ORIGINAL RESEARCH

Cardiac Resynchronization Therapy and Clinical Outcomes in Continuous Flow Left Ventricular Assist Device Recipients

Rakesh Gopinathannair, MD, MA, FAHA, FHRS; Henri Roukoz, MD; Adarsh Bhan, MD; Ashwin Ravichandran, MD; Mustafa M. Ahmed, MD; Dmitry Familtsev, MD, PhD; Geetha Bhat, MD; Jennifer Cowger, MD; Munazzah Abdullah, MD; Chirag Sandesara, MD; Rahul Dhawan, MD; Emma J. Birks, MRCP, PhD; Jaimin R. Trivedi, MD; Mark S. Slaughter, MD, FAHA

***Background*—**Many patients with heart failure continue cardiac resynchronization therapy (CRT) after continuous flow left ventricular assist device (CF-LVAD) implant. We report the first multicenter study to assess the impact of CRT on clinical outcomes in CF-LVAD patients.

***Methods and Results*—**Analysis was performed on 488 patients (58±13 years, 81% male) with an implantable cardioverter defibrillator (ICD) (n=223) or CRT-D (n=265) who underwent CF-LVAD implantation at 5 centers from 2007 to 2015. Effects of CRT on mortality, hospitalizations, and ventricular arrhythmia incidence were compared against CF-LVAD patients with an ICD alone. Baseline differences were noted between the 2 groups in age (60±12 versus 55±14, $P<0.001$) and QRS duration (159±29 versus 126±34, $P=0.001$). Median biventricular pacing in the CRT group was 96%. During a median follow-up of 478 days, Kaplan–Meier analysis showed no difference in survival between groups (log rank $P=0.28$). Multivariate Cox regression demonstrated no survival benefit with type of device (ICD versus CRT-D; $P=0.16$), whereas use of amiodarone was associated with increased mortality (hazard ratio 1.77, 95% confidence interval 1.1–2.8, $P=0.01$). No differences were noted between CRT and ICD groups in all-cause ($P=0.06$) and heart failure ($P=0.9$) hospitalizations, ventricular arrhythmia incidence (43% versus 39%, $P=0.3$), or ICD shocks (35% versus 29%, $P=0.2$). During follow-up, 69 (26%) patients underwent pulse generator replacement in the CRT-D group compared with 36 (15.5%) in the ICD group ($P=0.003$).

***Conclusions*—**In this large, multicenter CF-LVAD cohort, continued CRT was not associated with improved survival, hospitalizations, incidence of ventricular arrhythmia and ICD therapies, and was related to a significantly higher number of pulse generator changes. **(*J Am Heart Assoc*. 2018;7:e009091. DOI: 10.1161/JAHA.118.009091.)**

Key Words: cardiac resynchronization therapy • heart failure • implanted cardioverter defibrillator • left ventricular assist device • ventricular arrhythmia

Left ventricular assist devices (LVADs) are increasingly used as bridge-to-transplant, destination therapy, and in some cases as bridge-to-recovery in patients with advanced cardiomyopathy and heart failure (HF).[1] Continuous flow LVADs (CF-LVADs) have been shown to improve mortality, morbidity, functional status, and quality of life in patients with advanced HF.[2–4] Ventricular arrhythmias, however, are commonly seen in patients with LVAD,[5–7] and the vast majority of LVAD recipients who had implantable cardioverter defibrillators (ICDs) continue to receive ICD therapies post-LVAD implant.[8] Similarly, many patients with dilated cardiomyopathy and cardiac resynchronization therapy (CRT-D) who receive CF-LVADs continue to receive biventricular pacing following CF-LVAD implant. Cardiac resynchronization therapy (CRT), by improving electromechanical synchrony, has been shown to improve mortality, LV dimensions, functional status, and quality of life in patients with LVEF ≤35%, HF, and a wide QRS.[9–12] However, the benefit of CRT on clinical outcomes following CF-LVAD implantation remains unclear. Available data, from 2 observational studies evaluating this question show possible arrhythmic benefits but no overall survival benefit for CRT in a CF-LVAD population.[13,14] These single-center studies, however, were limited by very small sample

From the University of Louisville, Louisville, KY (R.G., R.D., E.J.B., J.R.T., M.S.S.); University of Minnesota, Minneapolis, MN (H.R.); Advocate Christ Medical Center, Oak Lawn, IL (A.B., G.B., M.A.); St. Vincent Heart Center, Indianapolis, IN (A.R.); University of Florida, Gainesville, FL (M.M.A.); University of Arizona, Tucson, AZ (D.F.); Henry Ford Hospital, Detroit, MI (J.C.); Inova Heart and Vascular Institute, Fairfax, VA (C.S.).

Correspondence to: Rakesh Gopinathannair, MD, MA, FAHA, FHRS, Division of Cardiovascular Medicine, University of Louisville, 550 So. Jackson St, ACB/A3L41, Louisville, KY 40202. E-mails: rakesh.gopinathannair@louisville.edu; drrakeshg@yahoo.com

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Clinical Perspective

What Is New?

- In patients with advanced heart failure receiving continuous flow left ventricular assist devices, continued cardiac resynchronization therapy was not associated with improved survival, all-cause and heart failure hospitalizations, and incidence of ventricular arrhythmias and implantable cardioverter defibrillator therapies, and was related to a significantly higher number of pulse generator changes during left ventricular assist device support.

What Are the Clinical Implications?

- Based on our results, it appears reasonable to turn off the left ventricular lead in patients undergoing cardiac resynchronization therapy following continuous flow left ventricular assist device implant to save battery life and limit frequent pulse-generator replacements.

size. Any additional benefit from CRT on myocardial recovery and clinical outcomes in CF-LVAD patients would be important to know. Conversely, lack of benefit could prompt turning off the LV lead following LVAD implant, thereby saving battery life and limiting generator replacements in this complex patient population at an already higher risk of bleeding and infection.

The primary objective of this large multicenter study was to investigate the long-term effects of CRT on survival, all-cause and HF hospitalizations, and incidence of ventricular arrhythmias (VA) and ICD shocks in CF-LVAD patients. A secondary objective was to assess the utility of CRT in bridge-to-transplant CF-LVAD patients when compared with those on destination therapy.

Methods

The present study was conducted at 5 high-volume LVAD centers in the United States (University of Louisville, Louisville, KY; University of Minnesota, Minneapolis, MN; Advocate Christ Medical Center, Oak Lawn, IL; University of Florida, Gainesville, FL; and St. Vincent Heart Center, Indianapolis, IN). The University of Louisville served as the data-coordinating center. The study protocol, including complete waiver of informed consent, was approved by the Institutional Review Boards at all the centers. Data collection and analysis were performed on 488 consecutive advanced HF patients with an existing ICD or CRT-D, who underwent CF-LVAD placement and subsequent follow-up at these institutions between 2007 and 2015. Patients who died during the index hospitalization for LVAD implant or had their LV lead turned off during the first 60 days after LVAD implant were excluded from the analysis. Also, those patients who underwent ICD or CRT-D implant after LVAD implant were excluded. All patients had CF-LVADs implanted either as a bridge-to-transplantation or as destination therapy. Implanted CF-LVADs included HeartMate II® (Abbott Medical, Chicago, IL) in 410 patients and Heartware® (HeartWare International, Inc., Framingham, MA) in 78 patients. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The LVAD study population was divided into a CRT-D group where biventricular pacing was maintained following LVAD implant (n=265) and an ICD-only group (n=223), which constituted patients with both single- and dual-chamber ICDs.

The study results represent a retrospective analysis of prospectively followed patients. The data variables collected include demographics, cause of HF, comorbidities, LVAD type, indication and date of implant, medications, ECG and echocardiographic parameters, and device-specific information on ICDs and CRT-Ds including type of device, percentage of biventricular pacing, as well as incidence of ICD shocks, atrial arrhythmia (AA), and VA. The day of CF-LVAD implant marked the start date for follow-up. The last day of follow-up was August 31, 2016, date of heart transplantation, CF-LVAD explantation, or date of death, whichever came first.

The effects of CRT on the primary outcome variables—Survival (at 1 year and end of follow-up), all-cause and HF hospitalizations, and incidence of VA and ICD shocks—were compared against CF-LVAD patients with an ICD alone. As a secondary analysis, patients in the CRT and ICD groups were stratified by LVAD indication (bridge-to-transplant or destination therapy) to better understand whether CRT impacts mortality in a specific LVAD subgroup when compared with the ICD-only group. The incidence of heart transplantation and LVAD explantation were also compared between groups. Patient charts were reviewed to assess utilization of cardiac medications during follow-up. Reported ECG and echocardiographic parameters during follow-up were assessed during the 6- to 12-month period post-LVAD implant. In those patients who had <6 months of follow-up, the latest available information on these parameters was selected. Patient medical records as well as institutional databases at each participating center were reviewed to assess the cause of death.

Adequacy of biventricular pacing before and after LVAD implant was confirmed by 12-lead ECG and device interrogation. Cardiac resynchronization therapy devices were kept in the DDD(R) (VVIR in patients with long-standing persistent or permanent atrial fibrillation) with atrioventricular delay settings to allow consistent biventricular pacing. CRT programming was left to the discretion of the patient's electrophysiologist. No specific programming protocol was used. ECGs and stored-device electrograms were analyzed for

incidence of AA, VA, and ICD shocks. VA was defined as sustained ventricular tachyarrhythmias lasting >30 s or requiring ICD therapy (antitachycardia pacing or shocks).[13] AA was defined as atrial tachycardia, atrial flutter, or atrial fibrillation lasting either >6 hours or ≥1% burden on device interrogation or requiring pharmacological or electrical therapy for termination. HF hospitalization was defined as any hospitalization secondary to clinical signs and symptoms of congestive HF (dyspnea, fatigue, volume overload, as well as use of intravenous diuretics and/or inotropes for volume) and included device malfunction (LVAD thrombosis) and aortic insufficiency–related HF.[13] All-cause and HF hospitalizations are reported as number of hospitalizations per 100 days of LVAD support.

Statistical Analysis

The effects of CRT on outcome variables were compared against CF-LVAD patients with an ICD alone. Continuous variables are reported as mean±SD or medians with interquartile ranges when appropriate. Categorical variables are reported as percentages. Categorical variables were analyzed using the Fisher exact and/or χ^2 tests. Continuous variables were analyzed using nonparametric (Kruskal–Wallis) tests. Within groups, pre- and post-LVAD parameters were compared using paired *t* tests. Kaplan–Meier curves were used to assess survival outcomes and the log-rank test was used to compare survival estimates. Multivariate Cox regression modeling was used to study the association between the treatment and the outcome after adjusting for clinically relevant covariates. Variables in Table 1 with $P \leq 0.1$ were included in the model and the variable coding for treatment (CRT and ICD) was forced in the model. Since QRS and QTC duration are likely to interact, only QRS duration was used in the model. A $P<0.05$ was considered statistically significant. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

A total of 488 patients with either an ICD or CRT-D underwent CF-LVAD implantation. Of these, 265 patients (age: 60.4±12.3 years, 82% male) had CRT-D and 223 patients (age: 55±14.1 years, 80% male) had an ICD. Of the 488 patients, 410 patients had a HeartMate II (Abbott Medical, Chicago, IL) and 78 patients had a HeartWare (HeartWare International, Inc., Framingham, MA) LVAD implanted. All CRT-D patients continued to receive biventricular pacing following LVAD implant. CF-LVAD was implanted as bridge-to-transplant in 234 patients (48%) and as destination therapy in 254 (52%) patients. Cause of HF was ischemic cardiomyopathy in 134/265 patients (51%) in the CRT-D and in 105/223 (48%) in the

Table 1. Baseline Characteristics in the ICD and CRT-D Groups

Variable	CRT-D Group (n=265)	ICD Group (n=223)	*P* Value
Mean age, y	60.4±12.3	55±14.1	<0.001*
Male sex, N (%)	217 (82)	178 (80)	0.56
White, N (%)	177 (68)	132 (60)	0.12
Mean BMI, kg/m^2	29.1±6.6	29.8±6.9	0.34
Medical history, N (%)			
Ischemic cardiomyopathy	134 (51)	105 (48)	0.65
LVAD as bridge to transplant	119 (46)	115 (52)	0.19
INTERMACS profile 2	42 (19)	42 (23)	0.12
INTERMACS profile 3	64 (28)	53 (29)	
Obstructive CAD	158 (60)	124 (56)	0.37
Hypertension	174 (66)	150 (67)	0.70
Dyslipidemia	181 (68)	135 (60)	0.08
Diabetes mellitus	117 (44)	99 (44)	0.95
Chronic kidney disease	119 (45)	96 (43)	0.71
COPD	55 (21)	49 (22)	0.74
Obstructive sleep apnea	92 (35)	78 (35)	0.95
Pulmonary hypertension	116 (44)	112 (50)	0.19
Pre-LVAD atrial arrhythmia incidence (AA)	144 (65)	88 (50)	0.003*
Pre-LVAD ventricular arrhythmia incidence (VA)	92 (35)	84 (38)	0.5
Cardiac medications, N (%)			
β-Blocker	215 (82)	194 (88)	0.05
ACEIs or ARB	147 (55)	116 (53)	0.53
Aldosterone antagonists	115 (44)	109 (50)	0.19
Amiodarone	106 (40)	64 (30)	0.009*
Digoxin	111 (42)	80 (37)	0.19
Pre-LVAD ECG			
Mean PR interval, ms	145±45	174±39	0.001*
Mean QRS duration, ms	159±29	126±34	0.001*
Mean QTc interval, ms	537±60	500±62	0.001*
Pre-LVAD echocardiography			
Mean LVEDD, cm	7.2±1.0	7±0.9	0.5
Mean LVESD, cm	6.5±1.1	6.3±1.0	0.12
LVEF, %	15.8±5.9	16.4±6.6	0.04*

AA indicates atrial arrhythmias; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; VA, ventricular arrhythmia.
*Significant *P* values.

ICD group (*P*=0.65). In the CRT-D arm, 19% and 28% of patients had an Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score of 2 and 3, respectively, whereas 23% and 29% of patients in the ICD arm had the same INTERMACS profile.

At baseline (before LVAD implant), significant differences were noted between the CRT-D and ICD groups in age (60.4±12.3 versus 55±14 years; *P*<0.001), incidence of AA (65% versus 50%; *P*=0.003), amiodarone use (40% versus 30%; *P*=0.009), ECG parameters (PR, QRS, and QTc intervals), and left ventricular ejection fraction (LVEF) (15.8±5.9 versus 16.4±6.6; *P*=0.04), whereas no significant differences were noted in LVAD indications, cause of HF, HF medications, left ventricular end-diastolic dimensions, and incidence of VA (Table 1). Pre-LVAD VA were present in 35% of patients in the CRT-D and 38% in the ICD group (*P*=0.5). Mean QRS duration (159±29 versus 126±34 ms; *P*=0.001) and QTc (537±60 versus 500±62 ms; *P*=0.001) at baseline were significantly greater in the CRT-D group versus the ICD group (Table 1). In the ICD group, 28/223 (12.5%) of patients had >80% right ventricular pacing at baseline.

Survival and Other Outcomes

Overall mean follow-up for both groups was 620±509 days (7776 patient-months); median follow-up was 478 days of LVAD support and was similar for both the CRT-D and ICD groups. Median biventricular pacing during follow-up for the CRT-D group was 96%. During follow-up, 75 patients (29%) died in the CRT-D group and 53 (25%) patients died in the ICD group. Severe sepsis with multiorgan failure, right ventricular failure, and stroke/cerebral hemorrhage were the 3 most common causes of death (Table 2). Forty-four patients (17%) in the CRT-D group and 39 (18%) in the ICD group underwent heart transplantation (*P*=0.53).

Table 2. Causes of Death in Both the CRT-D and ICD Groups

Cause of Death	CRT-D (n=75)	ICD Only (n=53)
Sepsis/multiorgan failure	18	12
Right ventricular failure/cardiogenic shock	16	5
Stroke/cerebral bleed	15	13
CF-LVAD malfunction/thrombus	6	6
Arrhythmic death	8	5
Liver/renal failure	2	1
Other	2	2
Unknown	8	9

CF-LVAD indicates continuous flow left ventricular assist device; CRT-D, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

Kaplan–Meier analysis showed no significant difference in survival between the 2 groups at end of follow-up (log rank *P*=0.28) (Figure 1). At 1-year follow-up (all patients who died within the first year of LVAD support or had completed 1-year of follow-up were included in this analysis), 46/200 (23%) patients died in the CRT-D group versus 22/149 (15%) in the ICD group. Kaplan–Meier analysis showed a trend towards worse survival in the CRT-D group, but this did not reach statistical significance (log rank *P*=0.054) (Figure 2). Continued CRT did not show any significant survival advantage when stratified by LVAD indication (bridge-to-transplant versus destination therapy; log rank *P*=0.7; Figure 3) or by cause of HF (ischemic versus nonischemic cardiomyopathy; log rank *P*=0.3).

Adjusted survival outcomes based on Cox-regression model showed that the type of cardiac implantable electronic device (ICD versus CRT-D hazard ratio 1.46 [0.85–2.51], *P*=0.16) was not significantly associated with all-cause mortality. Use of amiodarone was the only independent predictor of adverse survival (hazard ratio 1.77, *P*=0.01) (Table 3). In another analysis, we included high percentage right ventricular pacing in the Cox model and this was also not associated with survival (hazard ratio 0.928, *P*=0.92); however, this analysis was limited by the small size of the right ventricular pacing cohort.

No significant differences were found between the CRT-D and ICD groups in all-cause hospitalizations (0.46/100 days versus 0.59/100 days; *P*=0.06) and HF hospitalizations (0.1/100 days versus 0.2/100 days; *P*=0.9) during follow-up. The incidence of VA (43% versus 39%; *P*=0.3) and ICD shocks (35% versus 29%; *P*=0.2) were similar between the CRT-D and ICD groups, whereas AA incidence during follow-up was significantly higher in the CRT-D group (61% versus 47%; *P*=0.01) (Table 4). During follow-up, 69 (26%) patients underwent device pulse generator replacement in the CRT-D group compared with 36 (15.5%) in the ICD group (*P*=0.003). The median time from cardiac implantable electronic device implant to LVAD implant was 1080 days (range: 382–1942) in the ICD group and 1039 days (range: 378–1838) in the CRT-D group (*P*=0.4).

LV dimensions decreased with CF-LVAD support in both groups when compared with baseline. However, no significant differences in LV dimensions were noted between groups during follow-up. There was no significant difference between the CRT-D and ICD groups in β-blocker (65% versus 68%, *P*=0.4) and amiodarone (50% versus 45%, *P*=0.5) use post-LVAD implantation (Table 5).

Discussion

To our knowledge, this is the largest and only multicenter study to assess the impact of CRT on clinical outcomes in CF-

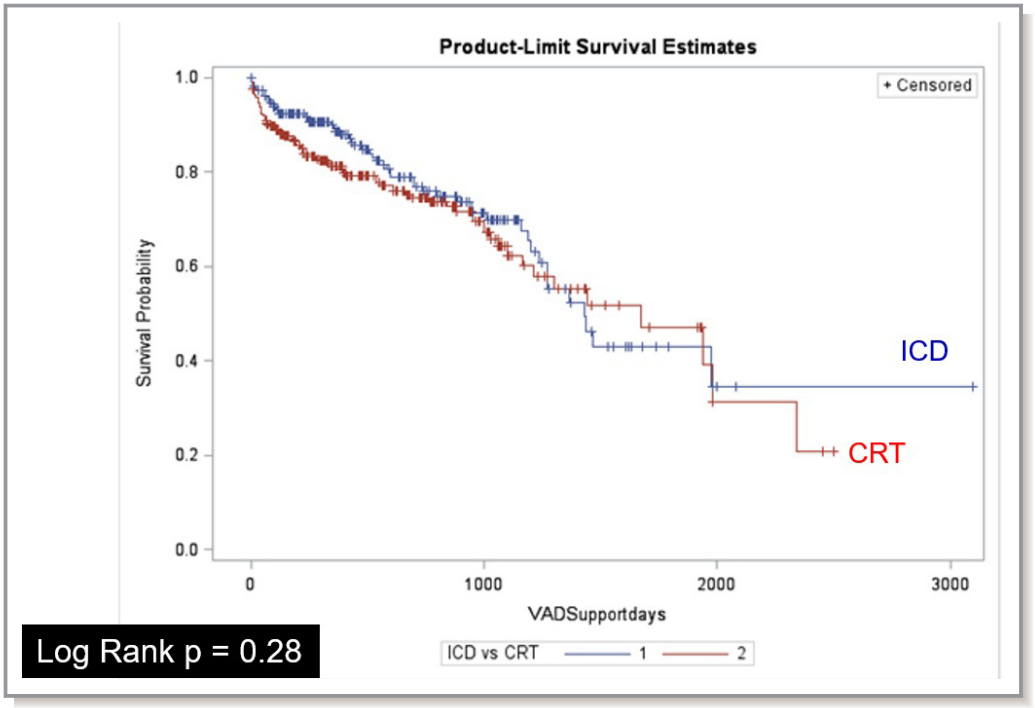

Figure 1. Kaplan–Meier analysis showing all-cause mortality in CF-LVAD patients stratified by the presence or absence of CRT. There was no significant difference in survival between the ICD and CRT-D groups. The log-rank test was used to assess differences in survival estimates between groups. CF-LVAD indicates continuous flow left ventricular assist device; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

LVAD patients. Our results show that continued CRT, when compared with a CF-LVAD group with ICDs only, was not associated with improved all-cause survival in CF-LVAD patients. There was a strong but nonsignificant trend towards higher mortality in the CRT group at 1-year follow-up. Subgroup analysis showed that CRT was not associated with improved survival whether the CF-LVAD was implanted as bridge-to-transplant or as destination therapy. Multivariate Cox regression analysis demonstrated that CRT was not associated with improved survival. Continued CRT was also not associated with reduction in all-cause and HF hospitalizations, VA incidence, or ICD shocks during CF-LVAD support.

Multiple large randomized trials have proven the salutary role of CRT in improving survival, morbidity, and quality of life in patients with ischemic and nonischemic cardiomyopathies, LVEF ≤35%, New York Heart Association class II-IV, and a QRS duration >120 ms.[9,10,15–17] A meta-analysis of available CRT trials shows that in eligible patients, CRT may significantly reduce the incidence of VA when compared with ICDs, and CRT responders had a significantly lower risk of VA when compared with nonresponders.[18]

The utility of CRT following LVAD implantation, however, is less well defined. One could argue that HF patients with an existing CRT-D needing a CF-LVAD are, by default, CRT nonresponders. However, the "resting LV" following CF-LVAD implant perhaps offers an opportunity for CRT to aid myocardial recovery. Therefore, a favorable additive effect of CRT on ventricular remodeling and outcomes in the CF-LVAD-supported patient would be valuable to know. So far, 2 single-center observational studies have evaluated this question. Gopinathannair et al, in 2015, reported the first data evaluating the role of CRT, when compared with ICD only, in 61 CF-LVAD patients. Over a mean follow-up of 682±45 days of LVAD support, 8 (26%) patients died in the CRT group and 5 (17%) died in the ICD group (P=0.53). No significant differences were seen in all-cause and HF hospitalizations as well in incidence of VA and ICD therapies.[13] Schleifer et al compared the arrhythmic outcomes between CF-LVAD patients with continued CRT (CRT-on, n=39) and those who had CRT turned off (CRT-off, n=27) before discharge. CRT was turned off for lead malfunction, phrenic nerve stimulation, infection requiring lead extraction, or battery preservation concerns. There was no significant difference in all-cause mortality, hospitalizations, VA per patient, incidence of inappropriate shocks, and incidence of ICD generator changes between groups. The CRT-off group had a higher incidence of total ICD shocks per patient, when compared with the CRT-on group (5.5±9.3 versus 1.5±2.7, P=0.014).[14]

Both of the prior single-center studies were limited by small sample size, thereby limiting robust multivariate analyses. In contrast, our study results are strengthened significantly by our large sample size and multicenter experience,

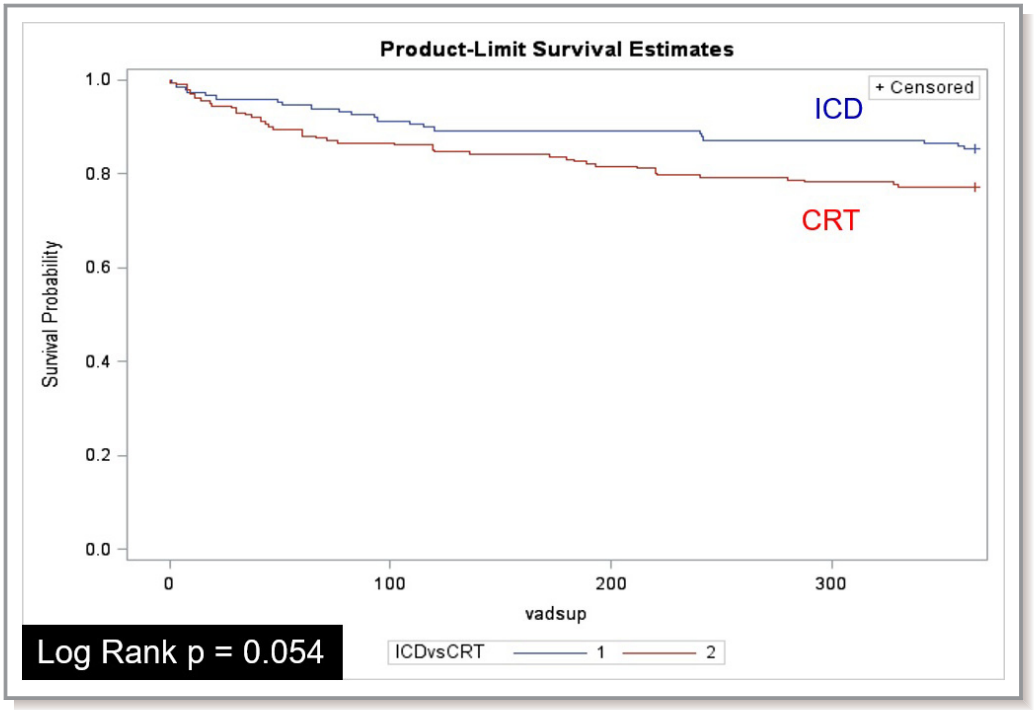

Figure 2. Kaplan–Meier analysis showing all-cause mortality at 1-year follow-up. The log-rank test was used to assess differences in survival estimates between groups. CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

allowing robust Cox regression analyses exploring the independent association of CRT with survival. Our study results concur with the prior studies[13,14] in that concomitant CRT following CF-LVAD did not offer any significant survival advantage. In fact, we noted a trend towards reduced survival in the CRT-D group at 1-year follow-up compared with the ICD group, suggesting early harm. Additional studies are required to explore this further. Additionally, when stratified by type of cardiomyopathy (ischemic versus nonischemic) or by LVAD indication (bridge-to-transplant versus destination therapy), no significant survival benefit for continued CRT was seen. Multivariate Cox regression analysis showed that the type of device (ICD versus CRT-D) was not associated with improved survival, further supporting our findings.

Multiple factors may explain the lack of benefit from continued CRT in CF-LVAD patients. In HF patients with wide QRS duration, the beneficial effects of CRT on LV systolic function and HF symptoms are primarily mediated by correction of electrical dyssynchrony leading to improved mechanical synchrony.[12] The significant LV unloading following LVAD implantation represents a completely different hemodynamic state and likely supersedes any benefits that CRT can offer. Change in LV myocardial fiber orientation from CF-LVAD inflow cannula placement as well as alterations in the orientation of cardiac chambers may have diminished any CRT effect.[13] Baseline characteristics and INTERMACS profiles were mostly similar between groups and any differences were adjusted for by multivariate analyses. Moreover, LV dimensions were the same in both groups at baseline and were decompressed to a similar degree following CF-LVAD implantation. Thus, it is unlikely that the CRT group was any more "sicker" than the ICD group. Survival, transplantation rates, and hospitalizations were similar during follow-up. Mortality rates noted in our study are comparable to randomized trials of CF-LVAD as well as prior studies evaluating ICD therapies in LVADs.[1,2,6,19,20]

VAs are commonly seen following LVAD implantation, with the incidence ranging from 24% to 52%.[2,13,21,22] Multiple mechanisms contribute but delayed incidence of VAs is mostly secondary to pre-existing substrate combined with a lack of favorable remodeling from the LVADs.[23,24] Sustained VAs are well tolerated by the LVAD-supported LV, but prolonged duration of VAs can result in right ventricular dysfunction and right heart failure, which can contribute to worse outcomes in LVAD patients.[25,26] Therefore, it is common practice to continue ICD therapies following CF-LVAD implantation and is supported by the 2013 mechanical circulatory support guidelines from the International Society of Heart and Lung Transplant.[8] Data regarding the impact of ICD therapy on survival in LVAD recipients, however, have been conflicting. Two recent meta-analyses of available observational studies show no significant survival benefit for ICD therapy in CF-LVAD recipients.[27,28] Our data also did not show any significant independent association between the type of cardiac

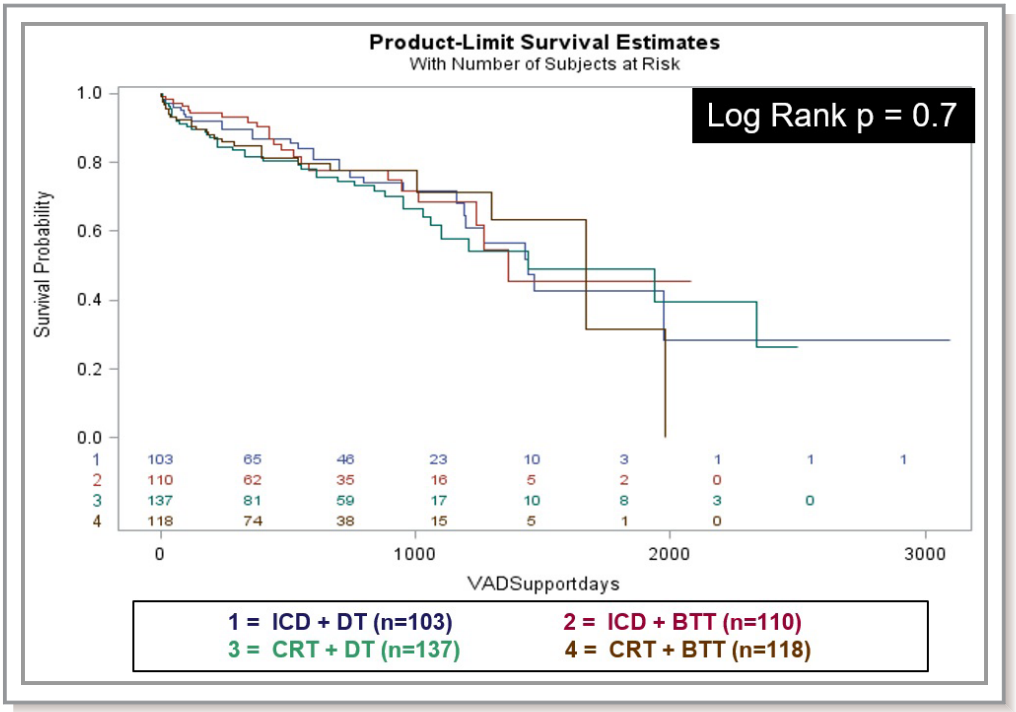

Figure 3. Kaplan–Meier analysis showing all-cause survival stratified by LVAD indication (bridge-to-transplant vs destination therapy). The log-rank test was used to assess differences in survival estimates between groups. BTT indicates bridge-to-transplant; CRT, cardiac resynchronization therapy; DT, destination therapy; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device.

implantable electronic device (ICD versus CRT) and survival. Randomized trials are clearly needed to assess this further.

Incidence of VA (defined as sustained ventricular tachyarrhythmias lasting >30 s or requiring ICD therapy) and ICD shocks following CF-LVAD implantation in our study was comparable to the previous studies evaluating this.[6,21,22,27,29] However, in contrast to the prior study from Schleifer et al,[14] we did not observe any significant reduction in the incidence of VA or ICD shocks in the CRT group. Antiarrhythmic drug and β-blocker use during CF-LVAD support were similar in both groups. It is likely that the smaller sample size in the Schleifer et al study (n=39 in the CRT group) resulted in a larger effect size that was not reproducible in a much larger (n=265 in the CRT group), more representative, multicenter cohort.

An interesting finding was the association of amiodarone use at baseline to worse survival. In our multicenter cohort, amiodarone use was common, with ≈35% of the patients taking the drug. Although the exact mechanism(s) of this

Table 3. Adjusted Survival Outcomes Based on Multivariate Cox-Regression Model

Parameter	Hazard Ratio	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Age at implant	1.009	0.987	1.032	0.41
Indication for CF-LVAD implant	0.782	0.486	1.259	0.31
QRS duration	0.995	0.988	1.003	0.24
PR interval	1.000	0.995	1.005	0.98
Pre-LVAD atrial arrhythmia	1.205	0.761	1.909	0.43
Amiodarone	1.772	1.104	2.845	0.018*
Dyslipidemia	0.971	0.569	1.656	0.9
β-Blocker use	0.560	0.309	1.014	0.055
ICD vs CRT	1.469	0.859	2.514	0.16

The type of device (ICD vs CRTD) was not significantly associated with all-cause mortality. Use of amiodarone was significantly associated with adverse survival (hazard ratio 1.77, *P*=0.01).
CF-LVAD indicates continuous flow left ventricular assist device; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.
*Significant *P* value.

Table 4. Differences in Clinical Outcomes Between the ICD and CRT-D Groups During Follow-Up

Variable	CRT-D Group (n=265)	ICD Group (n=223)	*P* Value
Heart transplantation, N (%)	44 (17)	39 (18)	0.53
All-cause hospitalizations, no./100 d	0.46/100 d	0.59/100 d	0.06
HF hospitalizations, no./100 d	0.1/100 days	0.2/100 days	0.9
Post-LVAD AA, N (%)	144 (61)	91 (47)	0.01*
Post-LVAD VA, N (%)	115 (43)	87 (39)	0.3
ICD shocks, N (%)	92 (35)	65 (29)	0.2

AA indicates atrial arrhythmias; CRT-D, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; VA, ventricular arrhythmias.
*Significant *P* value.

association remain unclear, we hypothesize that the following factors may be playing a role:

1. It is possible that those who were taking amiodarone were sicker at baseline. However, analysis of our data showed no significant differences in cardiomyopathy type, LV dimensions, and LVAD indication between those patients who were taking amiodarone at baseline versus those who were not.
2. Unrecognized systemic toxicity as well as drug interactions (especially with warfarin and digoxin) may have played a role, especially in patients without rigorous amiodarone surveillance.

Further studies are clearly needed to better understand the association between amiodarone use and survival in the CF-LVAD population.

Clinical Implications

Overall, our results show no significant additive effect of continued CRT following CF-LVAD implantation on clinical outcomes. Continued CRT was neither antiarrhythmic nor proarrhythmic. We also noted a significantly higher percentage of pulse generator changes in the CRT group during follow-up. Based on our results, it appears reasonable to turn off the LV lead in CRT-D patients following CF-LVAD implant to save battery life and limit frequent pulse generator replacements. This is especially important given the higher risk of infection[30] and periprocedural bleeding associated with procedures in the CF-LVAD population.

Limitations

Our study is limited by its observational, nonrandomized design. Baseline characteristics and duration of follow-up, however, were mostly similar between the ICD and CRT-D groups. The proportion of patients who received CF-LVADs for destination therapy or as bridge-to-transplant were equally represented in the ICD and CRT-D groups. Moreover, the large sample size and multicenter data add validity to the results. In our study, we did not follow a standard protocol for CRT programming. CRT-D group patients were mostly continued

Table 5. Differences in Echocardiographic and Electrocardiographic Parameters as Well as Medication Use Between CRT-D and ICD Groups During Post-LVAD Follow-Up

Post-LVAD Echocardiography	CRT-D Group	ICD Group	*P* Value
Mean left ventricular end-diastolic diameter, cm	6.2±1.4	6.0±1.1	0.12
Mean left ventricular end-systolic diameter, cm	5.6±1.5	5.3±1.2	0.16
LVEF, %	19.8±11.8	20.7±13.7	0.6
ECG parameters			
Mean QRS duration, ms	150.1±27.9	124.6±31	0.001*
Medications, N (%)			
β-Blocker	160 (65)	145 (68)	0.4
Amiodarone	123 (50)	100 (45)	0.5
Digoxin	38 (15)	56 (26)	0.003*

CRT-D, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction.
*Significant *P* values.

on their pre-LVAD biventricular pacing settings, and any programming changes were made on a case-by-case basis at the discretion of the patient's electrophysiologist. It is possible that a standardized CRT programming could have made a difference in outcomes in the CRT group, although no supporting evidence in this regard is available in the LVAD population. No accurate and consistent functional status or quality of life data were available to report. Although no significant difference in survival was noted in the CRT group when stratified by LVAD indication and type of cardiomyopathy, further study is required to identify specific subgroups of patients with CF-LVAD who may benefit from, or conversely be harmed by, continued CRT.

Conclusions

In this large, multicenter CF-LVAD cohort, continued CRT therapy was not associated with improved survival, all-cause and HF hospitalizations, and incidence of VA and ICD therapies, and was related to a significantly higher number of pulse-generator changes during follow-up. Baseline amiodarone use was associated with increased mortality. Our findings support discontinuing biventricular pacing following CF-LVAD implant to preserve battery life and reduce generator replacements. Large, prospective, randomized studies to evaluate the role of CRT on ventricular remodeling and clinical outcomes in CF-LVAD patients are warranted.

Disclosures

Dr Gopinathannair is a consultant and/or speaker for Abbott Medical, American Heart Association, Pfizer, Bristol Myers Squibb, and Zoll Medical. He also serves on the advisory board for HealthTrust PG. Dr Roukoz has served as a consultant for Boston Scientific Corp. Dr Slaughter has received research grant funding from Heartware Inc. and serves on the advisory board for Oregon Heart (no compensation). The remaining authors have no disclosures to report.

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