Impact of physiologic pacing versus right ventricular pacing among patients with left ventricular ejection fraction greater than 35%: A systematic review for the 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Evidence Review Committee Members

David J. Slotwiner, MD, FACC, FHRS (Chair), Merritt H. Raitt, MD, FACC, FHRS (Vice Chair), Freddy Del-Carpio Munoz, MD, MSc, FHRS, Siva K. Mulpuru, MD, FACC, Naseer Nasser, MD, Pamela N. Peterson, MD, MSPH, FACC

ACC/AHA Task Force Members

Glenn N. Levine, MD, FACC, FAHA, *Chair*
Patrick T. O'Gara, MD, MACC, FAHA, *Chair-Elect*
Jonathan L. Halperin, MD, FACC, FAHA, *Immediate Past Chair**
Sana M. Al-Khatib, MD, MHS, FACC, FAHA
Joshua A. Beckman, MD, MS, FAHA
Kim K. Birtcher, PharmD, MS, AACC
Biykem Bozkurt, MD, PhD, FACC, FAHA*
Ralph G. Brindis, MD, MPH, MACC*
Joaquin E. Cigarroa, MD, FACC
Lesley H. Curtis, PhD, FAHA*
Anita Deswal, MD, MPH, FACC, FAHA
Lee A. Fleisher, MD, FACC, FAHA
Federico Gentile, MD, FACC
Samuel Gidding, MD, FAHA*
Zachary D. Goldberger, MD, MS, FACC, FAHA
Mark A. Hlatky, MD, FACC, FAHA
John Ikonomidis, MD, PhD, FAHA*
José A. Joglar, MD, FACC, FAHA
Laura Mauri, MD, MSc, FAHA*
Mariann R. Piano, RN, PhD, FAAN, FAHA
Susan J. Pressler, PhD, RN, FAHA*
Barbara Riegel, PhD, RN, FAHA*
Duminda N. Wijeysundera, MD, PhD

**Former Task Force member; current member during the writing effort.*

KEYWORDS ACC/AHA Evidence Review Committee; ACC/AHA Clinical Practice Guideline; Atrioventricular block; Biventricular pacing; Cardiac resynchronization therapy; Dual chamber pacing; Heart block; His bundle pacing; Left ventricular ejection fraction; Right ventricular pacing (Heart Rhythm 2019;16:e280–e298)

This document was approved by the American College of Cardiology Clinical Policy Approval Committee, the American Heart Association Science Advisory and Coordinating Committee, and the Heart Rhythm Society Board of Trustees in August 2018, and the American Heart Association Executive Committee in October 2018. The Heart Rhythm Society requests that this document be cited as follows: Slotwiner DJ, Raitt MH, Del-Carpio Munoz F, Mulpuru SK, Nasser N, Peterson PN. Impact of physiologic pacing versus right ventricular pacing among patients with left ventricular ejection fraction greater than 35%: a systematic review for the 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2019;16:e280–e298. This article has been copublished in the *Journal of the American College of Cardiology* and *Circulation*.

1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2018.10.035

BACKGROUND It is unclear whether physiologic pacing by either cardiac biventricular pacing (BiVP) or His bundle pacing (HisBP) may prevent adverse structural and functional consequences known to occur among some patients who receive right ventricular pacing (RVP).

AIM Our analysis sought to review existing literature to determine if BiVP and/or HisBP might prevent adverse remodeling and be associated with structural, functional, and clinical advantages compared with RVP among patients without severe left ventricular dysfunction (>35%) who required permanent pacing because of heart block.

METHODS A literature search was conducted using MEDLINE (through PubMed) and Embase to identify randomized trials and observational studies comparing the effects of BiVP or HisBP versus RVP on measurements of left ventricular dimensions, left ventricular ejection fraction (LVEF), heart failure functional classification, quality of life, 6-minute walk, hospitalizations, and mortality. Data from studies that met the appropriate population, intervention, comparator, and outcomes of interest were abstracted for meta-analysis. Studies that reported pooled outcomes among patients with LVEF both above and below 35% could not be included in the meta-analysis because of strict relationships with industry procedures that preclude retrieval of industry-retained unpublished data on the subset of patients with preserved left ventricular function.

RESULTS Evidence from 8 studies, including a total of 679 patients meeting the prespecified criteria for inclusion, was identified. Results were compared for BiVP versus RVP, HisBP versus RVP, and BiVP+HisBP versus RVP. Among patients who received physiologic pacing with either BiVP or HisBP, the LV end-diastolic and end-systolic volumes were significantly lower (mean duration of follow-up: 1.64 years; −2.77 mL [95% CI −4.37 to −1.1 mL]; p=0.001; and −7.09 mL [95% CI −11.27 to −2.91; p=0.0009) and LVEF remained preserved or increased (mean duration of follow-up: 1.57 years; 5.328% [95% CI: 2.86%–7.8%; p<0.0001). Data on clinical impact such as functional status and quality of life were not definitive. Data on hospitalizations were unavailable. There was no effect on mortality. Several studies stratified results by LVEF and found that patients with LVEF >35% but ≤52% were more likely to receive benefit from physiologic pacing. Patients with chronic atrial fibrillation who underwent atrioventricular node ablation and pacemaker implant demonstrated clear improvement in LVEF with BiVP or HisBP versus RVP.

CONCLUSION Among patients with LVEF >35%, the LVEF remained preserved or increased with either BiVP or HisBP compared with RVP. However, patient-centered clinical outcome improvement appears to be limited primarily to patients who have chronic atrial fibrillation with rapid ventricular response rates and have undergone atrioventricular node ablation.

(Heart Rhythm 2019;16:e280–e298)

TABLE OF CONTENTS

Preamble

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, based on systematic methods to evaluate and classify evidence, provide a cornerstone of quality cardiovascular care. In response to reports from the Institute of Medicine[1,2] and a mandate to evaluate new knowledge and maintain relevance at the point of care, the ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) modified its methodology.[3–5]

Evidence Review

The Task Force recognizes the need for objective, independent evidence review committees (ERCs) that include methodologists, epidemiologists, clinicians, and biostatisticians who systematically survey, abstract, and assess the evidence to address systematic review questions posed in the PICOTS format (P=population, I=intervention, C=comparator, O=outcome, T=timing, S=setting).[2,4–6] Practical considerations, including time and resource constraints, limit the ERCs to evidence that is relevant to key clinical questions and lends itself to systematic review and analysis

that could affect the strength of corresponding recommendations. Recommendations developed by the writing committee on the basis of the systematic review are marked "SR."

Relationships With Industry and Other Entities

The ACC and AHA sponsor the guidelines without commercial support, and members volunteer their time. The Task Force avoids actual, potential, or perceived conflicts of interest that might arise through relationships with industry and other entities (RWI). All ERC members are required to disclose current industry relationships or personal interests, from 12 months before initiation of the writing effort. The ERC chair and all ERC members may not have any relevant RWI (Appendix 1). For transparency, ERC members' comprehensive disclosure information is available online, as is comprehensive disclosure information for the Task Force.

Glenn N. Levine, MD, FACC, FAHA, Chair
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

Introduction

In the United States, the annual number of first pacemaker implants is 990 for every million inhabitants.[7] This corresponds to an extrapolated 288,000 first implants each year. Evidence has shown that certain patient populations may experience adverse effects with conventional right ventricular pacing (RVP) even after implementing various algorithms to reduce unnecessary ventricular pacing.[8–14] RVP raises concern because it causes undesired effects such as left ventricular desynchronization, proarrhythmia, promotion of heart failure, and increased mortality for patients with reduced left ventricular function.[15,16] Biventricular pacing (BiVP), known as cardiac resynchronization therapy, has been shown to attenuate ventricular dyssynchrony and to improve symptoms and prognosis in patients with a left ventricular ejection fraction (LVEF) of <35% and left bundle branch block.[17–21] His bundle pacing (HisBP) has been postulated to mitigate many of the adverse effects of standard RVP and reduce dyssynchrony similar to BiVP.[22–25] It is unclear whether either BiVP or HisBP (i.e., physiologic ventricular pacing) is superior to RVP in patients with an LVEF of >35%. Therefore, an independent ERC was commissioned to perform a systematic review of this clinical question, the results of which were considered by the writing committee for incorporation into the current guideline. The ERC posted the clinical question for open public comment on the AHA website. Comments that were received were incorporated into the final question before the literature review was initiated. This systematic review is published in conjunction with the guideline.

Methodology

Study Selection

A trained medical librarian screened the titles and abstracts of studies against predefined selection criteria (Data Supplement 1) using a software environment with features such as color coding and ranking of relevant key words. The literature search was conducted using MEDLINE (through PubMed) and Embase to identify randomized trials and observational studies performed between January 1, 1974, and May 25, 2017, comparing the effects of BiVP or HisBP versus RVP (Data Supplement 2). Randomized controlled trials and crossover trials were included. A second medical librarian performed quality control using the above tools. The chief medical officer of Doctor Evidence, LLC (Santa Monica, CA) and the project methodologist reviewed all included abstracts and a random sample of excluded abstracts, managed discrepancies between librarians, and decided on studies of uncertain eligibility. ERC members were divided into pairs and performed dual independent review of full-text articles in the DOC Library software platform (Doctor Evidence. 2016. DOC Library. Santa Monica, CA: Doctor Evidence, LLC). During this review, ERC members identified an additional 4 articles in the bibliography of the originally identified articles that met the inclusion criteria. Disagreements were resolved by consensus between the 2 reviewers and the ERC chair and vice chair.

Data from several studies could not be included in the analysis because the original publication included a population with mixed baseline LVEF. Most notably, this prevented inclusion of BLOCK HF (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block).[26] Consideration was given to requesting the original data to permit subgroup analysis of patients with baseline LVEF of >35%. However, Task Force methodology does not permit data to be obtained for further analysis when it is in the possession of a commercial enterprise (in this case, Medtronic).

Data Extraction and Quality Assessment

Data extraction was performed using the DOC Data 2.0 (Doctor Evidence. 2016. DOC Data, Version 2.0. Santa Monica, CA: Doctor Evidence, LLC) software platform using a standard template for predefined data points. Included studies were extracted by an evidence analyst with software validation/data entry error prevention and with each data point verified against the source article by a quality control. Discrepancies were resolved by the project methodologist and/or chief medical officer. Subsequent dataset-level quality control (to identify outliers and ensure consistency of data across studies) was performed by an evidence audit specialist. An ontology specialist managed the naming of outcomes based on author-reported names and definitions.

For each included study, the following information was abstracted: study design, participant characteristics (age, race/ethnicity, sex, comorbid conditions), and duration of follow-up. Risk of bias was assessed for each study included using the Cochrane Risk of Bias tool and Newcastle Ottawa Scale (Data Supplements 3 and 4). Studies were considered

to have low risk of bias if there was low risk of bias for all domains or plausible bias was unlikely to alter results. Studies were considered to have high risk of bias if there was high risk of bias for ≥1 key domains and the plausible bias seriously weakened confidence in results.

Analysis

Meta-analysis was performed using the DOC Data 2.0 advanced web-based platform (Doctor Evidence. DOC Data, Version 2.0, Santa Monica, CA). For the primary analysis, a fixed-effect model was prespecified in the analysis plan because the search revealed only a small number of studies. In this scenario, the estimate of the between-studies variance would have poor precision and, therefore, a random-effects model could not be applied.[27] For continuous outcomes, reported means and associated variance were pooled using the mean difference (MD). For binary outcomes, reported events and sample size were pooled using the relative risk (RR). Because meta-analysis is not a valid technique when only 2 studies provide data on an outcome, when this arose, the results from each study were considered qualitatively and findings addressed in the discussion.

In each of the meta-analyses conducted, statistics related to heterogeneity were calculated when possible. The most common measure of heterogeneity is the I^2 statistic, which describes the percentage of variability that is attributable to heterogeneity rather than sampling error. The I^2 cut-off values of 25%, 50%, and 75% were used to assign low, moderate, and high degrees of heterogeneity, respectively. Funnel plots are common method to identify heterogeneity. These plot the treatment effect relative to some measure of precision (typically the sample size or the standard error). Points that fall outside of a predefined funnel indicate excess variability, and nonfunnel-shaped scatter indicate potential bias in the estimates. The use of either of these methods to assess heterogeneity is questionable in the context of this project, because there are too few studies in most meta-analyses. When there was insufficient evidence to estimate between-study heterogeneity, fixed-effects models were used. The cases in which it was not feasible to pool the results for meta-analysis, narrative summary from each study was reported qualitatively.

Results

The literature search identified 953 titles and abstracts through MEDLINE/Embase database, using various combinations of identifiers for physiologic pacing such as cardiac resynchronization therapy, BiVP, His bundle, and para-His bundle pacing as a comparator to RVP (either apical or septal). Nine hundred and thirty articles were excluded, leaving 23 for full-text analysis. Sixteen were excluded for the following reasons: population not of interest (n=5), comparison not of interest (n=3), duplicate publication (n=1), and outcome stratification not of interest (n=7) (Figure 1). Bibliography review of the included articles identified an additional 4 articles of the population of interest and 1 additional article with extended follow-up of an already included study. To avoid potential double counting of subjects, we excluded 4 studies that reported results for the same trial populations. Eight studies comprised the final analysis, 4 comparing BiVP versus RVP (N=438)[28–31] and 4 evaluated HisBP versus RVP (N=241)[25,32–34] (Figure 2). The characteristics of the studies are summarized in Data Supplements 5 and 6.

BiVP Versus RVP

Patients who received BiVP compared with RVP, after a mean duration of 1.91 years, were observed to have a smaller end-systolic volume (MD: –7.2039 mL; 95% CI: –11.95 to –2.46 mL; p=0.003; I^2=12.31%), a smaller end-diastolic volume (MD: –2.7027 mL; 95% CI: –4.35 to –1.06 mL; p=0.0013; I^2=0%) (Figures 3 and 4), and a higher LVEF (MD: 6.340%, 95% CI: 2.84–9.84%; p=0.0004; I^2=0%) (Figure 5). Three studies reported the impact of BiVP on 6-minute walk distances and detected no significant difference with BiVP (MD: 6.736 m; 95% CI: –2.82 to 16.29 m; p=0.167; I^2= 0%).[28–30] Two of the studies observed no significant improvement in 6-minute walk distances.[28,30] The third study, which evaluated patients with chronic atrial fibrillation (AF) who underwent atrioventricular node ablation, found that at 6 months there was a significant improvement with both RV or BiVP but that BiVP resulted in a greater improvement in 6-minute walk distance (61.2±90 m versus 82.9±94.7 m; p=0.04).[29] Further subgroup analysis revealed that patients with either a LVEF of ≤45% or New York Heart Association class II/III heart failure received the greatest improvement (55.9±96.1 m versus 96.9±97.7 m; p=0.04; and 51.6±86.3 versus 78.9±92.2; p=0.01).

One study reported quality of life assessed by the 36-Item Short-Form Health Survey (SF-36).[30] Investigators detected no significant difference in SF-36 domains between the BiVP and RV pacing groups. The effects on mortality were not statistically significant (RR: 1.0758; 95% CI: 0.51–2.27; p=0.848).

HisBP Versus RVP

Although 4 studies that compared HisBP versus RVP met our inclusion criteria, meta-analysis could only be performed for LVEF and New York Heart Association class because these were the only parameters reported by >2 studies. Overall, HisBP was associated with a significantly greater LVEF compared with RVP (MD: 4.33%; 95% CI: 0.85–7.81%; p<0.01; I^2= 0%; mean duration of follow-up: 8.36 months) (Figure 6), and an improvement in functional class (MD: –0.21; 95% CI: –0.4 to –0.02;

p=0.027; I^2=28.40%; mean duration of follow-up: 8.71 months) (Figure 7).[25,32,34] Two of the HisBP trials measured 6-minute walk distance and reached discordant findings.[32,34] The earlier study of patients with chronic AF who underwent atrioventricular node ablation[34] reported a significant superiority of HisBP in the distance walked (378±60 m at baseline to 431±73 m at 6-month follow-up; p<0.05), which was not confirmed by the larger and more recent double-blind randomized crossover study of patients in sinus rhythm with high-grade atrioventricular block (6-minute walk distance after 1 year of HisBP 560±97 m versus after 1 year of RVP which was 558±109 m; p=0.84).[32]

Quality of life was reported by 2 studies that compared HisBP to RVP: one using the SF-36 survey[32] and the other using the Minnesota Living with Heart Failure Questionnaire.[34] The studies reported discordant findings. Participants in the study that employed the SF-36 survey reported improvement in general health and vitality, regardless of treatment arm. Physiologic pacing did not confer additional benefit. Patients in the remaining study[34] reported a significant improvement in quality of life as assessed by their responses to the Minnesota Living with Heart Failure questionnaire. The baseline score for both groups was 32.5±15. A lower score indicates better quality of life. At 6 months' follow-up, among patients who received BiVP, quality of life improved with a mean score of 16.2±8.7 (p<0.05); among patients who received RVP, the improvement in quality of life was less, with a mean score of 20.6±8.5 (p=not significant).

There was no statistical evidence of any effect on mortality as reported by 2 of the studies.[32,33]

BiVP + HisBP Versus RVP

When both BiVP and HisBP patients were pooled and compared with RVP patients, the effect of physiologic versus RVP became more evident. After a mean follow-up duration of 1.64 years, both left ventricular end-systolic volume and end-diastolic volume were reduced with physiologic pacing (–7.09 mL; 95% CI: –11.27 to –2.91 mL; p=0.0009; I^2=12.98%; and –2.74 mL; 95% CI: –4.37 to –1.1; p=0.001; I^2=0%, respectively) (Figures 8 and 9),[28,30–32,34] and LVEF, which declined with RVP, remained preserved and in some studies increased (5.328%; 95% CI: 2.86–7.8; p<0.0001; I^2=39.11%) (Figure 10). Quality of life, as measured in 1 study using the Minnesota Living with Heart Failure questionnaire, also improved compared with baseline.[34] Among the 5 studies that measured 6-minute walk distances, meta-analysis demonstrated no improvement (7.81 m; 95% CI: –1.52 to 17.15; p=0.10; I^2=0%; mean duration of follow-up: 1.51 years).[28–30,32,34] There was no effect on mortality (RR: 0.926; 95% CI: 0.55–1.57; p=0.773; I^2=0%).[30–33]

Discussion

Our analysis of published trials indicates advantages of physiologic pacing for patients with intermediate and preserved LVEF and in particular for patients with chronic AF and rapid ventricular response rates who undergo atrioventricular node ablation (Table 1).

Patient-Centered Clinical Outcomes

Patients with chronic AF who underwent atrioventricular node ablation and pacemaker implant demonstrated improvement in 6-minute walk distances with either BiVP or HisBP, with only 1 study of 18 patients also observing improved quality of life and improved New York Heart Association functional class.[29,34] These findings are supported by results of a large, multicenter randomized trial that was not included in this meta-analysis. The study randomized 186 patients with AF and atrioventricular node ablation and a range of LVEF both above and below 35% to either RV or BiVP.[35] Patients in the cardiac resynchronization therapy arm were significantly less likely to reach the composite endpoint of death from heart failure, hospitalization for heart failure, or worsening heart failure symptoms regardless of whether their baseline LVEF was ≤35% or >35%.

Among patients in sinus rhythm, evidence indicates that physiologic pacing reduces the adverse remodeling observed with RVP (reduced end-systolic volume and end-diastolic volume and improved LVEF). The 1 study that measured quality of life also detected improvement as measured by the Minnesota Living with Heart Failure questionnaire.[34]

Intermediate Ejection Fractions

Several studies reported outcomes stratified by LVEF.[31,32,34] Two studies found the benefit of physiologic pacing to be greatest among patients with a LVEF of >35%, but ≤52%.[32,34] These patients were noted to have less of an increase in left ventricular end-systolic volume and no reduction in LVEF when they received physiologic pacing versus RVP. Patients who had normal left ventricular function at baseline and received physiologic pacing received no benefit compared with those who received right ventricular pacing. The remaining study found no benefit for physiologic pacing regardless of baseline LVEF.[31] Although we could not perform a meta-analysis of the data on this subgroup, the data suggest that patients with intermediate LVEFs are more likely to receive benefit.

Percentage of Ventricular Pacing

Individual study outcomes might have been affected by how much ventricular pacing patients received. To examine this, we reviewed each study to document the original indication for pacing as well as, when available, the percentage of ventricular pacing (Table 1). With the exception of 2 studies,[29,34] patients received pacemakers for standard indications of heart block or sinus node

dysfunction with the expectation of requiring frequent ventricular pacing.[34] Only 1 study stratified outcomes based on the percentage of ventricular pacing.[33] This study observed fewer heart failure hospitalizations among patients who received HisBP only if they received ventricular pacing ≥40% of the time.

Follow-up Duration

The duration of follow-up did not appear to correlate with an improvement in clinically significant outcomes with physiologic pacing (Table 1). Patients who underwent atrioventricular node ablation and physiologic pacing showed significant improvement in clinical outcomes with only 6 to 12 months' of follow-up.[29,34]

Complications From Physiologic Pacing Versus RVP

We sought to include studies with short as well as longer follow-up periods because these studies might be more likely to assess and report procedural complications associated with physiologic pacing to provide the writing committee with as much data as possible from which to draw their clinical recommendations. Table 2 lists reported complications requiring surgical revision or findings likely to impact battery longevity. These findings were not included in the meta-analysis but, overall, indicate physiologic pacing with either BiVP or HisBP to be associated with a slightly higher risk of lead revision because of either elevated pacing threshold or lead dislodgement. Battery longevity was not reported by any of the studies because of the follow-up period, but battery longevity is known to be reduced among patients who received BiVP given the need to pace the additional left ventricular lead. The effect of HisBP on battery longevity is unknown.

Existing Studies Excluded From Meta-Analysis

The ACC/AHA RWI procedures precluded retrieval of industry-retained unpublished data on the subset of patients with preserved left ventricular function for the patients with reduced left ventricular function (LVEF <50%), from the BLOCK HF study.[26]

The BioPace (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) trial is the largest study to evaluate the potential benefit of BiVP versus RVP for patients who present with heart block and require permanent pacing.[36] Study enrollment criteria permitted patients to enroll regardless of LVEF.[36] The primary endpoint is death or first heart failure hospitalization, but it did not include any left ventricular remodeling outcome. Enrollment is complete, and the results were presented at European Society of Cardiology Scientific and Educational Sessions in 2014.[37] However, the study remains unpublished. Therefore, we could not include the findings or data in our analysis. Similar studies are needed to definitively answer the same question for HisBP.

Limitations

Our meta-analysis is limited by small numbers and a preponderance of single-center studies. Also, the relatively short follow-up periods (1–3 years) limit the ability to assess potential benefits evident only over a longer period of time (e.g., hospitalizations and mortality) as well as potential costs of physiologic pacing (e.g., shorter battery longevity, device and/or lead malfunction, complications from more frequent generator replacements). Because of the limited number of studies, we included patients with chronic AF who underwent atrioventricular node ablation followed by pacemaker implantation, in addition to patients with atrial systolic function who required permanent pacing because of heart block. It is possible that the benefit of physiologic pacing may be different between these groups and that they should be considered separately.

Another potential limitation is that 2 of the studies used a crossover trial design. This methodology leaves the potential for bias based on the sequence in which patients receive the interventional therapy. It is possible that patients who were randomized to receive physiologic pacing first received a benefit that is maintained through the second half of the study when they are in the comparator arm (RVP). This potential for bias was considered but thought to be unlikely as evidence from 1 of the studies included found no statistical interaction between the order of study periods and the effect of physiologic pacing on LVEF.[32]

Summary

To summarize our findings, both methods of physiologic pacing appear to mitigate the deleterious structural and functional effects of RVP. Patients with chronic AF and a rapid ventricular rate who undergo atrioventricular node ablation receive benefit from physiologic pacing with improvement in structural findings and 6-minute walk distance. Patients in sinus rhythm also receive benefits from physiologic pacing as manifest by the absence of adverse structural remodeling and reduced LVEF, which were observed with RVP, although functional capacity and quality of life did not appear to be affected. Patients with LVEF between 36% and 52% may be more likely to receive clinical benefit from physiologic pacing.

Figures and Tables

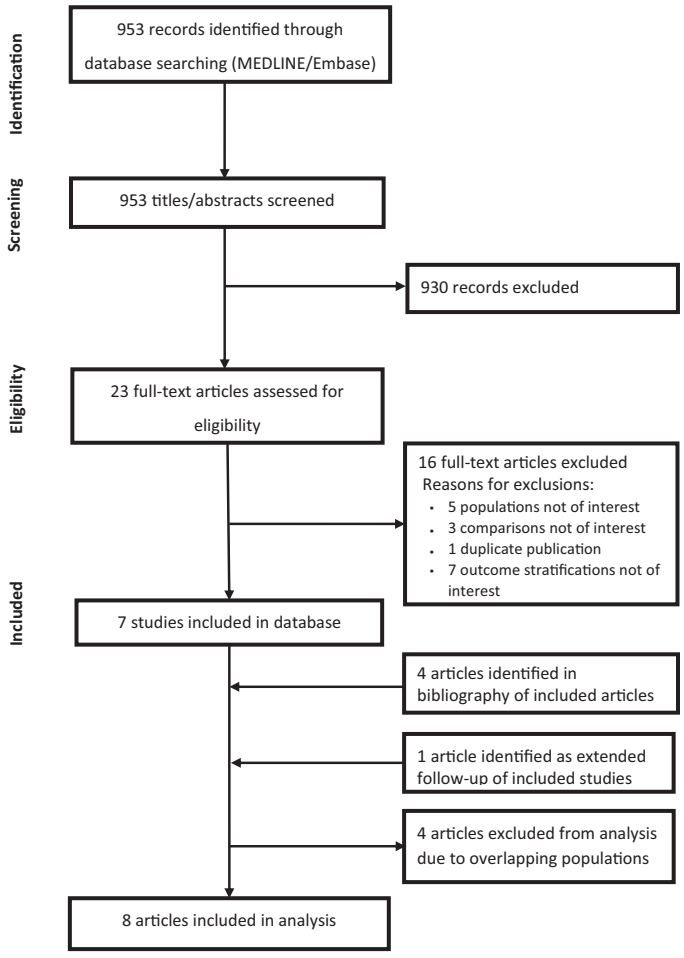

Figure 1 PRISMA Diagram.

Table 1 Pacing Modality and Clinical Outcomes

Study, Year	Intervention	No. of Patients	Indication for PM	Follow-up	% Ventricular Paced	6-Min Walk	QOL	Functional Status
Stockburger et al., 2011[31]	BiVP	108	Investigators asked to identify patients who were expected to require ventricular pacing ≥80%	1 y	NR	NR	NR	NR
Yu et al., 2014[30]	BiVP	177	AV block or SSS	>2 y Mean duration 4.8±1.5 y	■ RV 94±19.5% ■ BiVP 93±19.3%	No change	No change	NR
Albertsen et al., 2011[28]	BiVP	50	Complete heart block, permanent or paroxysmal	3 y	NR	No change	NR	NR
Kronborg et al., 2014[32]*	HisBP	38	High-grade AV block	1 y	>99% both groups	No change	Improved in both groups equally	No change
Occhetta et al., 2006[34]*	HisBP	18	AV node ablation	6 mo	NR	↑	↑	↑
Sharma et al., 2015[33]	HisBP	173	■ 38% SSS ■ 62% AV conduction disease ■ 25% Complete heart block	2 y	Reported outcomes for 2 groups based on % ventricular pacing: ■ The entire study population ■ The subgroup with >40% ventricular pacing (47 patients with HisBP [63%] and 62 patients with RVP [62%]). Among patients paced, >40% of the time they observed fewer heart failure hospitalizations (1 patient vs 9 patients, p=0.02)	NR	NR	NR
Doshi et al., 2005[29]	BiVP	103	AV node ablation	6 mo	>99%	↑	No change	No change
Zanon et al., 2008[25]	HisBP	12	■ AF with slow ventricular response rate (n=4) ■ Second-degree AV block (n=6) ■ Third-degree AV block (n=2)	Crossover design: 3 mo HisBP then 3 months RVP	AF group >97% Sinus rhythm group >90%	NR	NR	NR

AF = atrial fibrillation; AV = atrioventricular; BiVP = biventricular pacing; HisBP = His bundle pacing; NR = not reported; QOL = quality of life; RV = right ventricular; RVP = right ventricular pacing; SSS = sick sinus syndrome.

*Crossover study design.

Table 2 Complications Associated With Pacemaker Implantation

Study, Year	Pacing Modality	Complications of Physiologic Pacing
Stockburger et al., 2011[31]	BiVP	■ Survival free of first adverse event was similar in both groups (p=0.24). ■ Exact numbers not given, but authors report dual chamber pacemaker recipients had more atrial lead "issues," and BiVP had left ventricular lead problems (phrenic nerve pacing). ■ Problems were evenly balanced between the 2 groups.
Yu et al., 2014[30]	BiVP	■ Adverse events similar in RVP and BiVP groups (log-rank chi-squared=0.899; p=0.343).
Albertsen et al., 2011[28]	BiVP	NR
Doshi et al., 2005[29]	BiVP	■ BiVP had 21 complications (phrenic nerve, high threshold, left ventricular lead dislodgement). ■ RVP had 6 complications (RV lead dislodgement). ■ Note: Complications from RV lead were equal in both groups. So BiVP group had an excess 15 complications.
Kronborg et al., 2014[32]	HisBP	■ Pacing threshold rose among patients who received HisBP by the end of the study (1 y). Median threshold rose to 1.5 V (95% CI: 0.75-2.9); p=0.008. ■ 1 patient with HisBP developed exit block at 15 mo. ■ 2 patients had intermittent loss of capture for seconds on the HisBP lead documented on 24-h electrocardiographic monitoring. ■ No lead dislodgements
Occhetta et al., 2006[34]	HisBP	■ "Slight" dislodgement of 1 HisBP lead observed 1 mo after implant. Did not require surgical revision.
Sharma et al., 2015[33]	HisBP	■ 3 patients in HisBP group required ventricular lead revision (2 for loss of capture; 1 for high threshold). ■ 2 patients in RVP group required surgical revision of the RV lead because of dislodgement. ■ 1 pneumothorax in RVP group ■ 1 device infection in RVP group
Zanon et al., 2008[25]	HisBP	NR

BiVP = biventricular pacing; HisBP = His bundle pacing; NR = not reported; RV = right ventricular; RVP = right ventricular pacing.

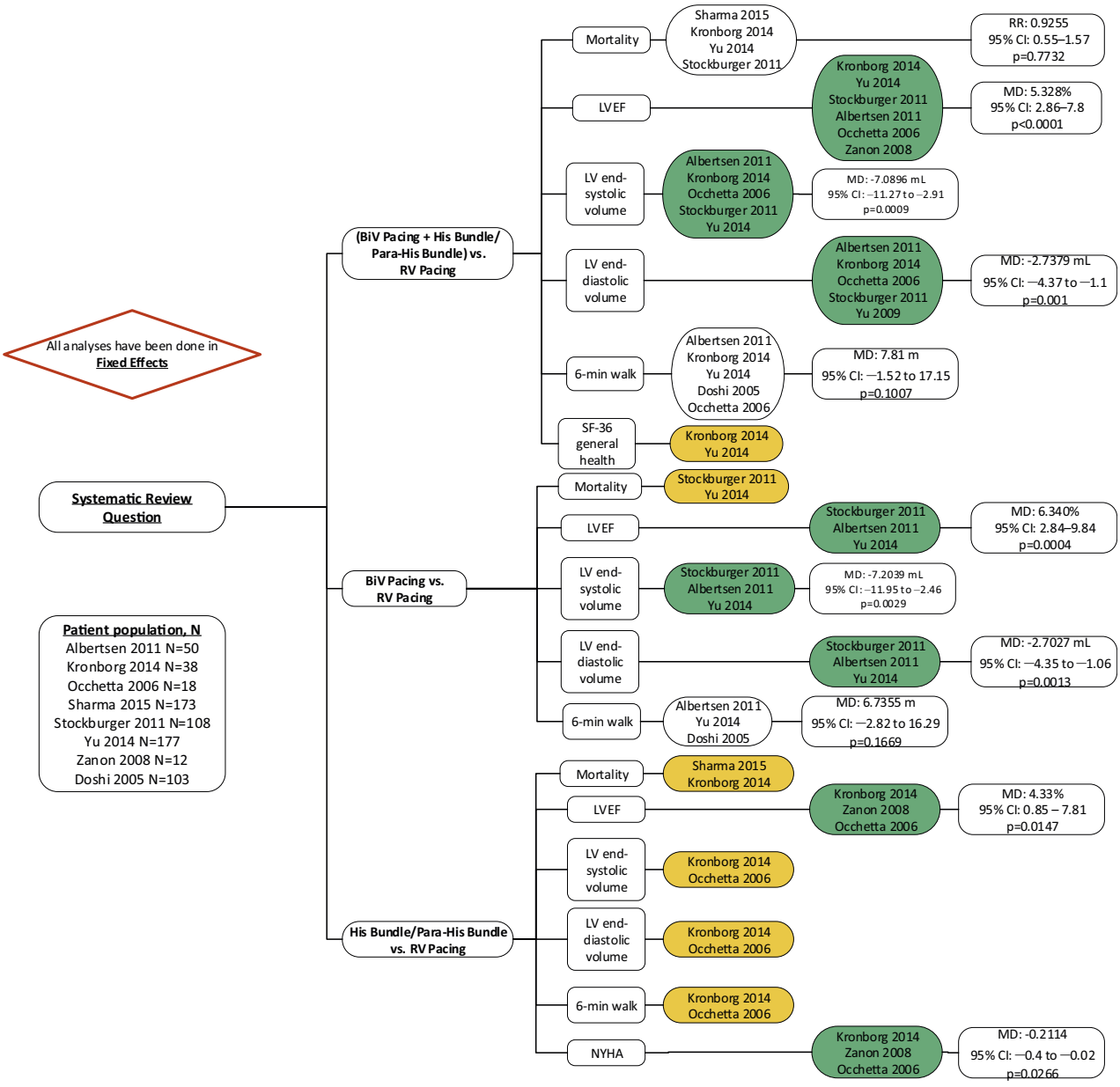

Figure 2 Studies Included in the Meta-Analyses With Selected Results. Green-shaded boxes indicate that the results are statistically significant ($p<0.05$). Orange-shaded boxes indicate that only 2 studies reported results. BiV = biventricular; CI = confidence interval; LV = left ventricular; LVEF = left ventricular ejection fraction; MD = mean difference; NYHA = New York Heart Association; RR = relative risk; RV = right ventricular; RVP = right ventricular pacing; SF-36 = 36-Item Short-Form Health Survey.

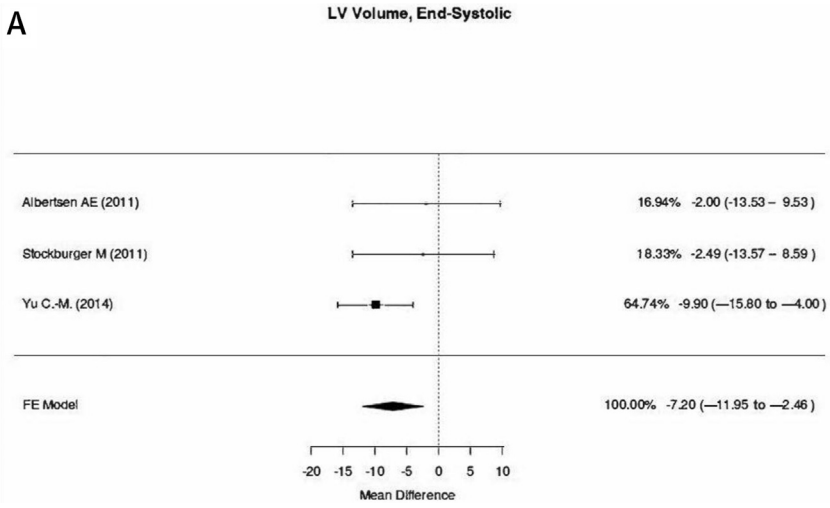

Figure 3A Forest Plots for BiVP Versus RVP, LV End-Systolic Volume. Heterogeneity is defined as: Q (df=2)=2.28; p=0.32; I^2=12.31%. BiVP = biventricular pacing; FE = fixed effects; LV = left ventricular; RVP = right ventricular pacing.

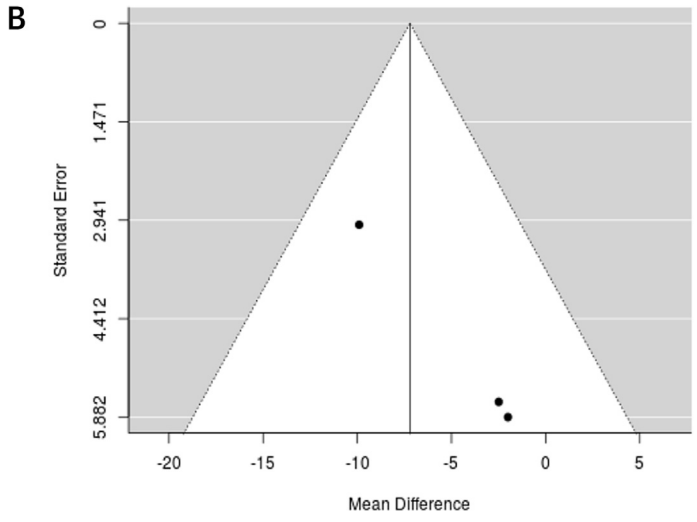

Figure 3B Funnel Plot for BiVP Versus RVP, LV End-Systolic Volume. BiVP = biventricular pacing; LV = left ventricular; RVP = right ventricular pacing.

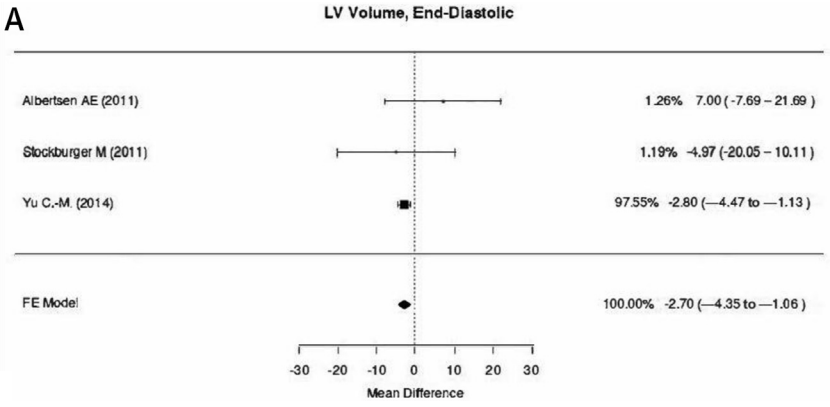

Figure 4A Forest Plots for BiVP Versus RVP, LV End-Diastolic Volume. Heterogeneity is defined as: Q (df=2)=1.78; p=0.41; I^2=0%. BiVP = biventricular pacing; FE = fixed effects; LV = left ventricular; RVP = right ventricular pacing.

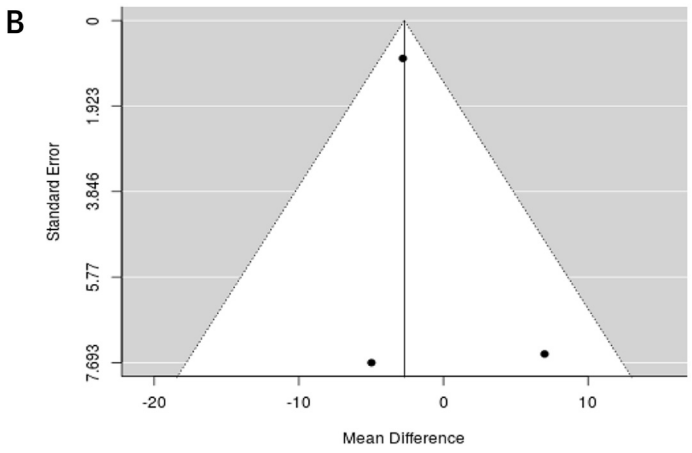

Figure 4B Funnel Plot for BiVP Versus RVP, LV End-Diastolic Volume. BiVP = biventricular pacing; LV = left ventricular; RVP = right ventricular pacing.

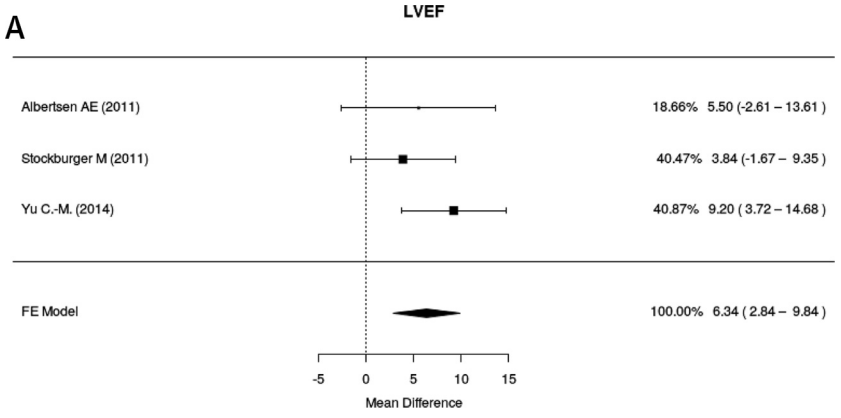

Figure 5A Forest Plot for BiVP Versus RVP, LVEF. Heterogeneity is defined as: Q (df=2)=1.88; p=0.39; I^2=0%. BiVP = biventricular pacing; FE = fixed effects; LVEF = left ventricular ejection fraction; RVP = right ventricular pacing.

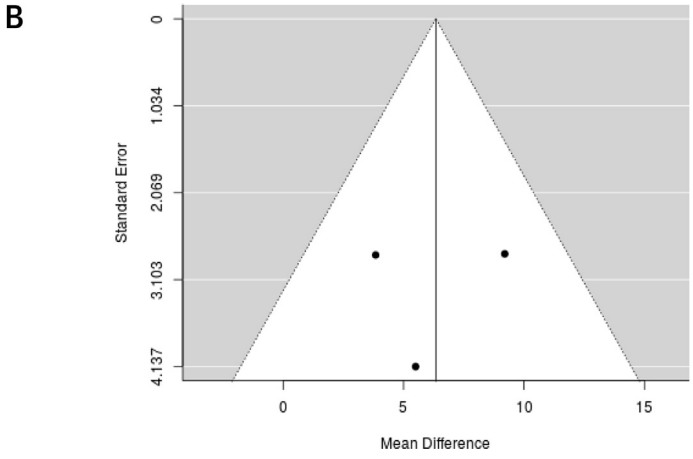

Figure 5B Funnel Plot for BiVP Versus RVP, LVEF. BiVP = biventricular pacing; LVEF = left ventricular ejection fraction; RVP = right ventricular pacing.

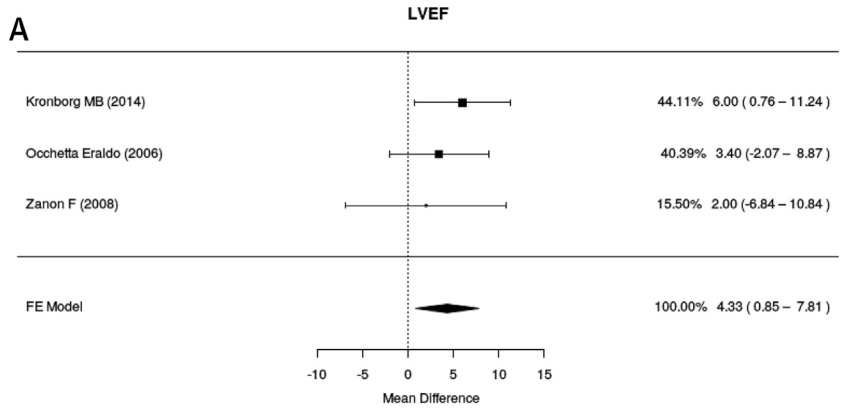

Figure 6A Forest Plot for HisBP Versus RVP, LVEF. Heterogeneity is defined as: Q (df=2)=0.77; p=0.68; I^2=0%. FE = fixed effects; HisBP = His bundle pacing; LVEF = left ventricular ejection fraction; RVP = right ventricular pacing.

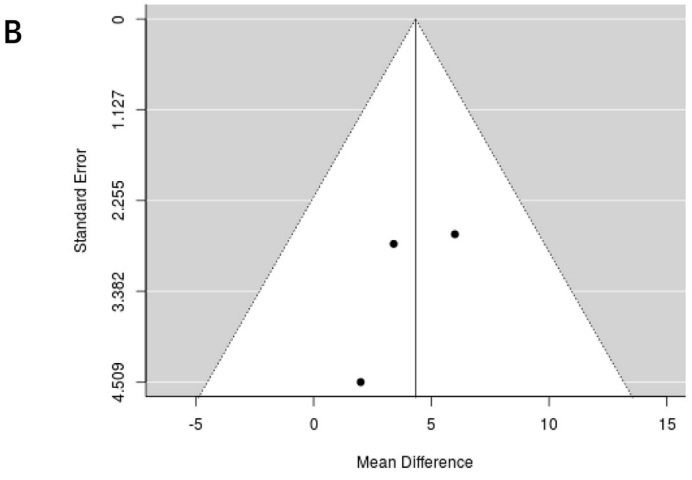

Figure 6B Funnel Plot for HisBP Versus RVP, LVEF. HisBP = His bundle pacing; LVEF = left ventricular ejection fraction; RVP = right ventricular pacing.

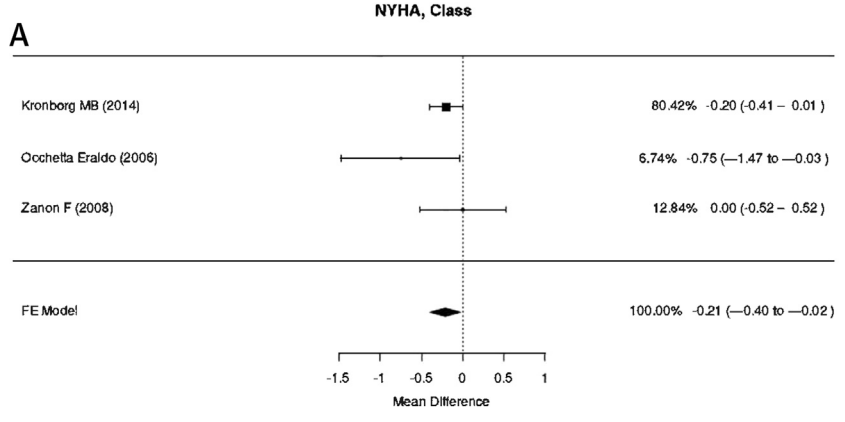

Figure 7A Forest Plot for HisBP Versus RVP, NYHA Class. Heterogeneity is defined as: Q (df=2)= 2.79; p=0.25; I^2=28.40%. FE = fixed effects; HisBP = His bundle pacing; NYHA = New York Heart Association; RVP = right ventricular pacing.

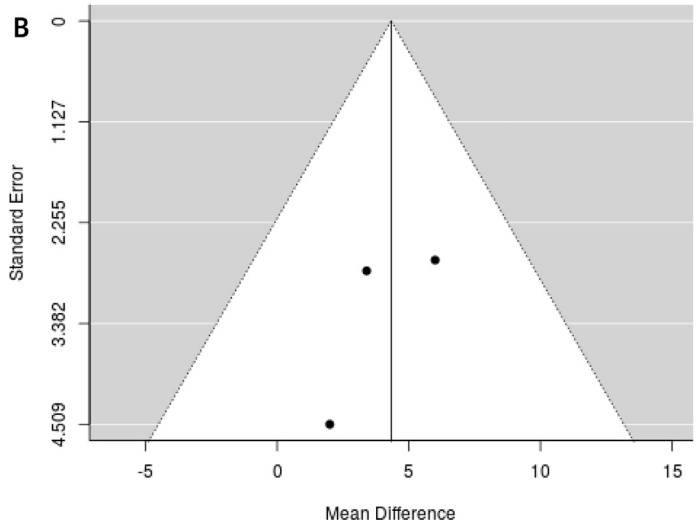

Figure 7B Funnel Plot for HisBP Versus RVP, NYHA Class. HisBP = His bundle pacing; NYHA = New York Heart Association; RVP = right ventricular pacing.

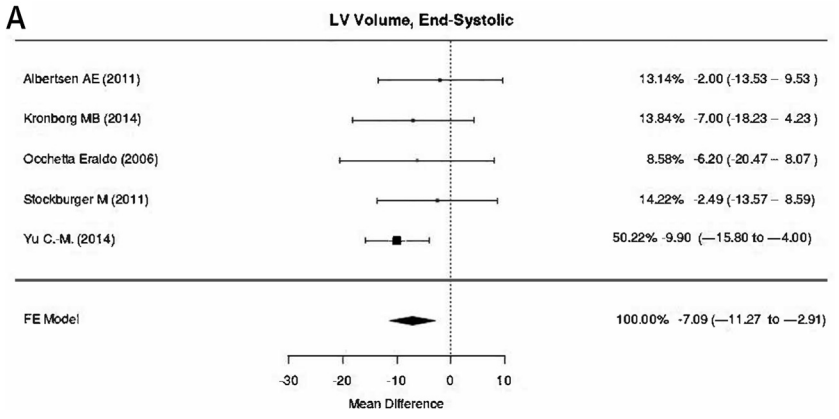

Figure 8A Forest Plot for BiVP and HisBP Versus RVP, LV End-Systolic Volume. Heterogeneity is defined as: Q (df=4)=2.30; p=0.68; I^2=12.98%. BiVP = biventricular pacing; FE = fixed effects; HisBP = His bundle pacing; LV = left ventricular; RVP = right ventricular pacing.

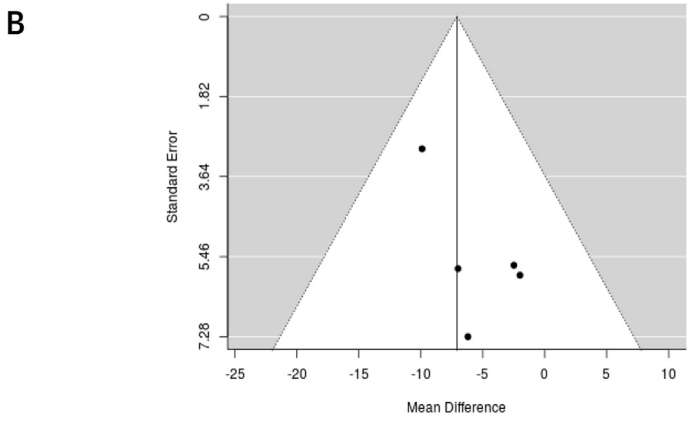

Figure 8B Funnel Plot for BiVP and HisBP Versus RVP, LV End-Systolic Volume. BiVP = biventricular pacing; HisBP = His bundle pacing; LV = left ventricular; RVP = right ventricular pacing.

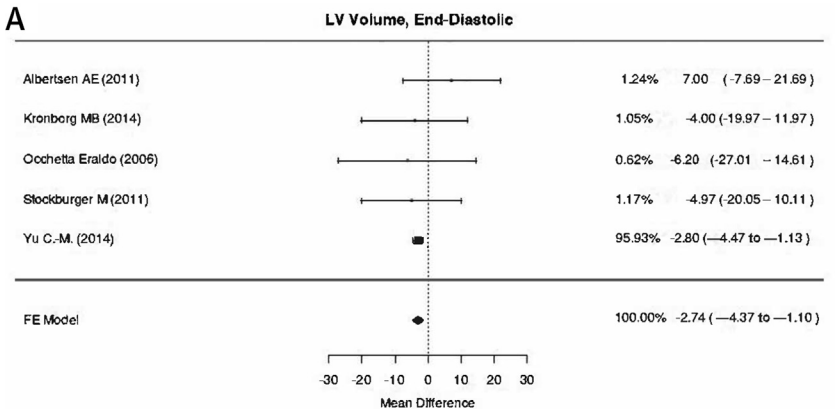

Figure 9A Forest Plot for BiVP and HisBP Versus RVP, LV End-Diastolic Volume. Heterogeneity is defined as: Q (df=4)=1.91; p=0.75; I^2=0%. BiVP = biventricular pacing; FE = fixed effects; HisBP = His bundle pacing; LV = left ventricular; RVP = right ventricular pacing.

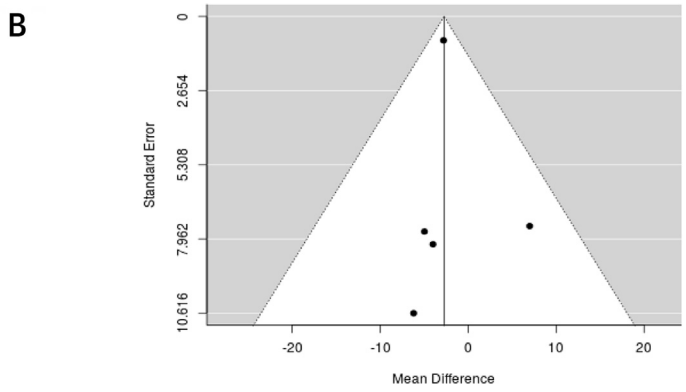

Figure 9B Funnel Plot for BiVP and HisBP Versus RVP, LV End-Diastolic Volume. BiVP = biventricular pacing; HisBP = His bundle pacing; LV = left ventricular; RVP = right ventricular pacing.

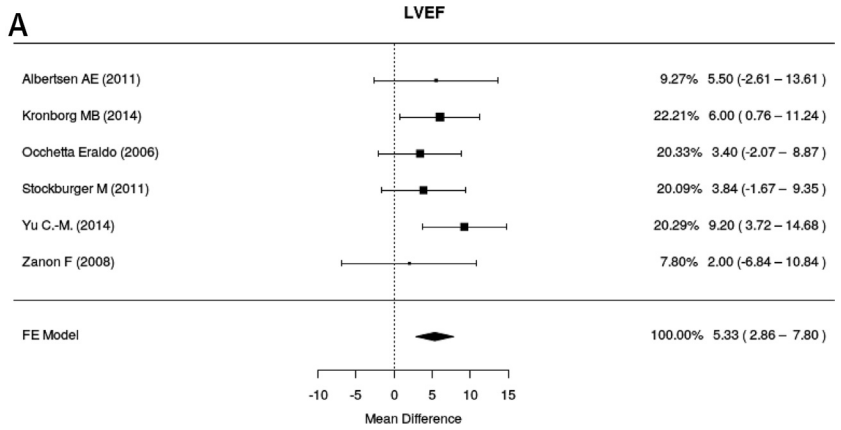

Figure 10A Forest Plot for BiVP and HisBP Versus RVP, LVEF. Heterogeneity is defined as: Q (df=5)=3.28; p=0.66; I^2=39.11%. BiVP = biventricular pacing; FE = fixed effects; HisBP = His bundle pacing; LVEF = left ventricular ejection fraction; RVP = right ventricular pacing.

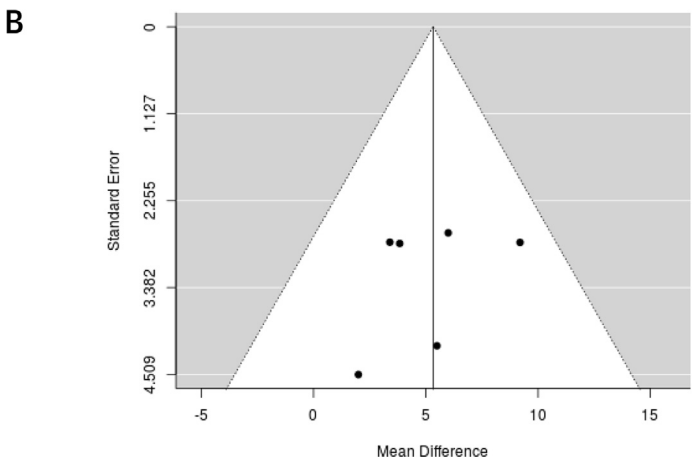

Figure 10B Funnel Plot for BiVP and HisBP Versus RVP, LVEF. BiVP = biventricular pacing; HisBP = His bundle pacing; LVEF = left ventricular ejection fraction; RVP = right ventricular pacing.

Presidents and Staff

American College of Cardiology

C. Michael Valentine, MD, FACC, President

Timothy W. Attebery, MBA, FACHE, Chief Executive Officer

William J. Oetgen, MD, MBA, FACC, Executive Vice President, Science, Education, Quality, and Publishing

MaryAnne Elma, MPH, Senior Director, Science, Education, Quality, and Publishing

Amelia Scholtz, PhD, Publications Manager, Science, Education, Quality, and Publishing

American College of Cardiology/American Heart Association

Katherine A. Sheehan, PhD, Director, Guideline Strategy and Operations

Abdul R. Abdullah, MD, Senior Manager, Guideline Science

Thomas S. D. Getchius, Manager, Guideline Science

Sam Shahid, MBBS, MPH, Associate Science and Medicine Advisor

Zainab Shipchandler, MPH, Associate Guideline Advisor, Clinical Practice Guidelines

American Heart Association

Ivor J. Benjamin, MD, FAHA, President

Nancy Brown, Chief Executive Officer

Rose Marie Robertson, MD, FAHA, Chief Science and Medical Officer

Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations

Paul St. Laurent, DNP, APRN, Science and Medicine Advisor

Jody Hundley, Production and Operations Manager, Scientific Publications, Office of Science Operations

Appendix

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018.10.035.

References

1. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (U.S.). Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.
2. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (U.S.). Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: National Academies Press; 2011.
3. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010. Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf and http://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf. Accessed: September 23, 2018.
4. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:213–265.
5. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;67:1572–1574.
6. Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:1373–1384.
7. Uslan DZ, Tleyjeh IM, Baddour LM, et al. Temporal trends in permanent pacemaker implantation: a population-based study. Am Heart J 2008;155:896–903.
8. Karpawich PP, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. Pacing Clin Electrophysiol 1999;22:1372–1377.
9. van Oosterhout MF, Prinzen FW, Arts T, et al. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 1998;98:588–595.
10. Thambo JB, Bordachar P, Garrigue S, et al. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. Circulation 2004;110:3766–3772.
11. O'Keefe JH Jr, Abuissa H, Jones PG, et al. Effect of chronic right ventricular apical pacing on left ventricular function. Am J Cardiol 2005;95:771–773.
12. Lee MA, Dae MW, Langberg JJ, et al. Effects of long-term right ventricular apical pacing on left ventricular perfusion, innervation, function and histology. J Am Coll Cardiol 1994;24:225–232.
13. Tse HF, Yu C, Wong KK, et al. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. J Am Coll Cardiol 2002;40:1451–1458.
14. Nielsen JC, Andersen HR, Thomsen PE, et al. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. Circulation 1998;97:987–995.
15. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline

QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932–2937.
16. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115–3123.
17. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–1853.
18. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–2150.
19. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–1549.
20. Kindermann M, Hennen B, Jung J, et al. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBI-PACE). J Am Coll Cardiol 2006;47:1927–1937.
21. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003;289:2685–2694.
22. Catanzariti D, Maines M, Cemin C, et al. Permanent direct His bundle pacing does not induce ventricular dyssynchrony unlike conventional right ventricular apical pacing. An intrapatient acute comparison study. J Interv Card Electrophysiol 2006;16:81–92.
23. Deshmukh P, Casavant DA, Romanyshyn M, et al. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation 2000;101:869–877.
24. Fang F, Zhang Q, Chan JY, et al. Early pacing-induced systolic dyssynchrony is a strong predictor of left ventricular adverse remodeling: analysis from the Pacing to Avoid Cardiac Enlargement (PACE) trial. Int J Cardiol 2013;168:723–728.
25. Zanon F, Bacchiega E, Rampin L, et al. Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study. Europace 2008;10:580–587.
26. Curtis AB, Worley SJ, Chung ES, et al. Improvement in clinical outcomes with biventricular versus right ventricular pacing: The BLOCK HF Study. J Am Coll Cardiol 2016;67:2148–2157.
27. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. West Sussex, UK: John Wiley & Sons; 2009.
28. Albertsen AE, Mortensen PT, Jensen HK, et al. Adverse effect of right ventricular pacing prevented by biventricular pacing during long-term follow-up: a randomized comparison. Eur J Echocardiogr 2011;12:767–772.
29. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 2005;16:1160–1165.
30. Yu CM, Fang F, Luo XX, et al. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. Eur J Heart Fail 2014;16:1016–1025.
31. Stockburger M, Gomez-Doblas JJ, Lamas G, et al. Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: results from a multicentre international randomized trial (PREVENT-HF). Eur J Heart Fail 2011;13:633–641.
32. Kronborg MB, Mortensen PT, Poulsen SH, et al. His or para-His pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, crossover study. Europace 2014;16:1189–1196.
33. Sharma PS, Dandamudi G, Naperkowski A, et al. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. Heart Rhythm 2015;12:305–312.
34. Occhetta E, Bortnik M, Magnani A, et al. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. J Am Coll Cardiol 2006;47:1938–1945.
35. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32:2420–2429.
36. Funck RC, Blanc JJ, Mueller HH, et al. Biventricular stimulation to prevent cardiac desynchronization: rationale, design, and endpoints of the 'Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace)' study. Europace 2006;8:629–635.
37. Funck RC, Mueller HH, Lunati M, et al. Characteristics of a large sample of candidates for permanent ventricular pacing included in the Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac Desynchronization Study (BioPace). Europace 2014;16:354–362.

Appendix 1 Author Relationships With Industry and Other Entities (Relevant)*—Impact of Physiologic Pacing Versus Right Ventricular Pacing Among Patients With Left Ventricular Ejection Fraction Greater Than 35%: A Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay (June 2017)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
David J. Slotwiner (*Chair*)	Chief, Division of Cardiology, Assistant Professor of Medicine, School of Health Policy & Research, New York Presbyterian Queens/Weill Cornell Medical College	None	None	None	None	None	None
Merritt H. Raitt (*Vice Chair*)	Chief of Cardiology, VA Portland Health Care System, Director, VA National Cardiac Device Surveillance Program	None	None	None	None	None	None
Freddy Del-Carpio Munoz	Assistant Professor of Medicine, Mayo Clinic College of Medicine and Science	None	None	None	None	None	None
Siva K. Mulpuru	Associate Professor of Medicine, Mayo Clinic College of Medicine and Science	None	None	None	None	None	None
Naseer Nasser	Attending Cardiac Electrophysiologist, South Bend Clinic	None	None	None	None	None	None
Pamela N. Peterson	Associate Professor, Medicine, University of Colorado School of Medicine, Cardiology	None	None	None	None	None	None

This table represents the relationships of evidence review committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq$5% of the voting stock or share of the business entity, or ownership of $\geq$$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document;* or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person, or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

CMS reported research payments to Dr. Del-Carpio Munoz in November 2016. Dr. Del-Carpio Munoz personally receives no money from Boehringer Ingelheim as the PI for the GLORIA registry; his hospital receives some reimbursement. Boehringer Ingelheim was deemed not relevant to the ERC report.

ACC = American College of Cardiology; AHA = American Heart Association; HRS = Heart Rhythm Society; VA = Veterans Affairs.

*For transparency, the ERC members' comprehensive disclosure information is available as an online supplement.

Appendix 2 Abbreviations

AF = atrial fibrillation
BiVP = biventricular pacing
CI = confidence interval
ERC = evidence review committee
HisBP = His bundle pacing
LV = left ventricular
LVEF = left ventricular ejection fraction
MD = mean difference
NYHA = New York Heart Association
PICOTS = population, intervention, comparator, outcome, timing, setting
RV = right ventricular
RVP = right ventricular pacing
RWI = relationships with industry and other entities
SF-36 = 36-Item Short-Form Health Survey