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RESEARCH ARTICLE

Cardiac implantable electronic devices with a defibrillator component and all-cause mortality in left ventricular assist device carriers: results from the PCHF-VAD registry

Maja Cikes[1]*, Nina Jakus[1], Brian Claggett[2], Jasper J. Brugts[3], Philippe Timmermans[4], Anne-Catherine Pouleur[5,6], Pawel Rubis[7], Emeline M. Van Craenenbroeck[8], Edvinas Gaizauskas[9], Sebastian Grundmann[10], Stefania Paolillo[11], Eduardo Barge-Caballero[12], Domenico D'Amario[13], Aggeliki Gkouziouta[14], Ivo Planinc[1], Jesse F. Veenis[3], Luc-Marie Jacquet[5,6], Laura Houard[5,6], Katarzyna Holcman[7], Arno Gigase[8], Filip Rega[4], Kestutis Rucinskas[9], Stamatios Adamopoulos[14], Piergiuseppe Agostoni[15], Bojan Biocina[16], Hrvoje Gasparovic[16], Lars H. Lund[17], Andreas J. Flammer[18], Marco Metra[19], Davor Milicic[1], and Frank Ruschitzka[18], on behalf of the PCHF-VAD registry

[1]Department of Cardiovascular Diseases, University of Zagreb School of Medicine and University Hospital Centre Zagreb, Zagreb, Croatia; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [4]University Hospital Leuven, Leuven, Belgium; [5]Division of Cardiology, Department of Cardiovascular Diseases, Cliniques Universitaires St. Luc, Brussels, Belgium; [6]Pôle de Recherche Cardiovasculaire (CARD) Institut de Recherche Expérimentale et Clinique (IREC) Université Catholique de Louvain, Louvain, Belgium; [7]Department of Cardiac and Vascular Diseases Krakow, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland; [8]Antwerp University Hospital, Antwerp, Belgium; [9]Clinic of Cardiac and Vascular Diseases, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [10]Faculty of Medicine, Heart Center Freiburg University, University of Freiburg, Freiburg, Germany; [11]Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy; [12]INIBIC, CIBERCV, Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain; [13]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [14]Onassis Cardiac Surgery Centre, Athens, Greece; [15]Centro Cardiologico Monzino IRCCS, Milan, Italy; [16]Department of Cardiac Surgery, University of Zagreb School of Medicine, Zagreb, Croatia; [17]Department of Medicine, Karolinska Institute, Stockholm, Sweden; [18]Clinic for Cardiology, University Hospital Zurich, Zurich, Switzerland; and [19]Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

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Aims To compare characteristics of left ventricular assist device (LVAD) recipients receiving a cardiac implantable electronic device (CIED) with a defibrillator component (implantable cardioverter-defibrillator and cardiac resynchronization therapy with defibrillation, CIED-D) vs. those without one, and to assess whether carrying such a device contiguously with an LVAD is associated with outcomes.

Methods and results Overall, 448 patients were analysed (mean age 52 ± 13 years, 82% male) in the multicentre European PCHF-VAD registry. To account for all active CIED-Ds during ongoing LVAD treatment, outcome analyses were performed by a time-varying analysis with active CIED-D status post-LVAD as the time-varying covariate. At the time of LVAD implantation, 235 patients (52%) had an active CIED-D. Median time on LVAD support was 1.1 years (interquartile range 0.5–2.0 years). A reduction of 36% in the risk of all-cause mortality was observed in patients with an active CIED-D [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.46–0.91; $P = 0.012$), increasing to 41% after

*Corresponding author. Department of Cardiovascular Diseases, University Hospital Centre Zagreb Kispaticeva 12, 10000 Zagreb, Croatia Tel: +385 1 2367 467, Fax: +385 1 2367 512, Email: maja.cikes@gmail.com

adjustment for baseline covariates (HR 0.59, 95% CI 0.40–0.87; $P = 0.008$) and 39% after propensity score adjustment (HR 0.61, 95% CI 0.39–0.94; $P = 0.027$). Other than CIED-D, age, LVAD implant as redo surgery, number of ventricular arrhythmia episodes and use of vasopressors pre-LVAD were remaining significant risk factors of all-cause mortality. Incident ventricular arrhythmias post-LVAD portended a 2.4-fold and 2.6-fold increased risk of all-cause and cardiovascular death, respectively; carrying an active CIED-D remained associated with a 47% and 43% reduction in these events, respectively.

Conclusions In an analysis accounting for all active CIED-Ds, including those implanted during LVAD support, carrying such a device was associated with significantly better survival during LVAD support.

Keywords Advanced heart failure • Left ventricular assist devices • Cardiac implantable electronic device • Implantable cardioverter-defibrillators • Cardiac resynchronization therapy • Ventricular arrhythmia • Mortality

Introduction

It is estimated that patients with advanced heart failure (HF) comprise 1–10% of the entire population of patients with HF, with increasing prevalence paralleling the growth of the HF population and the improvements in available treatments, prolonging survival.[1] Advances in long-term mechanical circulatory support with left ventricular assist devices (LVADs) have significantly improved outcomes in this rapidly expanding population.[2,3] However, several challenges in the clinical management of LVAD recipients remain and several opportunities exist to further optimize patient benefits,[4–6] including combined device therapy with cardiac implantable electronic devices (CIEDs).

Therapies for advanced HF are indicated with progression of the disease beyond adequate symptom management or adequate preservation of end-organ function, despite ongoing and optimised guideline-directed medical and device therapies.[1] For patients with HF with reduced ejection fraction (HFrEF), the guidelines mandate the use of implantable cardioverter-defibrillators (ICD) and, in selected patients, cardiac resynchronization therapy (CRT) devices.[7] Given the progressive nature of the disease, a certain amount of overlap of device-based treatment modalities is encountered – according to the INTERMACS database, 80% of LVAD recipients already have an ICD device *in situ*.[8] On the other hand, patients may receive an LVAD without having a CIED when the LVAD is indicated for an acute HF episode. Although the existing literature on patient outcomes with combined device therapy is growing, the results are conflicting; the majority of the studies were conducted in single-centre patient populations, with few exceptions.[8–15] Importantly, a perspective on the European landscape of combined device therapy in advanced HF is still lacking. The current International Society for Heart and Lung Transplantation (ISHLT) guidelines for mechanical circulatory support provide a class I recommendation for the reactivation of an ICD after LVAD surgery and a class IIa recommendation for ICD placement after LVAD for those without one.[16] However, more conservative strategies have recently been advocated.[17]

We compared characteristics among patients receiving a CIED with a defibrillator component (ICD and CRT-D devices) and those without one in a multicentre European registry of LVAD recipients to assess whether carrying a defibrillator component contiguously with an LVAD, including CIEDs implanted post-LVAD, was associated with improved outcomes.

Methods

Study population

This observational study enrolled patients through a network of 12 European HF tertiary referral centres, stemming from participants and alumni of the Postgraduate Course in Heart Failure (PCHF) of the Heart Failure Association of the European Society of Cardiology and the European Heart Academy, forming the PCHF-VAD registry. Each participating centre acquired the approval of their local institutional/ethics review board for the study protocol and retrospective acquisition of patient data, predominantly with a waiver of informed consent.

Currently, the registry consists of 488 patients who underwent durable ventricular assist device (VAD) implantation for advanced HF and are in regular follow-up by the participating centres. The variables collected in the registry include baseline demographic patient information, baseline device (VAD, ICD, CRT) information, patient physical status and functional class, electrocardiographic and echocardiography data, laboratory findings, right heart catheterisation data, data on medications and therapies as well as VAD and CIED parameters – except for baseline data, all other variables were collected at three time points: prior to VAD implantation, at discharge from VAD implantation, and 6 months after the last device implantation. In order to represent the currently most utilised form of durable mechanical circulatory support and to retain homogeneity of the studied cohort, data were analysed for patients implanted with a continuous-flow LVAD (cf-LVAD) – patients with pulsatile LVADs, right VADs and biventricular assist devices, as well as those with missing ICD/CRT carrier status (including missing implantation/potential inactivation dates) were excluded from the analysis. All cf-LVADs were implanted between 1 December 2006 and 15 April 2018. All-cause death was defined as the primary outcome. The secondary outcomes were cardiovascular mortality, hospitalisation for HF, the occurrence of clinically significant ventricular arrhythmias (VAs) after LVAD implantation (defined as symptomatic arrhythmias and/or arrhythmias leading to CIED therapy delivery, and/or arrhythmias requiring medical intervention), device-related (both LVAD and CIED) infections requiring antibiotic treatment, intracranial bleeding and non-cerebral bleeding events. The

adjudication of outcomes was performed by the teams of the registry centres.

The patient data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools – a secure, web-based application,[18] hosted at the University of Zagreb, School of Medicine, which served as the data coordinating centre.

Statistical analysis

Baseline characteristics are expressed as counts and percentages for categorical variables or as mean ± standard deviation [alternatively, median (25th–75th percentile) for those non-normally distributed] for continuous variables. At baseline, the inter-group differences were based on CIED with an active defibrillator component (CIED-D) carrier status before LVAD implantation and were assessed using the chi-square test or ANOVA (or Kruskal–Wallis test for non-normally distributed variables) for categorical and continuous variables, respectively.

Outcome analyses were performed using the primary endpoint of all-cause death as well as the secondary outcomes. For survival analyses, the time of LVAD implantation was considered as the index date; the time of follow-up was defined as time to last contact, heart transplant, weaning from LVAD or death (whichever came first). In order to include in the analysis all active ICD and CRT-D devices during the time of ongoing LVAD treatment (including those implanted and excluding those inactivated during LVAD support), outcome analyses were performed by a time-varying analysis with active CIED-D carrier status following LVAD implantation as the time-varying covariate to assess the association between active CIED-D carrier status post-LVAD and the occurrence and time course of the primary outcome. The incidence rate was estimated for the primary and secondary endpoints based on the time-varying covariate (active CIED-D carrier post-LVAD), and the hazard ratios (HR) were estimated using the Cox proportional hazards model with the group of patients with no active CIED-D post-LVAD serving as the referent group. A Cox regression model based on a forward stepwise selection process with a significance level of 0.05 and 0.10 for entry and removal thresholds, respectively, was used to test the association of active CIED-D carrier status with 25 baseline covariates (online supplementary *Methods S1*) that significantly differed between the two patient groups at baseline and had less than 30% missing data: age, gender, CIED-D status, heart rate, LVAD type, LVAD intention, INTERMACS class, aetiology of HF, known history of: chronic kidney disease, atrial fibrillation/flutter, VAs; significant VAs pre-LVAD, prior cardiac surgery, concomitant procedure with LVAD implant, type of life support prior to LVAD, diuretic use, beta-blocker use, ivabradine use, mineralocorticoid receptor antagonist use, vasopressor use, ultrafiltration, type of mechanical ventilation, creatinine values, left ventricular internal dimension at end-diastole, and LVAD implant date quartile (*Table 1*).

Additional sensitivity analyses were performed to determine the consistency of the results. A multiple imputation was performed whereby missing data were managed using multiple imputation by chained equations (STATA mi impute chained). Imputation was performed for each variable with 1–30% of missing data; it was based on linear regression using 20 baseline clinical variables and 18 predictor variables and estimated over 30 imputations.[19] Furthermore, in order to additionally adjust for the differences between the patients grouped by CIED-D carrier status prior to LVAD implantation (*Table 1*), we created a propensity score to determine the possibility of having a CIED-D pre-LVAD. The propensity score was calculated using a multivariable logistic regression model including the following variables: ICD/CRT carrier status, age, gender, previous history of hypertension, diabetes, chronic kidney disease, coronary artery disease, myocardial infarction, cerebrovascular accident, atrial fibrillation and VAs; type of LVAD, intention of LVAD treatment, INTERMACS score, LVAD implant as redo surgery and concomitant surgical procedures. This was followed by a propensity score adjusted analysis to assess the relation of CIED-D carrier status and the occurrence of the primary and secondary outcomes. Finally, to control for immediate perioperative deaths, we have utilised the time-varying coefficient to test the interaction between the duration of follow-up and the CIED-D treatment effect at 30 and 90 days following LVAD implantation.

A *P*-value of < 0.05 was considered statistically significant. The statistical analyses were performed in Stata version 14 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

After excluding data from 14 patients with pulsatile LVADs and biventricular assist devices, as well as 26 patients with missing ICD/CRT carrier status (including missing implantation and potential inactivation dates), the analysed population consisted of 448 patients (*Figure 1*). The baseline clinical characteristics were collected prior to LVAD implantation; the patients were thus divided into two groups according to CIED-D status before LVAD implantation: 240 patients (54%) were an CIED-D carrier pre-LVAD, while the remaining 208 patients (46%) did not carry any of these devices pre-LVAD (of note, the discrepancies such as the 20 ICD patients in the non-CIED-D group are those that cross-over during the course of LVAD treatment) (*Figure 1*). Baseline characteristics of the patient population according to CIED-D status pre-LVAD are provided in *Table 1* and in the online supplementary *Table S1*. CIED-D carriers were older and more frequently male compared to those without CIED-D pre-LVAD. Of the patients receiving a CIED-D pre-LVAD, the majority were those implanted with an LVAD in the last quartile of LVAD implantation dates, i.e. from 21 July 2016 onwards (online supplementary *Figure S1*). The predominant disease aetiology was dilated cardiomyopathy in those with CIED-D, while ischaemic cardiomyopathy was more common in the other group. While chronic kidney disease was more represented in CIED-D carriers, other co-morbidities such as hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease and prior cerebrovascular accident did not differ significantly between the two groups. Known atrial fibrillation and previous VAs (defined as those requiring ICD therapy or external defibrillation prior to LVAD implantation verified in ICD memory or during patient monitoring) were more frequent in the CIED-D pre-LVAD group. Although left ventricular ejection fraction did not differ significantly between groups, patients with CIED-D pre-LVAD had larger left ventricles. Haemodynamic measurements did not reveal a significant difference between groups, nor did their blood pressure values. However, heart rate was significantly higher in those without CIED-D pre-LVAD.

Table 1 Baseline characteristics of the studied patients by CIED-D carrier status prior to left ventricular assist device implantation

	Overall average	No CIED-D pre-LVAD (*n* = 208)	CIED-D pre-LVAD (*n* = 240)	*P*-value
Age, years	52 ± 13	50 ± 14	54 ± 12	<0.001
Female sex	81 (18.1)	46 (22.1)	35 (14.6)	0.039
Geographical area				0.14
Northwest Europe (The Netherlands, Belgium, Germany)	303 (76.6)	148 (71.2) (48.8% of region)	155 (64.6) (51.2% of region)	
Southeast Europe (Croatia, Poland, Lithuania, Italy, Spain, Greece)	145 (32.4)	60 (28.8) (41.4% of region)	85 (35.4) (58.6% of region)	
Quartiles of date of LVAD implant				<0.001
1st quartile (6 Dec 2006–2 Jan 2012)	112 (25)	72 (34.6)	40 (16.7)	
2nd quartile (3 Jan 2012–8 Dec 2014)	112 (25)	62 (29.8)	50 (20.8)	
3rd quartile (9 Dec 2014–20 Jul 2016)	113 (25.2)	48 (23.1)	65 (27.1)	
4th quartile (21 Jul 2016–04 Apr 2018)	111 (24.8)	26 (12.5)	85 (35.4)	
ICD status				<0.001
No ICD	238 (53.1)	188 (90.4)	50 (20.8)	
Primary prevention	153 (34.2)	15 (7.2)	138 (57.5)	
Secondary prevention	57 (12.7)	5 (2.4)	52 (21.7)	
CRT status				<0.001
No CRT	345 (77.0)	188 (90.4)	157 (65.4)	
CRT-P carrier	16 (3.6)	16 (7.7)	0 (0.0)	
CRT-D carrier	87 (19.4)	4 (1.9)	83 (34.6)	
Heart rate, b.p.m.	85 ± 20	93 ± 21	80 ± 17	<0.001
SBP, mmHg	100 ± 15	101 ± 16	100 ± 14	0.71
DBP, mmHg	65 ± 11	65 ± 12	65 ± 10	0.91
BMI, kg/m^2	25.8 ± 4.6	25.3 ± 4.4	26.2 ± 4.8	0.050
NYHA class				0.06
II	15 (3.8)	5 (2.9)	10 (4.5)	
IIIa	132 (33.4)	58 (33.3)	74 (33.5)	
IIIb	105 (26.6)	37 (21.3)	68 (30.8)	
IV	143 (36.2)	74 (42.5)	69 (31.2)	
LVAD type				<0.001
Heart Mate II	246 (54.9)	144 (69.2)	102 (42.5)	
HeartWare HVAD	94 (21.0)	36 (17.3)	58 (24.2)	
Heart Mate 3	87 (19.4)	22 (10.6)	65 (27.1)	
Other	21 (4.7)	6 (2.9)	15 (6.2)	
LVAD intention				<0.001
BTT	305 (71.1)	137 (68.8)	168 (73.0)	
BTD	68 (15.9)	47 (23.6)	21 (9.1)	
DT	56 (13.1)	15 (7.5)	41 (17.8)	
INTERMACS class				<0.001
1	73 (16.7)	55 (27.4)	18 (7.6)	
2	121 (27.7)	63 (31.3)	58 (24.6)	
3	139 (31.8)	47 (23.4)	92 (39.0)	
4–7	104 (23.8)	36 (17.9)	68 (28.8)	
Aetiology of heart failure				<0.001
Dilated cardiomyopathy	190 (42.4)	68 (32.7)	122 (50.8)	
Ischaemic cardiomyopathy	206 (46.0)	104 (50.0)	102 (42.5)	
Other	52 (11.6)	36 (17.3)	16 (6.7)	

Table 1 Continued

	Overall average	No CIED-D pre-LVAD (n = 208)	CIED-D pre-LVAD (n = 240)	P-value
Co-morbidities				
Arterial hypertension	102 (22.8)	47 (22.6)	55 (22.9)	0.94
Diabetes mellitus	90 (20.1)	37 (17.8)	53 (22.1)	0.26
Chronic kidney disease	102 (22.8)	31 (14.9)	71 (29.6)	<0.001
Coronary artery disease	111 (24.8)	52 (25.0)	59 (24.6)	0.92
Prior MI	168 (37.5)	87 (41.8)	81 (33.8)	0.08
Prior coronary revascularization	132 (29.5)	66 (31.7)	66 (27.5)	0.33
COPD	42 (9.4)	14 (6.7)	28 (11.7)	0.07
Atrial fibrillation/flutter	128 (28.6)	31 (14.9)	97 (40.4)	<0.001
Ventricular arrhythmias	102 (22.8)	30 (14.4)	72 (30.0)	<0.001
Cerebrovascular events	33 (7.4)	12 (5.8)	21 (8.8)	0.23
Significant ventricular arrhythmias prior to VAD implant				<0.001
None	245 (66.9)	120 (83.3)	125 (56.3)	
1 episode	58 (15.8)	14 (9.7)	44 (19.8)	
2 episodes	25 (6.8)	5 (3.5)	20 (9.0)	
3 episodes	21 (5.7)	2 (1.4)	19 (8.6)	
≥ 4 episodes	17 (4.6)	3 (2.1)	14 (6.3)	
Prior cardiac surgery	55 (12.3)	33 (15.9)	22 (9.2)	0.031
Concomitant procedure with LVAD implant	79 (17.6)	50 (24.0)	29 (12.1)	<0.001
Life support prior to LVAD implant				<0.001
None	318 (73.6)	112 (56.0)	206 (88.8)	
ECMO	35 (8.1)	30 (15.0)	5 (2.2)	
Temporary LVAD	4 (0.9)	4 (2.0)	0 (0.0)	
Temporary BiVAD	1 (0.2)	1 (0.5)	0 (0.0)	
IABP	55 (12.7)	35 (17.5)	20 (8.6)	
Other	19 (4.4)	18 (9.0)	1 (0.4)	
Medications				
Diuretic	349 (90.6)	130 (79.3)	219 (99.1)	<0.001
Beta blocker	230 (64.1)	64 (43.5)	166 (78.3)	<0.001
ACEi/ARB	183 (49.5)	78 (49.7)	105 (49.3)	0.94
MRA	243 (72.8)	76 (55.9)	167 (84.3)	<0.001
Ivabradine	36 (11.6)	9 (7.1)	27 (14.7)	0.042
Inotrope	232 (65.5)	104 (68.9)	128 (63.1)	0.25
Vasopressor	36 (10.8)	23 (16.8)	13 (6.6)	0.003
Ultrafiltration	12 (3.6)	10 (7.4)	2 (1.0)	0.003
Mechanical ventilation				<0.001
None	310 (92.3)	116 (84.1)	194 (98.0)	
NIV/cPAP	2 (0.6)	2 (1.4)	0 (0.0)	
Intubation	24 (7.1)	20 (14.5)	4 (2.0)	
Laboratory values				
Creatinine, µmol/L	126 ± 57	117 ± 57	133 ± 56	0.004
Bilirubin, µmol/L	19.0 (12.0–30.8)	19.8 (12.0–34.0)	18.8 (12.0–28.0)	0.19
Echocardiographic data				
LVIDd, mm	70.4 ± 12.8	67.4 ± 13.1	72.5 ± 12.2	<0.001
LVEF, %	19 ± 7	19 ± 8	20 ± 7	0.46

Values expressed as mean ± standard deviation, number (%), or median (interquartile range).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BiVAD, biventricular assist device; BMI, body mass index; BTD, bridge to decision; BTT, bridge to transplantation; CIED-D, cardiac implantable electronic device with a defibrillator component; COPD, chronic obstructive pulmonary disease; cPAP, continuous positive airway pressure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator component; CRT-P, cardiac resynchronization therapy with a pacemaker component; DBP, diastolic blood pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; FAC, fractional area change; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVIDd, left ventricular intraventricular dimension in end-diastole; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NIV, non-invasive ventilation; NYHA, New York Heart Association; RVIDd, right ventricular intraventricular dimension in end-diastole; SBP, systolic blood pressure; VAD, ventricular assist device.

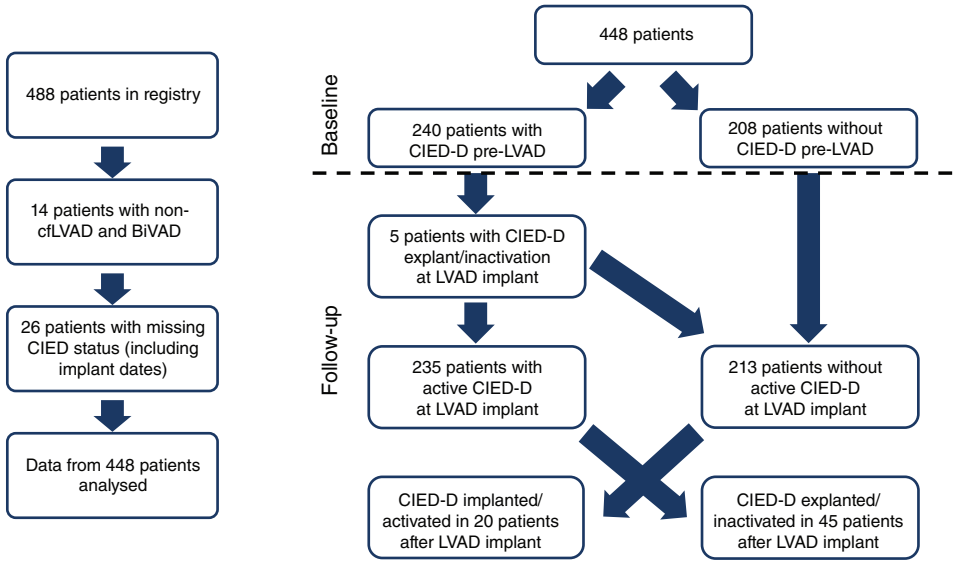

Figure 1 (*Left*) Selection of the study population from the PCHF-VAD registry. (*Right*) Patient flow during the follow-up period in respect to a cardiac implantable electronic device (CIED) with a defibrillator component (CIED-D). BiVAD, biventricular assist device; cfLVAD, continuous-flow left ventricular assist device; LVAD, left ventricular assist device.

The distribution of LVAD types differed significantly: those with CIED-D were more frequently carriers of HeartWare HVAD and HeartMate 3 devices than patients in the other subgroup, where HeartMate II was more common. The proportion with an LVAD as a bridge to decision was higher in those without a CIED-D; these patients were also more frequently in INTERMACS classes 1 and 2, while no significant difference in New York Heart Association (NYHA) class was noted. The proportion of patients on diuretics, beta-blockers and mineralocorticoid receptor antagonists was higher in those with a CIED-D pre-LVAD. A higher proportion of patients without a CIED-D pre-LVAD was treated with vasopressor medications (but not inotropes) and was on life support, predominantly intra-aortic balloon pump and extracorporeal membrane oxygenation. LVAD implantation as redo surgery as well as concomitant surgical procedures were more frequent in this group as well. In the group with CIED-D pre-LVAD, 58% of the patients carrying an ICD received it for primary prevention; 44% of the patients without a CIED-D pre-LVAD and 34% of those with such a device were transplanted (39% of the entire cohort).

Twenty patients received a CIED-D post-LVAD (9.6% of those without a CIED-D pre-VAD), at a median time to CIED-D implant of 57 days [interquartile range (IQR) 29.5–243.5 days, range 0–1068 days]. Forty-five patients (19% of those with a CIED-D pre-VAD) had their ICD or CRT-D device deactivated post-LVAD at a median time of deactivation of 252 days (IQR 77–379 days, range 0–981 days). Of these deactivations, 11 occurred during active LVAD support (median time to deactivation 40 days; IQR 0–368 days, range 0–664 days), while in the remaining 34 patients the deactivation occurred due to heart transplantation, i.e. on the day of transplantation (*Figure 1* and online supplementary *Figure S2*).

All-cause mortality and active CIED-D carrier status following left ventricular assist device implantation

The median time on LVAD support was 1.1 years (IQR 0.5–2.0 years) starting at the time of LVAD implantation (online supplementary *Figure S3*), which was similar in those with active CIED-D carrier status during LVAD support and those without one (median 1.1 years, IQR 0.5–2.0 years; and 1.1 years, IQR 0.4–2.0 years, respectively). At the time of LVAD implantation, 213 patients (48%) did not have a CIED-D and 235 patients (52%) had such a CIED *in situ* and activated (*Figure 1*). The primary outcome of all-cause death occurred in a total of 134 patients (30% of the overall study population). A total of 68 patients remained in the non-CIED-D group and 55 remained in the CIED-D group and suffered from all-cause death. Five patients had the CIED-D deactivated and six entered the CIED-D group before the event. The incidence rates for all-cause death were 28 events per 100 patient-years [95% confidence interval (CI) 22–36 events] and 18 events per 100 patient-years (95% CI 14–23 events) for those without and with a CIED-D after LVAD implant, respectively (*Table 2*). One-year survival in the overall cohort was 80.1%. The rate of all-cause death was the greatest in the first 30 days post-LVAD implant (event rate 7.3% per month; 95% CI 5.2–10.4%), declined between 30 and 90 days (event rate 3.0% per month; 95% CI 2.0–4.5%) and between 90 days and 1 year (event rate 1.3% per month; 95% CI 0.9–1.8%), remaining stable after 1 year (event rate 1.4% per month; 95% CI 1.0–1.9%). In a time-varying analysis, the unadjusted HR demonstrated a 36% reduction in the risk of all-cause mortality in patients with an active CIED-D following LVAD implantation (HR 0.64; 95%

Table 2 **Incidence rates and hazard ratios for the primary endpoint (all-cause death), cardiovascular mortality, heart failure hospitalisation, ventricular arrhythmias post-left ventricular assist device (LVAD), device-related infection requiring systemic antibiotics, non-cerebral and intracranial bleeding by time-updated CIED-D carrier status following LVAD implantation**

	No CIED-D at LVAD implant (n = 213)	CIED-D at LVAD implant (n = 235)	HR (95% CI)	
			Unadjusted	Adjusted[a]
All-cause mortality	28.2	18.1	0.64 (0.46–0.91)	0.59 (0.40–0.87)
(n of events = 134)	(22.4–35.5)	(14.1–23.2)	P = 0.012	P = 0.008
Cardiovascular mortality	16.7	11.9	0.72 (0.46–1.11)	0.65 (0.39–1.07)
(n of events = 83)	(12.4–22.5)	(8.7–16.2)	P = 0.13	P = 0.09
Heart failure hospitalisation	11.9	17.8	1.50 (0.96–2.38)	0.92 (0.56–1.51)
(n of events = 80)	(8.3–17.1)	(13.5–23.4)	P = 0.08	P = 0.74
Ventricular arrhythmias	14.0	31.3	2.20 (1.46–3.34)	1.57 (0.98–2.52)
post-LVAD	(9.9–19.8)	(24.9–39.2)	P < 0.0001	P = 0.06
(n of events = 107)				
Device-related infection requiring	39.1	28.1	0.76 (0.55–1.05)	0.96 (0.66–1.40)
systemic antibiotics	(31.1–49.2)	(22.4–35.2)	P = 0.09	P = 0.84
(n of events = 149)				
Non-cerebral bleeding	19.5	15.5	0.79 (0.52–1.20)	0.64 (0.40–1.03)
(n of events = 88)	(14.5–26.3)	(11.5–20.8)	P = 0.27	P = 0.07
Intracranial bleeding	6.3	4.8	0.75 (0.37–1.52)	0.55 (0.24–1.26)
(n of events = 32)	(3.9–10.3)	(3.0–7.9)	P = 0.42	P = 0.16

The incidence rates are presented as number of events per 100 patient-years (95% CI).
CI, confidence interval; CIED-D, cardiac implantable electronic device with a defibrillator component; HR, hazard ratio.
[a]Adjusted for age, number of ventricular arrhythmia episodes before LVAD implantation, use of vasopressors prior to LVAD implantation, LVAD type and LVAD implant as a redo surgical procedure.

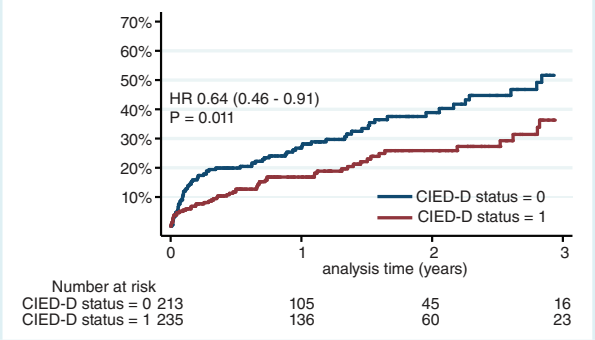

Figure 2 Kaplan–Meier plot of time to all-cause mortality, according to CIED-D carrier status following left ventricular assist device (LVAD) implantation. The analysis time begins at the time of LVAD implantation. CIED-D status 0 stands for no CIED-D present post-LVAD, CIED-D status 1 stands for CIED-D present post-LVAD. CIED-D, cardiac implantable electronic device with a defibrillator component; HR, hazard ratio.

CI 0.46–0.91, P = 0.012) (*Figure 2* and *Table 2*). No significant alteration in the treatment effect after 30 or 90 days following LVAD implantation was found (interaction P = 0.68 and P = 0.07, respectively).

Using stepwise regression, CIED-D carrier status, age, number of VA episodes before LVAD implantation, use of vasopressors prior to LVAD implantation, LVAD type and LVAD implant as a redo surgical procedure were identified as independently significant of all-cause mortality. After adjustment for these variables, the HR for CIED-D post-LVAD status remained significant (0.59, 95% CI 0.40–0.87; P = 0.008). Age, LVAD implant as redo surgery, number of VA episodes pre-LVAD and vasopressor use were the remaining significant predictors of the primary outcome (*Table 3*). Active CIED-D carrier status after LVAD implant remained significant after adding active CRT with a pacemaker component (CRT-P) carrier status post-LVAD implant to the model (HR 0.57, 95% CI 0.38–0.84; P = 0.005) (*Table 3*). Furthermore, the benefit of CIED-D treatment on all-cause mortality remained significant even after excluding patients with a CIED-D placed or deactivated/removed following LVAD implantation, both in unadjusted (HR 0.71, 95% CI 0.50–1.00; P = 0.048) and adjusted analysis (HR 0.63, 95% CI 0.41–0.96; P = 0.030). In a subgroup analysis, the effect of treatment with a CIED-D following LVAD implantation was consistent across various categorical subgroups at baseline (*Figure 3*). Of note, exposure to ultrafiltration at baseline was associated with a significant interaction P-value (0.0044), suggesting a possible interaction effect: CIED-D therapy post-LVAD was associated with a larger benefit in those not undergoing ultrafiltration pre-LVAD implant (HR 0.63, 95% CI 0.42–0.94) compared to those undergoing ultrafiltration (HR 7.76, 95% CI 1.07–56.0), however only five patients in the latter subgroup died during follow-up (hence not shown in the forest plot).

Table 3 Multivariate Cox regression models of risk factors for all-cause death by time-updated CIED-D carrier status following left ventricular assist device implantation

Variable	HR (95% CI)	*P*-value
CIED-D post-LVAD	0.59 (0.40–0.87)	0.008
Age	1.03 (1.02–1.05)	<0.0001
LVAD implant as redo surgery	1.69 (1.09–2.61)	0.019
LVAD type		0.35
Heart Mate II	Referent	
Heart Ware	1.28 (0.81–2.02)	
Heart Mate 3	0.73 (0.39–1.36)	
Other	0.76 (0.33–1.72)	
No. of VA episodes pre-LVAD		0.011
≥4	Referent	
None	0.51 (0.23–1.14)	
1	0.29 (0.11–0.79)	
2	0.75 (0.28–1.97)	
3	0.44 (0.14–1.38)	
Unknown	0.21 (0.08–0.58)	
Vasopressor use pre-LVAD		0.008
Yes	Referent	
No	0.49 (0.28–0.86)	
Unknown	0.89 (0.47–1.70)	
CIED-D post-LVAD	0.57 (0.38–0.84)	0.005
CRT-P post-LVAD	0.62 (0.25–1.59)	0.322
Age	1.03 (1.01–1.05)	<0.0001
LVAD implant as redo surgery	1.74 (1.12–2.71)	0.014
LVAD type		0.349
Heart Mate II	Referent	
Heart Ware	1.27 (0.80–2.00)	
Heart Mate 3	0.73 (0.39–1.36)	
Other	0.73 (0.32–1.66)	
No. of VA episodes pre-VAD		0.011
≥4	Referent	
None	0.51 (0.23–1.16)	
1	0.29 (0.11–0.79)	
2	0.75 (0.28–1.97)	
3	0.48 (0.15–1.50)	
Unknown	0.21 (0.08–0.58)	
Vasopressor use pre-LVAD		0.007
Yes	Referent	
No	0.48 (0.27–0.84)	
Unknown	0.85 (0.45–1.64)	

CI, confidence interval; CIED-D, cardiac implantable electronic device with a defibrillator component; CRT-P, cardiac resynchronization therapy with a pacemaker component; HR, hazard ratio; LVAD, left ventricular assist device; VA, ventricular arrhythmia; VAD, ventricular assist device.

Secondary outcomes and active ICD/CRT-D carrier status following left ventricular assist device implantation

The occurrence of one or more episodes of symptomatic VAs or those requiring intervention was noted in 24% of the entire cohort (107 patients): 30 patients remained in the non-CIED-D group and 73 remained in the CIED-D group and suffered from new-onset VAs, while two patients transitioned from the CIED-D group and two entered the CIED-D group before their event (the incidence rates are provided in *Table 2*). In patients with a CIED-D, a VA episode requiring anti-tachycardia pacing (ATP) occurred in 25 patients (median time to first ATP 231 days; IQR 25–495 days), while 42 patients received a shock (median time to first shock 121 days; IQR 7–231 days); 29% of the CIED-D cohort received at least one of these therapies. None of these patients died on the day of therapy delivery. Patients with a CIED-D post-LVAD had a nominally significant crude increased risk of post-LVAD VAs which was no longer significant after adjusting for the relevant baseline characteristics (HR 1.57, 95% CI 0.98–2.52, $P = 0.06$, adjusted by variable selection for the primary outcome; *Table 2* and online supplementary *Tables S2* and *S3*). We further used stepwise regression to detect variables that are independently significant of the occurrence of VAs post-LVAD. After additional adjustment for these variables, active CIED-D post-LVAD status remained unrelated to the occurrence of this secondary endpoint (online supplementary *Table S2*). An additional analysis of incident VAs post-LVAD as a time-varying covariate demonstrated that the occurrence of such arrhythmias portended a 2.4-fold increased risk of all-cause death and a 2.6-fold increased risk of cardiovascular death, while carrying an active CIED-D remained associated with a significant 47% reduction in all-cause death and 43% reduction in cardiovascular death. LVAD implant as redo surgery, vasopressor use prior to LVAD implant and increasing patient age were significantly associated with both of these outcomes, while the occurrence of VAs pre-LVAD was identified as an additional risk factor for all-cause death (online supplementary *Table S4*).

The incidence rates for cardiovascular mortality, HF hospitalisation, device-related infection requiring systemic antibiotics, as well as extracranial and intracranial bleeding events are presented in *Table 2*. Cardiovascular death occurred in 83 patients: 40 remained in the non-CIED-D group and 36 remained in the CIED-D group and suffered from cardiovascular death, while three patients transitioned from the CIED-D group and four entered the CIED-D group before death from cardiovascular cause. The crude risk for cardiovascular mortality was not modified by CIED-D status, while in the adjusted analysis there was a trend towards a reduction in the risk of cardiovascular death with active CIED-D status (HR 0.65, 95% CI 0.39–1.07; $P = 0.09$) (online supplementary *Tables S3* and *S4*). Both the crude and adjusted risks for the remaining outcomes were not significantly modified by CIED-D post-LVAD (*Table 2* and online supplementary *Table S3*; the full results of the multivariable regression models for the remaining outcomes are provided in the online supplementary *Tables S5* and *S6*).

Sensitivity analyses

In addition to a forward variable selection procedure, we have also performed a backwards selection, according to which CIED-D carrier status, age, disease aetiology, number of VA episodes before LVAD, LVAD type, intention of LVAD therapy, use of vasopressors,

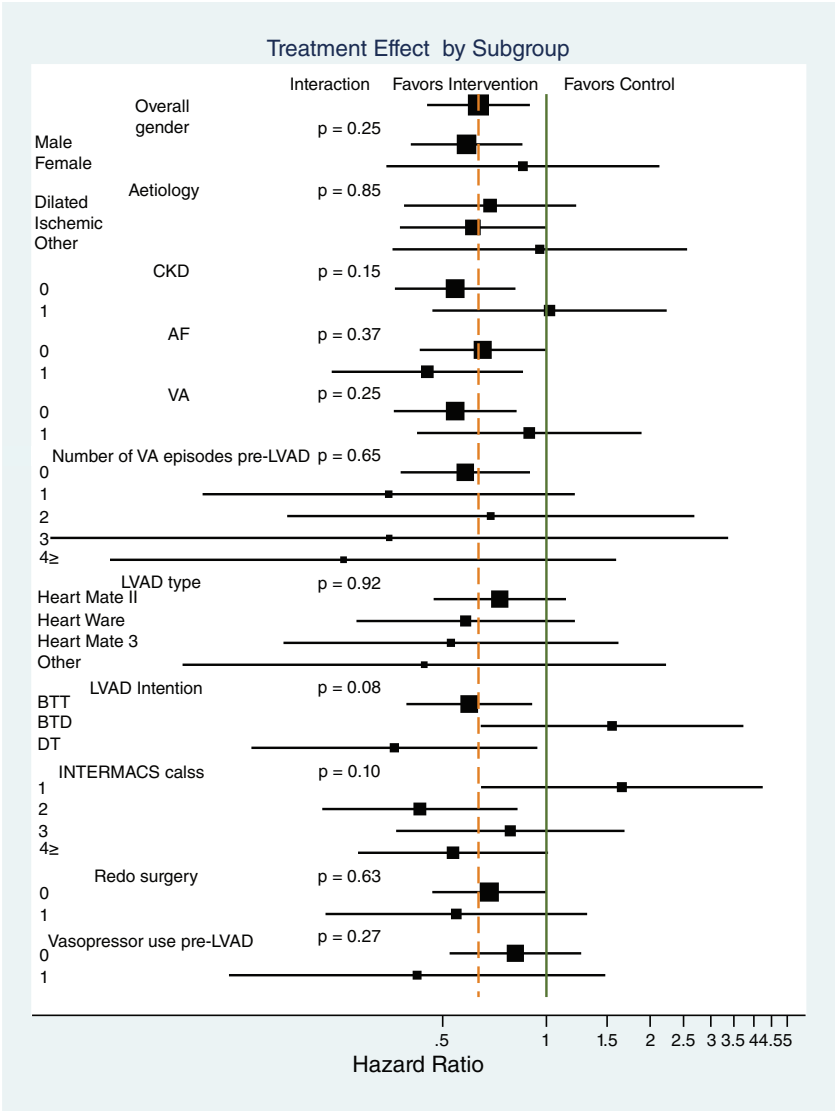

Figure 3 The effect of treatment with a cardiac implantable electronic device with a defibrillator component following left ventricular assist device (LVAD) implantation on all all-cause mortality for individual patient subgroups. 0 stands for absent, 1 for present. AF, atrial fibrillation; BTD, bridge to decision; BTT, bridge to transplant; CKD, chronic kidney disease; DT, destination therapy; VA, ventricular arrhythmia.

use of beta-blockers, type of mechanical ventilation implantation and intention of LVAD therapy were identified as independently significant of all-cause mortality. After adjustment for these variables, the results remained consistent with the primary analysis (HR 0.61, 95% CI 0.40–0.94; $P = 0.024$); the remaining significant predictors of the primary outcome were age (HR per 1 year change in age: 1.04, 95% CI 1.02–1.06; $P < 0.0001$), vasopressor use pre-LVAD ($P = 0.0007$), type of mechanical ventilation pre-LVAD ($P = 0.025$) and number of episodes of VAs pre-LVAD ($P = 0.028$) (online supplementary *Table S7*).

Given the significant differences in the baseline characteristics between the two patient groups, we have additionally performed a propensity score adjustment, following which the relative risk of all-cause death remained significantly reduced in the CIED-D carriers (HR 0.60, 95% CI 0.39–0.94; $P = 0.024$), while the propensity score itself was not significantly related to all-cause death. Strong predictors of CIED-D carrier status included having a history of atrial fibrillation [odds ratio (OR) 2.9] or VAs (OR 2.0), while having a prior myocardial infarction and a concomitant procedure with LVAD implant reduced the odds of carrying a CIED-D (OR 0.5 and 0.4, respectively). LVAD type, LVAD intention and INTERMACS class were additional predictors of CIED-D carrier status (all $P < 0.05$) (online supplementary *Table S8*).

In order to account for missing data, additional sensitivity analyses were performed by multiple imputation of missing values. The results were consistent with the original analyses – when adjusting by variable selection for the primary outcome, time-updated active CIED-D carrier status, patient age and LVAD implantation as

a redo surgical procedure remained the only significant predictors of all-cause mortality (online supplementary *Table S9*). In an additional stepwise multiple regression model obtained from the multiple imputation dataset, age and LVAD implantation as redo surgery remained additional predictors of all-cause mortality, in addition to active CIED-D status post-LVAD (online supplementary *Table S10*).

In an additional analysis of ICD-only carriers (excluding those with a CRT-D device) contiguously with an LVAD, the crude HR showed a trend towards a reduction in all-cause mortality (HR 0.73, 95% CI 0.51–1.04; $P = 0.077$). However, in adjusted analysis, carrying an ICD-only reached a significant reduction in all-cause mortality (HR 0.60, 95% CI 0.39–0.92; $P = 0.019$, online supplementary *Table S11*). After multiple imputation, the adjusted HR remained consistent, suggesting a 35% reduction in all-cause death in active ICD-only carriers during LVAD support (online supplementary *Table S11*).

Discussion

In this analysis of the PCHF-VAD registry, we have described the baseline characteristics and outcomes of 448 cf-LVAD carriers from 12 European academic centres in relation to carrying a CIED with an active defibrillator component (either in an ICD or CRT-D device) during the course of LVAD support. In patients enrolled in the registry, carrying an active defibrillator component during LVAD support was associated with a reduced crude and adjusted risk of all-cause mortality, compared to the patients without an active defibrillator component. This finding was consistent in several sensitivity analyses, including a propensity score adjusted analysis. Higher patient age, LVAD implantation as a redo surgical procedure, number of clinically significant VA episodes pre-LVAD and use of vasopressors recognized as other significant predictors of all-cause mortality.

The prevalence of either ICD or CRT-D carriers prior to LVAD implantation of 54% in this cohort is notably lower than that of >80% of LVAD carriers with an ICD in recent analyses of the INTERMACS and UNOS registries,[8,9] while it is more comparable to the EUROMACS population in which 58% carry an ICD.[20] This points out an important difference between LVAD carriers in Europe and the United States, while the currently available data predominantly originate from US centres. The source of this discrepancy is unclear but might be reflective of nearly four-fold higher ICD implantation rates in the United States, compared to Europe.[21] The clinical profile of CIED-D carriers pre-LVAD in our registry suggests a more chronic course of HF prior to the initiation of LVAD support – these patients were in higher INTERMACS classes with less need for life support therapies (vasopressors, ultrafiltration or mechanical ventilation) prior to LVAD; they had more remodelled left ventricles and a higher use of guideline-mandated HF therapies, including beta-blockers that may supress ventricular ectopy, compared to patients without an CIED-D pre-LVAD. A more chronic profile corresponds to ICD carriers described in other LVAD cohorts.[10,11,13–15] However, compared to several other analyses, the use of LVADs as bridge to transplantation was much more frequent in our cohort.[9,10] Furthermore, patients implanted with an LVAD more recently were more likely to have received an CIED-D, as well as those with a higher number of VAs pre-LVAD.

While the survival benefit of ICDs is well established in symptomatic HFrEF patients,[7] the data on the utility of defibrillators in LVAD carriers are still conflicting. Traditionally, LVAD patients are considered to tolerate life-threatening VAs,[22] possibly due to the Fontan-like circulation that occurs when the fibrillating right ventricle becomes a passive conduit.[17] Conversely, in some patients VAs may cause progressive right ventricular failure or lead to more gradual HF and death. 'Routine' implantation of ICDs post-LVAD is still debated and predominantly hindered by increased risk of bleeding and infection in this high-risk population.[23–25] Notwithstanding this, the replacement of exhausted generators of defibrillators implanted prior to onset of LVAD therapy is increasingly supported.[16,17]

While a meta-analysis of six observational studies assessing the impact of ICDs on survival of LVAD patients reported a significant reduction in mortality associated with ICD use, this finding was not significant when confined to the cf-LVAD population.[22] The results of one of these studies suggested that only patients who suffered potentially life-threatening VAs prior to LVAD implantation had recurring arrhythmias after LVAD implantation, thus benefiting from ICD therapy.[10] However, the rate of all-cause death in our multicentre cohort, and in particular the subgroup without CIED-D post-LVAD, was notably higher in comparison to this single-centre study, yet lower than reported from the EUROMACS data, and similar to the INTERMACS report.[8,10,26] In an analysis of the UNOS registry, the presence of ICDs at listing in durable LVAD recipients was not associated with lower waitlist mortality; however, numerically fewer arrhythmic deaths were noted in the ICD group.[27] As mentioned, the penetration of ICDs in this cohort is notably greater than in our European cohort which may portend differences among the populations. In the largest currently available analysis from the INTERMACS database, no survival benefit was associated with ICD in VAD carriers: in the primary analysis, ICD implantation was associated with increased mortality of unexpected death, which had not met significance levels in additional sensitivity analyses.[8] While we can only speculate on the aggregate causes of the discrepant results between our and the INTERMACS registry, several features clearly differ between these cohorts: the INTERMACS cohort was dominated by patients in NYHA class IV (around 83% of patients in the propensity score-matched cohort, as opposed to 36% of our cohort), a much larger proportion of destination therapy patients (40%, as opposed to only 13% of our population) and those with prior cardiac surgery (68% in INTERMACS compared to 12% in PCHF-VAD). Despite the fact that both studies identify clear differences in outcomes between those with and without an ICD, it is unclear whether the patient characteristics more typical for the INTERMACS registry portended potentially harmful effects of ICD therapy in that cohort. Importantly, in addition to a much larger penetration of ICDs within the LVAD population compared to our European registry, the INTERMACS analysis excluded patients with *de-novo* ICDs after LVAD implantation. As such, possible 'crossover', i.e. initiation and/or termination

of CIED therapy during active LVAD support warrants to be accounted for.

We have thus utilised a time-varying analysis that has provided consistent results: in an unadjusted analysis, carrying an active CIED with a defibrillator component was associated with a 36% reduction in all-cause death, which remained significant and comparable after adjustment for the relevant baseline covariates (41% reduction in all-cause death), after propensity score adjustment (40% reduction), after adjustment for the occurrence of VAs post-LVAD (47% reduction) and by utilising multiple imputation to compensate for the missing data (37% reduction). Our analysis was expanded to carriers of both ICD and CRT-D devices to include the effect of the defibrillator component in either type of CIED. After additional adjustment for CRT-P carrier status, the reduction in the risk of all cause-death remained significant and reached 43%. Furthermore, in a sub-analysis of the ICD-only subgroup, the crude HR suggested a trend towards reduced all-cause death, while the adjusted analysis confirmed a 40% reduction in all-cause death in active ICD-only carriers during LVAD support. The benefit of active CIED-D therapy with an LVAD remained consistent in subgroup analyses as well as with additional sensitivity analyses.

Ventricular arrhythmias post-LVAD occurred in 24% of our cohort, which is within the reported range of 22–52%.[8] In the MOMENTUM 3 trial, sustained ventricular tachyarrhythmias occurred relatively frequently (18% in centrifugal-flow VADs, 20% in axial-flow VADs), but rarely resulted in death.[3] While our data suggested a nominally increased crude risk of developing clinically significant VAs post-LVAD in CIED-D carriers (*Table 2*), this did not remain significant in adjusted analyses and was likely an effect of enhanced arrhythmia monitoring provided by the CIED. While we cannot infer causality between the delivery of defibrillator-driven therapies and reduction in mortality, we have noted that nearly one third of the CIED-D carriers received at least one of these therapies on at least one occasion, with a median time to first ATP or shock well beyond the arrhythmically fragile early post-surgical period. Moreover, in an analysis of incident VAs post-LVAD as a time-varying covariate, the occurrence of the arrhythmia was a strong predictor of all-cause and cardiovascular mortality as was increasing patient age, LVAD implant as redo surgery and vasopressor use prior to LVAD, while the presence of an active CIED-D device remained associated with a reduction in the risk of all-cause death. Whether the optimal timing of CIED-D implantation is before or after LVAD remains to be explored.

Limitations

Our analysis was limited by typical features of retrospective registry studies: incompleteness of the dataset which we aimed to account for by multiple imputation methods, possible selection bias and misclassification of events. Furthermore, the study was limited by lack of data on arrhythmic events in non-CIED-D carriers. We acknowledge the limited possibility of determining causality with a retrospective analysis, as well as the ability to adequately adjudicate the endpoints which also limits the possibility of determining the mitigation of risk of arrhythmic deaths by a CIED-D. Finally, this type of study design does not allow optimal control for multiple potential confounders, however extensive adjustments have confirmed the robustness of our results in terms of reduced all-cause mortality with CIED-D post-LVAD, whereby all adjusted models for all-cause death show a stronger treatment effect of CIED-D. However, only a randomised prospective trial, which we believe is warranted, would be able to adequately address this clinically relevant topic.

Conclusion

In an LVAD cohort with granularly described baseline data stemming from a multicentre European registry, we report a significant reduction in the crude and adjusted risk of all-cause death in patients carrying a CIED with an active defibrillator component during LVAD support, which was consistent across sensitivity analyses. Higher patient age, number of clinically significant VAs pre-LVAD, use of vasopressors and LVAD implantation as redo surgery were recognized as other significant predictors of all-cause mortality.

Finally, an analysis of incident VAs post-LVAD confirmed its occurrence as a strong predictor of all-cause and cardiovascular mortality, while in this analysis the presence of an active CIED-D remained associated with a reduction in the risk of all-cause and cardiovascular death.

Unambiguous disparities in CIED-D usage in LVAD recipients as well as its impact on outcomes exist between European and US cohorts. Further insight in the comparison of these populations should improve the understanding of (non-)response to CIEDs, while evidence from a randomised controlled trial would be anticipated to inform decisions on contiguous device usage in this growing patient population.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Methods S1. Supplementary methods.

Figure S1. The dates of LVAD implantation.

Figure S2. Kaplan-Meier plot of time to CIED-D implantation and deactivation following LVAD implantation (during active LVAD support).

Figure S3. Duration of follow-up.

Table S1. Baseline characteristics of the studied patients by CIED-D carrier status prior to LVAD implantation – additional variables with more than 30% missing data.

Table S2. Multivariate Cox regression model of risk factors for the secondary outcome of the occurrence of ventricular arrhythmias post-LVAD implantation from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection for the primary outcome and by outcome-specific variable selection.

Table S3. Unadjusted and adjusted hazard ratios for the primary endpoint (all-cause death) and secondary endpoints by time-updated CIED-D carrier status following LVAD implantation.

Table S4. Multivariate Cox regression model of risk factors for the primary outcome of all-cause death, using post-LVAD VAs as a time-varying covariate, and for the secondary outcome of cardiovascular death, using post-LVAD VAs as a time-varying covariate.

Table S5. Multivariate Cox regression model of risk factors for secondary outcome of cardiovascular death from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection for the primary outcome and by outcome-specific variable selection.

Table S6. Multivariate Cox regression model of risk factors for secondary outcome of heart failure hospitalisation, device-related infection requiring systemic antibiotics, non-cerebral bleeding and intracranial bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection for the primary outcome and by outcome-specific variable selection.

Table S7. Multivariate Cox regression model of risk factors for all-cause death based on a backward variable selection model, by time-updated CIED-D carrier status following LVAD implantation.

Table S8. Results of the propensity score model assessing the possibility of having a CIED-D pre-LVAD.

Table S9. Sensitivity analyses performed through additional multivariate Cox regression models of risk factors for all-cause death by time-updated CIED-D carrier status following LVAD implantation estimated by multiple imputation procedures.

Table S10. Sensitivity analysis performed through an additional multivariate Cox regression model obtained from the stepwise selection process of risk factors for all-cause mortality, based on multiple imputation methods.

Table S11. Multivariate Cox regression model of risk factors for all-cause mortality by time-updated ICD carrier status following LVAD implantation, adjusted by outcome-specific variable selection – sensitivity analysis based on multiple imputation.

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