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Cardiovascular implantable electronic device therapy in patients with left ventricular assist devices: insights from TRAViATA

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ABSTRACT

Background: There is conflicting observational data on the survival benefit cardiac implantable electronic devices (CIED) in patients with LVADs.

Methods: Patients in whom an LVAD was implanted between January 2008 and April 2017 in the multinational Trans-Atlantic Registry on VAD and Transplant (TRAViATA) registry were separated into four groups based on the presence of CIED prior to LVAD implantation: none ($n = 146$), implantable cardiac defibrillator (ICD) ($n = 239$), cardiac resynchronization without defibrillator (CRT-P) ($n = 28$), and CRT with defibrillator (CRT-D) ($n = 111$).

Results: A total of 524 patients (age 52 years ±12, 84.4% male) were followed for 354 (interquartile range: 166–701) days. After multivariable adjustment, there were no differences in survival across the groups. In comparison to no device, only CRT-D was associated with late right ventricular failure (RVF) (hazard ratio 2.85, 95% confidence interval [CI] 1.42–5.72, $p = 0.003$). There was no difference in risk of early RVF across the groups or risk of ICD shocks between those with ICD and CRT-D.

Conclusion: In a multinational registry of patients with LVADs, there were no differences in survival with respect to CIED subtype. However, patients with a pre-existing CRT-D had a higher likelihood of late RVF suggesting significant long-term morbidity in those with devices capable of LV-lead pacing post LVAD implantation.

1. Introduction

Continuous-flow left ventricular assist devices (CF-LVAD), specifically the HeartMate II (HMII) and the HeartWare (HVAD), have led to improvements in mortality and quality of life in those with advanced heart failure. [1,2] However, patients with CF-LVADs are at continued risk for adverse events, including ventricular arrhythmias, hospitalizations, and death. [3] Given the proven effectiveness of implantable

Abbreviations: CF-LVAD, continuous-flow left ventricular assist device; HM, HeartMate II; HVAD, HeartWare ventricular assist device; RVF, right ventricular failure; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; TRAVIATA, Trans-Atlantic registry on VAD and Transplant; CIED, cardiac implantable electronic device.

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cardiac defibrillator (ICD) therapy and cardiac resynchronization therapy (CRT) in select patients with heart failure, clinicians often continue use post LVAD implantation. [4]

However, the benefits of cardiac implantable electronic device (CIED) therapy in patients with a CF-LVAD remain controversial. While several studies involving United States cohorts demonstrated no survival benefit in those with a LVAD and ICD, a recent multicenter European study showed a survival advantage in those with LVAD and defibrillator. [5–7] Limited observational studies on CRT in patients with LVAD have largely showed no survival advantage and no impact on ventricular arrhythmias. [8,9] Despite the lack of clinical trial data, a class I recommendation currently exists per the International Society for Heart and Lung Transplantation (IHSLT) guidelines for reactivating the ICD after LVAD placement, while no guideline recommendations currently exist for CRT management post-LVAD. [10] Given the conflicting results along with the growing number of CIED in patients undergoing LVAD implantation, a focus on potential morbidity, particularly with regard to hemodynamic complications, associated with continued use of CIED in patients with CF-LVAD has not been previously described.

Using data from patients implanted with a CF-LVAD enrolled in the large, international Trans-Atlantic registry on VAD and Transplant (TRAViATA) registry, the aims of this study were to compare survival, early and late right ventricular failure (RVF), symptomatic ventricular arrhythmias, and ICD shocks across groups according to the presence or absence of cardiac implantable electronic device (CIED) therapy.

2. Methods

2.1. Study population

Consecutive patients that received a CF-LVAD enrolled in the TRAViATA registry between January 2008 to April 2017 were included in the analysis and stratified by the presence or absence of CIED prior to LVAD implant: none, ICD, CRT without defibrillator (CRT-P), and CRT with defibrillator (CRT-D). The methods and main findings from the registry have been described previously. [11] Briefly, patients in seven European (EU) hospitals and 3 United States (US) centers participated in the TRAViATA registry. Inclusion criteria consisted of: (1) age $\geq$ 16 years; (2) implantation of either HVAD (HeartWare, Minnesota, MN, US) or Heartmate II (HMII, Abbott, Pleasanton, CA, US); (3) and listing at any point for heart transplant while supported with CF-LVAD. Exclusion consisted of: (1) patients implanted with HeartMate 3 (HM3) device (Abbott Pleasanton, CA, US) as it was still under investigation in the US during the study period; (2) patients in which a biventricular VAD were planned at the time of implantation or total artificial heart; (3) patients never listed for heart transplant; and (4) prior heart transplant before CF-LVAD implantation. Patient selection and post-operative management were left at the discretion of the local investigators. The study was approved by the Institutional Review Board at each respective institution.

2.2. Definitions and outcomes

Data were organized using the Research Electronic Data Capture (REDCap), a secure web-based application for building an online database (www.project-redcap.org) managed by O.Ö.B. from Lund University in Lund, Sweden. University of California, San Diego (US) served as the coordinating center, and while the data were not monitored on-site, both E.A. and M.B. checked fidelity of the data and contacted local investigators for clarifications, if needed.

Primary endpoints assessed were survival to transplant and late RVF. Secondary endpoints included early RVF, symptomatic ventricular arrhythmia and ICD shocks. RVF was based on the INTERMACS definition as characterized by both of the following: 1) documentation of elevated central venous pressure (CVP) > 18 mmHg; and 2) manifestations of elevated CVP including clinical findings of peripheral edema, presence of ascites or palpable hepatomegaly, or worsening hepatic (total bilirubin >2.0 mg/dl) or renal dysfunction (creatinine >2.0 mg/dl). Furthermore, RVF was stratified based on occurrence into early (index hospitalization) and late. Early RVF was defined as either 1) moderate, as defined by need for post-implant intravenous (IV) inotropes and/or vasodilators beyond post-operative day 7; or 2) severe, requiring mechanical circulatory support or death due to RVF. Late RVF was defined as occurring after discharge from index hospitalization and requiring hospitalization for IV diuretics and/or inotropes for documented RVF as described above in those who did not develop early RVF. Symptomatic ventricular arrythmia was defined as clinically documented sustained ventricular arrythmia leading to syncope, cardioversion, or ICD shock. As device interrogation was not available, this diagnosis was obtained via chart review.

2.3. Statistical analysis

Patients were grouped according to presence of CIED: none, ICD, CRT-pacemaker (CRT-P), and CRT-defibrillator (CRT-D). Continuous variables were expressed as median (interquartile range) and categorical variables as percent. The Kruskal-Wallis and Pearson's Chi-squared tests were used to test differences across CIED categories for continuous and categorical variables, respectively. Survival analyses were completed via the Kaplan-Meier method and log-rank test to compare cumulative incidence curves across CIED categories. Univariate and multivariate Cox-proportional hazards models were used to test the association among CIED type and death before transplant and time to late RVF, after verifying proportionality assumptions. Patients were censored at last known follow-up date or time of transplant. Univariate and multivariate logistic regression were used to test the association among CIED and early RVF, symptomatic ventricular arrhythmia, and ICD shocks. Covariables in the adjusted models were chosen a priori based on prior literature, clinical knowledge, and availability, including age, body mass index, female sex, diabetes, LVAD type, ischemic etiology, INTERMACS profile, creatinine, prior cardiac surgery, prior stroke, tricuspid valve repair and continent (United States [US] vs Europe [EU]). Missing values were minimal (except in the case of the echocardiographic and right heart catheterization parameters) and roughly equivalent between groups for all variables and were thus omitted. For all tests, a p value $\leq$0.05 was considered significant. All statistical analyses were performed using statistical package for social science (SPSS) version 26 (IBM Corp).

3. Results

3.1. Baseline characteristics

Baseline characteristics of the 524 patients enrolled in the TRAViATA cohort are shown in Table 1. Overall, the mean age of the entire population was 52 years ±12, 84.4% were men, and 59.9% were implanted with HMII. Overall, 388/524 (74.0%) patients had a pre-existing CIED prior to LVAD implantation with subtype distribution as follows: no device (N = 146), ICD (N = 239), CRT-P (N = 28), and CRT-D (N = 111). Those with no device were more likely to be anemic, have a lower INTERMACS profile and require temporary mechanical circulatory support (t-MCS). Those with an ICD were more likely to have ischemic cardiomyopathy and tricuspid valve repair at the time of LVAD implantation. Patients with CRT-D were older and more likely to be implanted with HMII LVAD. Invasive hemodynamic (382/524, 72.9%) and echocardiographic measurements (444/524, 84.7%) prior to LVAD implantation were present in a subset of patients. There were no significant differences in invasive hemodynamics across groups. Those with no CIED were more likely to have a smaller LV end diastolic dimension and lower LV ejection fraction.

Table 1
Baseline characteristics.

Variable	No Device ($N = 146$)	ICD ($N = 239$)	CRT-P ($N = 28$)	CRT-D ($N = 111$)	*P*-Value
Age	49.9 (12.6)	52.6 (11.9)	52.6 (12.2)	55.1 (8.8)	0.005
Male	112 (76.7)	204 (85.4)	25 (89.3)	101 (91.0)	0.01
Body mass index (kg/m^2)	25.4 (4.6)	26.5 (5.2)	28.4 (5.3)	25.9 (4.3)	0.01
Race					0.07
Caucasian	111 (76.0)	165 (69.0)	18 (64.3)	89 (89.2)	
African American	14 (9.6)	36 (15.1)	4 (14.3)	5 (4.5)	
Asian	9 (6.2)	11 (4.6)	3 (10.7)	2 (1.8)	
Other	12 (8.2)	11 (4.6)	3 (10.7)	2 (1.8)	
Location					<0.001
United States	52 (35.6)	120 (50.2)	19 (67.9)	34 (30.6)	
Europe	94 (64.4)	119 (49.8)	9 (32.1)	77 (69.4)	
Ischemic cardiomyopathy	84 (57.5)	94 (39.3)	7 (18.4)	43 (38.7)	<0.001
Diabetes	27 (18.5)	70 (29.3)	7 (18.4)	27 (24.3)	0.13
Atrial Fibrillation					<0.001
Paroxysmal	18 (12.3)	48 (20.1)	6 (21.4)	26 (23.4)	
Persistent	6 (4.1)	16 (6.7)	3 (10.7)	5 (4.5)	
Permanent	1 (0.7)	16 (6.7)	1 (3.6)	16 (14.4)	
Prior gastrointestinal bleed	2 (1.4)	13 (5.4)	1 (2.6)	8 (7.2)	0.13
Prior stroke	11 (7.5)	30 (12.6)	1 (2.6)	13 (11.7)	0.26
Prior cardiac surgery	22 (15.1)	35 (14.6)	3 (7.9)	23 (22.7)	0.41
INTERMACS profile ≤2	105 (71.9)	84 (35.1)	13 (46.4)	37 (33.3)	<0.001
Prior home Inotrope	10 (6.8)	56 (23.4)	4 (14.3)	24 (21.6)	<0.001
Laboratory Results and Medications					
Creatinine, mg/dl	1.2 (0.9–1.6)	1.2 (1.0–1.7)	1.4 (1.2–1.7)	1.3 (1.0–1.7)	0.55
Bilirubin, mg/dl	1.1 (0.7–1.5)	1.1 (0.7–1.8)	1.2 (0.6–1.8)	1.0 (0.6–1.5)	0.90
INR	1.2 (1.1–1.4)	1.3 (1.1–1.6)	1.2 (1.0–1.5)	1.4 (1.2–1.7)	0.011
Hemoglobin, g/dl	10.6 (9.2–12.4)	12.0 (10.4–13.0)	12.1 (9.5–13.0)	11.9 (10.6–13.4)	0.001
ACEi/ARB at admission	54 (37.0)	137 (57.3)	16 (42.1)	73 (65.8)	<0.001
Beta blocker at admission	52 (35.6)	161 (67.4)	25 (65.8)	81 (80.0)	<0.001
Minerolocorticoid receptor antagonist at admission	38 (26.0)	147 (61.5)	19 (50.0)	81 (73.0)	<0.001
ACEi/ARB at 6 months	45 (30.8)	90 (37.7)	14 (50.0)	48 (43.2)	0.46
Beta blocker at 6 months	42 (28.8)	120 (50.2)	13 (46.4)	64 (57.7)	0.72
Minerolocorticoid receptor antagonist at 6 months	41 (28.0)	87 (36.4)	11 (39.2)	37 (33.3)	0.51
Procedural Information					
Left ventricular assist device type					0.75
HeartWare	54 (37.0)	101 (42.3)	12 (42.9)	43 (38.7)	
Heartmate II	92 (63.0)	138 (57.7)	16 (57.1)	68 (61.3)	
Tricuspid valve repair	5 (3.4)	30 (12.6)	2 (7.1)	7 (6.3)	0.01
Need for temporary mechanical circulatory support					
Intra-aortic balloon pump	31 (21.2)	21 (8.8)	5 (13.2)	22 (19.8)	0.003
Impella	6 (4.1)	6 (2.5)	1 (2.6)	2 (1.8)	0.70
ECMO	32 (21.9)	11 (4.6)	2 (5.3)	3 (2.7)	<0.001
Bridge to transplantation	142 (97.3)	226 (94.6)	28 (100)	105 (94.6)	0.37
Invasive Hemodynamic and Echocardiographic Measurements Pre-LVAD					
Right heart catheterization	***N* = 68**	***N* = 198**	**N = 23**	***N* = 93**	
Right atrial pressure, mmHg	11 (7–16)	10 (6–15)	11 (6–15)	10 (6–13)	0.30
Pulmonary arterial pressure, mean	33 (27–39)	36 (29–43)	34 (23–43)	36 (30–43)	0.13
Post capillary wedge pressure, mmHg	25 (20–29)	25 (20−31)	26 (17–30)	25 (21−31)	0.73
Cardiac index, L/min/m^2	1.9 (1.5–2.3)	1.8 (1.5–2.2)	2.0 (1.8–2.3)	1.7 (1.4–2.0)	0.54
Pulmonary vascular resistance, WU	2.4 (1.4–3.4)	2.9 (1.8–4.6)	2.0 (1.1–3.5)	3.1 (2.0–4.2)	0.15
Echocardiogram	***N* = 106**	***N* = 215**	**N = 23**	***N* = 100**	
Left ventricular end diastolic dimension, cm	6.2 (5.5–7.1)	7.0 (6.2–7.6)	7.2 (6.8–8.1)	7.1 (6.4–7.9)	<0.001
Ejection fraction, %	16 (14–22)	20 (15–25)	15 (11−22)	21 (17–26)	<0.001
Severe tricuspid regurgitation	6 (8.8)	24 (12.1)	2 (8.7)	8 (8.6)	0.01
Severe aortic regurgitation	1 (1.5)	2 (1.0)	1 (4.3)	1 (1.1)	0.11
Severe mitral regurgitation	16 (23.5)	50 (25.3)	3 (13.0)	21 (22.6)	0.27

Abbreviations: ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ECMO, extracorporeal membrane oxygenation.

3.2. Outcomes

3.2.1. Primary endpoints

Overall median follow-up was 354 days (Q1-Q3: 166–701). A total of 113 deaths occurred prior to transplant during the follow-up period: 29/146 (19.9%) in those with no device, 58/239 (24.3%) in ICD, 3/28 (10.7%) in CRT-P, and 23/111 (20.7%) in CRT-D. A total of 312 transplants occurred during the follow-up period: 93/146 (63.7%) in those with no device, 130/239 (54.4%) in ICD, 19/29 (67.9%) in CRT-P, and 70/111 (63.1%) in CRT-D. Kaplan-Meier analysis showed no significant difference across the groups (log-rank $p = 0.83$), as shown in Fig. 1A. Adjusted survival outcomes based on Cox regression analysis similarly showed that type of CIED vs no device was not associated with death prior to transplant (Fig. 2A).

A total of 72 patients developed late RVF at a median of 189 days (Q1-Q3: 72–364): 16/146 (11.0%) in those with no device, 29/239 (12.1%) in ICD, 1/28 (3.6%) in CRT-P, and 26/111 (23.4%) in CRT-D. Kaplan-Meier analysis showed a higher incidence of late RVF in CRT-D as compared to other the other groups (log-rank = 0.02) (Fig. 1B). Compared to no device, CRT-D was associated with nearly a three-fold increase in late RVF (HR 2.85, 95% CI 1.42–5.72, $p = 0.003$) after adjustment. In contrast, there was no difference in risk of late RVF in ICD

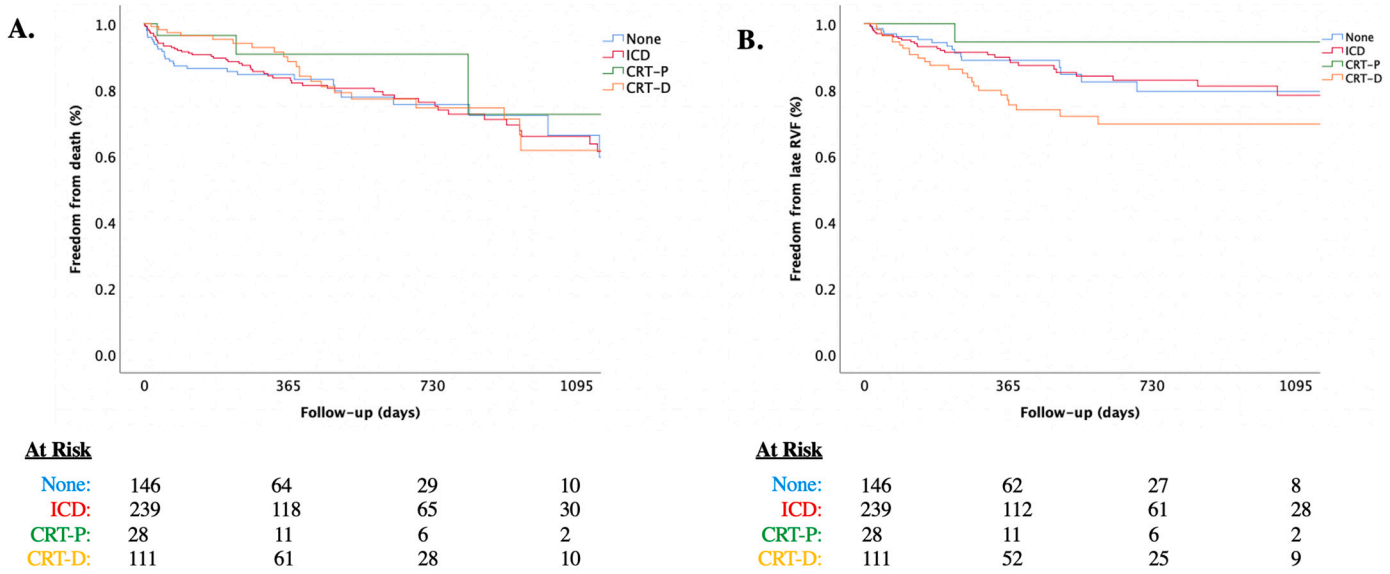

Fig. 1. Kaplan-Meier estimates for the cumulative incidence of **A.)** mortality and **B.)** late right ventricular failure as stratified by the presence or absence of cardiac implantable electronic device.
Captions: Log-rank *p* values; **A.)** 0.83 **B.)** 0.02.

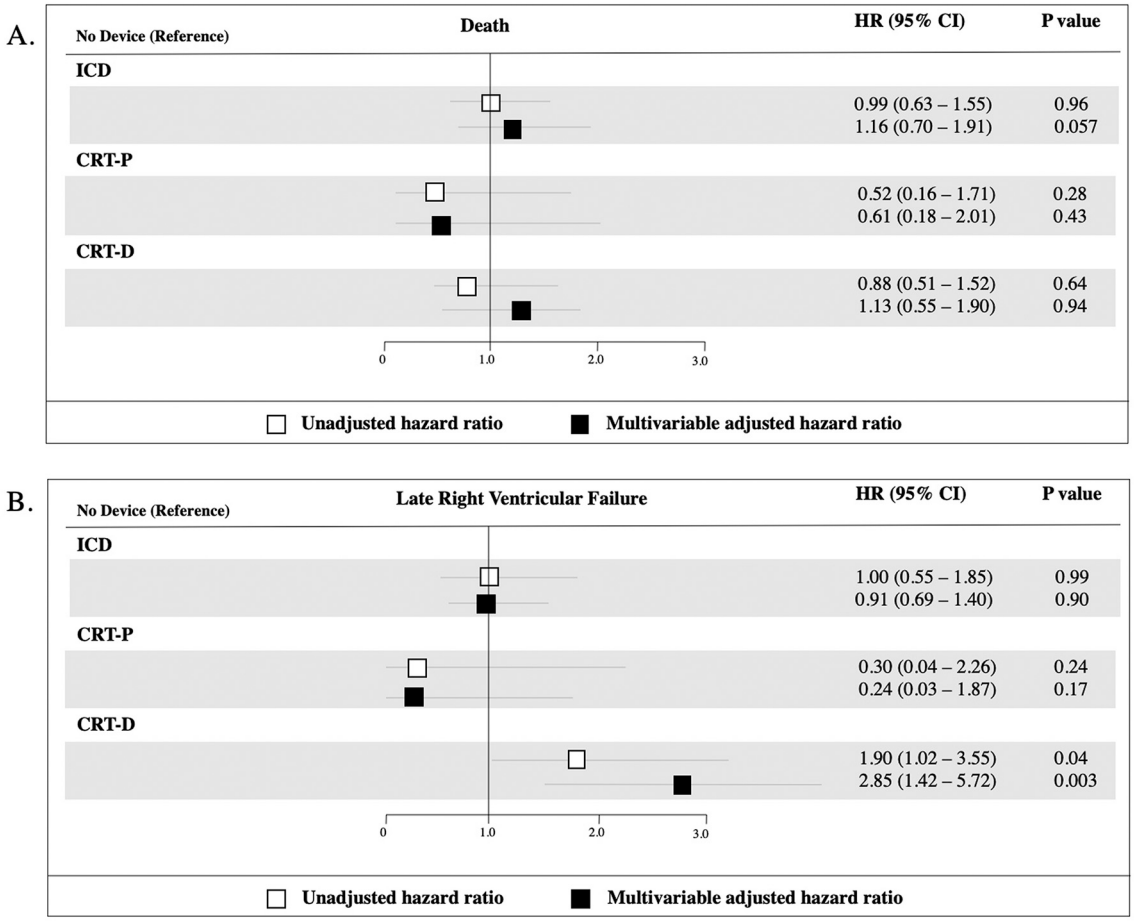

Fig. 2. Unadjusted and adjusted Cox regression models for primary endpoints as stratified by cardiac implantable electronic device, **A.)** Death and **B.)** late right ventricular failure.

and CRT-P as compared to no device (Fig. 2B). When stratified by LVAD type, CRT-D in patients with HVAD was associated with nearly a 5-fold increase in late RVF after adjustment (HR 4.73, 95% CI 1.71–13.1, p = 0.003), while no significant association with late RVF was observed across the groups in patients with HM2 (HR 1.41, 95% CI (0.49–4.06), *p* = 0.52). Furthermore, when stratified by continent, a nonsignificant

trend was observed with increased risk of late RVF in the United States in CRT-D (HR 2.31, 95% CI 0.96–5.53, $p = 0.06$), while no significant association with late RVF was observed in the European cohort (HR 1.71, 95% CI 0.46–6.42, $p = 0.43$).

3.2.2. Secondary endpoints

Early RVF occurred in 205 patients: 57/146 (39.0%) in those without a device, 96/239 (40.2%) in ICD, 11/28 (39.3%) in CRT-P, and 41/110 (37.3%) in CRT-D. After multivariable logistic regression, there were no differences in early RVF across CIED subtypes compared to no device (ICD: odds ratio [OR] 1.11, 95% confidence interval [CI] 0.67–1.85, $p = 0.7$; CRT-P: OR 0.95, 95% CI 0.37–2.41, $p = 0.9$; and CRT-D: OR 1.09, 95% CI 0.56–1.90, p = 0.9). A total of 109 (20.8%) patients experienced symptomatic VT and 73 (20.8% of those with a defibrillator device) patients experienced an ICD shock. There was over a three-fold and nearly five-fold higher likelihood of experiencing symptomatic VT in those with an ICD and CRT-D, respectively, when compared to no device. However, when compared to those with an ICD, patients with a CRT-D had no significant difference in experiencing ICD shocks (Table 2).

3.3. Sub-analysis: CIED with defibrillator vs no-defibrillator and CRT vs no-CRT

To further evaluate the independent association of defibrillator and CRT on long-term outcomes, the cohort was grouped by presence of defibrillator (CIED-D, including ICD and CRT-D) vs none ($N = 350$ and $N = 174$, respectively) and CRT (including CRT-D and CRT-P) vs none (N = 350 and $N = 179$, respectively). After multivariable adjustment, there were no differences in death for both groups. Lastly, presence of ICD was not associated with late RVF; however, the presence of CRT was associated with late RVF after adjustment (Fig. 3).

4. Discussion

Using a large, multicenter international registry we have demonstrated several key findings to advance our understanding of CIED therapy in patients with a CF-LVAD. First, there were no differences in mortality or rate of transplant with respect to the presence or absence of CIED. These findings remained when patients were grouped into CIED with defibrillator vs. without defibrillator and CRT vs. no-CRT. Secondly, there were no differences among CIED subtypes with early RVF, however only CRT-D was associated with a nearly three-fold increased risk of late RVF. Lastly, there was a higher likelihood of symptomatic VT in patients with CRT-D than ICD when compared to no device, although there was no difference in ICD shocks when CRT-D and ICD were compared. Taken together, these results suggest lack of mortality benefit with CIED and potential increased morbidity in those with CRT and CF-LVAD.

Table 2
Association of presence and absence of CIED and outcomes using logistic regression.

Outcomes	Groups	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Early right ventricular failure	None	Ref	–	Ref	–
	ICD	1.05 (0.69–1.60)	0.83	1.11 (0.67–1.95)	0.70
	CRT-P	0.44–2.31	0.98	0.95 (0.37–2.41)	0.90
	CRT-D	0.93 (0.56–1.55)	0.77	1.09 (0.56–1.90)	0.89
Symptomatic ventricular arrhythmia	None	Ref	–	Ref	–
	ICD	3.43 (1.78–6.66)	<0.001	3.22 (1.56–6.65)	0.002
	CRT-P	2.48 (0.79–6.66)	0.12	1.68 (0.51–5.64)	0.40
	CRT-D	5.03 (2.46–10.27)	<0.001	4.63 (2.12–10.11)	<0.001
ICD Shocks	ICD	Ref	–	Ref	–
	CRT-D	1.45 (0.85–2.49)	0.17	1.54 (0.85–2.78)	0.16

Abbreviations: HR, hazards ratio; CI, confidence interval.
Caption: Covariables in the adjusted model: age, BMI, male, diabetes, LVAD, ischemic etiology, INTERMACS profile, creatinine, prior cardiac surgery, prior stroke, tricuspid valve repair and continent.

Ventricular arrhythmias remain common after LVAD implantation, yet there remains uncertainty on the use of continued defibrillator in patients with an LVAD in the absence of randomized-controlled trials. [3] In a recent retrospective multicenter European study from the PCHF-VAD registry involving 448 patients with 54% with pre-existing defibrillator, contrasting results to the present data were reported showing a survival advantage in those patients with a CIED-D vs no defibrillator (HR 0.65, 95% CI 0.46–0.91, $p = 0.012$) [7]. However, there were several differences in the methodology as compared to the TRAViATA registry: the PCHF-VAD registry also included patients with LVADs as destination therapy and HeartMate 3 devices; and the outcome analysis was performed using a time-varying analysis, thus accounting only for CIEDs active during ongoing LVAD support. It is also important to note our cohort differs based on inclusion of US centers and a higher prevalence of CIED use prior to LVAD (74% with CIED, 67% with defibrillator), closer in line with prior studies with approximately 80% of LVAD recipients with ICD in the US [12]. Yet, this finding remained after stratification of our cohort into US and Europe cohorts (CIED-D vs no-defibrillator; Europe: OR 0.63, 95% 0.28–1.42, $p = 0.26$; US: OR 0.48, 95% CI 0.12–2.01, $p = 0.32$). While these conflicting results may suggest a more selective process for defibrillator placement in Europe in those that may benefit, it may also be influenced by other competing factors in those with a defibrillator, such as a more chronic and stable course allowing continuation of beta blocker therapy to suppress ventricular arrhythmias.

Our data supports the majority of increasing observational data, predominately from US centers, showing no survival advantage with continued ICD therapy [10]. In a meta-analysis of 937 patients from 6 retrospective observational studies from 2009 to 2015 consisting of both pulsatile and CF-LVAD, there was a significant 39% relative risk reduction in mortality in those with as compared to without ICD. However, no significant reduction was found when limited to CF-LVADs. [13] Other single-center, contemporary studies involving CF-LVAD have similarly shown no mortality reduction in the presence of an ICD [12,14]. Still, ventricular arrhythmias in the LVAD population represent a significant risk factor for mortality [15]. Whether ventricular arrhythmia post-LVAD is a marker of a sicker population or a modifiable risk factor with ICD therapy is unknown in the absence of randomized data.

The clinical benefit of CRT has been firmly established in preventing hospitalizations, improving symptoms, and reducing mortality in ambulatory HF patients; however, approximately one-third of patients are considered non-responders [4,16]. Similar to ICD therapy, many patients with pre-existing CRT continue biventricular pacing post LVAD implantation with no supporting mortality benefit in a group that may already be considered non-responders. In 488 patients with a CF-LVAD, Gopinathannair et al. demonstrated no difference in mortality, hospitalization, ventricular arrhythmias or ICD therapies in those with CRT-D as compared to ICD [8]. The present study confirms these previous findings suggesting no survival advantage of CRT in CF-LVAD. The LV unloading provided by the LVAD may overcome any potential benefit from CRT, thus awareness should be aimed toward potential morbidity associated with continued use.

Previous studies have shown CRT-D is associated with no difference or decreased risk of ventricular arrhythmias compared to those with an ICD or LV lead programmed off. In a recent randomized crossover study of 30 patients with an LVAD and CRT, patients were alternated on RV

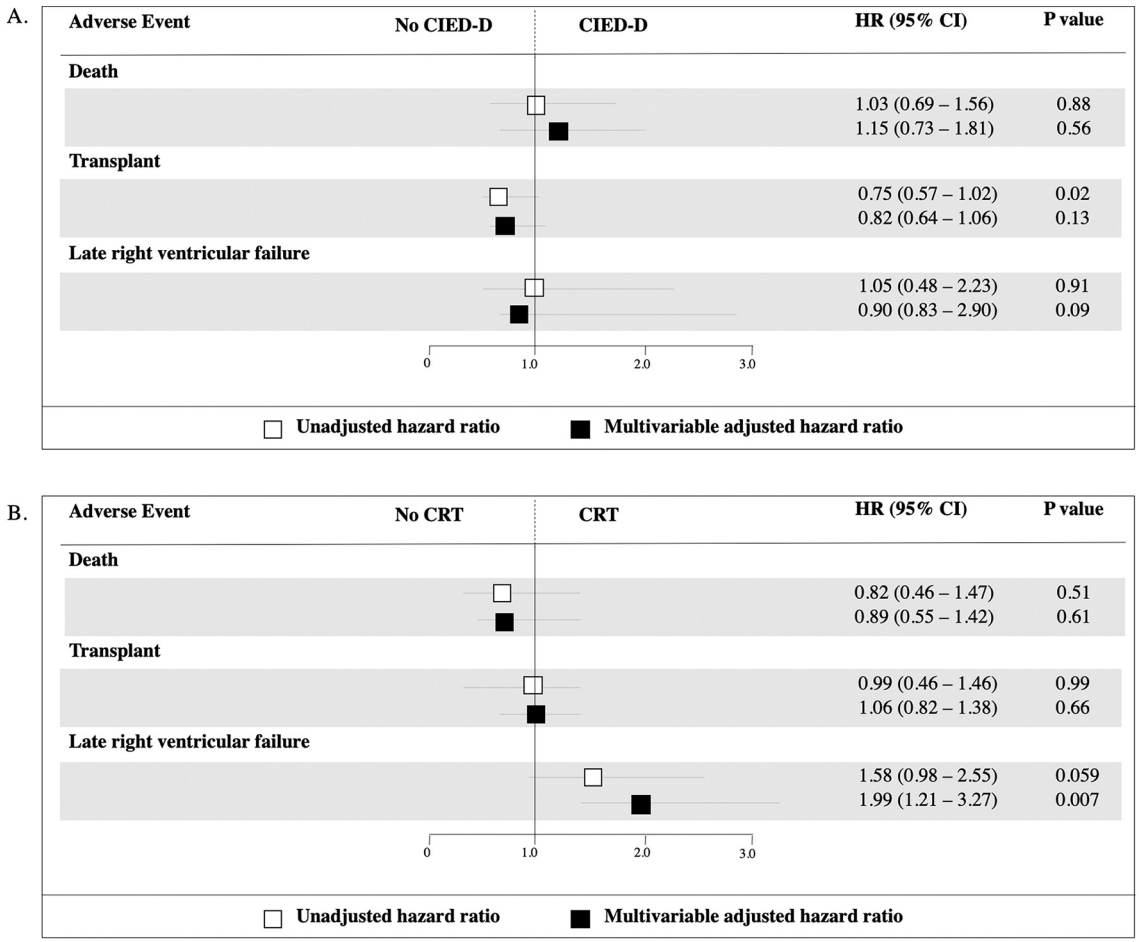

Fig. 3. Unadjusted and adjusted Cox regression models for primary endpoints as stratified by **A.)** Combined defibrillator vs no defibrillator **B.)** combined cardiac resynchronization vs no cardiac resynchronization therapy.

and biventricular pacing for 7–14 day periods [17]. In addition to improved functional status and quality of life, the investigators also demonstrated fewer ventricular tachyarrhythmias in the RV pacing as compared to biventricular pacing group (13% vs 30%, respectively, $p = 0.03$). We similarly describe a possible proarrhythmic effect with CRT-D. [8,9,18] It is important to note that ventricular arrhythmias are often tolerated in patients with an LVAD, therefore our analysis focused on clinically significant arrhythmias that lead to syncope, cardioversion, or ICD shocks [19]. While we demonstrated a higher overall risk of symptomatic ventricular arrhythmias in those with CRT-D than ICD as compared to no device, there was no difference in ICD shocks between CRT-D. Nevertheless, the higher overall risk of ventricular arrhythmias in those with CRT-D may reflect an overall sicker population not accounted for in the adjusted model, however plausible mechanisms may account for the proarrhythmic effect of CRT by altering the myocardial substrate LVAD population. Some studies have suggested that CRT, especially in non-responders, may potentially promote ventricular arrhythmias through increasing transmural dispersion of repolarization [20]. Following LVAD implantation, those with prolonged repolarization have been similarly shown to be at higher risk of ventricular arrhythmia [21]. As those with LVADs may be considered CRT non-responders by default, an unintended increase in repolarization dispersion caused by continued CRT may overtime lead to frequent ventricular arrhythmias.

The novel finding from the present study was the association with late RVF in those with CRT-D. Furthermore, this association remained when evaluating patients with CRT vs no CRT and not observed in ICD vs no ICD, further strengthening the independent role of CRT on late RVF. Affecting approximately 10% of LVAD recipients, late RVF is associated with frequent hospitalization, poorer quality of life, and worse survival than those without late RVF [22,23]. Although our study is not equipped to identify underlying mechanisms of late RVF, we hypothesize that the improved ventricular synchrony with biventricular pacing could paradoxically lead to increased suction events, dynamic obstruction, ventricular arrhythmias, and RVF, as the mechanical desynchrony and abnormal septal motion caused by the LVAD may be needed to prevent these adverse events [19]. Also, when the analysis was separated by VAD type, only those with an HVAD were at risk of late RVF, a finding that concurs with trial data demonstrating increased RVF in those HVAD [2]. As our overall model adjusted for LVAD type, this may suggest that CRT amplifies the risk of RVF in those with HVAD. Lastly, although an association with late RVF was not observed in those with CRT-P, it may suggest an important influence of the combined defibrillator on late RVF. Importantly, the small sample size and low number of events in this group limits adequate comparisons.

4.1. Study limitations

The present study must be interpreted in the context of several limitations. First, as a retrospective observational study, causality cannot be assumed, and these results should be interpreted as hypothesis-generating. Secondly, there is potential for selection bias as CIED therapy was not randomized and the reason for device implantation was unknown. To strengthen our findings, we performed separate analyses grouping all patients with a defibrillator (ICD and CRT-D) vs no defibrillator and all patients with CRT (CRT-P and CRT-D) vs no CRT

that demonstrated similar outcome observations as compared to predetermined CIED grouping analysis. Also, 12 patients with no device prior to LVAD received an ICD post-VAD. However, after exclusion of these patients in the outcome analyses, the results did not differ. Thirdly, CIED programming and interrogation data were not available. Therefore, information such as appropriate defibrillation, percentage of biventricular pacing, programming changes in the follow-up period, or if those with a CRT had an active LV lead were not available. Importantly, none of the centers included in our registry have adopted a policy to deactivate LV leads. Fourth, LVAD settings in the peri- and postoperative period and in follow-up were not captured in the registry. It remains unknown if LVAD settings contributed to late RVF in those with CRT-D. Fifth, we excluded patients with Heartmate 3 as it was still under investigation during the registry creation. Furthermore, we have excluded those with LVAD implanted as destination therapy, and important subgroup that warrants further investigation, particularly as the group may be at higher risk of long-term events, such as late RVF. Lastly, the multivariable models were adjusted for available risk factors based on prior literature and availability within the dataset. While additional factors may influence risk-relationships, such as invasive hemodynamic and echocardiographic parameters, these observations still inform the association between CIED and risk of adverse events in a large cohort of patients with an LVAD.

5. Conclusion

In patients with CF-LVAD awaiting transplant in a large, international cohort, CIED therapy was not associated with improved survival, however only those with CRT-D were at risk of late RVF. A prospective randomized study is needed to determine the role of continued ICD therapy on outcomes and if deactivating the LV lead in patients with pre-existing CRT will mitigate the risk of late RVF in patients with an LVAD.

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