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A Comprehensive Meta-Analysis of Clinical and Echocardio-graphic Outcomes of Physiological Versus Conventional Pacing

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 April 2025 and was last updated on 15 April 2025.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis was to compare the effectiveness of various cardiac pacing techniques (Intervention: CSP – HBP and LBBAP) with conventional techniques (Comparison: BVP, RVP) in adult patients with heart failure or indications for pacemaker implantation.

Rationale Addressing this issue is justified by the ambiguity of existing data and aims to provide a synthesized body of evidence that may support the optimization of device-based therapy in patients requiring chronic cardiac pacing.

Condition being studied Permanent cardiac pacing is indicated in patients with symptomatic bradyarrhythmias, including sick sinus syndrome, atrioventricular (AV) block, or atrial fibrillation with slow ventricular response, as well as in selected patients with heart failure requiring cardiac resynchronization therapy (CRT). The underlying conditions commonly include sinus node dysfunction, high-degree AV block, and heart failure with reduced ejection fraction (HFrEF), particularly in the presence of prolonged QRS duration or left bundle branch block (LBBB). This meta-analysis focuses on patients who met guideline-recommended indications for permanent pacing — either for bradyarrhythmia or for heart failure with reduced LVEF and electromechanical dyssynchrony — and were treated with physiological pacing techniques such as His bundle pacing (HBP) or left bundle branch area pacing (LBBAP), compared with those receiving conventional right ventricular pacing (RVP) or biventricular pacing (BVP).

METHODS

Search strategy A systematic search was conducted in the PubMed and Web of Science databases for studies published up to March 31, 2025. The literature search was performed twice in both databases by two independent reviewers. Advanced search strategies were employed, and the results were limited to the following publication

types: Full Text, Classical Article, Clinical Study, Clinical Trial (all phases), Clinical Trial Protocol, Comparative Study, Controlled Clinical Trial, Multicenter Study, Observational Study, and Randomized Controlled Trial.

Participant or population This review will include adult patients (≥18 years) with an indication for permanent cardiac pacing, either for bradyarrhythmia (e.g., sick sinus syndrome, high-grade atrioventricular block, atrial fibrillation with slow ventricular response) or for cardiac resynchronization therapy (CRT) in the setting of heart failure with reduced ejection fraction (HFrEF) and electrical dyssynchrony (typically wide QRS complex or left bundle branch block). Eligible populations include both patients undergoing de novo pacemaker implantation and those undergoing device upgrade (e.g., from RVP to HBP/LBBAP or CRT). Studies involving either selective or non-selective His bundle pacing (HBP), and/or left bundle branch area pacing (LBBAP, including LBBP and LBBAP with or without fascicular capture), will be included. Comparators will consist of conventional right ventricular pacing (RVP) or biventricular pacing (BVP). There will be no restriction regarding baseline LVEF, QRS duration, rhythm (sinus or atrial fibrillation), or device indication subgroup, as long as the intervention involves physiological pacing and appropriate comparator.

Intervention The intervention assessed in this review is physiological pacing, including His bundle pacing (HBP) and left bundle branch area pacing (LBBAP). These techniques aim to preserve or restore natural ventricular activation by engaging the intrinsic conduction system. The analysis includes both de novo implants and upgrade procedures in patients with indications for bradycardia pacing or cardiac resynchronization therapy (CRT). Interventions must involve pacing at the His bundle or left bundle branch region, regardless of specific lead type or pacing mode.

Comparator The comparators in this review are conventional non-physiological pacing modalities, including right ventricular pacing (RVP) and biventricular pacing (BVP), used in patients with similar clinical indications. These techniques serve as standard approaches in bradycardia pacing and cardiac resynchronization therapy (CRT), but may lead to non-physiological ventricular activation and dyssynchrony.

Study designs to be included This review will include prospective and retrospective studies with a comparative design, such as randomized controlled trials (RCTs), non-randomized controlled studies, and observational cohort studies comparing physiological pacing (HBP or LBBAP) with conventional pacing (RVP or BVP). Single-arm studies, case reports, editorials, and reviews will be excluded.

Eligibility criteria We will include studies involving adult patients (≥18 years) with an indication for permanent cardiac pacing due to bradyarrhythmia or heart failure requiring cardiac resynchronization therapy (CRT). Eligible studies must compare physiological pacing (His bundle pacing or left bundle branch area pacing) with conventional pacing (right ventricular or biventricular pacing) and report at least one relevant clinical or echocardiographic outcome. Only full-text, peer-reviewed studies published in English will be included. Single-arm studies, case series without comparators, editorials, conference abstracts, and reviews will be excluded.

Information sources We will search electronic databases including PubMed and Web of Science.

Main outcome(s) 29 studies (8,777 patients, 47 comparisons) were included. Conduction system pacing significantly improved LVEF, shortened QRS duration, reduced NYHA class, NT-proBNP levels, LVEDV and LVESV. Improvement in LVEF significantly correlated with longer follow-up.

Additional outcome(s) Conduction system pacing is more effective in patients with baseline low LVEF.

Data management All records identified during the systematic search were managed using PubMed and Web of Science platforms for initial screening and deduplication. Full-text articles selected for potential inclusion were collected and stored in a shared, access-controlled folder. Detailed extraction of relevant data (e.g., means, standard deviations, sample sizes, and clinical endpoints such as LVEF, QRS duration, NYHA class) was independently performed by two reviewers and recorded in a pre-specified Excel spreadsheet designed for meta-analytical synthesis. The final dataset was structured with variables appropriate for both pairwise meta-analysis and meta-regression, including study-level covariates such as follow-up duration, stimulation type, and patient characteristics. All data transformations (e.g., calculation of standardized mean differences, standard errors, and pooled standard deviations) were conducted using R (packages: metafor, meta, netmeta), with full reproducibility ensured via code versioning. Quality control procedures included independent

verification of 100% of the extracted data and sensitivity analyses to assess the robustness of results. Access to raw data was restricted to the core review team, while aggregated datasets and meta-analysis outputs may be shared upon reasonable request.

Quality assessment / Risk of bias analysis Publication bias tests (Egger's test and the trim-and-fill method) were performed for the main outcomes (LVEF, NYHA, BNP, QRS). Most analyses did not reveal significant signs of publication bias:
• Egger's test showed no funnel plot asymmetry for LVEF, BNP, QRS, and NYHA.
• The trim-and-fill method did not impute any additional studies, supporting the stability of the results.

Strategy of data synthesis Data synthesis was conducted using random-effects meta-analysis models, depending on the structure of the dataset. Standardized mean differences (SMD) with 95% confidence intervals were calculated for continuous outcomes such as LVEF, QRS duration, NYHA class. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. Subgroup analyses were performed based on the type of pacing (e.g., HBP, LBBP, BVP, RVP) and stimulation strategy (physiological vs conventional). Meta-regression was used to explore sources of heterogeneity, including follow-up duration and study quality. All analyses were performed using R software (packages meta, metafor, netmeta). Forest plots, bubble plots, and funnel plots were generated to visualize effect sizes, heterogeneity, and potential publication bias.

Subgroup analysis Subgroup analyses were conducted to explore differences in treatment effects across pacing modalities. The comparisons included His bundle pacing (HBP), left bundle branch pacing (LBBP or LBBAP), biventricular pacing (BVP), and right ventricular pacing (RVP), as well as grouped comparisons of physiological pacing (HBP, LBBP, LBBAP) versus conventional pacing (BVP, RVP). Key outcomes such as LVEF, QRS duration, NYHA class were analyzed separately within each subgroup. Where applicable, subgroup effects were further examined using meta-regression models with pacing modality included as a categorical moderator to assess potential effect modification.

Sensitivity analysis As part of the sensitivity analysis, we assessed the impact of individual studies on the overall effect estimate by comparing the results of random-effects and fixed-effect models. In the case of heterogeneous comparisons (e.g., HBP vs RVP and LBBAP vs BVP), we performed analyses excluding specific subgroups to evaluate the stability of the effect and to rule out a dominant influence of any single pacing modality.

Language restriction The review was conducted and reported only in English.

Country(ies) involved Poland.

Keywords His bundle pacing; left bundle branch area pacing; heart failure, biventricular pacing, right ventricular pacing, cardiac resynchronization therapy, atrial fibrillation.

Contributions of each author
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