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Cardiac resynchronization therapy in continuous flow left ventricular assist device recipients: A systematic review and meta-analysis from ELECTRAM investigators

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Cardiac Resynchronization Therapy in continuous flow Left Ventricular Assist Device Recipients: A Systematic Review and Meta-analysis from ELECTRAM Investigators

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Abstract

Introduction: Whether cardiac resynchronization therapy (CRT) continues to augment left ventricular remodeling in patients with the continuous-flow left ventricular assist device (cf-LVAD) remains unclear.

Methods: We performed a systematic review and meta-analysis of all clinical studies examining the role of continued CRT in end-stage heart failure patients with cf-LVAD reporting all-cause mortality, ventricular arrhythmias, and ICD shocks. Mantel-Haenszel risk ratio (RR) random-effects model was used to summarize data.

Results: Eight studies (7 retrospective and 1 randomized) with a total of 1,208 unique patients met inclusion criteria. There was no difference in all-cause mortality (RR 1.08, 95% CI 0.86 – 1.35, $p = 0.51$, $I^2=0\%$), all-cause hospitalization (RR 1.01, 95% CI 0.76-1.34, $p = 0.95$, $I^2=11\%$), ventricular arrhythmias (RR 1.08, 95% CI 0.83 – 1.39, $p = 0.58$, $I^2=50\%$) and ICD shocks (RR 0.87, 95% CI 0.57 – 1.33, $p = 0.52$, $I^2=65\%$) comparing CRT versus non-CRT. Subgroup analysis demonstrated significant reduction in ventricular arrhythmias (RR 0.76, 95% CI 0.64 – 0.90, $p = 0.001$) and ICD shocks (RR 0.65, 95% CI 0.44 – 0.97, $p = 0.04$) in “CRT on” group versus “CRT off” group.

Conclusion: CRT was not associated with a reduction in all-cause mortality or increased risk of ventricular arrhythmias and ICD shocks compared to non-CRT in cf-LVAD patients. It remains to be determined which subgroup of cf-LVAD patients benefit from CRT. The findings of our study are intriguing, and therefore, larger studies in a randomized prospective manner should be undertaken to address this specifically.

Introduction

Despite advances in pharmacologic and device therapies, heart failure is one of the foremost causes of hospitalization in the United States, accounting for high morbidity, mortality, and increased burden to health care cost utilization. It is estimated that nearly 6 million Americans are currently affected by heart failure, a number that is

expected to reach 8 million by 2030¹. Studies have shown that cardiac resynchronization therapy (CRT) improves the quality of life, decreases heart failure hospitalization, reduces left ventricular dimensions and overall mortality in patients left ventricular ejection fraction (LVEF) $\leq 35\%$, NYHA functional class I-III and wide QRS in addition to guideline-directed medical therapy²⁻⁴.

Key Words

Cardiac resynchronization therapy, LVAD, arrhythmias

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Given the limitations of organ availability, heart transplantation is not always the best therapeutic option in patients with end stage heart failure. Left ventricular assist device (LVAD) has been a viable alternative and has been increasingly used as destination therapy (DT), bridge to transplant (BT), and bridge to recovery in end-stage

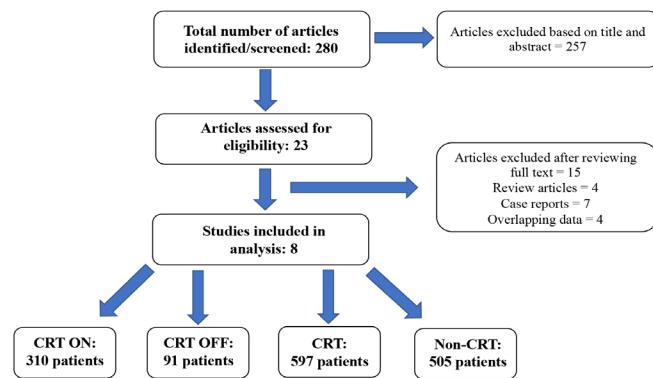


Figure 1: Flow Diagram illustrating the systematic search of studies

heart failure patients on guideline-directed medical therapy and CRT if indicated⁵. However, whether CRT continues to augment left ventricular remodeling in patients with end-stage heart failure on LVAD remains unclear. Based on current available literature, there are no strict guidelines (limited to consensus statement regarding device and arrhythmia management in patients with LVAD)⁶ on continued left ventricular pacing (as a part of CRT) in advanced heart failure patients with continuous-flow left ventricular assist device (cf-LVAD). Therefore, we performed a systematic review and meta-analysis of all the clinical studies examining the role of continued cardiac resynchronization therapy in end-stage heart failure patients with cf-LVAD.

Search Strategy

The reporting of this systematic review and meta-analysis complies with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (Supplement Table 1)⁷ and prospectively enrolled in the PROSPERO database.

We searched PubMed, Clinicaltrials.gov, the Web of Science, EBSCO database, Google Scholar, Cochrane Central Registry, and various major scientific conference sessions (American College of Cardiology, American Heart Association, Heart Rhythm Society, European Society of Cardiology and Cardiac Society) for published abstracts and manuscripts until May 30, 2020. We used the following keywords and medical subject heading: “left ventricular assist device,” “LVAD,” “CRT,” “cardiac resynchronization therapy”.

Study selection and data extraction

We included randomized clinical trials, prospective and retrospective studies. Considering the paucity of evidence, we decided to include abstracts. Any meta-analysis, review articles, studies with no comparator arm, or studies involving pulsatile flow LVAD (pf-LVAD) were excluded from our analysis. The data from included studies were extracted using a standardized protocol and a data extraction form. Any discrepancies between the two investigators were resolved through consensus and arbitration with the co-senior investigators (D.L. and J.G.). The following data were extracted: author name, study design, publication year, follow-up duration, number of patients, age, gender, biventricular percent pacing, comorbidities, etiology of cardiomyopathy, INTERMACS score, indications of cf-LVAD, left ventricular ejection

fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), ventricular arrhythmias, implantable cardioverter-defibrillator (ICD) shocks, medications, and outcomes. The Newcastle Ottawa Risk bias assessment tool was used to appraise the quality of non-randomized studies (Supplement Table 2). The Cochrane – Risk bias assessment tool was used to appraise the quality of a randomized controlled trial (Supplement Table 3).

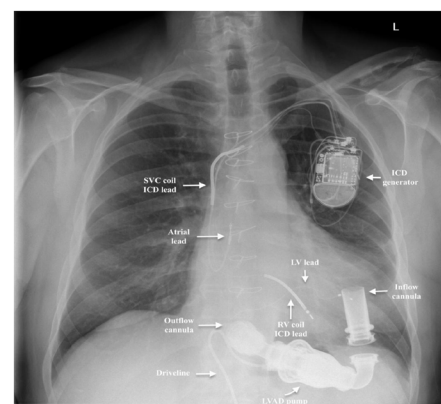
Clinical outcomes

The primary outcome of our study was – (i) all-cause mortality (ii) all-cause hospitalization (composite of heart failure and ventricular arrhythmia related hospitalization), (iii) ventricular arrhythmias, and (iv) appropriate ICD shocks between the CRT and non-CRT groups with cf-LVAD.

Subgroup analysis was performed comparing “CRT on” versus “CRT off” (to assess long term effect sequela of wide QRS in cf-LVAD patients, if any). Outcomes studied were all-cause hospitalizations per patient, ventricular arrhythmia, and appropriate ICD shocks.

Statistical analyses

The meta-analysis was performed using a meta-package for R version 4.0 and Rstudio version 1.2. Mantel-Haenszel risk ratio (RR) random-effects model (DerSimonian and Laird method) was used to summarize data between the two groups⁸. For continuous variables, weighted mean difference (WMD) was calculated to evaluate the difference in clinical outcomes between relevant subgroups in patients with cf-LVAD. Heterogeneity of effects among the included studies was assessed by Higgins I-squared (I^2) statistic⁹. A value of I^2 of 0–25% represented insignificant heterogeneity, 26–50% represented low heterogeneity, 51–75% represented moderate heterogeneity, and more than 75% represented high heterogeneity, as set forth by the Cochrane Collaboration. Publication bias was visually and formally assessed using funnel plots. A two-tailed $p < 0.05$ was considered statistically significant for all analyses.



Clinical Outcomes	CRT versus non-CRT		“CRT on” versus “CRT off”	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
All-cause mortality	1.08 (0.86 – 1.35)	P = 0.51	-	-
All-cause hospitalization	1.01 (0.76 – 1.34)	P = 0.95	-1.07 (-3.97 – 1.82)	0.47
Ventricular arrhythmias	1.08 (0.83 – 1.39)	P = 0.58	0.76 (CI 0.64 – 0.90)	0.001
Appropriate ICD shocks	0.87 (0.57 – 1.33)	P = 0.52	0.65 (CI 0.44 – 0.97)	0.04

Figure 2: Cardiac Resynchronization Therapy in end-stage heart failure patients with cf-LVAD

Table 1: Baseline characteristics of the studies included in our analysis

Study	Schleifer et al		Richardson et al		Roukoz et al		Choi et al		Kutyifa et al		Mai et al		Rao et al		Gopinathannair et al	
Study Period	2007-2012		2013 - 2016		2007 - 2015		2006 - 2009		2008 - 2014		2009 - 2015		2005 - 2013		2007 - 2015	
Type	Retrospective		Randomized controlled trial		Retrospective		Retrospective (abstract)		Retrospective (abstract)		Retrospective (abstract)		Retrospective (abstract)		Retrospective	
Follow up	2.1 years		11 (4-18)months		2.4 ± 2.0 years		49 days		25 months		59 days (median)		Up to 1 year		651 ± 528 days	
Biventricular pacing (%) Mean ± SD			99 (94-99)		96 ± 5.3										96 ± 5	
Groups	CRT on	CRT off	CRT on	CRT off	CRT on	CRT off	CRT	Non-CRT	CRT	Non-CRT	CRT	Non-CRT	CRT	Non-CRT	CRT	Non-CRT
N	39	26	20	21	251	44	22	13	61	130	40	47	135	118	280	106
Age Mean ± SD (years)	62±13	62±14	.	.	60±0.8	63±1.8	56±12		58.9±9.7		55.3±27		57.7	54.4	60±12	60±13
Males (N, %)	31 (79)	24 (92)	.	.	208 (82.9)	37 (84.1)	29 (total) (82.85)		162		74 (85.1)		.		232 (82.9)	86 (81)
Ischemic cardiomyopathy (N, %)	15 (38)	16 (62)	.	.	130 (51.9)	24 (54.8)		151 (53.9)	66 (62)
Hypertension (N, %)	11 (28)	8 (31)	.	.	174 (69.3)	23 (52.3)		185 (66.1)	78 (74)
Diabetes (N, %)	15 (38)	10 (38)	.	.	112 (44.6)	19 (43.2)		123 (43.9)	47 (44)
LVEF % Mean ± SD	17±6	18±6	.	.	15.8±5.8	16.6±7.7	.		.		20 (total)		16.9	19.1	16±6	16±6
LVEDD-mm Mean ± SD	72±9	71±12	.	.	72±10	73±12	.		.		.		71.4	67.8	70±10	70±10
Primary prevention ICD (N, %)	33 (85)	17 (65)	.	.	139 (55.5)	15 (35.1)
Bridge to Transplant (N, %)	18 (46)	8 (31)	.	.	115 (45.7)	21 (48.8)		126 (45)	53 (50)
INTERMACS profile 1-2 (N, %)	71(28.1)	6 (14.3)
QRS duration (msec) Mean ±SD	141±27	138±43	.	.	160±29	152±29		159±29	155±26
Beta-blockers (N, %)	15 (38)	13 (50)			206 (82.3)	36 (81.8)									230 (82)	91 (86)
ACEi or ARB's (N, %)	139 (55.3)	26 (59.1)	109 (39)	42 (40)
Aldosterone antagonists (N, %)	56 (22.5)	8 (19.1)
Nitrates (N, %)	35 (14.1)	4 (9.5)
Hydralazine (N, %)	83 (33.2)	7 (16.7)
Antiarrhythmic drugs (N, %)	16 (41)	13 (50)	.	.	153 (60.95)	23 (52.27)	.		.		.		104 (77)	76 (64)	112 (40)	36 (34)

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker

Results

Search results

A total of 280 citations were identified (Figure 1) during the initial search. Two hundred seventy-two records were excluded. After a detailed evaluation of these studies, eight articles: ⁷retrospectives¹⁰⁻¹⁶ and 1 randomized clinical trial¹⁷ ultimately met the inclusion criteria, constituting 1,208 unique patients with a mean follow-up of

424.36±425.25 days. Table 1 summarizes the baseline characteristics of the included trials in our meta-analysis. Studies by Gopinathannair et al.(published in 2015¹⁸ and 2018¹⁹) enrolled patients from the same institution and overlapping years. Therefore, we only included the study by Gopinathannair et al published in 2019, as it was more contemporary of the three¹⁶. Patients in the “CRT off” subgroup were included in the non-CRT group for the overall analysis. Studies by Gopinathannair et al and Roukoz et al enrolled patients from the same

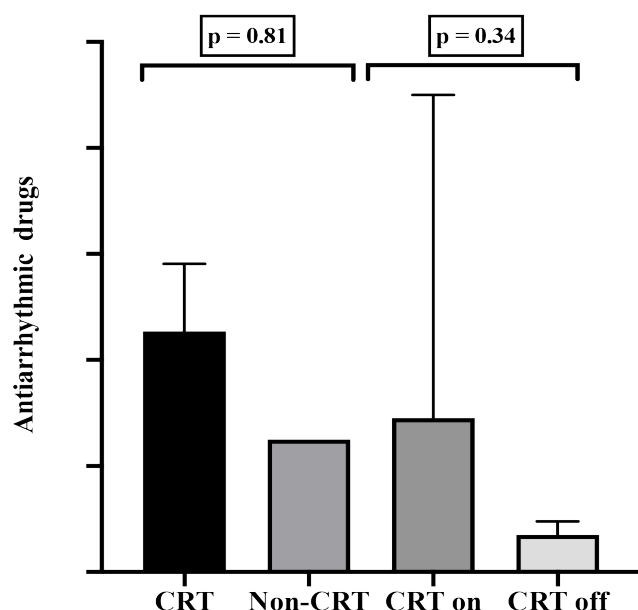


Figure 3: Antiarrhythmic drug use in end-stage heart failure patients on cf-LVAD.

institution and overlapping years; hence we included Gopinathannair et al for comparing CRT versus non-CRT and Roukuz et al for “CRT on” vs “CRT off”. While comparing overall analysis (CRT vs. non-CRT), Roukuz et al was excluded due to overlapping data with Gopinathannair et al.

Study characteristics

Of eight studies included in our analysis, five studies evaluated CRT versus non-CRT in cf-LVAD patients (CRT = 597 patients, non-CRT = 505 patients)¹²⁻¹⁶; while 3 studies evaluated “CRT on” versus “CRT off” in cf-LVAD patients (“CRT on” = 310 patients, “CRT off” = 91 patients)^{10,11,17}. Overall, the mean age of the patients was 58.04 ± 12.84 years. Bridge to transplantation (BTT) as the indication for LVAD placement was available in three trials ($n = 341, 45.7\%$)^{10,11,16}.

Data on antiarrhythmic drugs was available only in 4 studies, with 51% patients (232/454) in CRT vs 50% patients (125/250) in non-CRT group ($p=0.81$); while 58.27% patients (169/290) in “CRT on” vs 51.42% (36/70) in “CRT off” sub-group ($p=0.35$) (Table 1 and Figure 3).

Outcomes (Figure 4-6, Supplement figure 1-2)

All-cause mortality

The data for all-cause mortality was available in 3 trials^{13,15,16}. The presence of CRT was not associated with any difference in all-cause mortality as compared to non-CRT in patients with cf-LVAD (30.67% vs. 27.4%, RR 1.08, 95% CI 0.86 – 1.35, $p=0.51$). No heterogeneity was observed between trials ($I^2=0\%$) (Figure 4).

All-cause hospitalization

Two studies reported data on all-cause hospitalization^{15,17}. Rates of hospitalization were not significantly different between CRT and non-CRT group in cf-LVAD patients (67.10% vs. 68.88%, RR 1.01, 95% CI 0.76-1.34, $p = 0.95$, $I^2 = 11\%$) (Figure 5A).

In studies comparing “CRT on” vs “CRT off”^{10,11}, all-cause hospitalization per patient was not significantly different between “CRT on” versus “CRT off” in cf-LVAD patients (WMD -1.07, 95% CI -3.97 – 1.82, $p = 0.47$, $I^2=63\%$) (Figure 5B).

Ventricular arrhythmias

The data for the incidence of ventricular arrhythmias after cf-LVAD was available in 5 trials^{10,12,14-16}. The CRT group was not associated with increased risk of ventricular arrhythmias as compared to the non-CRT group in cf-LVAD patients (44.76% vs. 40.32%, RR 1.08, 95% CI 0.83 – 1.39, $p=0.58$). Moderate heterogeneity was observed between trials ($I^2=50\%$) (Figure 6).

When comparing “CRT on” vs “CRT off”^{10,11}, “CRT on” group was associated with a lower incidence of ventricular arrhythmias as compared to “CRT off” group in cf-LVAD patients (57.9% vs. 75.7%, RR 0.76, 95% CI 0.64 – 0.90, $p = 0.001$). No heterogeneity was observed between trials ($I^2=0\%$) (Supplement Figure 1).

Appropriate ICD shocks

Four studies reported data on the ICD shocks^{10,15-17}. The incidence of ICD shocks did not differ between CRT and non-CRT group in cf-LVAD patients (35.86% vs 33.58%, RR 0.87, 95% CI 0.57 – 1.33, $p = 0.52$). Moderate heterogeneity was observed between trials ($I^2=65\%$) (Figure 7).

In studies comparing “CRT on” versus “CRT off”^{10,11,17}, “CRT on” group was associated with a lower incidence of ICD shocks as compared to “CRT off” in cf-LVAD patients (33.87% vs. 47.25%, RR 0.65, 95% CI 0.44 – 0.97, $p = 0.04$). Mild heterogeneity was observed between trials ($I^2=28\%$) (Supplement Figure 2).

Discussion

The main findings in this analysis are: (1) all-cause mortality and hospitalizations did not differ between CRT and non-CRT groups

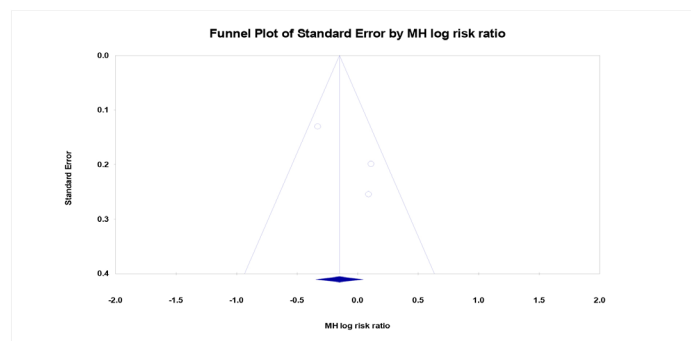
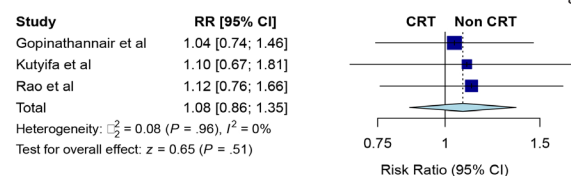


Figure 4: All-cause mortality. The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. The funnel plot demonstrates no publication bias.

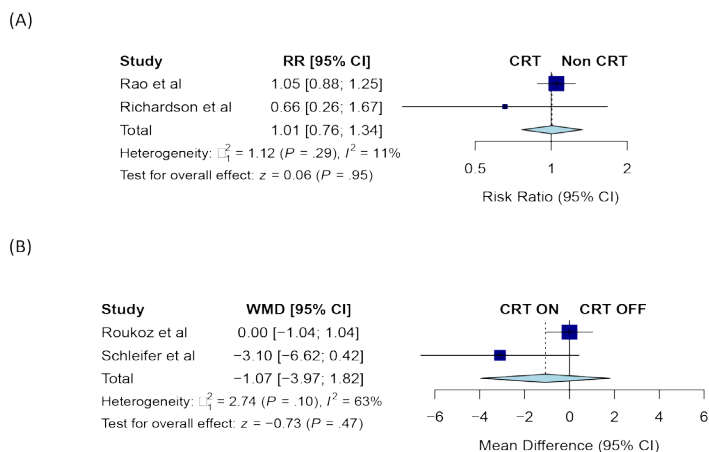


Figure 5:

All-cause hospitalization. (A) The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. (B) The forest plot shows all-cause hospitalization per patient was not significantly different between “CRT on” versus “CRT off” in cf-LVAD patients. Point estimates to the left favor “CRT on”.

in end-stage heart failure patients with cf-LVAD; (2) no reduction in ventricular arrhythmias and ICD shocks was observed; (3) Significant reduction in ventricular arrhythmias and ICD shocks was observed in cf LVAD patients with “CRT on” as compared to “CRT off” (Figure 2). The findings of our study are important clinically and indicate that cf LVAD patients with active CRT did not derive any long term any benefit with continued LV pacing; however, there was significant reduction in ventricular arrhythmias and ICD shocks in cf-LVAD patients with “CRT on” versus “CRT off”. Nonetheless, due to reduction in battery longevity requiring multiple procedures, risks and benefits must be judiciously contemplated.

MADIT-CRT post hoc analysis demonstrated that patients with $\geq 97\%$ biventricular are at reduced risk of heart failure hospitalization and mortality as compared to patients with $< 97\%$ biventricular pacing²⁰. In addition, cf-LVAD improves overall survival in end-stage heart failure patient; however, the benefit of CRT in cf-LVAD may not be additive. Whether or not continued LV pacing post LVAD implantation for maximal LV remodeling remains controversial. There are several potential explanations for the findings observed in our study. First, lack of randomized clinical trials may have caused a selection bias towards sicker patients, resulting in no observed mortality benefit with CRT. Second, advanced heart failure patients on cf-LVAD are at increased risk of mortality from non-arrhythmic causes such as device infection, pump failure, or pump thrombosis, factors that may outweigh the net clinical benefits of CRT. Third, hemodynamic effects observed with cf-LVAD might offset the electromechanical effects and the long-term sequelae seen with CRT. The RV and LV shares oblique fibers within the interventricular septum, thereby augmenting RV contractility with LV contraction^{21,22}. With a decline in LV function, oblique septal fibers orient in a more transverse orientation due to spherical shaped LV (given volume overload), thereby reducing RV contractility. Therefore, CRT (in non-LVAD patients) by reverse LV modeling may in turn improve septal fibers orientation and improve RV function. It is worthwhile to notice that hemodynamic benefits of CRT in improvement on LV systolic function are predominantly mediated

by the improvement of electrical dyssynchrony resulting in improved mechanical synchrony in a setting of wide QRS. Acute LV unloading, change in LV fiber orientation/cardiac chambers from LVAD inflow cannula, and limited pulsatility of LV might counterpoise the hemodynamic effect and long-term sequelae observed with CRT^{16,23}. Fourth, improved patient care, care transition teams, and improvement in LVAD design (over the last decade), resulting in enhanced patient survival, might offset the effects of biventricular pacing.

Studies have shown that CRT may exhibit proarrhythmic effect²⁴ [thought to be due to differential activation and creation of two different wavefronts (from RV and LV pacing), resulting in a unidirectional functional block and initiating reentrant arrhythmias], with an increased risk of ventricular arrhythmias in CRT non-responders²⁵. Besides, ventricular arrhythmia prior to LVAD implantation is an independent predictor of recurrent arrhythmia after LVAD implantation²⁶. In our pooled analysis, although the non-CRT group had a lower incidence of ventricular arrhythmias and ICD shocks, it did not reach statistical significance. The findings of our study corroborate with the study from Gopinathannair et al. demonstrating no significant association between QRS duration or RV pacing or LV pacing on long term outcomes (i.e., hospitalization or development of ventricular arrhythmias)¹⁶.

It is well known that a wide QRS (left bundle block or right bundle branch block) and resultant inter/intraventricular dyssynchrony is associated with adverse clinical outcomes in patients with heart failure^{27,28}. Acute LV unloading, thereby reducing wall stress from cf-LVAD, surpasses the potential electrical remodeling benefit derived from either narrow QRS or biventricular pacing. However, in subgroup analysis, there was a statistically significant reduction in episodes of ventricular arrhythmias and ICD shock in “CRT on” group versus “CRT off”. The precise pathophysiology of the observed finding remains unclear and could represent Type 1 error. Also, there was

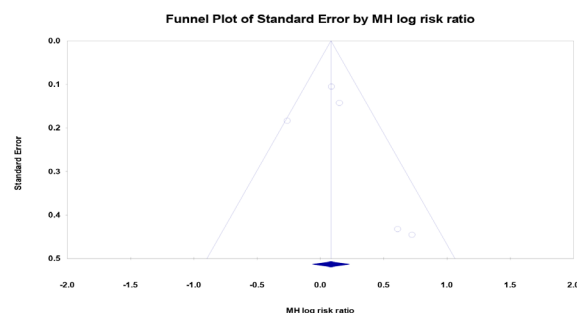
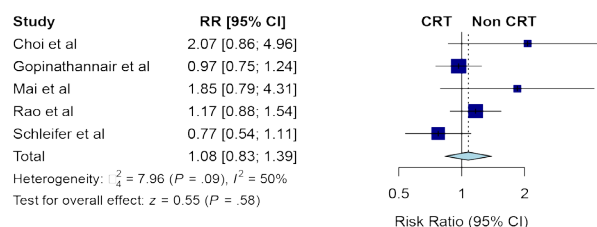


Figure 6:

Ventricular arrhythmias. The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. The funnel plot demonstrates no publication bias.

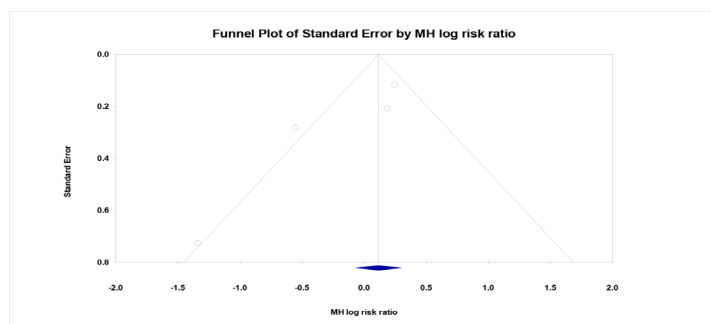
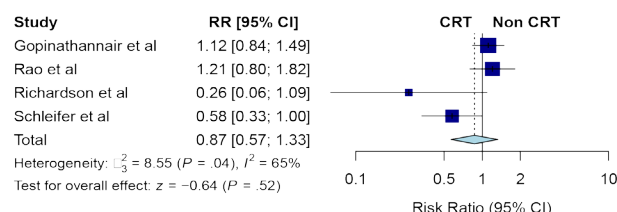


Figure 7: Appropriate ICD shocks. The forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. Funnel plot demonstrates publication bias

Proposed CRT-D programming post cf-LVAD

- Consider programming LV pacing lead off.
- Consider minimizing RV pacing (unless pacer dependent).
- Conservative ICD programming approach to minimize ICD shocks.
- Set up remote monitor if not done previously.
- Assess battery life and multi-disciplinary team approach for battery replacement in future.
- Maximize beta-blockers and minimize antiarrhythmic drugs as tolerated.

Figure 8: Clinical practice approach on CRT-D in patients with cf-LVAD ⁶

a substantially higher number of primary prevention ICDs in the “CRT on” patients which could contribute to the lower incidence of ICD shocks and ventricular arrhythmias in those groups as opposed to the “CRT off” group. Variation in device programming could be another potential explanation for the differences in arrhythmia detection in both groups. Also, no significant difference was observed in terms of antiarrhythmic use between the “CRT on” and “CRT off” groups (Figure 3). If the antiarrhythmic effect of CRT is the possible explanation for the reduction in ventricular arrhythmias and ICD shocks as highlighted by Richardson et al.¹⁷, then similar findings should have been observed in CRT versus non-CRT group in our analysis. The findings of our study are intriguing, and therefore, we feel that larger studies in a randomized prospective manner should be

undertaken to address this specifically.

Because of the lack of definite clinical data assessing the role of CRT in LVAD patients, it remains controversial at this time regarding optimal device programming settings. Therefore, in our clinical practice, we typically deactivate the LV pacing (and reprogram to minimize RV pacing unless otherwise pacer dependent) to preserve battery life and minimize generator changes¹⁹, which by themselves carry a risk of infections or anticoagulation related issues (pocket hematoma or LVAD pump thrombosis) in this high-risk population (Figure 8).

This systematic review and meta-analysis has several important limitations. First, patient selection bias due to limited data (retrospective nature of included studies and conference abstracts) could not be excluded. Also, the trials that evaluated “CRT on” versus “CRT off” had a small size and lacked sufficient statistical power to draw realistic conclusions. Second, information on arrhythmia burden/morphology and its timing in relation to LVAD were obscure. Third, variations in the LV lead position depending underlying anatomy and operator experience, device programming parameters in cf-LVAD patients were not well defined. Fourth, QRS duration, change in QRS post LVAD, and change in LVEF was not available in all trials to thoroughly understand hemodynamic effects between CRT on and off groups. Fifth, data on antiarrhythmic and other medications, etiology of death (cardiac, or non-cardiac), generator changes, and LVAD/CRT related complications were not outlined in all trials. Finally, patient-level data to perform more detailed analyses are not available.

Conclusion

Cardiac resynchronization therapy was not associated with a reduction in all-cause mortality, increased risk of ventricular arrhythmias, and ICD shocks as compared to non-CRT in end-stage heart failure patients with cf-LVAD. However, it remains to be determined which subgroup of cf-LVAD patients may benefit from cardiac resynchronization therapy. Future research should be directed to study the role of CRT in end-stage heart failure patients with cLVAD in a dedicated randomized controlled study.

[Please Click for Supplemental Material](#)

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