Heart Failure Reviews (2019) 24:229–236
https://doi.org/10.1007/s10741-018-9740-x

Cardiac resynchronization therapy and outcomes in patients with left ventricular assist devices: a systematic review and meta-analysis

Dinesh Chandra Voruganti[1] · Alexandros Briasoulis[2] · Mohsan Chaudhry[1] · Paulino Alvarez[2] · Vlad Cotarlan[3] · Jay K. Bhama[4] · Michael Giudici[2]

Published online: 27 September 2018

Abstract

The impact of cardiac resynchronization therapy (CRT) on clinical outcome in patients with a continuous-flow left ventricular assist device (LVAD) is currently not well understood. We conducted a systematic literature review and meta-analysis with an intention to summarize all published clinical evidence. We searched MEDLINE and EMBASE databases through March 2018 for studies that compared the outcomes in patients with LVAD and CRT. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random-effects model, inverse variance method. The between-study heterogeneity was assessed using the Q statistic and I^2. A total of seven studies that included 1157 (575 CRT; 582 non-CRT) patients were identified. Our meta-analysis did not demonstrate a significant difference in the risk of mortality (pooled OR = 1.21, 95% CI 0.90–1.63, $P = 0.21$), ventricular arrhythmia incidence (pooled OR = 1.36, 95% CI 0.99–1.86, $P = 0.06$), hospitalization (pooled OR = 1.36, 95% CI 0.59–3.14, $P = 0.48$), or implantable cardioverter defibrillator therapies (pooled OR = 1.08, 95% CI 0.51–2.30, $P = 0.84$) among the CRT group compared with the non-CRT group. There was high heterogeneity with an I^2 of 75% for ICD therapies. Among LVAD patients, CRT combined did not significantly affect mortality, re-hospitalization, ventricular arrhythmia incidence, and ICD therapies.

Keywords Left ventricular assist device (LVAD) · Cardiac resynchronization therapy (CRT) · Implantable cardioverter defibrillator (ICD) · Mortality · Hospitalization

Introduction

Heart failure (HF) is a condition with high morbidity and mortality contributing to a major cause of death in the USA. Approximately 6 million Americans are currently affected by HF, and it is estimated that the prevalence will increase to 8 million by 2030 [1].

Cardiac resynchronization therapy (CRT) was shown to reduce mortality, improve quality of life and functional capacity, and decrease hospitalizations [2–4]. CRT has also been shown to address intra-ventricular dyssynchrony and improve cardiac function without increasing myocardial oxygen demand [5]. Left ventricular assist devices (LVAD) are implanted in selected patients with end-stage heart failure and have been shown to significantly improve survival and quality of life [6].

The benefit for the continuation of CRT post-LVAD implant is unknown. Some observational studies have shown that CRT may reduce ventricular arrhythmias post-LVAD implant while others have shown no significant change in ventricular tachycardia (VT) burden, heart failure hospitalization, or mortality [7]. To consolidate the evidence, we conducted a systemic review and meta-analysis to assess the clinical benefits for CRT post-LVAD implantation.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10741-018-9740-x) contains supplementary material, which is available to authorized users.

✉ Dinesh Chandra Voruganti
dinesh-voruganti@uiowa.edu

[1] Department of Internal Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Dr., Iowa City, IA 52242, USA

[2] Division of Cardiovascular Diseases, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

[3] Division of Cardiovascular Diseases, Section of Heart Failure and Transplant, University of Cincinnati Hospitals, Cincinnati, OH, USA

[4] Department of Surgery, Division of Cardiothoracic Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Methods

Data sources

This study was conducted by following PRISMA (preferred reporting items for systematic reviews and meta-analysis) statement. A systematic literature search of MEDLINE and EMBASE was carried out from inception in March 2018 to identify original studies that investigated the association between LVAD and outcomes after CRT as described in the supplementary table. No language limitation was applied. A manual search for additional potentially relevant studies using references of the included articles was also performed.

Study selection

We initially reviewed the title and abstract of retrieved citations. The title with eligible studies was to be cohort studies that investigated the relationship between LVAD and CRT. They must have provided effect estimates (odds ratios (OR), relative risks (RR), or hazard ratios (HR)) with 95% confidence intervals (CI). Study size did not restrict inclusion. When more than one article using the same database/cohort was available, the study with the most comprehensive data/analyses was included. Inclusion criteria also included the following: (i) observational studies that involved LVAD patients who had CRT and (ii) studies that reported ventricular arrhythmia incidence, mortality, hospitalization, and implantable cardioverter defibrillation therapies outcomes. We excluded case reports and case series. Retrieved articles were independently reviewed for their eligibility by the same investigators. Conference with all investigators resolved any disagreement. Newcastle-Ottawa quality assessment scale was used to appraise the quality of study in three areas including study selection, study comparison, and determination of the outcome of interest for the cohort study [8].

Data extraction

Two co-authors (D.V and M.C) independently extracted data from the included full-text citations. A structured data collection form was used to extract the following data from each study: title of this study, name of the first author, publication year, year of this study, country where this study was conducted, number of subjects, demographic data of subjects, effect estimates with 95% CI, and covariates that were adjusted in the multivariable analysis. To ensure the accuracy, this data extraction process was reviewed by a third investigator (A.B).

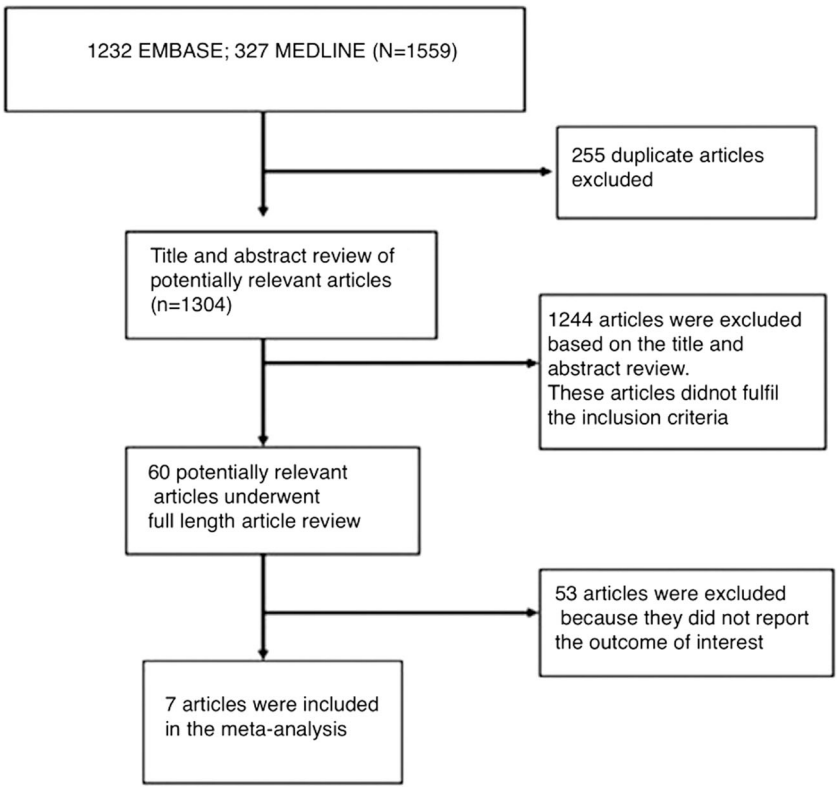

Fig. 1 Search strategy. 1559 studies were initially identified from database search. Seven articles were included in the systematic review and meta-analysis

Table 1 Table of contents of studies included in the systematic review and meta-analysis

Study (publication year)	Gopinathannir (2017)	Richardson (2018)	Kutyifa (2016)	Mai TV (2016)	Rao P (2015)	Choi (2010)	Hottigoudar (2013)
Country	USA	USA	USA	USA	USA	USA	USA
Study design (publication type)	Retrospective chart review analysis (conference abstract)	Prospective randomized trial (article)	Retrospective chart review analysis (conference abstract)	Retrospective chart review analysis (conference abstract)	Retrospective chart review analysis (conference abstract)	Retrospective chart review analysis (conference abstract)	Retrospective chart review analysis (conference abstract)
Study time period (year)	2007–2015	2013–2016	2008–2014	2009–2015	2005–2013	2006–2009	2008–2011
Mean age of participants in years	Total 58 ± 13 (SD); CRT-D 60 ± 12 (SD); ICD 55 ± 14 (SD)	Not available	CRT 58.9 ± 9.7 (SD)	Total 55.3 ± 27 (SD)	CRT 57.7 non-CRT 54.5	Total 56 ± 12 (SD)	CRT-D 59 ± 15 (SD) ICD 57 ± 13 (SD)
Gender	Total males 395; total females 93	Not available	Not available	Not available	Not available	Total males: 29; total females: 6	Total males 48; total females 13
Number of participants	Total 488; CRT-D 266; non CRT (ICD) 223	Total 41; CRT 20; non-CRT 21	Total 191; CRT 61; non CRT: 130	Total 105; CRT-D 50; ICD 55	Total 253; CRT 135; non-CRT 118	Total 35; ICD 13; CRT-D 22	Total 61; ICD 30; CRT-D 31
Outcomes included in the meta--analysis	Mortality, all-cause and cardiac hospitalization, ventricular arrhythmia incidence	Time to first ICD shock, rates of inappropriate shocks, arrhythmic hospitalization, hospitalization for congestive heart failure	All-cause mortality	Ventricular arrhythmias and therapies	Morality, time to first hospitalization, ventricular arrhythmias, ICD shocks	Ventricular arrhythmias	All-cause hospitalization

Table 2 Newcastle-Ottawa scale quality assessment of cohort studies

Study	Representation of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of co-horts	Aggregate score
Choi et al. 2010	*	*	*	*	/	*	*	NA	******
Gopinathannair et al. 2017	*	*	*	*	*	*	*	NA	*******
Kutyifa et al. 2016	*	*	*	*	*	*	*	NA	*******
Mai TV et al. 2016	*	*	*	*	/	*	*	NA	******
Rao P et al. 2015	*	*	*	*	/	*	*	NA	******
Richardson et al. 2018	*	*	*	*	/	*	*	NA	******

Statistical analysis

Data analysis was performed using the review manager 5.3 software from the Cochrane Collaboration (London, UK). Considering the high likelihood of between-study variance because of different study designs, populations, and random-effect model was used. Cochran's Q test and I^2 statistic were used to determine the between-study heterogeneity. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity [9]. Subgroup analysis was performed for ICD therapies outcome to assess the heterogeneity. For all analyses, a P value of < 0.05 was considered statistically significant.

Results

The initial search yielded 1559 potentially relevant articles (1232 articles from EMBASE and 327 articles from MEDLINE). After the exclusion of 255 duplicated articles, 1304 articles underwent title and abstract review. A total of 1244 articles were excluded at this stage, as they did not fulfill the eligibility criteria, leaving 60 articles for full-length review. Fifty-three articles were excluded after the full-length review, for the following reasons: 29 studies did not recruit our subjects of interest; 12 studies were reviews, case reports, or letters; 2 studies included the same population, and ten studies did not report the outcome of interest. Therefore, seven studies [7, 10–15] (all cohort studies) that included 1157 patients (575 in the CRT group and 582 in the non-CRT group) were included in the meta-analysis. Figure 1 outlines the search methodology and study selection process. All studies were performed in the USA. Table 1 summarizes the individual studies.

Quality assessment

Table 2 summarizes the quality assessment of the included studies. Newcastle-Ottawa scale for cohort studies tool was used.

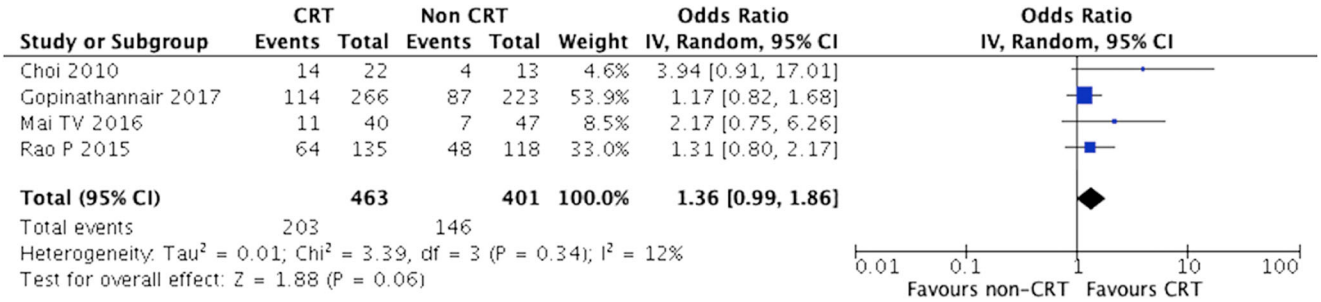

Fig. 2 Random effect meta-analysis for ventricular arrhythmia incidence. The figure represents the pooled odds ratio (black diamond) of 1.36, 95% CI (0.99–1.86) after analyzing outcomes of four studies (blue dots for odds ratio; extending black lines indicate 95% CI for each study) for incidence of ventricular arrhythmia for 463 patients with CRT and 401 patients without CRT. The observed heterogeneity was insignificant at 12% (I^2)

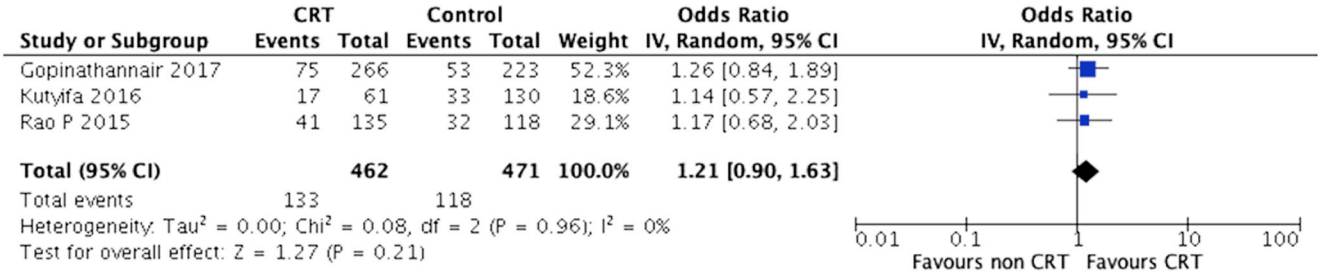

Fig. 3 Random effect meta-analysis for all-cause mortality. The figure represents the pooled odds ratio (black diamond) of 1.21, 95% CI (0.90–1.63) after analyzing outcomes of three studies (blue dots for odds ratio; extending black lines indicate 95% CI for each study) for incidence of all-cause mortality for 462 patients with CRT and 471 patients without CRT. The observed heterogeneity was insignificant at 0% (I^2)

Ventricular arrhythmias

Four studies reported data on the ventricular arrhythmias. There was no significant difference in the rate of ventricular arrhythmias between the two groups. Among the CRT group, 203 out of 463 patients (43.8%) experienced ventricular arrhythmia when compared to 146 patients out of 401 (36.4%) among the non-CRT group yielding a pooled OR of 1.36, 95% CI 0.99–1.86; $P = 0.06$; (Fig. 2) with insignificant heterogeneity between studies ($I^2 = 12\%$, $P = 0.34$).

All-cause mortality

Three of the included studies reported data on all-cause mortality. The incidence of all-cause mortality was not significantly different between the CRT and non-CRT groups. Among the CRT group, there were 133 events out of 462 (28.7%), and 118 out of 471 (25%) in the non-CRT group resulting in a pooled OR of 1.21, 95% CI 0.90–1.63; $P = 0.21$; (Fig. 3), with insignificant heterogeneity between studies (I^2 0%, $P = 0.96$).

ICD therapies

Four studies reported data on the ICD shocks. The incidence of ICD shocks did not differ significantly between the two groups of patients with and without CRT. The pooled OR is 1.08, 95% CI 0.51–2.30; $P = 0.84$; (Fig. 4) with high heterogeneity between studies (I^2 75%, $P = 0.007$). One hundred forty-seven out of 461 had an ICD

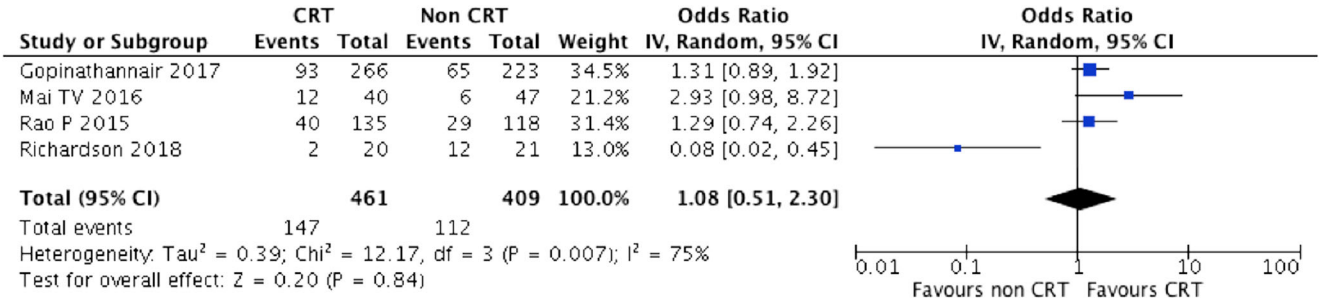

Fig. 4 Random effect meta-analysis for ICD therapies. The figure represents the pooled odds ratio (black diamond) of 1.08, 95% CI (0.51–2.30) after analyzing outcomes from four studies (blue dots for odds ratio; extending black lines indicate 95% CI for each study) for incidence of ICD therapies for 461 patients with CRT and 409 patients without CRT. The observed heterogeneity was high at 75% (I^2)

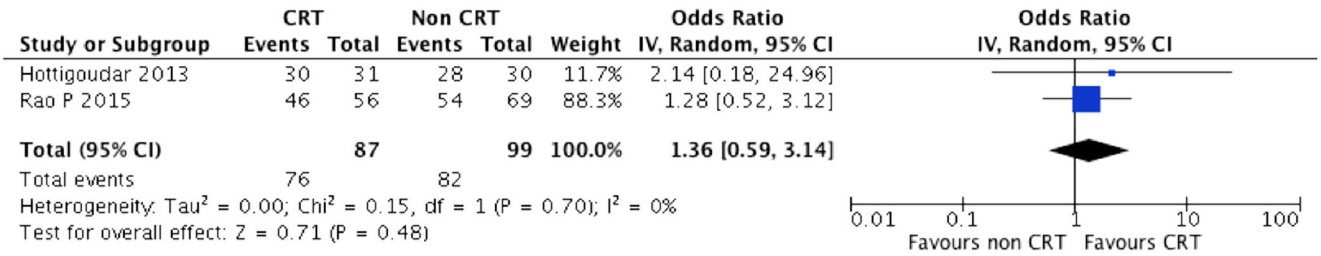

Fig. 5 Random effect meta-analysis for hospitalizations. The figure represents the pooled odds ratio (black diamond) of 1.36, 95% CI (0.59–3.14) after analyzing outcomes from two studies (blue dots for odds ratio; extending black lines indicate 95% CI for each study) for incidence of hospitalizations for 87 patients with CRT and 99 patients without CRT. The observed heterogeneity was insignificant at 0% (I^2)

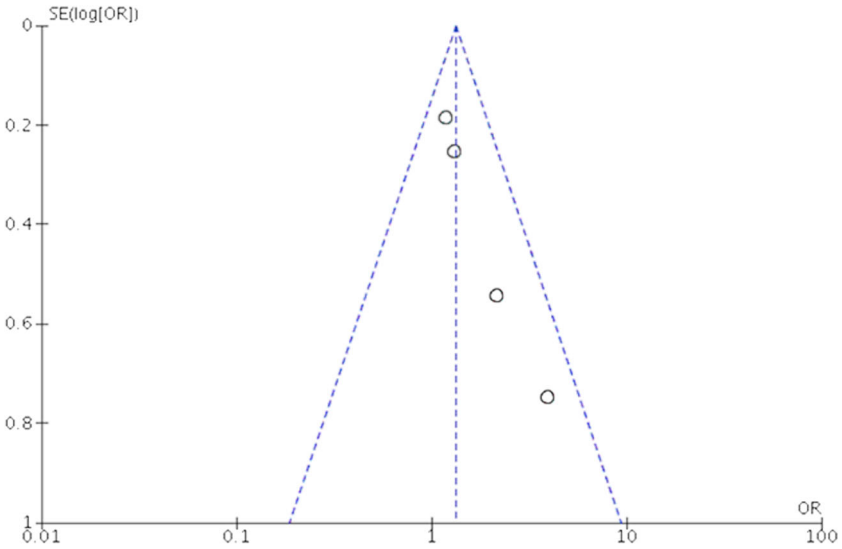

Fig. 6 Funnel plot for publication bias—ventricular arrhythmia incidence. Most of the studies (black circles) are scattered around the mid-line at the apex and middle with no studies missing on the bottom of the funnel plot indicating less likelihood of publication bias

therapy (31.8%) in the CRT group, while 112 out of 409 had an ICD therapy (27.3%) in the non-CRT group. Subgroup analysis of the retrospective cohort studies (excluding the prospective study by Richardson et al. 2018) reduced the heterogeneity to $I^2 = 0\%$.

Hospitalization

Two studies reported data on the incidence of hospitalization. Hospitalization rates were not significantly different between groups, 76 of 87 (87.3%) patients with CRT were hospitalized vs. 82 of 99 (82.8%) patients in the non-CRT group, yielding a pooled OR 1.36, 95% CI 0.59–3.14; $P = 0.48$; (Fig. 5) with insignificant heterogeneity between study (I^2 0%, $P = 0.70$).

Publication bias

The funnel plots (Figs. 6, 7, 8, and 9) reveal the studies scattered in the apex and the middle, without any missing studies in the bottom of the plot. This demonstrates a less likelihood of publication bias.

Discussion

The main findings from our study are (1) ventricular arrhythmia incidence in the CRT and the non-CRT did not differ significantly in patients with LVAD, (2) all-cause mortality rate was not statistically different in the CRT and non-CRT groups in LVAD patients, (3) no difference was noted from two studies reporting outcomes on the influence of all-cause hospitalizations, and (4) CRT did not influence the difference in the incidence of ICD shocks. Overall, we can conclude that

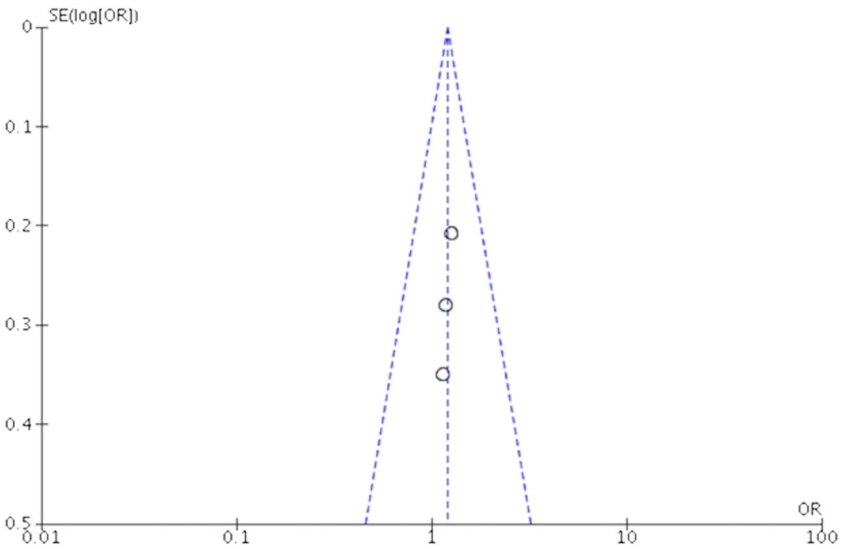

Fig. 7 Funnel plot for publication bias—mortality. Most of the studies (black circles) are scattered around the mid-line in the middle with no studies missing on the bottom of the funnel plot indicating less likelihood of publication bias

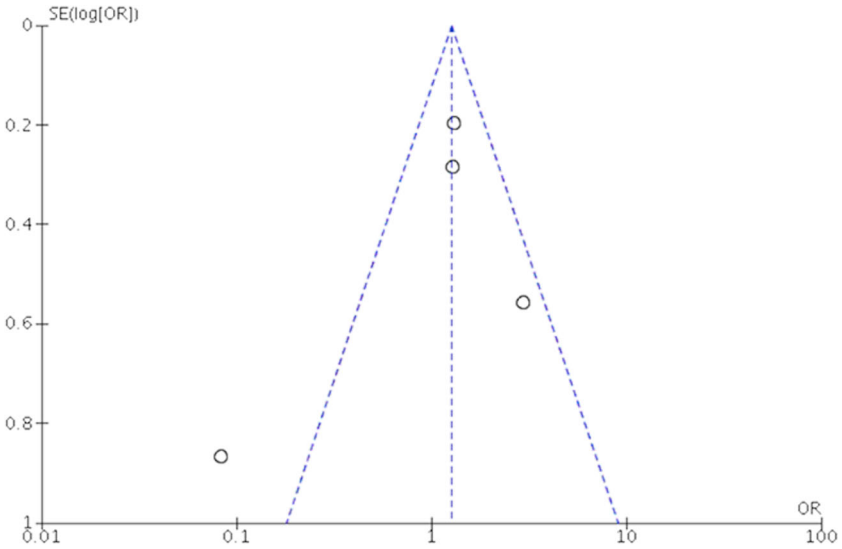

Fig. 8 Funnel plot for publication bias—ICD therapy. Most of the studies (black circles) are scattered around the mid-line at the apex and middle with one study missing on the bottom of the funnel plot indicating a chance of publication bias

the recipients who have CRT continued after LVAD implantation were not found to have a significant benefit from CRT in the outcomes as mentioned above.

Both CRT's and LVAD's isolations have shown to improve the survival, quality of life, and functional aspects of the failing left ventricle. However, the benefit is not additive. A plausible explanation might be that left ventricular dyssynchrony and abnormal septal motion in patients with LVADs may prevent dynamic obstruction of the inflow cannula, prevent suction events, and provide some support to the right ventricle. For these patients, biventricular pacing may adversely affect the left ventricular hemodynamics. Furthermore, most of the LVAD recipients who have a CRT device and particularly those with a substantial burden of a left ventricular scar are likely poor responders to resynchronization therapy. Besides, one recognized reason for the lack of response to CRT is inadequate biventricular pacing. Previous studies have demonstrated improved outcomes associated with higher percentage of biventricular pacing [16–18]. A recent post hoc analysis of the MADIT-CRT trial suggested that patients with biventricular pacing ≥ 97% of the time were at a 50% lower risk of heart failure or death compared with those with biventricular pacing < 97% of the time [18]. In LVAD recipients, inadequate biventricular pacing may explain the findings of our analysis as for many of these patients, the presence of atrial arrhythmias, ventricular ectopy, high capture thresholds, lead dislodgement, or malfunction can reduce biventricular pacing rate. Finally, the effects of left ventricular unloading and the presence of continuous flow, often with closed aortic valve and limited pulsatility of the left ventricle diminish the beneficial effects of electromechanical remodeling associated with CRT.

The approach to biventricular pacing may vary within institutions. Deactivation of the coronary sinus lead is often performed to either preserve battery life and prevent generator change and

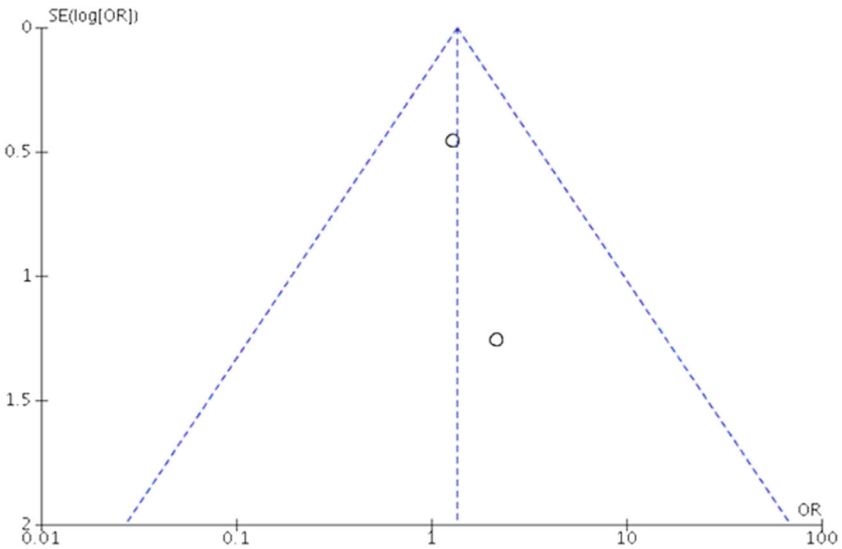

Fig. 9 Funnel plot for publication bias—hospitalization. Most of the studies (black circles) are scattered around the mid-line at the apex and middle with no studies missing on the bottom of the funnel plot indicating less likelihood of publication bias

risk of infection or because of higher capture thresholds, arrhythmias, and poor biventricular pacing rates. However, a portion of LVAD recipients who are pacemaker dependent or the ones with potential for recovery after LVAD implantation may benefit hemodynamically and prognostically from biventricular pacing. Optimization of pacing function can be guided by echocardiographic or hemodynamic parameters on the right heart catheterization. Regarding patients with a high burden of ventricular arrhythmias, right ventricular or backup pacing modes can be attempted.

There are some limitations to the interpretation of our data analysis. First, due to lack of data, most of the included studies in the analysis are conference abstracts with limited information available on the included patients (gender frequency missing in some studies, missing description of associated comorbidities). Second, publication bias may still exist despite our best efforts to conduct a comprehensive search and despite the lack of statistical evidence for the existence of bias. Third, any meta-analysis based on pooling of data from different studies with different inclusion criteria, different designs, populations, variable follow-up duration with differing attrition rates, and not being unified in definition and validation of endpoints in individual studies presents challenges. The comparator groups in included studies were not consistent, and it includes patients who had ICD, and in some studies, no CRT and ICD. Due to limited data, only two studies were included in the analysis of hospitalizations. Additionally, we could not exclude the possibility of differential CRT response in our patients depending on the presence or absence of left ventricular dyssynchrony which might have introduced a selection bias in the included cohort. Finally, variable electrical and structural substrates may affect response to CRT before LVAD implantation and introduce confounding.

In conclusion, among LVAD recipients, CRT alone or with CRT-D did not appear to improve mortality, hospitalization, and incidence of VA and ICD therapies. Our results suggest that the continuation of CRT in LVAD patients should be individualized. In patients that do not seem to derive substantial benefit or have poor biventricular pacing rates, left ventricular lead inactivation may prevent future generator change. Further studies, ideally randomized trials, are needed to identify patients who would derive benefit from biventricular pacing after LVAD implantation.

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