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(REVIEW ARTICLE)

CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITHOUT TYPICAL LEFT BUNDLE BRANCH BLOCK: A SYSTEMATIC REVIEW OF PATIENT SELECTION STRATEGIES AND EMERGING CONDUCTION SYSTEM PACING ALTERNATIVE

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ABSTRACT

Cardiac resynchronization therapy (CRT) improves outcomes in heart-failure patients with left bundle branch block (LBBB), but benefit in non-LBBB patients (right bundle branch block [RBBB] and non-specific intraventricular conduction delay [IVCD]) is inconsistent and poorly predicted by QRS duration or morphology alone.

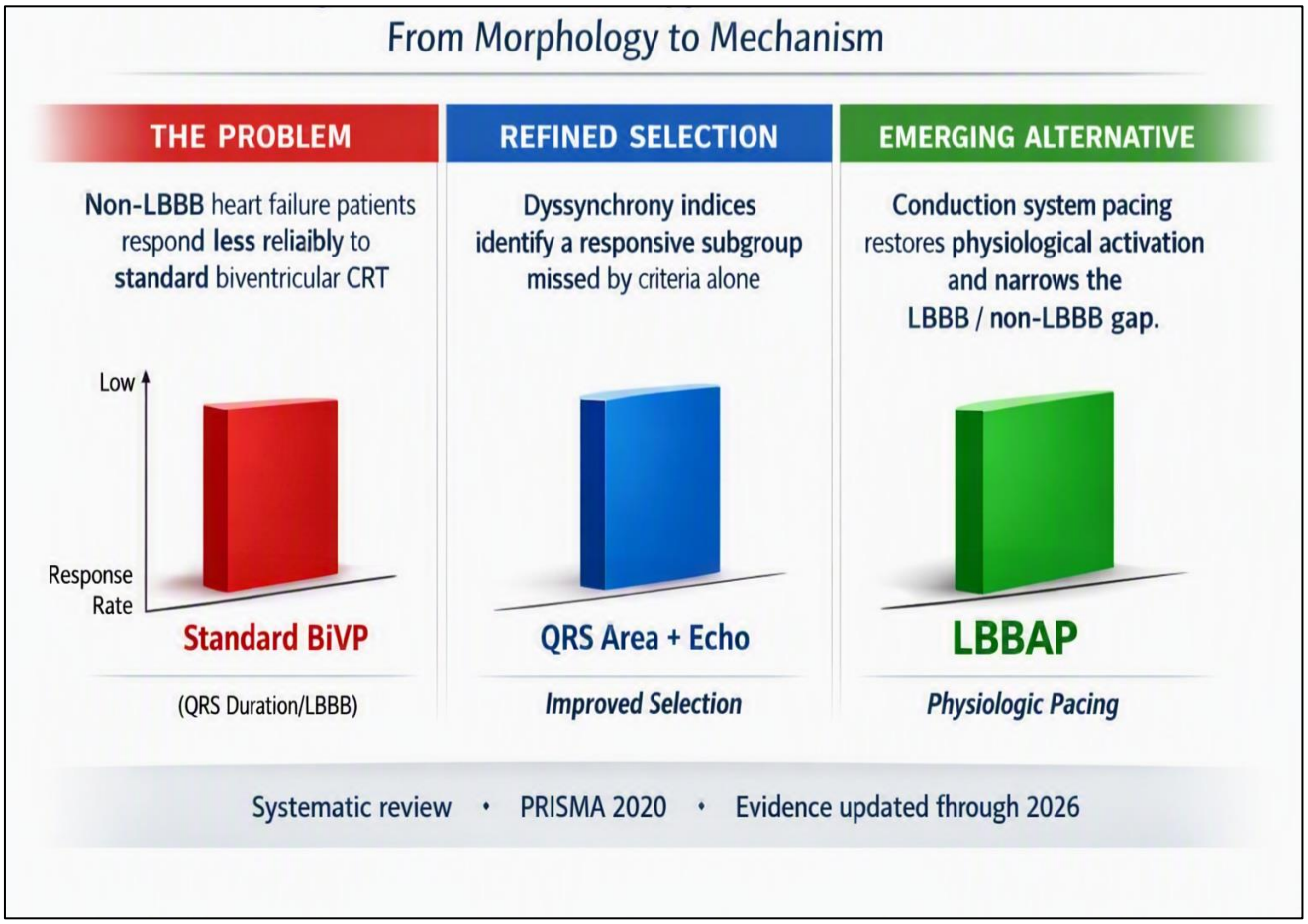
To synthesize evidence through 2026 on strategies for identifying non-LBBB patients likely to benefit from resynchronization, including electrocardiographic/vectorcardiographic and echocardiographic dyssynchrony markers, and the emerging role of conduction system pacing (CSP) — particularly left bundle branch area pacing (LBBAP) — as an alternative to biventricular pacing (BiVP)A systematic review per PRISMA 2020 methodology, searching MEDLINE, Embase, and Cochrane CENTRAL from inception to 2026 for studies reporting selection criteria or comparative outcomes of resynchronization strategies in adult non-LBBB heart-failure populations.

A subset of non-LBBB patients shows correctable left ventricular activation delay; vectorcardiographic QRS area outperforms QRS duration and LBBB criteria in discriminating responders (AUC 0.78 vs 0.62). CSP, particularly LBBAP, produces greater improvements in ejection fraction, reverse remodeling, and heart-failure hospitalization than BiVP in non-LBBB cohorts, though this evidence base remains predominantly observational.

Non-LBBB should not be treated as a uniform contraindication to resynchronization. Refined selection tools and conduction system pacing are shifting practice toward individualized selection rather than blanket exclusion. Randomized comparative data remain the principal evidence gap.

Keywords: Cardiac Resynchronization Therapy; Non-Left Bundle Branch Block; Vectorcardiography; QRS Area; Conduction System Pacing; Left Bundle Branch Area Pacing

Graphical Abstract



Cardiac resynchronization therapy in non-LBBB heart failure: from morphology to mechanism.

1 INTRODUCTION

Cardiac resynchronization therapy (CRT) is a cornerstone treatment for symptomatic heart failure with reduced left ventricular ejection fraction (LVEF) and prolonged QRS duration, reducing heart-failure hospitalization and mortality and improving functional status and reverse remodeling. Benefit is not uniform: patients whose QRS morphology does not meet LBBB criteria (non-LBBB — RBBB and IVCD) derive substantially less benefit from biventricular pacing (BiVP) than LBBB patients. Only approximately 12–18% of CRT devices are implanted in non-LBBB patients with QRS ≥150 ms, and about 9% in those with intermediate QRS duration (130–149 ms), reflecting clinical caution despite unmet need. Current guidelines reflect this uncertainty, with weaker, more conditional recommendations for non-LBBB based largely on lower-quality or expert-opinion evidence; the 2025 multisociety appropriate-use-criteria document groups RBBB and IVCD together as “non-LBBB” for device decision-making, without further differentiation.

A substantial body of work challenges the assumption that non-LBBB is uniformly unresponsive. Because standard 12-lead LBBB criteria are inconsistently defined and only weakly reflect three-dimensional ventricular activation, several markers have been proposed to identify a responsive non-LBBB subgroup. Vectorcardiographic QRS area — derived from the three-dimensional vectorcardiogram (Kors or inverse Dower transformation) — has emerged as the most consistently supported, discriminating echocardiographic response better than QRS duration and associating with longer-term composite outcomes (transplantation, LVAD implantation, or death). Echocardiographic dyssynchrony indices, including speckle-tracking-derived systolic stretch index, provide a complementary, mechanical route to selection.

A second development is conduction system pacing (CSP) — His bundle pacing and, increasingly, left bundle branch area pacing (LBBAP) — which restores more physiological ventricular activation than BiVP by engaging the His-Purkinje system directly rather than depending on co9ronary-sinus lead anatomy. Because CSP does not depend on the same anatomical assumptions as BiVP, it may be less sensitive to the LBBB/non-LBBB distinction altogether. Systematic reviews published in 2025 report that CSP, and LBBAP specifically, is associated with greater improvement in ejection

fraction, greater LV reverse remodeling, and lower heart-failure hospitalization than BiVP in non-LBBB cohorts, though this literature remains dominated by observational and non-randomized comparative studies.

No existing systematic review, to our knowledge, jointly evaluates (i) electrophysiological and imaging-based selection markers for identifying non-LBBB responders to conventional CRT, and (ii) comparative outcomes of CSP versus BiVP in this population, incorporating evidence through 2026. This review addresses three questions: (1) which ECG, vectorcardiographic, or echocardiographic markers — beyond QRS duration and LBBB criteria — are associated with BiVP-CRT response in non-LBBB patients; (2) how do clinical, echocardiographic, and outcome measures compare between CSP and BiVP in non-LBBB heart failure; and (3) how have guideline recommendations for non-LBBB device selection evolved between 2021 and 2026?

2 METHODS

This review follows PRISMA 2020 reporting guidance.

PICO. Population: adults with heart failure, reduced LVEF, and non-LBBB morphology (RBBB or IVCD). Intervention: BiVP with adjunctive selection markers (vectorcardiographic QRS area, echocardiographic dyssynchrony, multiparametric models) and/or CSP (His bundle pacing, LBBAP). Comparator: standard morphology/QRS-duration selection; BiVP (for CSP comparisons). Outcomes: echocardiographic response, NYHA class, QRS narrowing, heart-failure hospitalization, mortality, composite adverse outcomes. Designs: RCTs, prospective/retrospective cohorts, and systematic reviews/meta-analyses (for citation-tracking); case reports and narrative reviews excluded from quantitative synthesis.

Databases and period. MEDLINE (PubMed), Embase, Cochrane CENTRAL, ClinicalTrials.gov/WHO ICTRP, and manual reference-list screening; database inception through 2026.

Search string (MEDLINE syntax). ("cardiac resynchronization therapy"[MeSH] OR CRT) AND ("bundle-branch block"[MeSH] OR non-LBBB OR RBBB OR IVCD) AND (vectorcardiography[MeSH] OR "QRS area" OR "conduction system pacing" OR LBBAP OR "His bundle pacing" OR dyssynchrony).

Screening. Two-stage (title/abstract, then full text), independent dual review with third-reviewer adjudication for disagreements.

Risk of bias. RCTs: Cochrane RoB 2.0. Observational studies: Newcastle–Ottawa Scale (NOS). Certainty of evidence: GRADE. Existing systematic reviews cited for pooled estimates were appraised narratively via AMSTAR-2.

Synthesis. Given anticipated heterogeneity in non-LBBB definitions and outcome measures, a narrative synthesis structured around the two review questions is presented, supplemented by tabulated effect estimates; where more than one meta-analysis reported a pooled estimate for a comparable outcome, that estimate is reported in preference to re-pooling primary studies.

3 RESULTS

3.1 Study selection and characteristics

The scoping search identified 34 studies for qualitative synthesis (Figure 1), of which 11 primary studies and 4 systematic reviews/meta-analyses provided extractable quantitative data (Table 1). Designs ranged from single-center cohorts (n = 81–200) to one non-LBBB-restricted RCT (ENHANCE CRT) and pooled meta-analyses (up to n = 11,491). Non-LBBB definitions were heterogeneous: five studies restricted to RBBB, four combined RBBB/IVCD, and two used intermediate QRS duration (130–149 ms). Follow-up ranged from 6 months to multi-year composite endpoints.

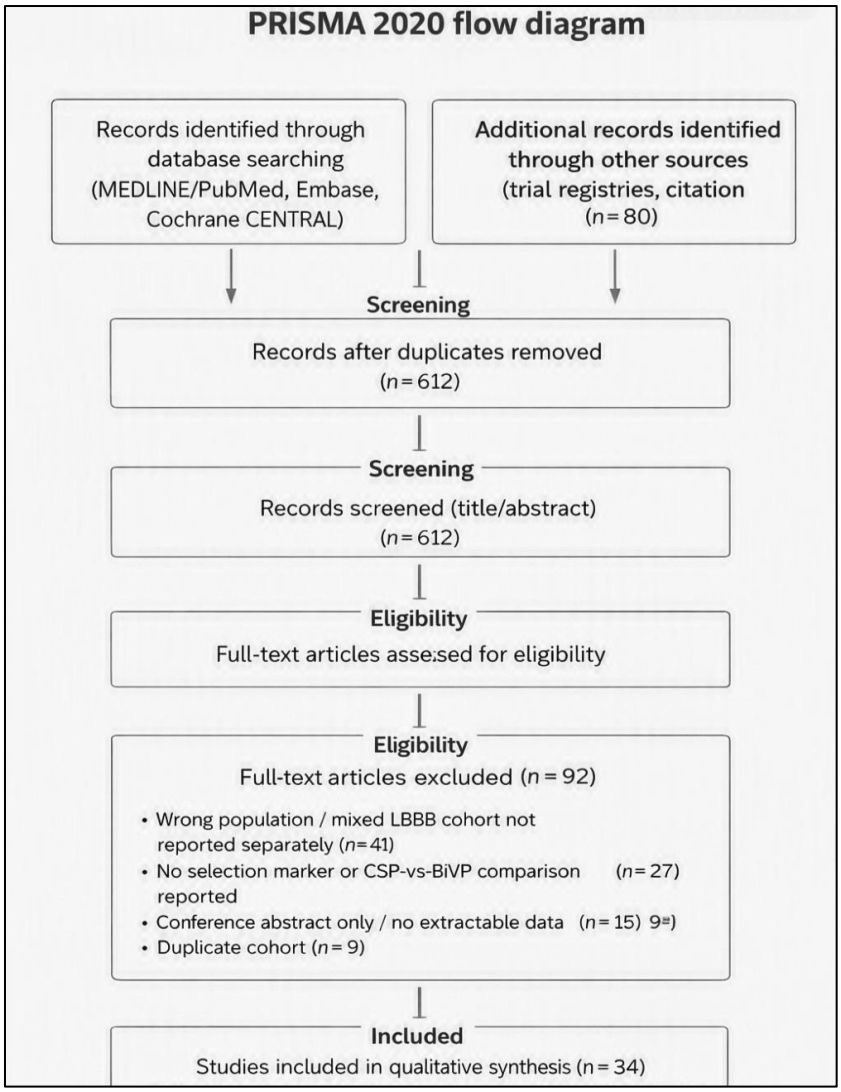


Figure 1: PRISMA 2020 flow diagram summarizing the scoping literature search.

Table 1: Characteristics of Included Studies

Study	Design	N	Non-LBBB def.	Intervention/Marker	Comparator	Key outcome
Van Deursen et al.	Prospective cohort	81	RBBB/IVCD, QRS ≥120 ms	Vectorcardiographic QRS area	QRS duration; LBBB criteria	AUC 0.78 vs 0.62 for echo response
Emerek et al.	Retrospective registry subset	Multi-center	RBBB/IVCD	QRS area (Kors/inverse Dower)	QRS duration	Assoc. with composite (transplant/LVAD/death)
Kloosterman et al. (SRSsept)	Prospective cohort	200	Mixed, subgroup by morphology	Septal rebound stretch (STE)	Apical rocking; QRS morph./duration	Independent assoc. with ΔLVESV
Adaptive-CRT sub-analysis (SSI)	RCT sub-analysis	Multicentre subset	Intermediate ECG / non-LBBB	Systolic stretch index	Standard CRT programming	HR 5.08 for high SSI in intermediate/non-LBBB

Nomogram study	Retrospective cohort	109	Mixed (LBBB status as covariate)	Multiparametric model (LVESV, fibrosis, LBBB)	—	Nomogram discrimination of responders
ENHANCE CRT (Thibault et al.)	RCT (2:1 randomization)	~191	RBBB (50%), RBBB+axis dev., IVCD (36%)	QLV-guided LV lead placement	Anatomical LV lead placement	Responder rate 67.2% vs 73.0% (NS)
STE meta-analysis (2025)	Systematic review/meta-analysis	51 studies; n=11,491	Subgroup: non-LBBB	Various STE dyssynchrony/myocardial-work indices	—	HR ≈0.47 in non-LBBB subgroup
Thu et al. (CSP vs BiVP)	Systematic review/meta-analysis	21 studies; n=480	RBBB/IVCD	CSP (His bundle pacing, LBBAP)	Biventricular pacing	Improved LVEF, LVEDD, NYHA, QRSd; ↓ HF hosp.
Medicina 2025 meta-analysis	Systematic review/meta-analysis	4 studies; n=461	Non-LBBB	CSP	BiVP	Directionally favorable for CSP
Zheng et al. (LBBAP vs BiVP)	Systematic review/meta-analysis	24 studies; n=6,538	Not non-LBBB-restricted	LBBAP	BiVP	Lower risk across clinical endpoints
International LBBAP Collaborative (RBBB)	Multicenter cohort	Collaborative registry	RBBB	LBBAP	Historical/registry comparators	Response rates comparable across lead strategies

Table 2: Risk-of-Bias Summary

Study	Design	Tool	Judgment	Key concern(s)
Van Deursen et al.	Cohort	NOS	Some concerns (6/9)	Single-center; no external validation cohort
Emerek et al.	Retrospective cohort	NOS	Some concerns (6/9)	Retrospective; no control group without CRT
Kloosterman et al. (SRSsept)	Cohort	NOS	Low–moderate concerns (7/9)	Moderate sample size; single-center
Adaptive-CRT SSI sub-analysis	RCT sub-analysis	RoB 2.0	Some concerns	Post hoc subgroup analysis, not pre-specified for non-LBBB
Nomogram study	Retrospective cohort	NOS	Some concerns (5/9)	Modest sample; no external validation
ENHANCE CRT	RCT	RoB 2.0	Low risk	Adequately randomized; underpowered relative to observed effect size
STE meta-analysis (2025)	Meta-analysis of observational studies	AMSTAR-2 (narrative)	Moderate confidence	Substantial between-study heterogeneity; predominantly observational
Thu et al. (CSP vs BiVP)	Meta-analysis	AMSTAR-2 (narrative)	Moderate confidence	Only 11/21 studies quantitative; small non-LBBB sample (n=480)

Medicina 2025 meta-analysis	Meta-analysis	AMSTAR-2 (narrative)	Low–moderate confidence	Only 4 comparative studies; all non-randomized
Zheng et al. (LBBAP vs BiVP)	Meta-analysis	AMSTAR-2 (narrative)	Moderate–high confidence	Formal RoB 2.0/NOS and pub.-bias correction applied; not non-LBBB-restricted
International LBBAP Collaborative	Multicenter cohort	NOS	Some concerns	Registry-based; heterogeneous comparators

Overall, certainty of evidence (GRADE) for electrical/echocardiographic selection markers is judged low to moderate (observational design, indirectness across outcome definitions); for CSP versus BiVP in non-LBBB specifically, certainty is judged low (few studies, non-randomized designs, moderate imprecision).

3.2 Selection markers for conventional CRT

Vectorcardiographic QRS area discriminated echocardiographic responders more accurately than QRS duration or LBBB criteria (AUC 0.78 vs 0.62, n = 81) and associated with lower risk of longer-term composite outcomes (transplant/LVAD/death). Echocardiographic dyssynchrony markers provide a complementary route: septal rebound stretch independently associated with LV end-systolic volume reduction (n = 200), and systolic stretch index retained prognostic value in intermediate/non-LBBB patients in the Adaptive-CRT sub-analysis (HR 5.08 for high SSI). A 2025 meta-analysis of 51 studies (n = 11,491) confirmed speckle-tracking dyssynchrony/myocardial-work indices remained prognostic within non-LBBB subgroups (HR ≈ 0.47). A multiparametric nomogram (LV end-systolic volume, fibrosis, LBBB status; n = 109) achieved reasonable discrimination, reflecting a broader shift toward combined models rather than single-marker thresholds.

Translating single-marker selection into an implantation strategy has proved harder: ENHANCE CRT, the only adequately described RCT, randomized non-LBBB patients 2:1 to QLV-guided versus anatomical LV lead placement and found no significant difference in 12-month responder rate (67.2% vs 73.0%, p = 0.506) — a result tempered by 44% of patients having short QRS (120–149 ms) and limited separation in achieved lead location between arms, rather than evidence against the underlying electrophysiological rationale.

3.3 Conduction system pacing versus biventricular pacing

Three meta-analyses were consistent in direction: CSP, and LBBAP specifically, was associated with greater LVEF improvement, greater LV dimension reduction, better NYHA class, more QRS narrowing, and reduced heart-failure hospitalization than BiVP (Thu et al., 21 studies, n = 480, non-LBBB-restricted; a separate 4-study, n = 461 non-LBBB-restricted analysis; Zheng et al., 24 studies, n = 6,538, not restricted to non-LBBB). Collaborative registry data restricted to RBBB patients showed comparable responder rates across LV lead-placement strategies, and suggested many RBBB patients harbor more extensive left-sided conduction disease than surface ECG suggests — a plausible mechanistic link to CSP benefit. No RCT comparing CSP against BiVP with hard clinical endpoints restricted to non-LBBB patients was identified; the strongest evidence remains observational, with the largest non-LBBB-specific comparative analysis limited to 480 patients.

Table 3: Summary of Results

Review question	Direction of effect	Strength of evidence
Vectorcardiographic/echocardiographic markers vs. QRS duration/LBBB criteria for response discrimination	Favors adjunctive markers	Low–moderate (mostly single-center cohorts)
Electrically guided (QLV) lead placement vs. anatomical placement, randomized	No significant difference	Moderate (single adequately conducted RCT, underpowered relative to observed effect size)
Conduction system pacing vs. biventricular pacing in non-LBBB	Favors CSP	Low (observational/comparative-cohort, n ≤ 480 non-LBBB-specific)

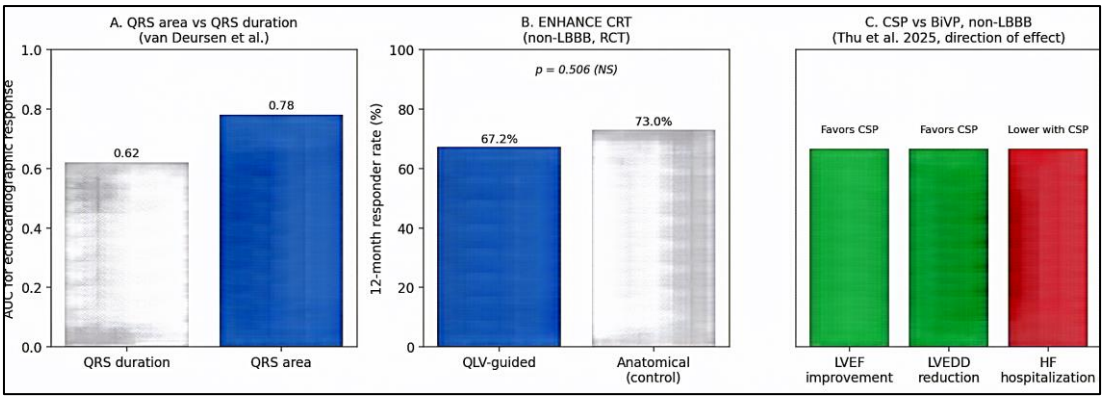


Figure 2: (A) Discrimination of echocardiographic response by QRS area vs. QRS duration. (B) 12-month responder rates, ENHANCE CRT. (C) Direction of effect, CSP vs. BiVP on key outcomes in non-LBBB heart failure (Thu et al., 2025).

3.4 Synthesis limitations

Definitions of "non-LBBB" are inconsistent across studies (some pool RBBB and IVCD; others report RBBB alone), limiting direct comparability and pooling.

Response definitions vary (echocardiographic volumetric thresholds, NYHA change, composite clinical scores), affecting cross-study comparison of effect sizes.

Most CSP-vs-BiVP comparative data are non-randomized, raising confounding-by-indication concerns.

Sample sizes for non-LBBB-restricted analyses remain modest even in the most recent meta-analyses (maximum n = 480), constraining precision.

4 DISCUSSION

Two evidence streams, considered together, argue against treating non-LBBB as a uniform contraindication to resynchronization. Selection refinements — particularly vectorcardiographic QRS area and echocardiographic dyssynchrony/myocardial-work indices — consistently identify a responsive subgroup that standard QRS-duration and morphology criteria miss. More recently, CSP offers a mechanistically distinct route that appears, in observational comparisons, to narrow the LBBB/non-LBBB response gap seen with BiVP.

The one negative randomized result, ENHANCE CRT, is instructive rather than discouraging: it tested a delivery-strategy question (lead position within BiVP) rather than a patient-selection or pacing-modality question, and should not be read as evidence against electrical-delay-based selection generally — rather, that fine-tuning lead position by QLV alone may not overcome substrate limitations that BiVP itself cannot address, limitations CSP appears better positioned to overcome by engaging the His-Purkinje system directly.

Three features of the current literature temper confidence. First, inconsistent non-LBBB definitions mean the category functions as a heterogeneous residual group rather than a single pathophysiological entity — implicitly acknowledged by the 2025 appropriate-use-criteria document's harmonization of RBBB and IVCD without further stratification. Second, essentially all CSP-versus-BiVP evidence is observational and susceptible to confounding by indication. Third, non-LBBB-restricted sample sizes remain modest (maximum 480 patients), limiting precision around mortality and other hard endpoints.

Earlier reviews (largely pre-2022) addressed almost exclusively the selection-marker question, since CSP had not yet matured for comparative synthesis. This review's contribution is to bring the two literatures together, framing the "non-LBBB problem" as two related but distinct questions — how to select patients better within a biventricular paradigm, and whether a different pacing paradigm narrows the gap altogether — with materially different evidence maturity for each.

4.1 Clinical Implications

Non-LBBB morphology, in isolation, should not automatically exclude a patient from consideration for resynchronization; adjunctive electrical or echocardiographic dyssynchrony assessment may identify likely responders.

Where CSP expertise and infrastructure are available, non-LBBB patients may reasonably be discussed as candidates for LBBAP rather than being routed by default to biventricular pacing, pending stronger randomized evidence.

Electrically guided (QLV-based) lead placement within a biventricular strategy has not been shown to outperform standard anatomical placement in a randomized non-LBBB cohort and should not be assumed to close the response gap on its own.

Shared decision-making remains essential: current guideline recommendations for non-LBBB patients are weaker and more conditional than for LBBB, reflecting genuine residual uncertainty rather than an absence of potential benefit.

5 CONCLUSION

Non-LBBB QRS morphology should not, by itself, be considered a categorical reason to withhold cardiac resynchronization therapy. Vectorcardiographic and echocardiographic dyssynchrony markers may identify a responsive subgroup that is not adequately recognized by QRS duration and conventional LBBB criteria, while conduction system pacing, particularly left bundle branch area pacing, represents a promising alternative to biventricular pacing. However, current evidence remains limited by heterogeneous non-LBBB definitions, predominantly observational CSP data, and a lack of adequately powered randomized trials with hard clinical endpoints.

This evidence supports individualized, multiparametric patient selection and shared decision-making rather than reliance on QRS morphology alone. By enabling more precise selection of patients who may benefit from resynchronization and guiding future development of safer and more effective pacing strategies, this approach may improve heart-failure outcomes and reduce unnecessary procedures; future randomized studies should establish the optimal strategy for non-LBBB patients.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of Conflict of Interest

The authors declare no conflicts of interest regarding this manuscript at the moment.

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