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Clinical and echocardiographic response of apical vs nonapical right ventricular lead position in CRT: A meta-analysis

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Abstract

Background: Traditionally the right ventricular (RV) pacing lead is placed in the RV apex in cardiac resynchronization therapy (CRT). It is not clear whether nonapical placement of the RV lead is associated with a better response to CRT. We aimed to perform a meta-analysis of all randomized controlled trials (RCTs) that compared apical and nonapical RV lead placement in CRT.

Methods: We searched PubMed, EMBASE, Cochrane, Scopus, and relevant references for studies and performed meta-analysis using random effects model. Our main outcome measures were all-cause mortality, composite of death and heart failure hospitalization, improvement in ejection fraction (EF), left ventricle end-diastolic volume (LVEDV), left ventricle end-systolic volume (LVESV), and adverse events.

Results: Seven RCTs with a total population of 1641 patients (1199 apical and 492 nonapical) were included in our meta-analysis. There was no difference in all-cause mortality (5% vs 4.3%, odds ratio (OR) = 0.86; 95% confidence interval (CI) 0.45-1.64; $P = .65$; $I^2 = 11\%$) and a composite of death and heart failure hospitalization (14.2% vs 12.9%, OR = 0.92; 95% CI: 0.61-1.38; $P = .68$; $I^2 = 0$) between apical and nonapical groups. No difference in improvement in EF (Weighted mean difference (WMD) = 0.37; 95% CI: -2.75-3.48; $P = .82$; $I^2 = 68\%$), change in LVEDV (WMD = 3.67; 95% CI: -4.86-12.20; $P = .40$; $I^2 = 89\%$) and LVESV (WMD = -1.20; 95% CI: -4.32-1.91; $P = .45$; $I^2 = 0$) were noted between apical and nonapical groups. Proportion of patients achieving >15% improvement in EF was similar in both groups (OR = 0.85; 95% CI: 0.62-1.16; $P = .31$; $I^2 = 0$).

Conclusion: In patients with CRT, nonapical RV pacing is not associated with improved clinical and echocardiographic outcomes compared with RV apical pacing.

KEYWORDS
apical pacing, cardiac resynchronization therapy, nonapical pacing, right ventricular pacing

1 | INTRODUCTION

Heart failure is the most common cause of hospitalization in patients older than 65 years in the United States.[1] Cardiac resynchronization therapy (CRT) has been found to improve symptoms and cardiac function in some heart failure patients with New York Heart Association (NYHA) III-IV symptoms, left ventricular (LV) ejection fraction (EF) <35% and electrocardiographic QRS widening of at least

120-130 ms.[2-4] Successful CRT has also been associated with significant reduction in morbidity and mortality.[5] Recently, several retrospective and prospective studies have also suggested similar benefits in patients with NYHA functional class I and II heart failure.[6,7]

The presence of left ventricular dyssynchrony as manifest by left bundle branch block (LBBB) is common in heart failure[8] and is associated with a better outcome and LV reverse remodeling after CRT.[9,10] However, a significant proportion of heart failure patients do not respond to CRT.[11] Although response to CRT is at least partly dependent upon left ventricular lead location, other factors may play a significant role. One of these factors is right ventricular (RV) lead placement. Although the RV lead is commonly placed at or near the apex; septal, outflow tract and para-hisian sites (nontraditional) have also been used with RV pacing leads. These nontraditional pacing sites in the right ventricle have been postulated to simulate a more physiologic electrical activation of the heart, to reduce ventricular dyssynchrony and to potentially obtain more favorable hemodynamics.[12] The RV septum, RV outflow tract, RV midseptum have been used as alternatives to RV apical pacing.[13-15] The impact of alternate RV lead position on the outcome of CRT is largely unknown. Studies comparing RV apical with alternative site RV pacing have found conflicting evidence. To understand this issue further, we performed a meta-analysis on this subject.

2 | METHODS

2.1 | Data sources and search strategy

This review was constructed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses.[16] We searched Medline/PubMed, Embase, Scopus, and the Cochrane Library for publications. Databases were searched from inception to October 20, 2017, with keywords "Right ventricular apical lead placement" OR "Right ventricular nonapical lead placement" OR "Right ventricular septal lead placement" OR "Right ventricular outflow tract lead placement" OR "Right ventricular apical stimulation" OR "Right ventricular nonapical stimulation" AND "Cardiac resynchronization therapy" OR "CRT" in various combinations. The search strategy did not include the MeSH term and it was adapted for each database as necessary. In addition to the computer search, we manually reviewed the reference list of all included studies and published reviews to complete the search. The search strategy, study selection, and meta-analysis were guided by a written protocol. Two investigators (SPS and KD) independently performed the database search and agreed on the final study selection.

2.2 | Inclusion and exclusion criteria

We included studies that met all of the following criteria (i) randomized controlled studies comparing RV apical pacing with non-apical sites in right ventricle (septum, midseptum, RV outflow tract) for CRT; (ii)a report of at least one of the outcomes of interest (All-cause mortality, composite of all-cause mortality or heart failure hospitalization, change in EF, change in left ventricular end-systolic volume [LVESV] or left ventricular end-diastolic volume [LVEDV]) . We excluded abstracts without full-text publications and nonrandomized studies. Also excluded were abstracts from annual meeting as our protocol prespecified inclusion of full-text articles only.

2.3 | Data extraction

First, items for data collection and the methodology for event count extraction were standardized. Two authors (SPS and KD) extracted data from the selected studies in duplicate using a standardized data extraction table. Data were extracted on study characteristics (author, journal, year of publications, number of patients, study design, follow-up duration, inclusion/exclusion criteria, primary and secondary outcomes), patients' characteristics (age, gender, types of cardiomyopathy, sites of nonapical lead placement, baseline EF, QRS duration); outcomes of interest and adverse events. Event counts for the primary and secondary outcomes were extracted as reported by the individual studies.

2.4 | Major outcomes

The primary endpoints of our meta-analysis were all-cause mortality and a composite of all-cause mortality and heart failure hospitalizations. Secondary endpoints were echocardiographic measures of reverse ventricular remodeling (change in EF, LVESV, and LVEDV and >15% improvement EF), and adverse events related to RV lead placement, including arrhythmias.

2.5 | Statistical analysis

The meta-analysis was performed using a random effects model with the help of Review Manager (RevMan 5.2, Cochrane Collaboration, Nordic Cochrane Center, and Copenhagen, Denmark) for statistical analyses. Categorical variables were pooled as an odds ratio (OR) with 95% confidence interval (CI). For the continuous variable, mean difference was calculated with corresponding 95% confidence interval. The P value <.05 (2 tailed) was considered statistically significant. Study heterogeneity was evaluated by Cochrane's Q and I^2 index. We used the Cochrane Collaborations' tool for assessing risk of bias in the individual studies.

2.6 | Quality assessment

We used the Cochrane Collaboration tool for assessing risk of bias to determine the quality of included randomized controlled trials (RCTs). This tool assesses the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each RCT is categorized on the basis of criteria determining the likelihood of potential threats to validity. Quality assessment was independently performed by 2 reviewers (SPS and KD).

3 | RESULTS

3.1 | Description of individual studies

We retrieved 82 citations from electronic database and manual searches as shown in Figure 1. We reviewed 16 citations for full-text articles; 7 full-text articles were included in the final analysis.[17-23] Four of the included studies were post hoc analyses of the RCTs[19-22] and one was randomized crossover trial.[21] All the included studies were published between 2011 and 2016. There were a total of 1641 patients included in our meta-analysis. A total of 1199 patients had apical lead placement while 492 had nonapical placement (midseptum, high septum, RV outflow tract, and RV free wall). The study by Miranda et al[23] compared patients with uniform RV apical pacing to patients with maximal electric separation (MES)-guided pacing. Although majority of MES-guided pacing occurred in nonapical sites, the greatest MES was found in RV apex in some patients. All the studies had biventricular lead placement except for 2 patients in the study by Asbach et al[19] who were excluded from the final analysis. Left ventricular lead position was provided in all studies except for the study by Asbach et al[19]. LV lead positions were variable across the studies. The average age of study patients was 66 years and ma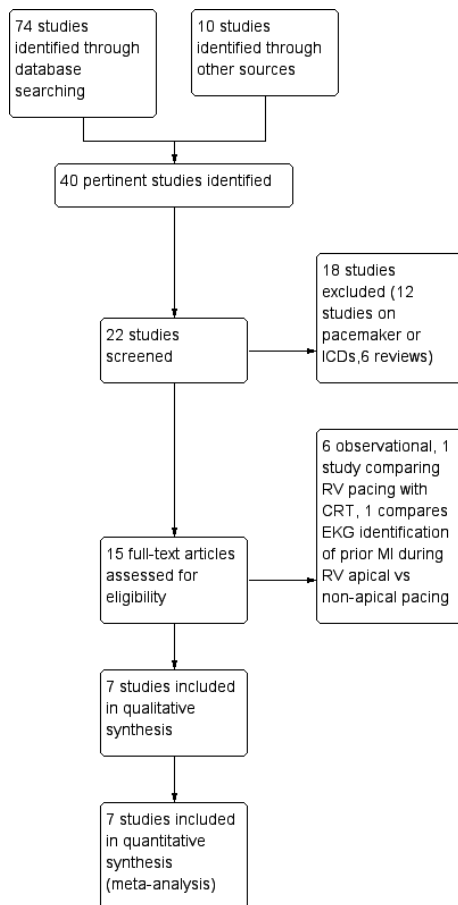les comprised of more than 75% of the total population. Details of the included studies and baseline characteristics of patients are summarized in Table 1. The details about pooled outcomes and adverse events are summarized in Table 2.

3.2 | Primary outcomes

There was no difference in all-cause mortality between apical and nonapical RV lead placement (5% vs 4.3%, OR = 0.86; 95% CI: 0.45-1.64; $P = .65$; $I^2 = 11\%$) (Figure 2). We did not find a significant difference in the composite of death or heart failure hospitalization between 2 groups (14.2% vs 12.9%, OR = 0.92; 95% CI: 0.61-1.38; $P = .68$; $I^2 = 0$) (Figure 2).

3.3 | Secondary outcomes

3.3.1 | Change in EF, LVEDV, and LVESV

No difference in improvement in EF was noted between apical and nonapical group (Weighted mean difference = 0.37; 95% CI: −2.75-3.48; $P = .82$; $I^2 = 68\%$) (Figure 3).

There was no difference in LVEDV between apical and nonapical (WMD = 3.67; 95% CI: −4.86-12.20; $P = .40$; $I^2 = 89\%$) group as shown in (Figure 3). Because of significant heterogeneity in change in EF and LVEDV, sensitivity analysis was performed by excluding 1 study at a time to evaluate the effect of any individual study in the overall heterogeneity. We found that the Miranda et al study[23] contributed to significant heterogeneity in both our endpoints. However, even after removal of this study, there was no significant difference in the weighted mean between the 2 groups. Similarly, no difference was noted in change of LVESV between apical and nonapical groups (WMD = −1.20; 95% CI: −4.32-1.91; $P = .45$; $I^2 = 0$) (Figure 3).

3.3.2 | Number of patients with >15% improvement in LVESV

The proportion of patients who achieved >15% improvement in LVESV was no different between the apical and nonapical groups (OR = 0.85; 95% CI: 0.62-1.16; $P = .31$; $I^2 = 0$) (Figure 4).

3.3.3 | Adverse events

Only 2 studies[19,20] reported on the occurrence of ventricular arrhythmias. It was more common in nonapical group but was not statistically significant (16% vs 20%; $P = .7$). Only a few studies reported on the RV lead-related complications. RV lead complication rates were low and similar between 2 groups (0.5% vs 0.6%) (Table 2).

3.4 | Sensitivity analysis

We performed the sensitivity analyses by assessing the contribution of each study to the overall estimate from the pooled

FIGURE 1 Flow diagram of included studies

TABLE 1 Patient and study characteristics

	Asbach et al	Leclercq et al	Kutyifa et al	Thebault et al	Kristiansen et al	Ronn et al	Miranda et al
Study design	Randomized (Post hoc analysis)	Randomized	Randomized (Post hoc analysis)	Randomized (Post hoc analysis)	Randomized	Randomized	Randomized
Total population	98	263	742	345	85	58	50
Participating countries	Germany	France and Spain	USA, Canada, and Europe	USA, Canada, and Europe	Norway	Sweden	Canada
RVA population	53	132	656	237	43	28	25
RVNA population	45	131	86	108	42	30	25
Follow-up (months)	12	12	12	12	6	6	3
Inclusion	Patients of MADIT trial with indications for ICD with CRT according to local guidelines	Patients with EF < 35%, QRS > 120 ms	Patients with EF < 30% with QRS > 130 ms	Patients with EF < 40% with QRS > 120 ms	NYHA III or IV patients with EF ≤ 35% and QRS ≥ 120	18-80 y with chronic AFib with NYHAIII-IV CHF with EF ≤ 35% and QRS ≥ 150	EF < 35% in sinus rhythm, QRS > 120 ms with LBBB
Exclusion	Preexisting RV pacemaker or ICD leads, pacemaker dependency	NA	Implanted ICD, CRT, or PPM, NYHA I with nonischaemic cardiomyopathy, NYHA III, IV in the past 90 d or at enrollment, CABG or PCI or enzyme-positive MI in the past 90 d, AFib, 2nd or 3rd degree heart block	Preexisting pacing device, presence of persistent, and chronic atrial fibrillation	NA	Patients with conventional indication for pacemaker, heart failure not related to systolic dysfunction or cardiac events within last month	Preexisting device, atrial arrhythmias, inability to place LV lead
Primary endpoint	Echocardiographical and electrocardiographic outcome at the end of follow-up	Septal pacing is noninferior to apical pacing in terms of End-systolic volume, mortality, and HF hospitalization	Heart failure or death	Proportion of patients with a worsened HF clinical composite response, scored as improved, unchanged, or worsened	Effect of the apical and right ventricular outflow tract lead position in CRT on clinical status, the haemodynamic effects, and LV dyssynchrony	Improvement in heart failure score	Change in Echocardiogram, 6-min walk distance, functional class
RVNA site	Midseptum	Septal	Septal or RVOT	Midseptum, high septum, and free wall	High septum	RVOT	Septum and RVOT [b]

(Continues)

TABLE 1 (Continued)

	Asbach et al	Leclercq et al	Kutyifa et al	Thebault et al	Kristiansen et al	Ronn et al	Miranda et al
LV site	NA	Lateral or anterolateral	Anterior and posterior	Lateral or posterolateral	Anterior, anterolateral, posterolateral, and posterior	Anterior or anterolateral	Posterolateral and lateral
Age (mean)	69/66	64/63	65/63	62/63	67/66	69[a]	67/67
Male (%)	60/80	74/71	75/66	76/74	88/86	97[a]	80/76
Ischemic cardiomyopathy (%)	45 /47	27/26	55/52	57/56	60/60	58[a]	56/60
NICM (%)	55/53	73/74	45/48	43/44	40/40	42[a]	44/40
EF% (mean)	22/24	30/29.6	29/26	26/27	25/24	23[a]	25/23
CRT-D (%)	100/100	100/100	100/100	90/61	NA	0[a]	100/100
LBBB (%)	55/74	81/80	70/79	NA	84/88	76[a]	100/100
QRS duration in ms (mean)	155/162	161/161	157/159	155/151	173/165	179[a]	165/163
LVEDD (mm)	64/67	NA	NA	67/67	NA	NA	NA

[a]Only average of total population (both apical and nonapical group) available in the study.

[b]Electrode was placed based on maximal electrical separation.

NA, not available; RVNA, Right ventricle nonapical; NICM, Nonischemic cardiomyopathy; LV, left ventricle; EF, ejection fraction; CRT-D, cardiac resynchronization therapy-defibrillator; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; PPM, permanent pacemaker; NYHA, New York Heart Association; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CHF, congestive heart failure; RVOT, right ventricular outflow tract.

TABLE 2 Outcomes of interest pooled from included studies

	Asbach et al	Leclercq et al	Kutyifa et al	Thebault et al	Kristiansen et al	Ronn et al	Miranda et al
Improvement in LVEF %	15.8 ± 14.6/ 9.7 ± 12.6	8.21 ± 10.04/ 6.78 ± 9.67	NA	NA	6 ± 7.2/7 ± 8.9	7.9 ± 12.21/ 6.5 ± 14.46	5.1 ± 8.4/9.5 ± 3.9
Change in LVEDV	NA	−37.16 ± 55.87/ −32.63 ± 53.68	−20.97 ± 11.48/ −21.43 ± 12	NA	−33 ± 86/−38 ± 99.7	−7.7 ± 27/ −9.9 ± 41.91	−11 ± 4/−23 ± 6
Change in LVESV	NA	−38.55 ± 50.92/ −32 ± 43.21[a]	−34.85 ± 21.27/ −32.99 ± 16.26	−18.2 ± 30.4/ −19.9 ± 26.22	−36 ± 66.2/ −40 ± 82.76	−15 ± 50/15.7 ± 39	NA
Implant success rate (%)	NA	86.8/90	NA	NA	100/100	100/100	NA
Ventricular arrhythmia	6/3	NA	111/23	NA	NA	NA	NA
Total mortality	6/0	4/5	39/7	4/5	3/2	NA	NA
RV lead-related adverse events	NA	4/3	NA	NA	1/0[b]	1/0[b]	0/0 [b]
Death or HF hospitalizations	NA	17/20	116/14	13/8	NA	NA	NA
Procedural time (minutes)	NA	112 ± 47/ 118 ± 55	NA	NA	116 ± 38/132 ± 63	NA	NA
>15% improvement of LVESV	NA	66/65	NA	101/56	26/25	NA	NA

[a]Per protocol analysis.

[b]Dislodgement.

n/n, apical/nonapical; NA, not available; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RV, right ventricle; HF, heart failure.
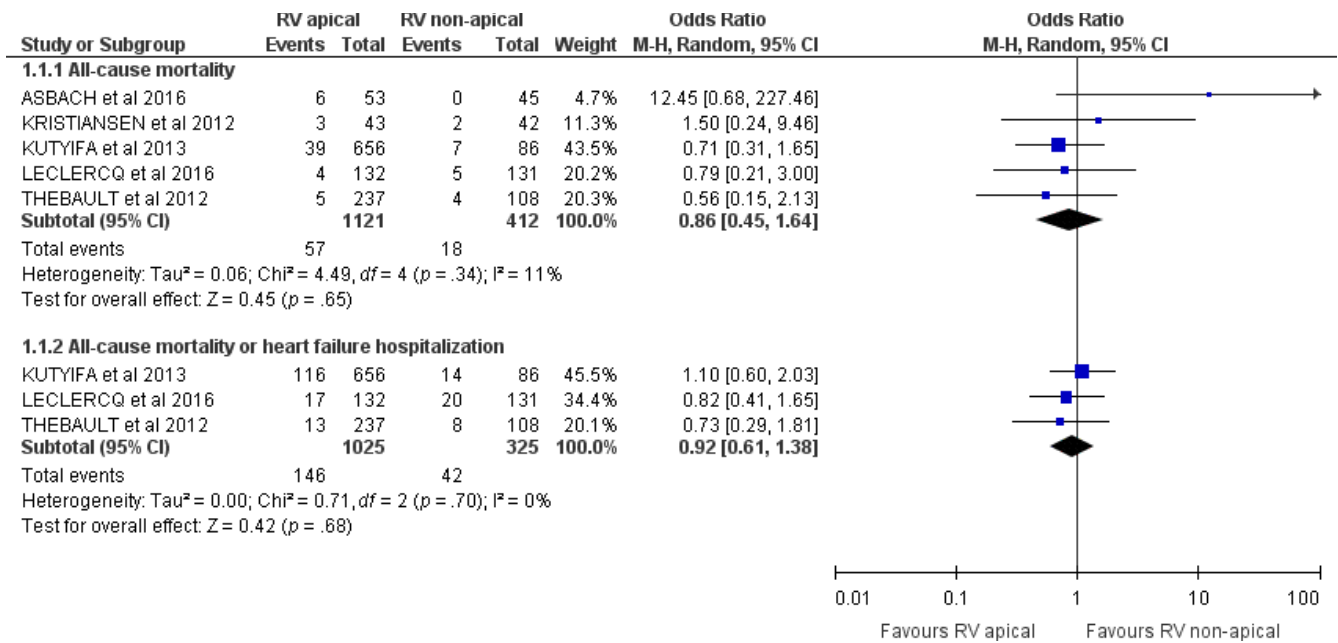
FIGURE 2 Forest plot of all-cause mortality and composite of all-cause mortality and heart failure hospitalization
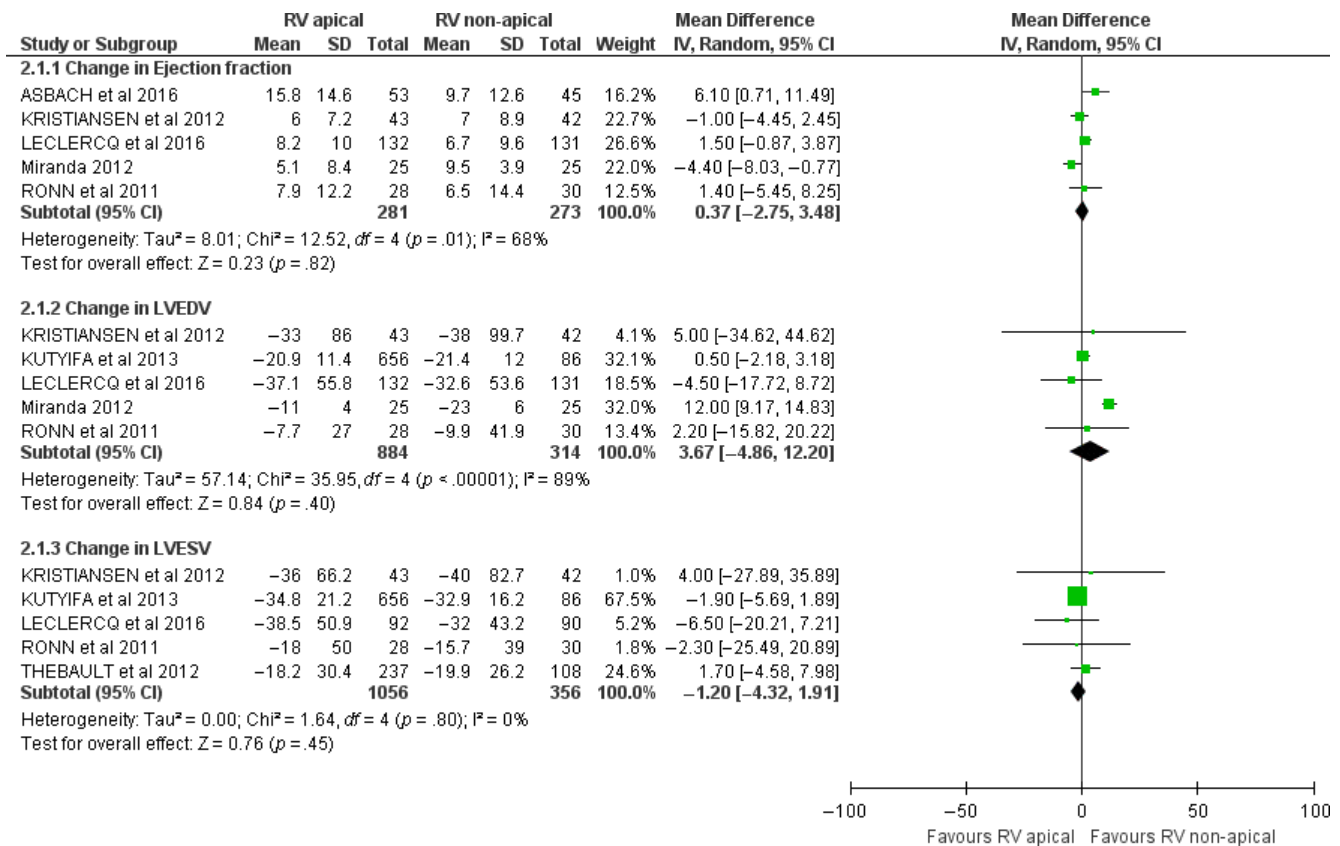

FIGURE 3 Forest plot of change in echocardiographic parameters

estimate and by excluding individual study one at a time and recalculating the pooled odds ratio for the remaining. It did not substantially change the pooled point estimate on any endpoints. As prespecified in our methodology, we performed meta-analysis using random effect model. However, as there was extremely low heterogeneity in primary outcomes, we also analyzed data using fixed-effect model. Final results did not differ between 2 models for all the outcomes.
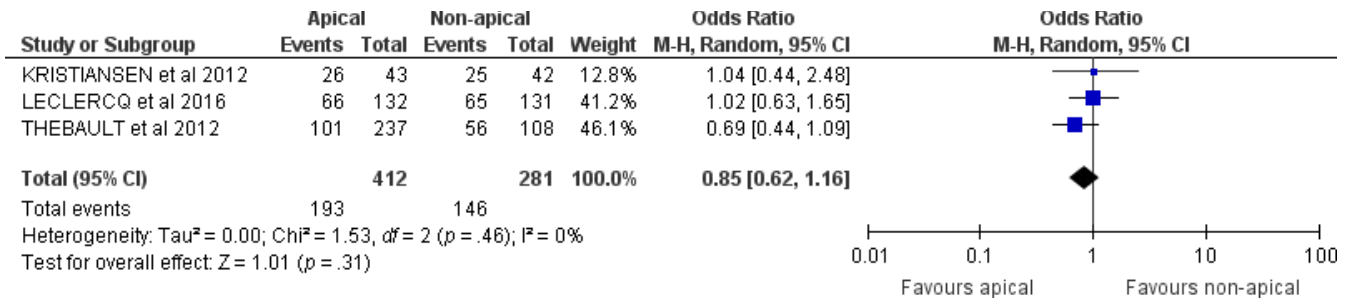
Study or Subgroup	Apical Events	Apical Total	Non-apical Events	Non-apical Total	Weight	Odds Ratio M-H, Random, 95% CI
KRISTIANSEN et al 2012	26	43	25	42	12.8%	1.04 [0.44, 2.48]
LECLERCQ et al 2016	66	132	65	131	41.2%	1.02 [0.63, 1.65]
THEBAULT et al 2012	101	237	56	108	46.1%	0.69 [0.44, 1.09]
Total (95% CI)		412		281	100.0%	0.85 [0.62, 1.16]
Total events	193		146			

Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 2 (p = .46); I² = 0%
Test for overall effect: Z = 1.01 (p = .31)

Odds Ratio M-H, Random, 95% CI

Favours apical | Favours non-apical

FIGURE 4 Forest plot of >15% improvement in Ejection fraction

3.5 | Qualities of studies

Assessment of risk of bias was conducted by investigating random sequence generation, allocation concealment, blinding, completeness of outcome data, and potential for selective reporting. We found no evidence of significant bias (Figure 5). Publication bias was not assessed because the included number of RCTs was less than 10.[24]

4 | DISCUSSION

To our knowledge, this is the first meta-analysis evaluating the impact of RV lead positions on clinical and echocardiographic outcomes in heart failure patients undergoing CRT. A previous meta-analysis on the topic by Zografos et al[25] included both RCTs and observational studies and did not report on the hard clinical outcomes because of lack of available data. In comparison, our study included only RCTs and assessed both hard clinical outcomes and echocardiographic parameters. Our main results suggest that there are no differences in the clinical endpoints of all-cause mortality and a composite of all-cause mortality or heart failure hospitalization between apical and nonapical RV lead placement. There were also no differences in echocardiographic parameters between 2 groups.

Mortality data were similar between the 2 groups in all studies except for the study by Asbach et al where all mortality was seen in the apical pacing group. Patients in the midseptal group were younger (66.2 ± 9.5 years vs 69.4 ± 10.1 years, P = .042) and more likely to be male (80% vs 60%, P = .048) in this study. It is arguable that since in this study, a significantly greater number of younger

patients were in the midseptal group, mortality was lower. An earlier study had hypothesized that the elderly would not benefit as much from CRT as the younger patients.[26] However, this effect might have been balanced by the proportion of men in the midseptal group, who have in general been found to have a lower benefit with CRT-ICD in MADIT-CRT trial compared with women.[27] In the study by Asbach et al, both apical and nonapical groups had a similar extent of reverse remodeling; therefore the mechanism which may have promoted heart failure and death in apical group remains unclear. In general, the finding of no significant change in mortality rates between different RV lead positions is in keeping up with the result of an observational study that used mortality and morbidity as endpoints.[28]

The study by Kutfiya et al who did post hoc analysis on the MADIT-CRT trial showed a significant number of ventricular arrhythmias in the nonapical RV lead position with no difference in the primary endpoints of heart failure or death. This was attributed to nonapical pacing-induced increase in electrical heterogeneity of the preexisting arrhythmogenic substrate in the patients with left ventricular dysfunction.[20]

Overall, there were identical benefits between 2 groups in terms of improvement in echocardiographic findings. The study by Miranda et al showed marked benefit for nonapical pacing group for LVEDV improvement. This may be because the study compared traditional RV apical lead placement with nonapical placement guided by MES. However, in this study, MES-guided pacing sites were found in RV apex in some patients. Thus, this might not fully reflect the real effect of nonapical pacing. Previous studies have shown electric delay from the onset of the QRS complex to the left ventricular (LV) lead electrogram correlates with improved response to CRT.[10,29,30]

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

0% 25% 50% 75% 100%

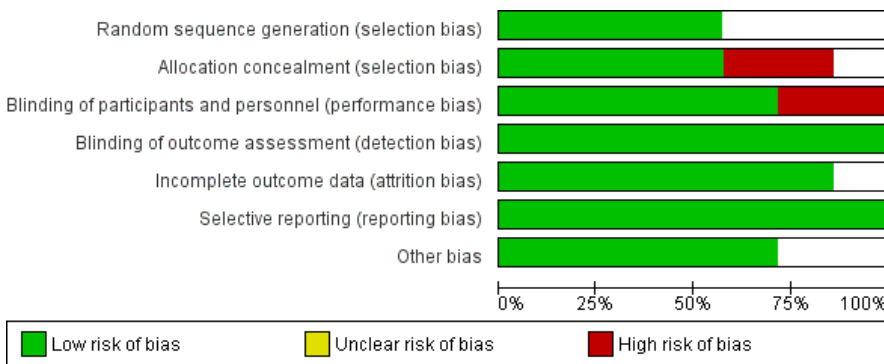■ Low risk of bias ■ Unclear risk of bias ■ High risk of bias

FIGURE 5 Risk of Bias diagram

An observational study that is not based on MES-guided electrode placement had also found midseptal RV lead position to be associated with greater improvement in left ventricular end-diastolic diameter.[31] In the study, patients from both groups showed similar improvement in functional NYHA class and improvement in LVEDV was mostly seen in subgroup of dilated cardiomyopathy patients.

A recently published Danish registry study found nonapical RV lead position in CRT to be associated with improved outcome of death and heart failure hospitalization in patients with nonischemic heart disease only.[32]

It has been suggested that optimal RV lead location may be tailored according to LV lead position when RV lead implantation occurs after LV lead. Apical or nonapical RV lead placement may derive maximal clinical benefit if a particular LV lead position is achieved, to create maximal lead separation. Apical RV and nonapical RV lead positions have been associated with better outcome when they were stimulated in the presence of anterolateral and posterolateral LV leads, respectively.[33] Included studies used different LV lead locations. There is lack of details regarding which LV lead position was stimulated in the presence of RV apical or nonapical lead. The position of the LV lead has significant impact on events and parameters assessed in this study, which could not be considered in the analysis. For a fixed LV site, there is substantial RV site-specific inter- and intraindividual variability in acute hemodynamic response to biventricular pacing.[34] Such variability in the acute hemodynamic response may lead to variable CRT response during long-term follow-up. Such variable response may warrant strategies to incorporate individualized RV lead placement.[34] In some patients, apical pacing may result in greater MES when compared to septal or outflow tract pacing and this may counter any measurable benefit from nonapical lead position.

All the studies included in our meta-analysis used fluoroscopy to assess the RV lead position. Cardiac computed tomography (CT) is considered to be more accurate to determine the RV lead position when compared to fluoroscopy. Many early studies of non-RV apical pacing sites are considered possibly flawed due to inaccuracies of lead position reporting by fluoroscopy.[35] In these studies, use of fluoroscopy alone can misclassify a true apical lead position as basal/mid-RV and a free wall RV lead position as septal.[30] There are concerns that RV free wall lead positions may actually be worse than RV apical positions, possibly resulting in a dilution of benefits of cardiac resynchronization. The confounding effects of possible RV lead misclassification may need to be considered in the results of our meta-analysis.

Reverse remodeling and improvement in left ventricular function are postulated to occur over a period of 3-6 months, but the improvement in left ventricular function beyond a year has been described, and the included studies do not address this.

5 | LIMITATIONS

Our meta-analysis has several limitations. A shorter and variable duration of follow-up, inherent weakness of using data from post hoc analysis of RCTs and crossover trial, smaller sample sizes in the nonapical group, small number of primary events are some important shortcomings in the included studies. Studies are also limited by use of fluoroscopy alone for lead placement evaluation, but this likely reflects clinical practice well. Absence of details on LV lead position relative to RV for determining clinical outcomes is other major limitation.

6 | CONCLUSION

This meta-analysis shows that nonapical RV pacing in CRT is not associated with improvement in clinical and echocardiographic endpoints compared with apical RV pacing. Our conclusion is drawn from small number of events noted in the included studies with short follow-up. So, further studies with longer follow-up might be needed to provide strong evidentiary base to draw firm conclusion.

Further studies should focus on detailed analysis of the LV with RV apical and nonapical lead locations based on MES and confirmation of lead location by cardiac CT.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

AUTHORS' CONTRIBUTION

Conception and design: SPS and RSS; Provision of study material: SPS and KD; Collection and assembly of data: SPS, KD; Data analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of manuscript: All authors.

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