Y.H., M.R.M., B.M.H., M.Q., and Q.S.) independently screened titles and abstracts in pairs, with full-text reviews for potentially eligible records. Disagreements were resolved by consultation with a senior reviewer (A.S.). The process is presented in a PRISMA flow diagram (Fig. 1).

Data extraction and outcomes

Data were independently extracted by eight reviewers (A.A., A.M., M.H., Y.H., M.R.M., B.M.H., M.Q., and Q.S.) using a standardised and pilot-tested data extraction form, with conflicts resolved by consensus. The extracted information included:

Study-level characteristics. The data extracted included study ID, study design, blinding status, RCT registration number, countries and centres involved, sample size, pacing strategies, inclusion and exclusion criteria, baseline cardiac resynchronization therapy (CRT) exclusion, and outcome definitions (which varied across studies).

Baseline characteristics. For each study arm, we extracted group size (n, %), age (y, mean $\pm$ SD), male proportion (n, %), QRS morphology (normal, right bundle branch block [RBBB], left bundle branch block [LBBB]), baseline QRS duration (ms, mean $\pm$ SD), BMI (kg/m^2 , mean $\pm$ SD), LVEF (%), mean $\pm$ SD), anticipated pacing burden, electrode locations (LBBAP, HBP, para-RBBB, deep septal, right ventricular [RV] septum or apex), comorbidities, pacing indications, New York Heart Association (NYHA) functional class, and medications.

Outcomes. Outcomes were extracted at the longest available follow-up (preferring 1-year data when available). For outcomes presented only in graphic form, WebPlotDigitizer¹⁹ was used to extract quantitative data. The following outcomes were collected for each arm: 1) clinical outcomes: all-cause mortality, HFH, new-onset atrial fibrillation, PICM (as defined per study [Supplemental Table S1]), and CRT upgrades; 2) safety outcomes: wound infection, lead dislodgement, pericardial effusions, lead revision, and composite complications (Supplemental Table S2); 3) procedural outcomes: procedure time (min), fluoroscopy time (min), radiation dose (mGy), pacing success rate (Supplemental Table S3), paced QRS (ms), QRS change from baseline, and LVEF change (%); and 4) device parameters: capture threshold (V), impedance (Ω), R-wave amplitude (mV), and ventricular pacing burden (%), mean $\pm$ SD).

For continuous outcomes, data were extracted as mean $\pm$ SD. When trials reported medians and range or interquartile range, values were converted to mean $\pm$ SD with the use of the Meta-Analysis Accelerator website.²⁰

Risk of bias and certainty of evidence

Risk of bias (RoB) was assessed independently with the use of the Cochrane RoB 2.0 tool²¹ across 5 domains: randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Four reviewers (A.E., M.S.E., A.M., and A.A.) performed assessments, with at least 2 independent evaluations per trial. Conflicts were resolved through another reviewer (A.S.). Certainty of evidence for all critical outcomes was evaluated by 2 authors (M.S.E. and A.S.) using the GRADE framework.²² Each outcome was rated as high, moderate, low, or very low based on risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Statistical analysis

Statistical analyses were performed in R (version 4.4.2) with the "meta" and "metafor" packages. Categorical outcomes were pooled as risk ratios (RRs) with the use of the Mantel-Haenszel method, and continuous outcomes were pooled as mean differences (MDs) by means of the inverse variance method, both with 95% confidence intervals (CIs). Random-effects models were used for all meta-analyses to account for

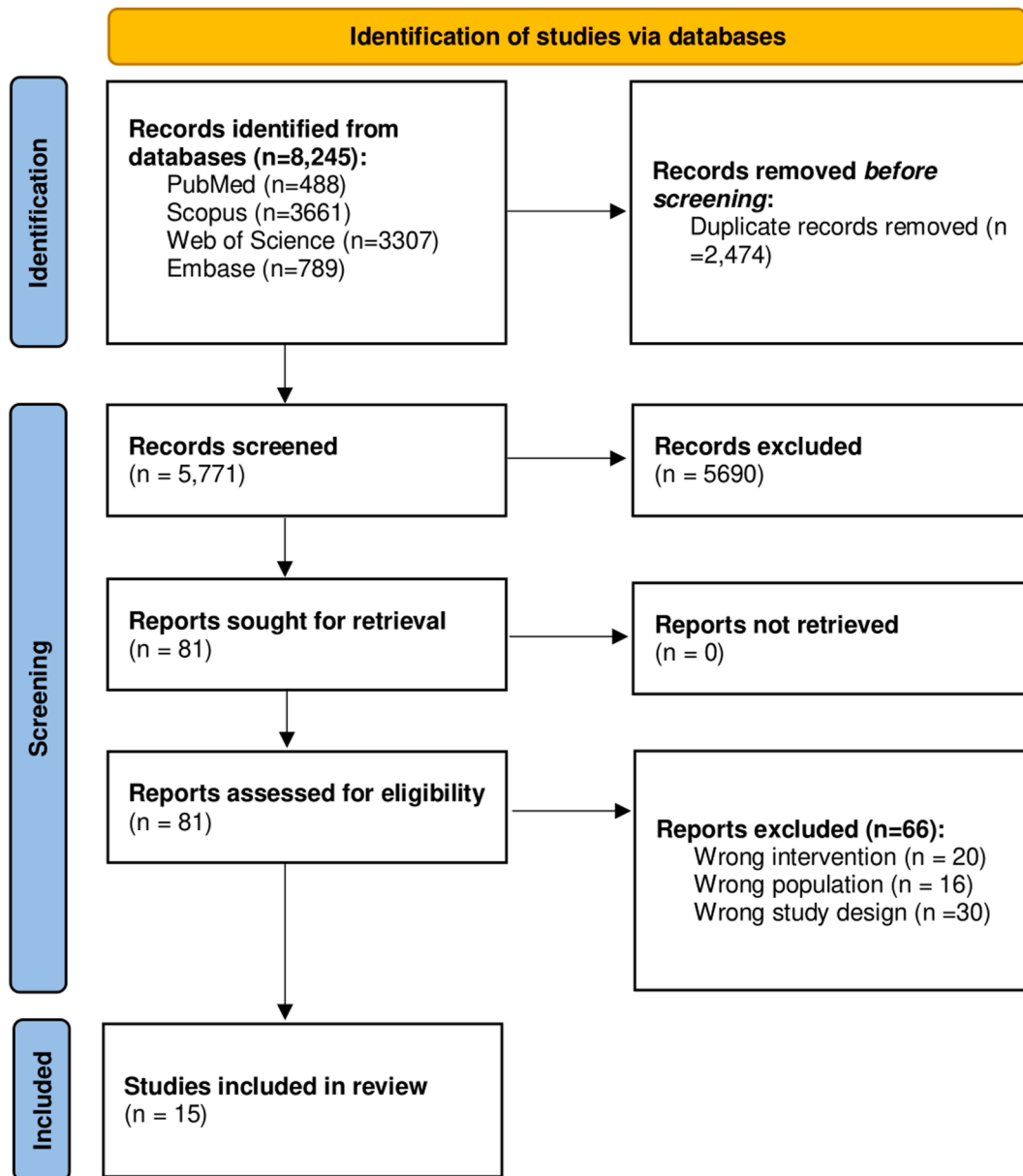


Figure 1. PRISMA flow diagram of study selection, showing identification, screening, eligibility assessment, and final inclusion of studies in this systematic review and meta-analysis, including reasons for full-text exclusion.

anticipated between-study variability, with between-study variance estimated by means of the DerSimonian-Laird method. In studies that included zero-event data, a 0.5 continuity correction was applied. Heterogeneity was quantified with the use of both the I^2 statistic (low: 0%-30%; moderate: 30%-50%; substantial: > 50%) and τ^2 . Publication bias was assessed via Egger test and funnel plots. Pre-specified subgroup analyses were performed by CSP type (eg, LBBAP-only) when feasible.

Meta-regression

Random-effects meta-regression (restricted maximum-likelihood estimator) was performed for PICM, HFH, mortality, and LVEF change with the use of prespecified moderators (mean age, male %, baseline LVEF, baseline QRS

duration, ventricular pacing burden). Ventricular pacing burden was treated as a trial-level proxy for anticipated burden. Results were visualised with bubble plots (bubble size = inverse-variance weight) with fitted regression lines and 95% CIs. Power was limited by the number of available trials.

Results

Search results

The search identified 8245 records across four databases. After removing 2474 duplicates, 5771 unique records were screened, and 81 full-text articles were assessed for eligibility. Fifteen RCTs^{13,14,15,16,23,24,25,26,27,28,29,30,31,32,33} were included in the meta-analysis. The selection process is shown in the PRISMA flow diagram (Fig. 1).

Characteristics of the included studies

Fifteen RCTs enrolling 1466 patients were included. Trials were conducted in Europe (Spain, Czech Republic, Greece), Asia (China, India), and Australia and were mostly single- or 2-centre studies. CSP primarily involved LBBAP or HBP (with some protocols permitting deep septal or LV septal pacing), whereas conventional RVP targeted the septum, apex, or outflow tract. Most studies were open-label, frequently with blinded echocardiographic outcome assessment when specified. Most enrolled patients had a high anticipated ventricular pacing burden. Trial-level characteristics are summarised in Table 1 and Supplemental Table S5.

Overall, 738 participants (50.3%) were randomised to CSP and 728 (49.7%) to RVP. Where baseline data were reported, the pooled mean age was 72.9 ± 12.3 years ($n = 1186$) and mean LVEF was $59.4 \pm 7.0\%$ ($n = 1186$). Men composed 62.6% of participants (730/1166). QRS morphology ($n = 745$) was normal (< 120 ms) in 65.1%, RBBB in 24.6%, and LBBB in 8.7%, with a pooled baseline QRS of 118.3 ± 27.0 ms ($n = 1114$). Common comorbidities included hypertension (71.6%, 677/946), diabetes mellitus (31.5%, 298/946), and ischemic heart disease or coronary artery disease (25.3%, 215/850). Detailed baseline and pacing characteristics are presented in Table 2 and Supplemental Tables S6 and S7.

Risk of bias

Most trials had a low risk of bias. Six (Qiu 2025,³³ Zhao 2024,³¹ Mizner 2023,²⁷ Riano Ondiviela 2021,³² Wang 2020,²⁹ and Du 2015²⁵) were judged to have some concerns, primarily in the randomisation process or deviations from intended interventions. The Das 2020 trial was rated as having a high risk of bias owing to issues with the randomisation process (Fig. 2).²⁴

Primary outcomes

Compared with RVP, CSP was associated with 66% lower risk of PICM (4 RCTs, 564 patients; 4.6% [13/280] vs 16.2% [46/284]; RR 0.34, 95% CI 0.19-0.60; $P = 0.0003$), with no heterogeneity ($I^2 = 0\%$). HFH (5 RCTs, 665 patients) was reduced by 66% with CSP (3.3% [11/336] vs 9.1% [30/329]; RR 0.34, 95% CI 0.17-0.70; $P = 0.0034$), with low heterogeneity ($I^2 = 13.6\%$). There was no significant difference in all-cause mortality (4 RCTs; RR 0.56; $P = 0.21$). CSP also resulted in a greater improvement in LVEF from baseline (11 RCTs; MD 2.96%, 95% CI 1.18%-4.73%; $P = 0.0011$; $I^2 = 84\%$) (Fig. 3).

When analysing the data after excluding studies that may have included some patients with LVEF $< 40\%$ based on the baseline mean $\pm$ SD (Yao 2022³⁰ and Shroff 2025¹⁴), the reduction in HFH was no longer statistically significant, although the effect estimate remained directionally favourable for CSP (4 RCTs; 2.9% [8/276] vs 6.7% [18/269]; RR 0.43, 95% CI 0.15-1.26; $P = 0.1258$; $I^2 = 29.0\%$). After further exclusion of the small Pujol-López 2025 pilot study,¹⁵ the reduction in HF hospitalisation became statistically significant and remained in favour of CSP (3 RCTs; 1.9% [5/264] vs 6.6% [17/257]; RR 0.27, 95% CI 0.10-0.71; $P = 0.0079$), with no heterogeneity ($I^2 = 0.0\%$; P for heterogeneity =

0.9553). In contrast, after exclusion of Yao 2022³⁰ and Shroff 2025,¹⁴ the change in LVEF from baseline remained significantly in favour of CSP (9 RCTs; MD 2.39%, 95% CI 0.61%-4.16%; $P = 0.0083$), although substantial heterogeneity persisted ($I^2 = 78.8\%$). This analysis was performed as an exploratory analysis, because current guideline recommendations for CSP are even stronger in patients with LVEF 36%-50%;⁸ however, we sought to examine how the results would appear when the analysis was restricted as much as possible to patients with preserved LVEF, acknowledging that a minority with mildly reduced EF may still have been included because the baseline mean $\pm$ SD can overlap that range.

Secondary Outcomes

Electrical synchrony. CSP significantly shortened paced QRS duration (11 RCTs; MD -30.10 ms, 95% CI -35.46 to -24.74 ms; $P < 0.0001$; $I^2 = 93\%$) and produced a larger reduction in QRS duration from baseline (9 RCTs; MD -29.78 ms, 95% CI -36.18 to -23.38 ms; $P < 0.0001$; $I^2 = 87.9\%$) (Figs. 4 and 6).

Procedural metrics and feasibility. Procedural feasibility favoured RVP. CSP had a lower pacing success rate (13 RCTs; 93.6% [616/658] vs 99.5% [640/643]; RR 0.95, 95% CI 0.91-0.99; $P = 0.0081$; $I^2 = 78.2\%$) (Fig. 6). CSP was also associated with a longer procedure time (7 RCTs; MD 32.44 min, 95% CI 21.22-43.67 min; $P < 0.0001$; $I^2 = 97.8\%$), longer fluoroscopy time (11 RCTs; MD 5.27 min, 95% CI 3.89-6.65 min; $P < 0.0001$; $I^2 = 98.3\%$), and higher radiation dose (4 RCTs; MD 24.91 mGy, 95% CI 10.27-39.55 mGy; $P = 0.0009$; $I^2 = 98\%$) (Fig. 5).

Lead performance and pacing characteristics. There were no significant differences in ventricular pacing burden (7 RCTs; MD 1.68%, 95% CI -0.92% to 4.28%; $P = 0.2051$) (Fig. 5). Pacing parameters at time of implantation were similar between groups, including pacing threshold (12 RCTs; MD 0.11 V, 95% CI -0.00 to 0.22 V; $P = 0.0504$), R-wave amplitude (8 RCTs; MD -1.27 mV, 95% CI -3.14 to 0.59 mV; $P = 0.1812$), and impedance (7 RCTs; MD -5.18 Ω , 95% CI -36.32 to 25.97 Ω ; $P = 0.7447$) (Fig. 4).

Safety and procedural complications. There was no significant difference in new-onset atrial fibrillation (4 RCTs; RR 0.79, 95% CI 0.23, 2.66; $P = 0.70$) (Fig. 6). Procedure-related complications were similar, including the composite procedural complications (10 RCTs; RR 1.09; $P = 0.83$) (Fig. 5), lead revision (6 RCTs; RR 1.78; $P = 0.25$), acute lead dislodgement (9 RCTs; RR 1.97; $P = 0.20$), pericardial effusion (4 RCTs; RR 0.99; $P = 0.99$), and wound infection (6 RCTs; RR 0.89; $P = 0.88$) (Fig. 7). CRT upgrade did not differ between the 2 groups (2 RCTs; RR 0.27; $P = 0.25$) (Fig. 6).

Subgroup analysis (LBBAP only). In the LBBAP-only subgroup, CSP produced a greater reduction in QRS duration from baseline (5 RCTs; MD -32.10 ms, 95%

Table 1. Summary overview of the included trials

Study	Design	Country	No. of centres	No. of patients	Arms		Inclusion criteria	Primary outcome(s)	Max follow-up
					Intervention	Control			
Chow 2025 ¹⁶	RCT	Australia	2	202	CSP (HBP and/or LBBP/LVSP allowed)	RVSP (RV apex discouraged)	Pacing indication for AVB without CRT indication	Composite end point: PICM, CRT upgrade, HFH, all-cause mortality	25.2 ± 11.8 mo
Pujol-López 2025 ¹⁵	RCT	Spain	1	24	LBBP (CSP)	RVAP	Age > 18 y, post-TAVI persistent high-degree AVB with PPM indication, LVEF ≥ 50%	Survival and either Δ NYHA ≥ 1 (12 mo vs 30 d) or ≥ 25% increase in 6MWT distance	12 mo
Shroff 2025 ¹⁴	RCT	Australia	1	120	LBBAP (Medtronic 3830; LBBP/LVSP/ DSP accepted)	RVP (mid-apical interventricular septum)	Age ≥ 18 y; LVEF > 40%; indication for PPM owing to AVB, tachy-brady with anticipated VP > 40%, or permanent AF undergoing pace-and-ablate	Change in LVEF at 12 mo (core lab blinded)	12 mo
Qiu 2025 ³³	RCT	NR	NR	160	LBBP (CSP)	RVP	Patients dependent on VP undergoing pacemaker implantation	Composite: PICM + all-cause mortality + HF readmission at 12 mo	12 mo
Curila 2025 ²³	RCT	Czech Republic	2	249	CSP (HBP or LBBAP)	RVSP	AV conduction disease with expectation of high RV pacing burden; echocardiographic window sufficient for Simpson LVEF; LVEF > 45%; life expectancy ≥ 2 y	Change in LVEF at 1 y vs baseline	12 mo
González-Matos 2024 ¹³	RCT	Spain	1	75	CSP (HBP or LBBP; deep septal allowed)	RVAP	Age ≥ 18 y, LVEF > 40%, high-degree AVB with anticipated VP > 80%	Evolution of LVEF and LVEDD (baseline to 6 mo)	6 mo
Mizner 2023 ²⁷	RCT	Czech Republic	1	92	CSP (HBP)	RVSP	Conduction disease + indication for PPM (ESC 2013)/ anticipated high RVP burden + life expectancy > 2 y or ≥ 1 if LVEF ≤ 60%, QRS > 115 ms, or ischemic heart disease	Change in LVEF at 6 mo (also collagen-metabolism biomarkers at baseline and 6 mo)	6 mo
Riano Ondiviela 2021 ³²	RCT	Spain	1	120	LBBP (CSP)	RVOTP (RVP)	Pacemaker indication + preserved LVEF; AVB anticipated for high-burden RVP	Acute success, feasibility, safety (success in LBBP defined as paced ECG < 120 ms or ≥ 20% reduction vs baseline)	3 mo
Wang 2020 ²⁹	RCT	China	1	131	LBBAP (CSP)	RVSP	Class I indication for single (VVI) or dual-chamber (DDD) pacemaker implantation	Paced vs intrinsic ECG repolarisation measures (QT, QTc, QTD, QTcD, TpTe, TpTe/QT); procedural metrics; lead parameters and complications	6 mo

Continued

Table 1. Continued.

Study	Design	Country	No. of centres	No. of patients	Arms		Inclusion criteria	Primary outcome(s)	Max follow-up
					Intervention	Control			
Yao 2022 ³⁰	RCT	China	1	50	LBBP (CSP)	RVSP (RVP; RV outflow tract septum)	Age > 18 y with ECG-confirmed 3rd-degree AVB and pacing indication	Outcomes: 3D-speckle tracking (GLS/GRS/GCS), LV dyssynchrony (Tmsv16-SD/RR), QRS duration, LVEF	18 mo
Das 2020 ²⁴	RCT	India	1	50	LBBAP (CSP)	RVAP	Conventional pacemaker indications; enrolled Jul-Dec 2018	Procedure and fluoroscopy times, paced QRS duration, LV function (LVEF, LVIDd), lead parameters; assessed HFH and AF occurrence	6 mo
Du 2015 ²⁵	RCT	China	1	41	Para-right bundle branch pacing	RVAP	Persistent AF + complete AVB with slow ("torpid") ventricular rate + junctional escape rhythm (to allow mapping of right bundle branch potential)	LV performance and synchrony (echocardiographic measures) + clinical HF/NYHA assessment	24 mo
Zhao 2024 ³¹	RCT	China	1	72	LBBAP (CSP)	RVOTP septal pacing (RVP)	Pace-dependent patients with 2nd-degree AVB, high AVB, or 3rd-degree AVB; symptomatic bradyarrhythmias consenting to pacemaker	Left atrial structure and function (echocardiography + strain/strain-rate) over follow-up	6 mo
Leventopoulos 2022 ²⁶	RCT	Greece	1	20	LBBP (CSP)	RVSP	Patients with AVB and preserved LVEF	LV dyssynchrony indices: global myocardial work efficiency (GWE) and peak systolic dispersion (PSD), assessed at 24 h after procedure (follow-up planned 1 y)	1 y
Tang 2019 ²⁸	RCT	China (Guangzhou)	1	60	HBP	RVAP	Age > 18 y; bradyarrhythmia without prior pacemaker; class I/IIa pacing indication; baseline QRS < 120 ms; synchronous LV contraction; LVEF > 50%; NYHA I-II	LV mechanical synchronisation after procedure and during 6-mo follow-up	6 mo

6MWT, 6-minute walk test; AF, atrial fibrillation; AVB, atrioventricular block; CRT, cardiac resynchronization therapy; CSP, conduction system pacing; DSP, deep septal pacing; ECG, electrocardiogram; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; HBP, His bundle pacing; HF, heart failure; HFH, heart failure hospitalisation; LBBAP, left bundle branch area pacing; LBBP, left bundle branch pacing; LVEDD, left ventricular end-diastolic diameter; LVIDd, left ventricular internal diameter in diastole; LVEF, left ventricular ejection fraction; LVSP, left ventricular septal pacing; NYHA, New York Heart Association functional class; PICM, pacing-induced cardiomyopathy; PPM, permanent pacemaker; RCT, randomised controlled trial; RV, right ventricular; RVAP, right ventricular apical pacing; RVOTP, right ventricular outflow tract pacing; RVP, right ventricular pacing; RVSP, right ventricular septal pacing; TAVI, transcatheter aortic valve implantation; Tmsv16-SD/RR, LV dyssynchrony index; VP, ventricular pacing.

Table 2. Baseline Characteristics of the Included Trials

Study	Group	Patients, n	Age, y	Male sex	QRS morphology			Baseline QRS duration, ms	Medical history				LVEF, %
					< 120 ms	RBBB	LBBB		DM	HTN	AF	IHD/CAD	
Chow 2025 ¹⁶	CSP	101	77.0 ± 8.1	65 (64.4)	40 (39.6)	42 (41.6)	13 (12.9)	124.1 ± 28.5	39 (38.6)	86 (85.1)	32 (31.7)	26 (25.7)	60.9 ± 7.8
	RVP	101	77.2 ± 9.3	70 (69.3)	39 (38.6)	44 (43.6)	13 (12.9)	125.1 ± 27.7	42 (41.6)	80 (79.2)	35 (34.7)	22 (21.8)	60.9 ± 6.9
Pujol-López 2025 ¹⁵	CSP (LBBP)	12	82.77 ± 6.88	9 (75)	7 (58.3)	NR	NR	158.67 ± 11.74	1 (8.3)	8 (67)	1 (8.3)	NR	60.33 ± 7.55
	RVAP	12	81.67 ± 8.39	10 (83.3)	8 (66.7)	NR	NR	161.33 ± 21.8	3 (25)	10 (83)	3 (25)	NR	58 ± 5.87
Shroff 2025 ¹⁴	CSP (LBBAP)	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	51.43 ± 8.14
	RVSP	60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	51 ± 6.22
Qiu 2025 ³³	LBBP (CSP)	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR (largely preserved)
	RVP	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR (largely preserved)
Curila 2025 ²³	CSP	124	75 ± 9	93 (75)	79 (63)	33 (27)	12 (10)	117 ± 27	47 (38)	96 (77)	22 (18)	37 (30)	61 ± 6
	RVP	125	76 ± 7	89 (71)	73 (59)	39 (31)	12 (10)	115 ± 25	44 (35)	96 (77)	17 (14)	33 (26)	61 ± 5
González-Matos 2024 ¹³	CSP	40	75 ± 10.2	26 (65)	NR	NR	NR	136.6 ± 25.5	20 (50)	32 (80)	13 (32.5)	7 (17.5)	58.5 ± 7.6
	RVAP	35	80 ± 6.9	23 (65.2)	NR	NR	NR	138.2 ± 21.5	11 (31.4)	31 (88.6)	7 (20)	11 (31.4)	60.7 ± 6.9
Mizner 2023 ²⁷	CSP	53	78 ± 8	38 (88)	20 (38)	NR	NR	125 ± 25	20 (38)	51 (96)	NR	23 (43)	60 ± 5
	RVP	39	78 ± 7	31 (80)	12 (31)	NR	NR	126 ± 27	16 (41)	38 (97)	NR	15 (38)	58 ± 7
Riano Ondiviela 2021 ³²	LBBP (CSP)	60	76.7 ± 9	37 (62)	NR	NR	9 (15)	112.6 ± 29.6	NR	NR	NR	NR	NR (preserved)
	RVOTP (RVSP/ RVOTP)	60	79.7 ± 8	36 (60)	NR	NR	8 (13.3)	109.9 ± 25.8	NR	NR	NR	NR	NR (preserved)
Wang 2020 ²⁹	LBBAP	66	71.12 ± 13.14	38 (57.6)	66 (100)	0 (0)	0 (0)	99.24 ± 13.60	11 (16.7)	34 (51.5)	14 (21.2)	10 (15.2)	61.3 ± 5.7
	RVSP	65	72.03 ± 12.11	41 (63.1)	65 (100)	0 (0)	0 (0)	101.88 ± 11.72	15 (23.1)	37 (56.9)	12 (18.5)	12 (18.5)	62.1 ± 6.3
Yao 2022 ³⁰	LBBP	25	66.3 ± 11	13 (52)	NR	NR	NR	139.44 ± 10.07	NR	NR	NR	NR	52.48 ± 4.4
	RVSP	25	69.2 ± 12.8	14 (56)	NR	NR	NR	140.28 ± 8.93	NR	NR	NR	NR	53.24 ± 3.57
Das 2020 ²⁴	LBBAP	22	63.36 ± 7.82	12 (54.5)	9 (40.9)	7 (31.8)	6 (27.3)	131.64 ± 17.80	NR	NR	NR	NR	61.15 ± 4.04
	RVA	28	61.64 ± 5.9	16 (57.1)	10 (35.7)	10 (35.7)	8 (28.6)	132.73 ± 16.71	NR	NR	NR	NR	62.50 ± 4
Du 2015 ²⁵	Para-RBB (not CSP)	19	54 ± 11	7 (36.8)	19 (100)	0 (0)	0 (0)	88.11 ± 6.64	5 (26.3)	10 (52.6)	19 (100)	7 (36.8)	58.37 ± 4.81
	RVP	22	51 ± 9	8 (36.4)	22 (100)	0 (0)	0 (0)	88.82 ± 6.26	6 (27.3)	12 (54.5)	22 (100)	8 (36.4)	57.77 ± 4.24
Zhao 2024 ³¹	CSP (LBBAP)	36	64.26 ± 14.1	20 (55.56)	29 (80.56)	6 (14.29)	1 (2.78)	NR	9 (21.43)	25 (69.44)	NR	NR	62.27 ± 7.23
	RVP (RVOTP septal)	36	68.11 ± 10.04	18 (50)	34 (94.44)	2 (4.76)	0 (0)	NR	7 (16.67)	21 (58.34)	NR	NR	63.18 ± 5.8
Leventopoulos 2022 ²⁶	LBBP (CSP)	10	79.8 ± 2.0	NR	NR	NR	NR	125 ± 11.2	NR	NR	NR	NR	59.7 ± 1.4
	RVSP (RVP)	10	80.5 ± 1.5	NR	NR	NR	NR	113.9 ± 9.5	NR	NR	NR	NR	59 ± 2.1
Tang 2019 ²⁸	HBP (CSP)	30	55.3 ± 17.1	10 (31.8)	NR	NR	NR	94.7 ± 12.3	0 (0)	6 (20)	1 (3.3)	2 (6.7)	59.1 ± 6.4
	RVAP (RVP)	30	55.2 ± 19.2	6 (20)	NR	NR	NR	101.7 ± 20.9	2 (6.7)	4 (13.3)	0 (0)	2 (6.7)	60.4 ± 6.4

Data are presented in mean ± SD or n (%).

AF, atrial fibrillation; CAD, coronary artery disease; CSP, conduction system pacing; DM, diabetes mellitus; HBP, His bundle pacing; HTN, hypertension; IHD, ischemic heart disease; LBBAP, left bundle branch area pacing; LBBP, left bundle branch pacing; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NR, not reported; RBB, right bundle branch; RBBB, right bundle branch block; RVAP, right ventricular apical pacing; RVOTP, right ventricular outflow tract pacing; RVP, right ventricular pacing; RVSP, right ventricular septal pacing.

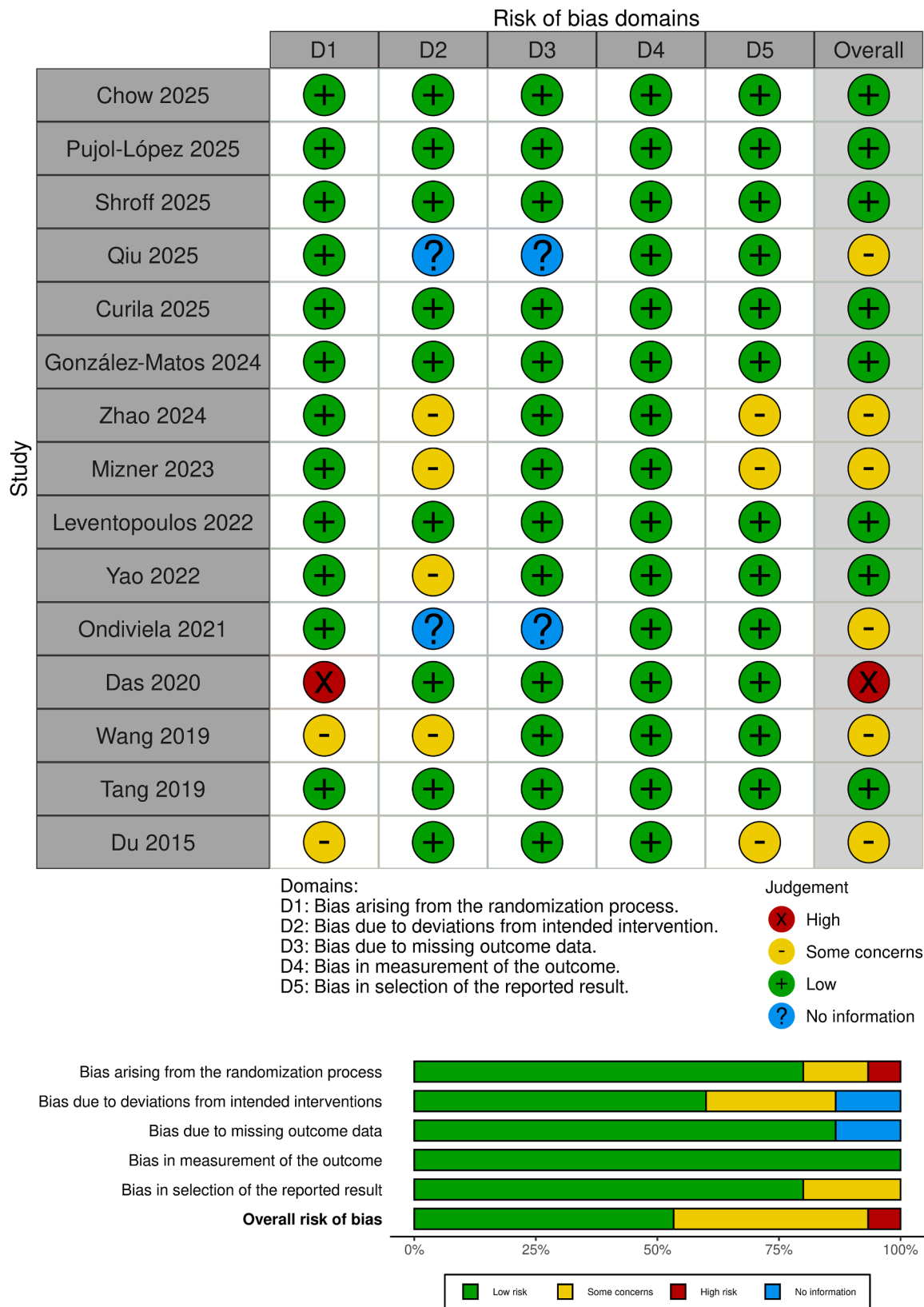


Figure 2. Risk-of-bias (RoB) assessment of the included randomised trials. RoB 2 domains: bias arising from the randomisation process (D1), bias due to deviations from intended interventions (D2), bias due to missing outcome data (D3), bias in measurement of the outcome (D4), and bias in selection of the reported result (D5). The top panel shows study-level judgements, and the bottom panel summarises the proportion of studies rated as low risk, some concern, high risk, or no information across domains and overall.

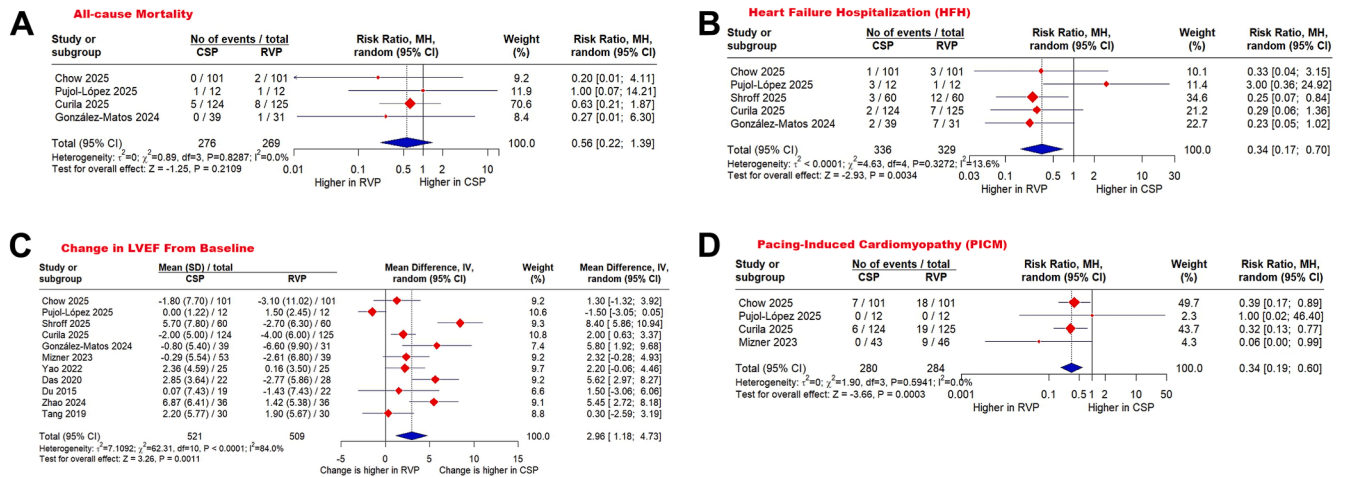


Figure 3. Forest plots of primary clinical outcomes comparing conduction system pacing (CSP) vs right ventricular pacing (RVP). Pooled analyses of (A) all-cause mortality, (B) heart failure hospitalisation, (C) change in left ventricular ejection fraction from baseline, and (D) pacing-induced cardiomyopathy. Dichotomous outcomes are presented as risk ratios and continuous outcomes as mean differences, both with 95% confidence intervals (CIs), according to random-effects models. IV, inverse variance; MH, Mantel-Haenszel.

CI -44.13 to -20.07 ms; $P < 0.0001$; $I^2 = 93\%$), whereas the change in LVEF was not significantly different (4 RCTs; MD 2.83%, 95% CI -0.82% to 6.48% ; $P = 0.1286$) (Fig. 8).

It is worth noting, however, that the studies included in these subgroup analyses were small. Moreover, after exclusion of the Das 2020²⁴ and Pujol-López 2025¹⁵ pilot studies, the LBBAP subgroup showed a statistically significant improvement in LVEF change (2 RCTs; MD 3.73%, 95% CI 0.55%-6.91%; $P = 0.0215$; $I^2 = 69.0\%$; P for heterogeneity = 0.0726). Likewise, the favourable reduction in QRS duration from baseline remained significant (4 RCTs; MD -33.64 ms, 95% CI -48.60 to -18.68 ms;

$P < 0.0001$), although substantial heterogeneity persisted ($I^2 = 94.7\%$; P for heterogeneity < 0.0001).

Subgroup analysis (HBP only). The only 2 studies in which HBP was used exclusively as the pacing modality in the CSP arm were Tang 2019²⁸ and Mizner 2023.²⁷ Although pooling was not feasible for most outcomes, Mizner 2023 reported a lower PICM event rate with HBP than with RVP (0/43 [0.0%] vs 9/46 [19.6%]).²⁷ Both studies contributed data for LVEF, and the meta-analysis showed no statistically significant difference in LVEF change between HBP and RVP (2 RCTs; MD 1.41%, 95% CI -0.56% to 3.39% ; $P = 0.1598$), with no important heterogeneity ($I^2 = 3.6\%$; P for

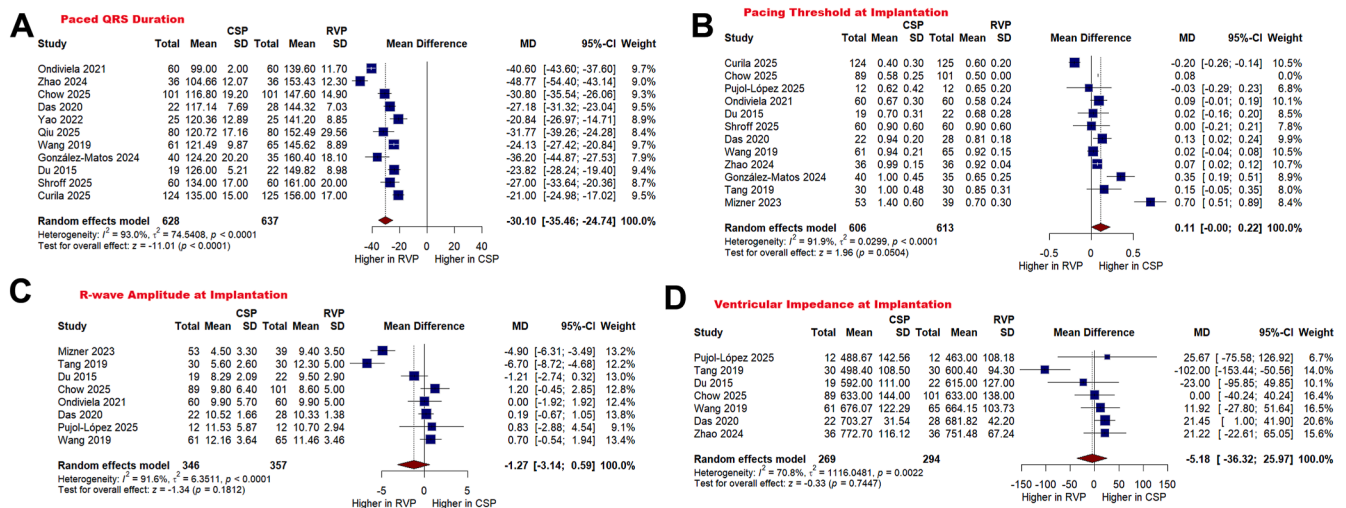


Figure 4. Forest plots of paced electrical and implantation performance parameters comparing conduction system pacing (CSP) vs right ventricular pacing (RVP). Pooled analyses of (A) paced QRS duration, (B) pacing threshold at implantation, (C) R-wave amplitude at implantation, and (D) ventricular impedance at implantation. Continuous outcomes are expressed as mean differences (MDs) with 95% confidence intervals (CIs) according to random-effects models.

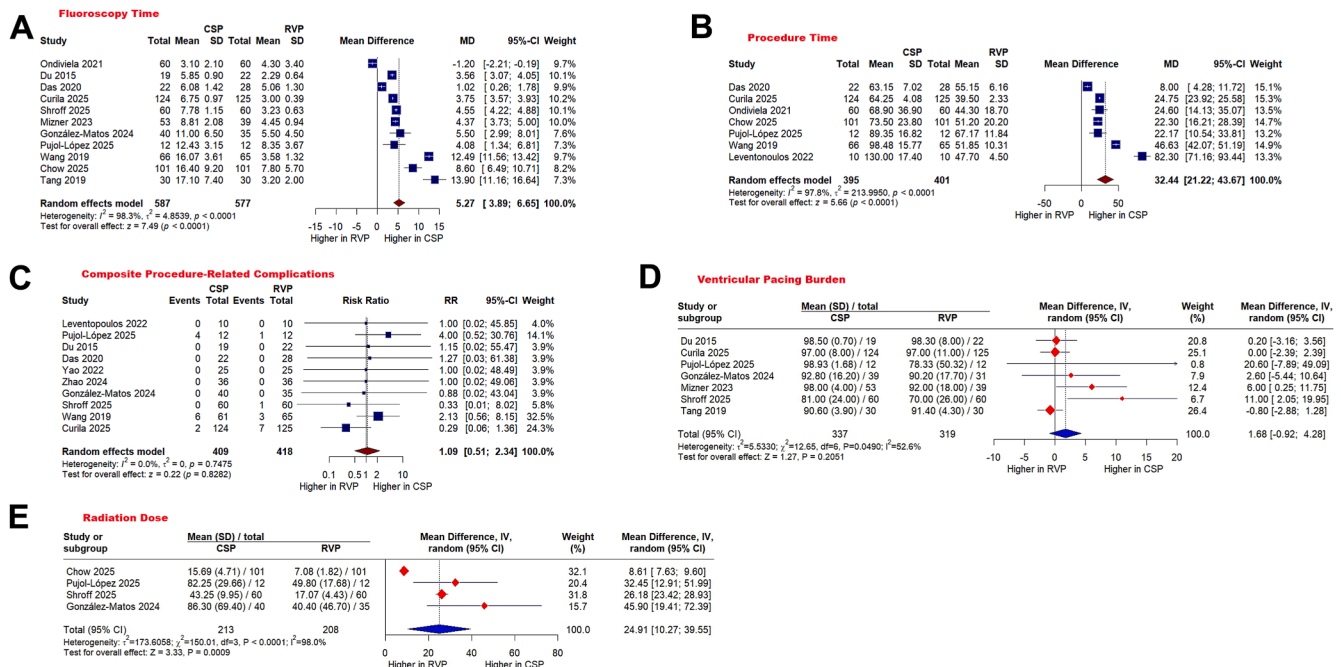


Figure 5. Forest plots of procedural characteristics and peri-procedural outcomes comparing conduction system pacing (CSP) vs right ventricular pacing (RVP). Pooled analyses of (A) fluoroscopy time, (B) procedure time, (C) composite procedure-related complications, (D) ventricular pacing burden, and (E) radiation dose. Effect estimates are shown as mean differences or risk ratios (RRs) with 95% confidence intervals (CIs) according to random-effects models. IV, inverse variance.

heterogeneity = 0.3085). However, these findings should be interpreted cautiously, given the small number and size of the included studies.

Publication bias

Egger tests showed no evidence of publication bias for most outcomes (fluoroscopy time, procedural complications, pacing threshold, paced QRS duration, and LVEF change; all $P > 0.05$). Small-study effects were suggested for pacing success (intercept = -1.54 ; $t = -2.695$; $P = 0.021$). Corresponding funnel plots are presented in Supplemental Figures S1-S6.

Meta-regression

Univariable random-effects meta-regression showed no statistically significant effect modification by trial-level covariates (age, sex, baseline LVEF, baseline QRS duration, or ventricular pacing burden) across outcomes, including all-cause mortality, PICM, change in LVEF, and HFH. Bubble plots are presented in Supplemental Figures S7–S10 (Supplemental Table S4). These analyses are exploratory given the limited number of trials and the risk of ecologic bias.³⁴

Sensitivity analysis (leave-one-out)

Leave-one-out analyses showed that the benefit of CSP on PICM and LVEF remained directionally consistent and statistically significant across all study exclusions. For HFH, the pooled effect remained directionally consistent, although statistical significance was attenuated in some iterations. For all-cause mortality, directionality was consistent, and no

single study materially altered the nonsignificant pooled estimate. Leave-one-out plots are presented in Supplemental Figures S11-S29.

Certainty of evidence

Certainty of evidence (GRADE) ranged from low to moderate across outcomes. It was moderate for PICM and HFH owing to imprecision and for paced QRS duration owing to inconsistency. It was low for the change in LVEF and all-cause mortality owing to both inconsistency and imprecision. The GRADE evidence profile is summarised in Table 3.

Discussion

This meta-analysis of 15 randomised controlled trials ($n = 1466$) demonstrates that CSP offers a principal clinical advantage over conventional RVP in preservation of left ventricular (LV) systolic function and in reducing PICM and HFH in patients who predominantly present with preserved or mildly reduced ejection fraction (mean baseline LVEF = 59.4%). In our analysis, CSP improved LVEF (MD +2.96%), narrowed paced QRS duration (MD -30.10 ms) and yielded substantial RR reductions in PICM (RR 0.34) and HFH (RR 0.34), despite neutral effects on all-cause mortality. These RCT-derived benefits provide randomised-level support for CSP as a preventive strategy in this population with preserved or mildly reduced LVEF ($> 40\%$).

This prevention framing is clinically paramount: Most pacemaker recipients have baseline LVEF $> 40\%$, where the goal is to avoid iatrogenic LV decline rather than reverse established heart failure with reduced ejection fraction

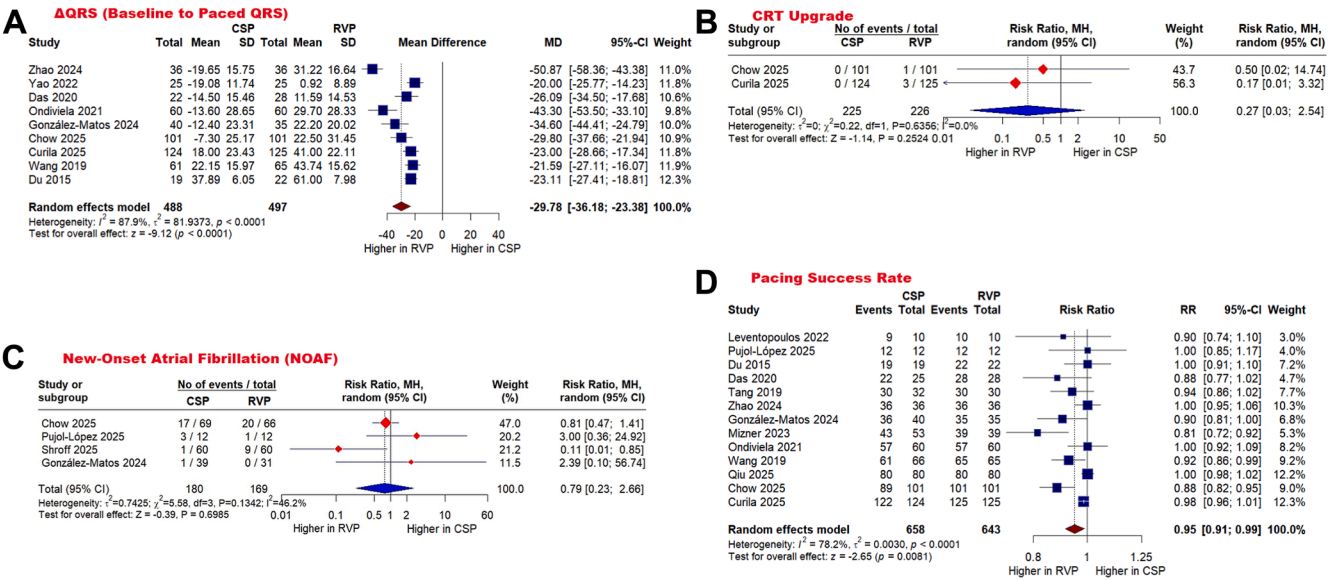


Figure 6. Forest plots of additional electrophysiologic and clinical outcomes comparing conduction system pacing (CSP) vs right ventricular pacing (RVP). Pooled analyses of (A) change in QRS duration from baseline to paced QRS, (B) cardiac resynchronisation therapy upgrade, (C) new-onset atrial fibrillation, and (D) pacing success rate. Dichotomous outcomes are presented as risk ratios (RRs) with 95% confidence intervals (CIs) according to random-effects models. MH, Mantel-Haenszel.

(HFREF). The mechanistic underpinning of our results is coherent and strongly supported by electrophysiologic principles. Chronic RVP induces electrical and mechanical dyssynchrony via slow myocardial conduction, producing LBBB-like activation, QRS widening, inter- and intraventricular dyssynchrony, reduced mechanical efficiency, functional mitral regurgitation, altered wall stress, and maladaptive remodelling—hallmarks of PICM.³⁵ A recent systematic review and meta-analysis reported PICM prevalence of ~ 12% among chronically paced patients, with strong associations with higher RVP percentage, wider paced QRS, and comorbidities.³⁶ CSP, by engaging the His-Purkinje system, restores near-physiologic activation,

shortens QRS, and mitigates these adverse effects.³⁷ The large QRS narrowing in our analysis is an electrocardiographic marker, and it likely reflects improved ventricular synchrony that mechanistically mediates the reductions in PICM and HFH observed in this analysis.³⁷ Importantly, the absolute LVEF improvement of ~ 3% should be interpreted in context. Although modest at the individual level, such preservation across a population exposed to chronic pacing may translate into clinically meaningful reductions in remodelling and heart failure events over time.

Previous strategies to mitigate RVP harm—alternative RV sites (septal or outflow) or upfront biventricular pacing (BiV-CRT)—have yielded inconsistent or limited benefits in

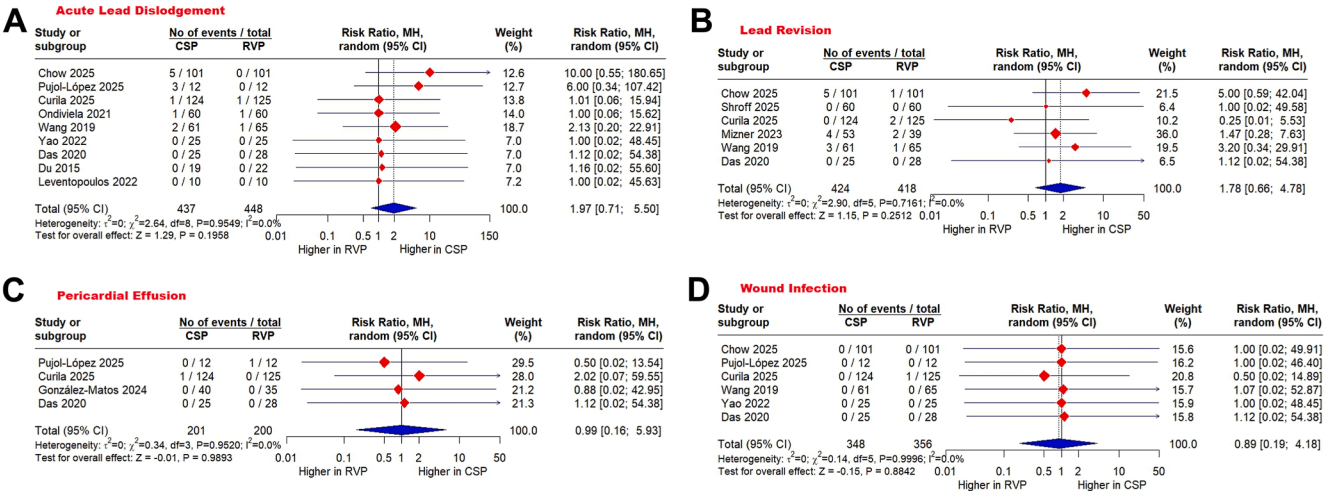


Figure 7. Forest plots of device- and procedure-related safety outcomes comparing conduction system pacing (CSP) vs right ventricular pacing (RVP). Pooled analyses of (A) acute lead dislodgement, (B) lead revision, (C) pericardial effusion, and (D) wound infection. Effect estimates are presented as risk ratios (RRs) with 95% confidence intervals (CIs) according to random-effects models. MH, Mantel-Haenszel.

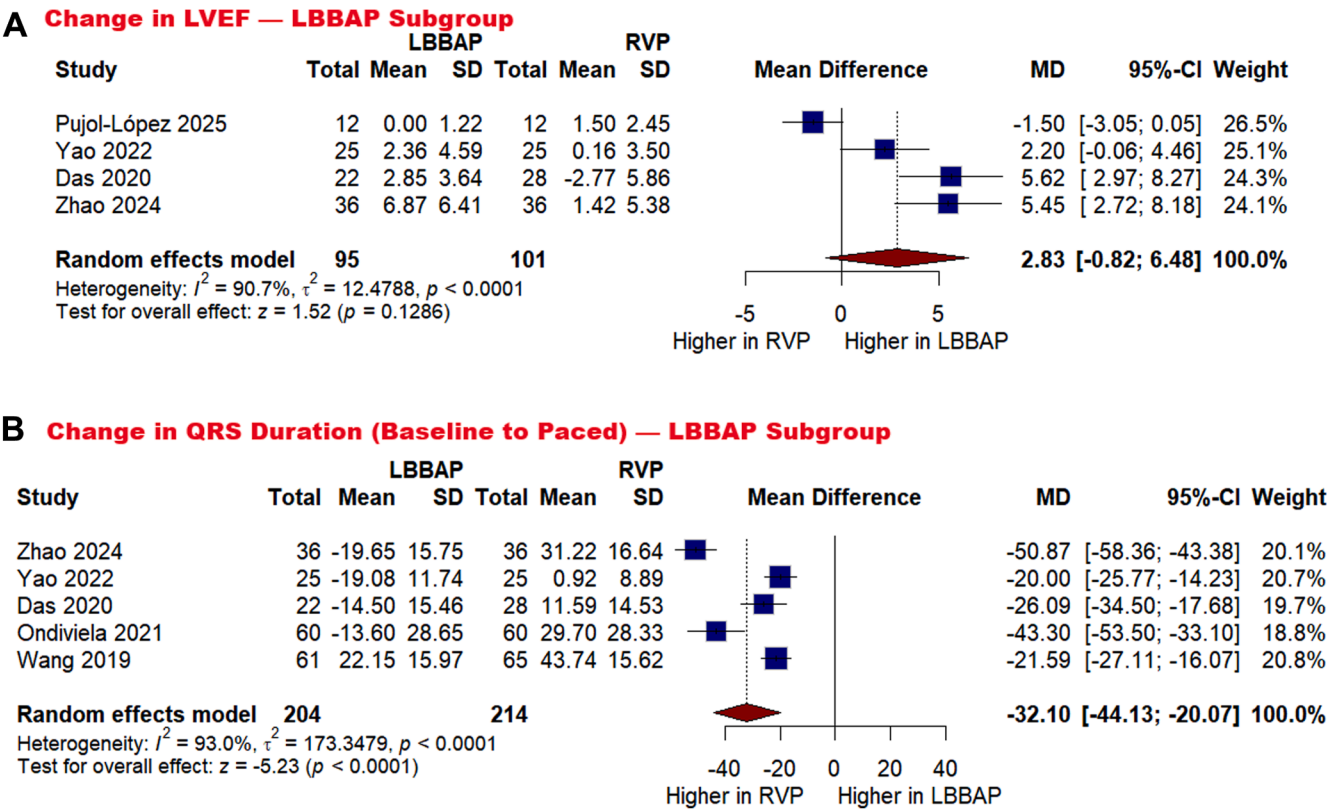


Figure 8. Subgroup analyses of left bundle branch area pacing (LBBAP) vs right ventricular pacing (RVP). Forest plots showing the LBBAP subgroup for (A) change in left ventricular ejection fraction (LVEF) from baseline and (B) change in QRS duration from baseline to paced QRS. Continuous outcomes are expressed as mean differences (MDs) with 95% confidence intervals (CIs) according to random-effects models.

preserved LVEF cohorts.^{38,39,40} RV septal pacing shows no clear LV systolic advantage over apical pacing in randomised comparisons, whereas BiV pacing benefits are more established in reduced LVEF with LBBB (eg, BLOCK HF)⁴¹ but equivocal in preserved LVEF (eg, BioPace).⁴² The long-awaited BioPace report re-energized debate about whether routine upfront BiV pacing is necessary or efficient for many pacemaker recipients anticipated to have frequent ventricular pacing.⁴² Within this landscape, CSP can be conceptualized as a middle path or a physiologic activation strategy that may deliver HF prevention without the full complexity of BiV lead placement, albeit with its own technical challenges. Observational and registry evidence has also increasingly favoured CSP over conventional pacing, reporting lower HF events and better LV function preservation in bradycardia patients requiring ventricular pacing.⁴³ Our RCT-based synthesis strengthens causal inference and addresses a key limitation of earlier nonrandomised comparisons. However, most included trials were single- or 2-centre studies, which may limit the generalisability of the findings to broader practice settings. Differences in institutional expertise, patient selection, implantation workflows, and operator experience may influence both procedural and clinical outcomes; therefore, larger multicentre pragmatic trials are needed to confirm the reproducibility of these benefits across diverse health care environments.

Within CSP modalities, LBBAP has gained traction owing to high implant success rates and stable pacing parameters

achieved by capturing the conduction system distal to proximal His disease. Comparative data suggest that LBBAP may provide lower capture thresholds and more durable sensing parameters compared with HBP, potentially improving battery longevity and reducing revision rates.³⁵ However, CSP entails procedural trade-offs.³⁵ Compared with RVP, it is associated with longer procedure and fluoroscopy times, greater radiation exposure, and slightly lower acute success in early adoption phases. This likely reflects not only the intrinsic technical complexity of CSP, but also the operator learning curve and the relatively early stage of adoption represented in several included trials. Accordingly, these procedural disadvantages should be interpreted in context, as contemporary real-world experience suggests that implant success, efficiency, and fluoroscopy exposure may improve with growing operator expertise, dedicated training, and standardised implantation workflows. HBP in particular may be limited by higher baseline capture thresholds and threshold rise over time, with some studies reporting higher lead revision or abandonment rates in selected cohorts.^{35,44} These technical realities likely explain why pooled RCTs can show clinical benefit but still report lower procedural success rates and less favourable procedural metrics.

Our findings support an LVEF-centred pacing strategy. In patients with preserved or mildly reduced LVEF (> 40%) and anticipated high ventricular pacing burden, CSP functions primarily as a preventive intervention against PICM and HFH. In contrast, among patients with established HFrEF or CRT

GRAPHICAL ABSTRACT · META-ANALYSIS · 15 RANDOMISED CONTROLLED TRIALS

Conduction System Pacing Versus Right Ventricular Pacing
in Patients With Preserved or Mildly Reduced LVEF

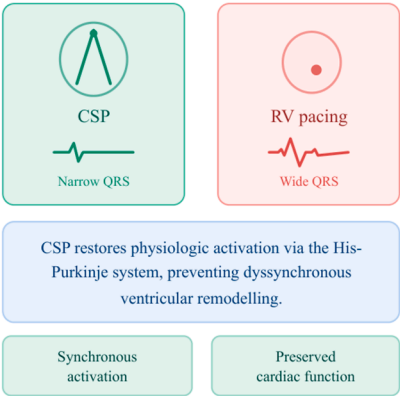
STUDY POPULATION

Included RCTs	15
Total patients	1,466
Mean age	72.9 ± 12.3 yrs
Baseline LVEF	59.4 ± 7.0%

TRIAL DESIGN



PHYSIOLOGICAL MECHANISM



CLINICAL OUTCOMES

HF HOSPITALISATION vs RV pacing · RR 0.34	66% ↓
PACING-INDUCED CARDIOMYOPATHY (PICM) vs RV pacing · RR 0.34	66% ↓
LVEF CHANGE FROM BASELINE Echocardiographic benefit	+2.96%
QRS REDUCTION FROM BASELINE Electrical synchrony	-29.78 ms
No difference in all-cause mortality	



PROCEDURAL TRADE-OFFS
Technically demanding approach

PROCEDURE TIME

+32 min

RADIATION DOSE

+25 mGy

PACING SUCCESS

93.6%
vs 99.5%

CLINICAL BENEFIT
VS COMPLEXITY

CSP significantly reduces HF hospitalisation and pacing-induced cardiomyopathy while improving ventricular synchrony, with procedural trade-offs compared with RV pacing.

Central Illustration. Design and principal findings of this meta-analysis of randomised controlled trials comparing conduction system pacing (CSP) with right ventricular (RV) pacing in patients requiring permanent pacing with preserved or mildly reduced left ventricular ejection fraction. Across 15 trials including 1466 patients, CSP was associated with lower risks of pacing-induced cardiomyopathy and heart failure (HF) hospitalisation, greater preservation of left ventricular ejection fraction, and improved electrical synchrony as reflected by shorter paced QRS duration and a greater reduction in QRS duration from baseline. These benefits were offset by lower acute implant success and less favourable procedural metrics, including longer procedure duration, longer fluoroscopy time, and higher radiation exposure. PICM, pacing-induced cardiomyopathy.

indications, CSP—particularly LBBAP—has emerged as a viable alternative or complement to BiV pacing within the broader cardiac physiologic pacing paradigm. Emerging randomised and prospective comparative data suggest that LBBP-based CRT can achieve LVEF improvement similarly to BiV-CRT in selected patients. The recent CSP-SYNC randomised study demonstrates the feasibility of head-to-head CSP vs BiV comparisons in CRT candidates.⁴⁵ Although these CRT data are not directly interchangeable with bradycardia populations, they reinforce a consistent mechanistic principle that improvements in electrical synchrony tend to precede reverse remodelling and symptomatic benefit.

Finally, leadless pacing deserves brief mention as a competing trend. Leadless atrioventricular synchronous RV pacing reduces pocket and lead complications and is expanding in use, but it still produces nonphysiologic RV myocardial activation and may not address dyssynchrony-driven HF risk in high-burden pacing patients.⁴⁶ This highlights a future design tension between minimising hardware complications and optimising ventricular

activation, motivating innovation toward leadless physiologic pacing solutions.

The certainty of evidence for the principal outcomes ranged from moderate to low. Although the trials consistently enrolled the target population of patients with bradyarrhythmias requiring pacing, the evidence should be interpreted with caution because several outcomes were limited by small sample sizes, low event rates, variable end point definitions, and differences in procedural technique and follow-up. Thus, although the findings support CSP as a physiologic pacing strategy, larger ongoing trials remain necessary.

These sources of heterogeneity are also relevant to clinical utility. Because PICM definitions, CSP qualification criteria, and procedural protocols were not uniform across trials, the pooled estimates should not be interpreted as applying identically to every clinical setting or implantation strategy. Rather, they provide an aggregate estimate of benefit across related physiologic pacing approaches while underscoring the need for standardised end point definitions and implantation criteria in future trials.

Table 3. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Evidence Profile

No. of studies	Study design	Certainty assessment					Patients, n (%)		Effect		Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CSP	RVP	RR (95% CI)	Absolute (95% CI)	
Pacing-induced cardiomyopathy 4	Randomised trials	Not serious	Not serious	Not serious	Serious*	None	13/280 (4.6)	46/284 (16.2)	0.34 (0.19-0.60)	107 fewer per 1000 (from 131 fewer to 65 fewer)	Moderate
Heart failure hospitalisation 5	Randomised trials	Not serious	Not serious	Not serious	Serious*	None	11/336 (3.3)	30/329 (9.1)	0.34 (0.17-0.70)	60 fewer per 1000 (from 76 fewer to 27 fewer)	Moderate*
Change in left ventricular ejection fraction 11	Randomised trials	Not serious	Serious†	Not serious	Serious‡	None	521	509	—	MD 2.96% higher (1.18% higher to 4.73% higher)	Low,‡,§
Paced QRS duration (electrical synchrony) 11	Randomised trials	Not serious	Serious†	Not serious	Not serious	None	628	637	—	MD 30.1 ms lower (35.46 ms lower to 24.74 ms lower)	Moderate†
All-cause mortality 4	Randomised trials	Not serious	Not serious	Not serious	Very serious*,§	None	6/276 (2.2)	12/269 (4.5)	0.56 (0.22-1.39)	20 fewer per 1000 (from 35 fewer to 17 more)	Low*,§

CI, confidence interval; MD, mean difference; RR, relative risk.

*The total accrued sample size did not reach the required/optimal information size, indicating imprecision and that further trials are needed to confirm the effect.

† $I^2 \geq 50\%$; shows significant heterogeneity.

‡Wide CI, which may not exclude the risk of appreciable benefit/harm.

§Cross no-effect line (1.0), does not exclude the risk of appreciable benefit or harm.

Study limitations

Several limitations should temper interpretation. First, trial-level heterogeneity is unavoidable: CSP techniques (eg, HBP vs LBBAP), confirmation criteria for conduction capture, RV pacing sites (apical vs septal), operator experience, and follow-up duration likely varied meaningfully across trials, potentially influencing both event rates and procedural performance. In addition, most included studies were single- or 2-centre trials, which may limit external validity and reduce the generalisability of the findings to centres with different expertise, procedural volume, and implementation practices. Second, definitions of PICM have historically been inconsistent across studies, with 15 unique criteria reported in a recent systematic review and meta-analysis³⁶; substantial variability in PICM criteria can affect absolute incidence estimates and treatment effects.

In addition, what qualified as CSP was not entirely consistent across trials, with differences in modality (HBP, LBBAP, or mixed CSP approaches) and in the criteria used to confirm conduction system capture. Similar variability also existed in how procedural success was defined. Together, these issues may reduce the direct clinical utility and bedside portability of the pooled estimates, although they do not negate the overall signal favouring CSP across the principal randomised comparisons. Third, most pacing trials are underpowered for mortality, and short follow-up (often 12-24 months) plus low event rates can explain the neutral all-cause mortality signal despite improvements in HFH and remodelling surrogates. Fourth, blinding is challenging in device trials, which may influence softer end points and follow-up management (eg, thresholds for HF admission or upgrade decisions). Finally, our pooled procedural outcomes likely reflect a mixture of early- and late-adopter experience, and therefore may partly capture the CSP learning curve rather than inherent limitations of the technique alone; as programs mature, operator experience increases, and implantation workflows become more standardised, success rates and radiation exposure may improve, potentially narrowing the gap with RVP.

Future directions

Pragmatic, adequately powered RCTs with extended follow-up in preserved or mildly reduced LVEF (> 40%) populations are needed to confirm the durability of PICM and HFH reductions observed in the present meta-analysis. Such studies could provide the high-quality evidence needed to potentially elevate CSP from its current class 2b recommendation (may be considered) in the 2023 HRS/APHRS/LAHS guideline for bradycardia indications with anticipated high RVP burden (> 20%-40%) to stronger endorsement. Direct head-to-head comparisons of CSP subtypes (LBBAP vs HBP) in bradycardia populations are warranted, incorporating standardised criteria for conduction system capture confirmation and longitudinal assessment of lead performance, thresholds, revisions, and extractability—persistent knowledge gaps noted in professional consensus statements. In parallel, implementation science initiatives focused on operator learning curves, fluoroscopy and radiation minimisation strategies, structured training frameworks, and real-world adoption barriers will be

as critical as technologic advances in enabling safe widespread CSP integration into clinical practice.

Conclusion

This meta-analysis of 15 RCTs ($n = 1466$) supports CSP as a physiologic LVEF-preserving strategy over RVP in patients with baseline LVEF $> 40\%$ and anticipated high ventricular pacing burden—reducing PICM and HFH. These benefits align with current guidelines, which assign CSP a class 2a recommendation in patients with LVEF 36%–50% and substantial anticipated ventricular pacing and a class 2b recommendation in those with normal LVEF, while underscoring the need for larger pragmatic RCTs to confirm long-term outcomes, device performance, and potential guideline evolution.

Data Availability

All required data are included in the manuscript or the supplemental material. Any additional data can be obtained from the corresponding author on reasonable request.

Ethics Statement

This meta-analysis used only previously published data; therefore, ethics approval was not required.

Patient Consent

The authors confirm that patient consent was not required for this article, because it is a meta-analysis of previously published randomised trials and does not involve any new data collection or identifiable patient information.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at <https://doi.org/10.1016/j.cjca.2026.04.009>.