Combined device therapy for advanced heart failure

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The Dissertation was written at the Department of Cardiovascular Diseases, University Hospital Centre Zagreb, University of Zagreb School of Medicine, under the mentorship of Associate Professor Maja Čikeš, MD, PhD, and the co-mentorship of Professor Frank Ruschitzka, MD, of the Clinic for Cardiology, University Hospital Zurich, Zurich, Switzerland.

Dissertation mentor: Associate Professor Maja Čikeš, MD, PhD
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List of abbreviations

ACEi	Angiotensin-converting enzyme inhibitors
ADL	Activities of daily living
ARNi	Angiotensin receptor neprilysin inhibitor
AoV	Aortic valve
AR	Aortic regurgitation
ATP	Anti-tachycardia pacing
BiVAD	Bi-ventricular VAD
BMI	Body mass index
BTC	Bridge to candidacy
BTR	Bridge to recovery
BTT	Bridge to transplantation
CAD	Coronary artery disease
cf-LVAD	Continuous flow left ventricular assist device
CI	Confidence interval
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
CIED	Cardiac implantable electronic device
COPD	Chronic obstructive pulmonary disease
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
CRT	Cardiac resynchronization therapy
CVP	Central venous pressure
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DT	Destination therapy
E	Era
ECMO	Extracorporeal membrane oxygenation
ELEVATE	Evaluating the HeartMate 3™ in a Post-Market Approval Setting: The HeartMate 3 Registry
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction
EMPHASIS	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
ESC	European Society of Cardiology
EU	Europe
EUROMACS	European Registry for Patients with Mechanical Circulatory Support
FF	Frequent flyer
GDMT	Guideline-directed medical treatment
GIB	Gastrointestinal bleedings
HCS	Haemocompatibility score
HM II	HeartMate II
HM 3	HeartMate 3
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HRAE	Haemocompatibility-related adverse events
HW	HeartWare

IABP	Intra-aortic balloon pump
ICD	Implantable cardioverter defibrillator
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ISHLT	International Society for Heart and Lung Transplantation
IQR	Interquartile range
LATERAL	A Prospective, Single-Arm, Multi-Center Study in Collaboration With INTERMACS to Evaluate the Thoracotomy Implant Technique of the HeartWare™ HVAD™ System in Patients With Advanced Heart Failure
LBBB	Left bundle branch block
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MCS	Mechanical circulatory support
MOMENTUM 3	Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3
MRA	Mineralocorticoid receptor antagonists
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal fragment of B-type natriuretic peptide
NYHA	New York Heart Association
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PCHF-VAD	Postgraduate Course in Heart Failure – Ventricular Assist Device
RALES	Randomized Aldactone Evaluation Study
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
REDCap	Research Electronic Data Capture
ROADMAP	Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device (LVAD) and Medical Management
RVF	Right ventricular failure
SOLVD	Studies of Left Ventricular Dysfunction
SGLT2i	sodium-glucose cotransporter-2 inhibitors
STS	Society of Thoracic Surgeons
TAH	Total artificial heart
TCS	Temporary Circulatory Support
TRAViATA	TRans-Atlantic registry on VAd and TrAnsplant
UNOS	United Network for Organ Sharing
USA	United States of America
VA	Ventricular arrhythmias
6MWT	6-minute walk tests

List of scientific Publications included in the PhD thesis

1. Cikes M, Jakus N, Claggett B, Brugts JJ, Timmermans P, Pouleur AC, Rubis P, Van Craenenbroeck EM, Gaizauskas E, Grundmann S, Paolillo S, Barge-Caballero E, D'Amario D, Gkouziouta A, Planinc I, Veenis JF, Jacquet LM, Houard L, Holcman K, Gigase A, Rega F, Rucinskas K, Adamopoulos S, Agostoni P, Biocina B, Gasparovic H, Lund LH, Flammer AJ, Metra M, Milicic D, Ruschitzka F; PCHF-VAD registry. Cardiac implantable electronic devices with a defibrillator component and all- cause mortality in left ventricular assist device carriers: results from the PCHF-VAD registry. Eur J Heart Fail. 2019 Sep;21(9):1129-1141.

2. Jakus N, Brugts JJ, Claggett B, Timmermans P, Pouleur AC, Rubiś P, Van Craenenbroeck EM, Gaizauskas E, Barge-Caballero E, Paolillo S, Grundmann S, D'Amario D, Braun OÖ, Gkouziouta A, Meyns B, Droogne W, Wierzbicki K, Holcman K, Planinc I, Skoric B, Flammer AJ, Gasparovic H, Biocina B, Lund LH, Milicic D, Ruschitzka F, Cikes M; PCHF-VAD registry. Improved survival of left ventricular assist device carriers in Europe according to implantation eras: results from the PCHF-VAD registry. Eur J Heart Fail. 2022 Jul;24(7):1305-1315.

3. Gasparovic H, Jakus N, Brugts JJ, Pouleur AC, Timmermans P, Rubiś P, Gaizauskas E, Van Craenenbroeck EM, Barge-Caballero E, Grundmann S, Paolillo S, D'Amario D, Braun OÖ, Meyns B, Droogne W, Wierzbicki K, Holcman K, Planinc I, Lovric D, Flammer AJ, Petricevic M, Biocina B, Lund LH, Milicic D, Ruschitzka F, Cikes M. Impact of progressive aortic regurgitation on outcomes after left ventricular assist device implantation. Heart Vessels. 2022 Dec;37(12):1985-1994

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6. Ammirati E, Brambatti M, Braun OÖ, Shah P, Cipriani M, Bui QM, Veenis J, Lee E, Xu R, Hong KN, Van de Heyning CM, Perna E, Timmermans P, Cikes M, Brugts JJ, Veronese G, Minto J, Smith S, Gjesdal G, Gernhofer YK, Partida C, Potena L, Masetti M, Boschi S, Loforte A, Jakus N, Milicic D, Nilsson J, De Bock D, Sterken C, Van den Bossche K, Rega F, Tran H, Singh R, Montomoli J, Mondino M, Greenberg B, Russo CF, Pretorius V, Liviu K, Frigerio M, Adler ED. Outcome of patients on heart transplant list treated with a continuous-flow left ventricular assist device: Insights from the TRans-Atlantic registry on VAd and TrAnsplant (TRAViATA). Int J Cardiol. 2021 Feb 1;324:122-130.

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1. Introduction and background

1.1. Heart failure

Heart failure (HF) is defined by the European Society of Cardiology (ESC) as a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema), which are due to a structural and/or functional abnormality of the heart, resulting in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise (1).

It is estimated that 64.3 million people are affected by HF worldwide (2). Currently, the incidence of HF in Europe in all age groups is estimated around 3/1000 person-years, and around 5/1000 person-years in adults (3,4). Epidemiological surveys and studies estimate the prevalence of symptomatic HF in the developed countries to be between 1 to 2% (5), with an exponential increase with age, where the prevalence increases to 4 to 8% in patients older than 65 years (6). While age-adjusted incidence of HF in developed countries seems to be on the decline, possibly due to better management of cardiovascular diseases, the overall incidence is increasing with the aging population (7,8). Factors such as better care of cardiac pathologies (acute coronary syndrome, valvular disease, arrhythmias), as well as improvements in HF treatment, are allowing patients to reach older age, resulting in a growing prevalence of HF, as well.

Older patients with advanced and acute HF often pose a therapeutic challenge given the age cut-offs most institutions have for certain treatment options. With the growing experience of advanced HF centres, proper selection of older patients who might benefit from this treatment is gaining importance.

There are some differences in the incidence and aetiology of HF between men and women. Some population-based studies have noted a lower incidence and prevalence of HF in women (9); on the other hand, given the longer expected survival in women, others report a similar prevalence in both sexes (6,10). Women are considered to predominate the heart failure with preserved ejection fraction (HFpEF) population, possibly due to a different response of the myocardium to injury, as well as the lower prevalence of coronary artery disease in women (11). Additionally, there are some aetiologies of HF that are specific for the female gender,

such as peripartal cardiomyopathy. Notably, there is an underrepresentation of women in clinical trials (10,11,12,13), possibly leading to lesser utilisation of some therapies in women. Given the large number of affected patients, the economic burden of HF is an important aspect of the disease. It is already highly significant and is expected to further increase, stressing the importance of adequate and timely implementation of treatment options that improve the morbidity and mortality of patients with HF.

1.1.1. Types of heart failure

According to presentation, HF can be categorized into acute or chronic, where acute HF could be a presentation of new onset or *de novo* HF, or on the other hand, it can be a manifestation of worsening of chronic HF (1). Further categorizations include the differentiation of HF according to ejection fraction; despite the known shortcomings of this parameter, such phenotyping is routinely used in everyday practice. Patients are distinguished into those with heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF). A patient is considered to have HFrEF if signs and symptoms of HF are present, as well as ejection fraction ≤40% is verified on echocardiography or magnetic resonance imaging (MRI), while HFmrEF and HFpEF include symptomatic patients with EF 40-49% and ≥50%, respectively, as well as some additional criteria required for the diagnosis of HFpEF (objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, raised natriuretic peptides) (1). Epidemiological studies indicate that almost half of the total number of HF patients have HFpEF (14). Given that the focus of this thesis is cardiac devices and ventricular assist devices, which are currently approved for use only in HFrEF patients, only HFrEF will be discussed in detail.

When assessing the symptomatic severity of HF, it is common to categorize patients according to functional class into the New York Heart Association (NYHA) classes. The NYHA classification designates a patient as NYHA I if they have no limitation in physical activity, NYHA II if there is light limitation of physical activity (the patient is comfortable at rest, but usual physical activity leads to undue dyspnoea of fatigue), NYHA III if the patient reports a marked limitation of physical activity (comfortable at rest, but less than usual activities lead to dyspnoea or fatigue), or NYHA IV if the patient is unable to carry out any

physical activity without symptoms, which can even be present at rest (1). This gradation is utilised in everyday cardiological practice but was found insufficient for the assessment of patients with advanced HF, i.e. potential mechanical circulatory support (MCS) candidates. For this purpose, an additional grading system was created in 2009 by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) (Table 1) (15,16).

Table 1. INTERMACS profiles. ADL – activities of daily living; ECMO – extracorporeal membrane oxygenation; IABP – intra-aortic balloon pump; ICD – implantable cardioverter defibrillator; NYHA – New York Heart Association (15).

Profile	**Title**	**Description**
1	Critical cardiogenic shock	Life-threatening hypotension refractory to IV inotropes. “crash and burn”
2	Progressive decline	IV inotropes required with worsening end-organ function. “sliding on inotropes”
3	Inotrope dependent	Stable blood pressure and end-organ function but failure to wean from IV inotropes. “dependent stability”
4	Resting symptoms	Daily symptoms of congestion at rest or with ADLs. High doses of diuretics.
5	Exertion intolerant	Unable to engage in any activity above ADLs.
6	Exertion limited	Can participate in minor activities, but quickly fatigues. “walking wounded”
7	Advanced NYHA III	Comfortable with meaningful activity, limited to mild exertion.
Modifiers for profiles		
TCS (Temporary Circulatory Support) – including IABP, ECMO, TandemHeart, Levitronix, Impella, suitable only for hospitalised patients, modifies profiles 1-3.		
A (Arrhythmia) – recurrent ventricular tachyarrhythmia that cause clinical compromise, including frequent ICD shocks and external defibrillations, usually more than twice weekly. A can modify any profile.		
FF (Frequent flyer) – patients requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration or temporary vasoactive therapy. FF can modify profiles 3-6.		

This system provided a subclassification of NYHA III and IV classes into 7 profiles of severity, according to severity of clinical symptoms and inotrope requirement, with higher profiles (profiles 1-3) indicating more acutely ill patients with advanced HF, thus providing better guidance in the optimal timing of MCS implantation in potential candidates (Table 1). Some additional factors can modify, i.e. enhance the severity of the current INTERMACS profile of the patient, such as the need for temporary circulatory support, life-threatening arrythmias and the need for frequent HF hospitalizations, usually referred to as the "frequent flyer" status. Several clinical trials provided insight into the outcomes of LVAD recipients depending on the INTERMACS profile, with those in the most acute profiles (INTERMACS profile 1) having worse outcome (17), but LVADs are also not recommended in patients on the other side of the spectrum (INTERMACS 7), with the optimal candidates being those in INTERMACS profiles 2-3/4. Further reports of satisfactory outcomes in non-inotrope dependant patients receiving LVAD therapy (18) confirmed favourable outcomes in selected patients in the intermediate INTERMACS classes.

1.1.2. Aetiology of heart failure

Several risk factors predisposing the development of HF have been identified, including coronary artery disease (CAD), arterial hypertension, diabetes mellitus, obesity and smoking (6). Aetiology of HF differs somewhat depending on the type of HF (HFrEF vs. HFpEF), but there is some overlap.

Regarding HFrEF, most common aetiologies include (6):

a) ischaemic heart disease,
b) dilated cardiomyopathy (idiopathic),
c) HF due to pressure overload (hypertensive, stenotic valvular disease),
d) HF due to volume overload (regurgitant valvular disease, shunting),
e) postinflammatory (postmyocarditic),
f) toxic/drug related (alcohol, chemotherapy),
g) HF due to rhythm disturbances
h) infiltrative disease
i) other types of HF (peripartal)

Defining the aetiology of HF is especially important in cases of potentially reversible advanced HF where temporary MCS could be sufficient; on the other hand, a durable support modality should be considered in irreversible pathology.

1.1.3. Outcomes and treatment options for patients with heart failure with reduced ejection fraction

Heart failure is a clinical entity with a severe and an unfavourable natural course, resulting in reduced quality of life and premature death, comparable to the outcomes of malignant diseases. Large observational studies reported mortality rates of HF populations: the Olmsted County Cohort reported 1-year and 5-year mortality rates for all types of HF, after the diagnosis has been established, of 20% and 53%, respectively, in the period between 2000 and 2010 (19). Similarly, an analysis combining findings from the Framingham Heart Study and the Cardiovascular Health Study found a 67% mortality rate at 5-year follow-up following the diagnosis of HF (20). The effect of sex on survival has been studied as well, and opposing findings have been noted, with some reporting better overall prognosis in female HF patients (6), which was contradicted by other reports, especially in advanced HF (21).
There have been significant changes in the treatment of HF starting decades ago, with the landmark clinical trials, such as SOLVD (22), CIBIS II (23), COPERNICUS (24), RALES (25) and EMPHASIS (26), which introduced the use of angiotensin-converting enzyme inhibitors (ACEi), beta-receptor blockers and mineralocorticoid receptor antagonists (MRA), to reduce the risk of HF hospitalization and death in patients with HFrEF (1). Recently, further advancements in the field occurred, with the publication of PARADIGM-HF (27), DAPA-HF (28) and EMPEROR-Reduced (29) trails, which ushered the angiotensin receptor neprilysin inhibitor (ARNi) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) into the therapeutic medical armamentarium for HF, in aggregate often referred as guideline-directed medical treatment (GDMT).
Great advancements in improved outcomes in HF have been made with the implementation of cardiac implantable electronic devices (CIED), such as implantable cardiac defibrillators (ICD), validated through the MADIT II trial (30) and cardiac resynchronization therapy (CRT) devices, both with a defibrillator lead (CRT-D) and without (CRT-P), introduced by the MADIT-CRT trial (31), all of which further improved outcomes in the HFrEF population. Despite the significant advances in the GDMT and CIED fields, a certain number of patients

reach the advanced HF stage, where GDMT is no longer sufficient to prevent deterioration and death, making them candidates for advanced HF treatment options, such as mechanical circulatory support (MCS), either short-term or long-term, or heart transplantation.

1.1.4. Advanced heart failure

Advanced heart failure denotes a stage of HF where standard treatment options such as GDMT, devices or conventional surgery cannot successfully alleviate the patient's symptoms nor improve their outcomes, making advanced therapies such as heart transplantation, MCS or palliative therapies necessary (16). "Refractory" and "end-stage" HF are considered synonyms for advanced HF (16). It is estimated that patients with advanced HF comprise 1–10% of the entire HF population, with increasing prevalence paralleling the growth of the HF population and the improvements in available treatments, prolonging survival, (16), thus increasing the pool of candidates for advanced HF treatment. Heart transplantation is still the gold standard for treatment of advanced HF, with a 1-year survival of 90% and the median survival of 12.2 years (32), as well as a very favourable post-transplantation course, regarding the functional capacity and quality of life (16). These results are only replicable when patients are adequately selected, and some comorbidities can present a contraindication for heart transplantation, such as a recent history of malignancy or an irreversibly high value of pulmonary vascular resistance (PVR) (16). The utilisation of heart transplantation is, in part, also limited by donor organ availability, due to a stagnating number of donor organs (33) and an increasing pool of recipients and is thus not accessible to all patients who require it. Some of these patients will then be referred to LVAD implantation, as a permanent treatment option or as a bridge to transplantation (or candidacy).

1.2. Left ventricular assist devices (LVAD)

Ventricular assist devices (VADs) are mechanical devices designed to provide circulatory support, i.e. supplement the native cardiac function of the left, right or both ventricles. They do so by unloading the affected ventricle(s) and deriving blood into the corresponding large blood vessel (aorta or pulmonary artery), thus providing cardiac output and decreasing congestion, the two main pathophysiological mechanisms of heart failure (34,35). Depending on the expected duration of support, short-term (usually extracorporeal) or long-term

(implantable) devices can be utilised. When the support is provided for the left ventricle, left ventricular assist devices (LVAD) are utilised, and these patients comprise the vast majority of the VAD population (according to the 2020 INTERMACS STS report (36), isolated LVADs comprised 93.6% of the 27.298 patients implanted in the 10-year period), and will be the primary focus of the publications comprising this thesis. According to the architecture of the device, durable VADs have been designed as pulsatile or continuous pumps.

1.2.1. History of VAD therapy

Mechanical circulatory support (MCS) has been successfully implemented in practice since 1953, initially as treatment for post-cardiotomy failure. With the increase in the number of heart transplantations, MCS became a viable option for bridging of patients with terminal HF, until availability of an adequate donor heart. After the approval of the Novacor LVAD, the first device used as BTT, approval of several other pulsatile devices followed, such as Thoratec HeartMate XVE, HeartMate IP, and IVAD/PVAD. In 2001, after the publication of the landmark REMATCH trial, the HeartMate XVE was approved for DT, thus expanding the utilisation of LVADs beyond heart transplantation candidates (37). Despite the significant limitations of these first-generation devices (large size, loud mechanism, short durability of certain pump parts), they have paved the way for the more sophisticated devices of the second and third generation, the latter being exclusively used today.

The need for smaller and more durable devices led to the creation of the second-generation devices, which operate as continuous flow pumps, such as the HeartMate II (HM II), the axial flow device first introduced in 2001 (38). The clinical introduction of continuous-flow LVADs (cf-LVADs) resulted in improved reliability and superior outcomes in comparison to first generation pulsatile-flow LVADs (39). These devices revolutionised the field of MCS, allowing for patients to increase functional capacity and resume everyday activities, with favourable overall survival. The superiority of the second-generation device, HM II, as compared to the first generation has been demonstrated in a clinical trial (HEARTMATE II) published in 2009 (40). Despite the significant improvement in patient outcomes with the new device, there was still room for improvement, especially with regard to pump thrombosis, which led to further developments in pump design.

The third-generation devices introduced intrapericardial pump placement, and a major development including the total magnetic/hydrodynamic levitation of the pump propeller

(38). The third generation devices are represented by the HeartWare (HW) HVAD, a centrifugal flow device, which was approved by the Food and Drug Administration in 2012, and the HM 3, a fully magnetically levitated pump, with significant structural improvements, which eliminated some of the shortcomings present in the earlier generations of devices (less shear stress due to wider blood flow gaps, an artificial pulse which prevents blood stasis, elimination of wear and heat generation). The superiority of the HM 3 device has been demonstrated in the MOMENTUM 3 trial series, which randomised 1028 advanced HF patients 1:1, to either HM II or the HM 3 pump. At 2-year and 5-year follow-up the HM 3 was superior compared to the HM II regarding the composite primary endpoint of survival free of disabling stroke or reoperation for device malfunction (41, 42). Other findings included reduction in pump thrombosis, major surgical and non-surgical bleeding, and stroke in HM 3 carriers, most benefits linked to improved haemocompatibility (43). Currently, the HM 3 is the only LVAD approved for clinical use by regulatory agencies in Europe (EU) and the United States of America (USA). Another potential benefit of the newer generation devices was the possibility of implantation utilising minimally invasive surgery (38), which was shown to reduce the duration of hospitalization, as demonstrated in the LATERAL trial (44).

1.2.2. LVAD design

There have been significant alterations in device architecture, but most modern pumps consist of several parts (38):

a) inflow cannula (which derives blood from the ventricle);
b) the blood pump with an electrical motor (which accelerates the blood forward);
c) outflow cannula (which injects the blood into the aorta / pulmonary artery);
d) percutaneous driveline (connects the pump with an external power source and controller);
e) controller (displays current pump settings, as well as any alarms);
f) external power source (rechargeable batteries).

In case of the LVAD, the inflow cannula is placed on the apex of the left ventricle, and depending on the type of the device, it can be placed within the pericardium or not. The inflow cannula is connected to the blood pump which accelerates the blood towards the outflow cannula, connected to the ascending aorta. The pump receives power through the percutaneous cable, often referred to as the driveline, which is connected to an external power

source, such as rechargeable batteries. The driveline usually exits the body of the patient on the abdominal wall, on the right side of the umbilicus, but in some devices, the exit site was placed retroauricular. The driveline also connects the pump to the controller which displays basic pump settings and alarms.

1.2.3. Indication for LVAD implantation

The indication for LVAD implantation includes advanced HF, refractory to medical therapy, usually including patients in the most advanced INTERMACS profiles (profiles 1-4) (16). Given the success of LVAD treatment, some studies suggested extending the indication beyond the most acute patients, to ambulatory, inotrope independent, NYHA IIIB and IV patients, as suggested by the ROADMAP study (18).
Regarding the perceived strategy of treatment, the indication for LVAD implantation can also be differentiated further, as described in the current HF guidelines (1):
a) bridge to candidacy (BTC) - use of MCS to make an ineligible patient eligible for heart transplantation
b) bridge to transplantation (BTT) - used for candidates for heart transplantation, who require stabilization while waiting for the donor heart
c) bridge to recovery (BTR) - use of MCS until cardiac function recovers
d) destination therapy (DT) - use of durable MCS as a final treatment option, usually for patients ineligible for heart transplantation
The treatment strategy is usually set prior to LVAD implantation, but it may change during the course of LVAD support. Availability of each device for a certain treatment indication varied over time, as most of the devices were initially approved for BTT and then DT. The only currently commercially available device, the HeartMate 3 (HM 3) is approved in Europe for both BTT and DT strategy.

1.2.4. Age and sex of the LVAD candidates

Although the overall lifetime risk of developing HF is comparable between men and women, women are underrepresented in HF trials (10-13). Additionally, women are less likely to be treated with GDMT, and some reports indicated potential underutilization of CIEDs for HF in women (11, 45-51). Even though approximately one third of the advanced HF population is

female, several studies have also shown lower utilization of LVADs in women (52-55). Women are hospitalised more frequently than men, and, according to some sources, they more often die as a result of HF, particularly in cases of advanced HF (21). It was reported that women more frequently receive an LVAD in INTERMACS 1 profile, or the "crash-and burn" stage of advanced HF (56). Possibly relating to this, women have prolonged intensive care stays, with longer duration of ventilation, as well as extended need for inotropic support (56). There is a higher risk for postoperative adverse events such as neurologic complications and RV failure (RVF) requiring RV support in women (56-58). Women are also fitted with smaller pump sizes (59).

Furthermore, studies investigating sex-related differences in LVAD outcomes provided conflicting results. Analyses of large US and European LVAD registries demonstrated worse clinical outcomes in women, while a smaller study and a meta-analysis showed similar survival for women and men (52,53,60-62). However, these previous studies contained only a very small proportion of the newest HM3 LVADs and primarily included data on US patients. It is important to raise awareness of any potential disparities in LVAD utilization between the sexes, thus possibly helping physicians make informed clinical decisions regarding female patients.

Age is an important determinant of the therapeutic success in advanced HF patients. LVADs are now more often used as DT in older patients and those not deemed eligible for heart transplantation (36,40,63-66), but the use of LVADs as BTT has increased in older patients as well (67). With the increasing use of LVADs and the expected number of patients who could benefit from LVAD support, risk stratification is essential for proper patient selection, especially in elderly patients. Several risk scores have been developed, but with improvements in LVAD technology and patient management, new insights into the impact of an ageing LVAD population on clinical management and outcomes are essential (68,69). Moreover, outcomes other than mortality are particularly relevant for older recipients and destination therapy candidates, as they affect quality of life and healthcare costs.

1.2.5. General direction of LVAD therapy in Europe

Improvement in survival and other outcomes achieved over the years of LVAD use has been previously described and has been attributable to the inevitable learning curve (70,71), development of surgical techniques with lower rates of surgical complications (44), technical

advances in pump architecture (41) as well as the evolution of treatment indications (72,73) and improved patient selection (63). A shift of utilization of LVADs from treating acutely ill patients, towards including the more 'stable' chronic HF patients has occurred over the past decade(s) (18,41) powered by the early data suggesting worse outcomes in INTERMACS profile 1 patients (74). An 'era effect' that amalgamates such progress in LVAD therapies was described in the latest INTERMACS registry report, with the improvement of outcomes in patients implanted in the more recent years (36). Since similar analyses were lacking for Europe, one of the publications comprising this thesis evaluated the progress of LVAD therapy during a course of 13 years, as well as providing a better insight into the European LVAD landscape.

1.2.6. Differences in outcomes in LVAD patients across continents – EU and US disparities

Two of the publications comprising this thesis are based on a multicentric, transatlantic registry of LVAD carriers, comparing data on practices and outcomes in several European centres, as well as some VAD centres in the United States of America (US), especially focusing on the BTT LVAD population. This is novel since most current large registries evaluating LVADs as BTT do not report survival after transplantation (75-77); similarly, the United Network for Organ Sharing (UNOS) only collects data at the time of listing and at the time of heart transplantation, without reporting baseline characteristics at the time of LVAD implantation (78). Hence, there is a critical knowledge gap regarding the impact of LVAD on the long-term outcomes of patients bridged to transplantation. Despite the overall benefit of LVAD therapies, extended duration of support increases the rates of device-related complications, which could potentially increase the risk of exclusion from the heart transplantation list or ultimately lead to worse posttransplantation outcomes (79).
The US and EU differ in a variety of factors related to LVAD-strategy and heart transplantation indications (80), the most obvious being the older age of transplant recipients in the US and older age of donors in the EU. Furthermore, there is some heterogeneity in heart transplantation and LVAD volumes between the centers in US and EU, with the number of LVAD implants being nearly 4-fold greater in the US (1700/year in the US compared with 430/year in EU) (81), even though the EU population is roughly twice the size of the US population (741 million compared to 328 million respectively). It is challenging to quantify

and compare the practices between LVAD centres, and to compare outcomes between two different patient populations, but such studies could elucidate some crucial points and provide knowledge that could be beneficial in improving practices on both sides of the Atlantic.

1.2.7. Effect of valvular disease on outcomes in LVAD carriers

One of the more prominent adverse events that has been associated with durable LVAD support is aortic regurgitation (AR), as seen in approximately one third of LVAD recipients (82-84). The mechanism of AR in LVAD recipients is multifactorial. The pathological correlates of non-pulsatile flow at the level of the aortic valve (AoV) are commissural fusion and leaflet thinning (85), accentuated in the absence of AoV opening and the ensuing continuous exposure to an increased transvalvular gradient (86), the net result being progressive valvular dysfunction (85). Size mismatches between the outflow graft and native aorta result in high velocity jets that create mosaics of high pressure and shear stress (87). These flow patterns manifest as chaotic eddy currents which may lead to aortic root dilatation and shortening of aortic valve coaptation lengths (87,88). Greater angles between the outflow graft and the aorta have also been associated with greater regurgitant volumes (89). Other known predictors of *de-novo* AR include older age, female gender, and systemic hypertension (82,90).

Conventional semiquantitative echocardiography underestimates the severity of AR, as it does not take into account its pancyclic nature. Ostensibly small regurgitant orifices may therefore translate into significant AR, and potentially induce clinically relevant hemodynamic sequelae (83). The importance of AR-induced reduction of forward flow is proportional to the duration of support (82). An increase in LVAD output may counteract the adverse effects of inefficient flow, but this may come at the expense of reduced durability of older generation devices (91). The clinical impact of AR after LVAD support is subject to debate and remains an important issue, as does the appropriate management strategy for such complications.

1.3. Cardiac implantable electronic devices (CIEDs)

The most commonly utilised CIEDs for treatment of HFrEF include ICD and CRT, with and with a defibrillator lead and without (1). These devices are fully implantable and are usually positioned transvenously, although certain types of ICDs are placed subcutaneously. The

main role of ICDs is to prevent sudden cardiac death due to malignant arrhythmias, which are among the more prevalent causes of death in HF patients with milder symptoms (1). The current HF Guidelines recommend implanting an ICD in patients with HFrEF, who have experienced a hemodynamically unstable ventricular arrhythmia and who are expected to survive more than 1 year with good functional status (secondary prevention), or those patients, in which an increased risk of arrhythmia exists, due to symptomatic HF (NYHA II-III) with reduced LV ejection fraction (LVEF≤35%), despite 3 months of GDMT (primary prevention).

CRT devices with biventricular pacing have been primarily recognised as an effective adjunctive therapy to GDMT, in reducing HF hospitalization rates in symptomatic HF patients (NYHA III-IV class), with LVEF ≤ 35%, and an intraventricular conduction delay of more than 120ms (92-94). The MADIT-CRT trial then demonstrated that implanting a CRT-D device compared to implanting an ICD resulted in a significant reduction of the combined outcome of death and HF events, especially in those with a significantly prolonged QRS interval (>150 ms), even in mildly symptomatic patients (31). Some beneficial effects have been demonstrated in the echocardiographic study, such as a significant decrease in the left ventricular end-diastolic and end-systolic volumes, as well as the improvement in LVEF seen 1 year after the initiation of CRT therapy. The current HF guidelines recommend implantation of a CRT device in symptomatic HFrEF (LVEF ≤ 35%) patients in sinus rhythm, with an increased QRS duration (≥150) and left bundle branch block (LBBB) morphology in order to improve symptoms and reduce morbidity and mortality (Class I recommendation, Level of evidence A). CRT therapy is recommended in other subsets of patients with a somewhat lower class of recommendation. Both types of devices are considered as an adjunct to maximally tolerated GDMT.

1.4. Combined device therapy

Given the progressive nature of HFrEF, a certain amount of overlap of device-based treatment modalities is encountered. As stated earlier, CIEDs are indicated in symptomatic HF as an adjunct to GDMT, while LVADs enter at the final stage of HF, advanced HF. According to the INTERMACS database, 80% of LVAD recipients already have an ICD device *in situ* (95) 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 expanding, the results are conflicting; the majority of the studies were conducted in single-centre patient populations, with few exceptions (95-102). Importantly, a perspective on the European landscape of combined device therapy in advanced HF is lacking. Limited observational studies on CRT in patients with LVAD have largely showed no survival advantage and no impact on ventricular arrhythmias (103,104). The current International Society for Heart and Lung Transplantation (ISHLT) guidelines for MCS 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 (105), while the current 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend ICD implantation in secondary prevention in LVAD carriers with symptomatic ventricular arrhythmias (106). Currently, no guideline recommendations exist for CRT management post-LVAD (105). In some instances, more conservative strategies have recently been advocated (107), particularly, bearing in mind the potential morbidity involved with CIED replacement.

2. Hypothesis

Combined device therapy improves outcomes in patients with advanced heart failure.

- Cardiac resynchronization therapy provides additional clinical benefit to VAD carriers with clinical characteristics evidenced to be beneficial of CRT response.
- ICD implantation and/or generator replacement in VAD carriers reduces total mortality

3. Aims and purposes of the research

General aim: To obtain better insight into outcomes of combined treatment strategies (ICD/CRT/CRT-D and VAD) in advanced heart failure patients through a European network of heart failure centres.

Specific aims:

- to describe the LVAD landscape in a European cohort of LVAD carriers as a function of implantation date and to investigate the relevance of the era of LVAD implantation on outcomes in Europe.
- to describe differences in preimplant patients' characteristics, as well as donors' aspects, between US and EU.
- to characterize overall outcomes from the time of cf-LVAD implant to the posttransplant period, focusing on survival and adverse events, while controlling for regional variations between US and EU.
- to assess sex-related differences in LVAD utilization and outcomes in a contemporary European cohort of LVAD patients.
- to assess the associations between age and cause-specific clinical outcomes after continuous-flow LVAD (cf-LVAD) implantation.
- to identify the mortality burden of progressive AR and its impact on the clinical and functional status in patients receiving cf-LVADs.
- to explore the association between use of a combination of devices and overall and cardiovascular mortality, frequency of HF hospitalizations, atrial and/or ventricular arrhythmias, and functional status, as well as safety of combined device therapy.

4. Materials and Methods

4.1. Design of the thesis

The thesis is based on the data from two large registries: the Postgraduate Course in Heart Failure – Ventricular Assist Device (PCHF-VAD) registry and the TRans-Atlantic registry on VAd and TrAnsplant (TRAViATA), retrospective, multicentric registries dedicated to accumulating data on VAD carriers.

This thesis elaborates on (Figure 1):
- baseline characteristics of the LVAD population in the investigated regions (EU and US), providing an insight into the landscape of European LVAD carriers, as well as a comparation of outcomes with the US cohort,
- outcomes of LVAD patients according to certain patient characteristics (age, sex, valvular disease),
- comparison of the utility of CIED implantation and therapy continuation in LVAD carriers, i.e. combined device therapy.

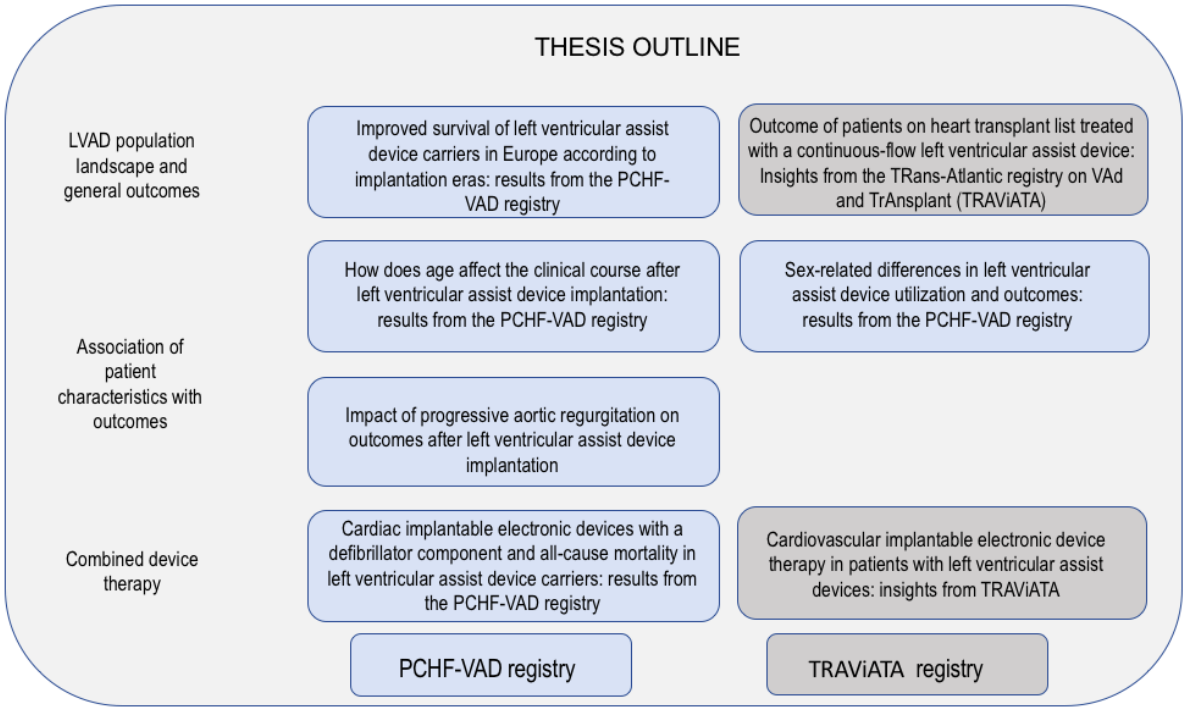

Figure 1. Thesis outline depicting the publications comprising the thesis. The publications are sequestered into three general topics. The publications stemming from the PCHF-VAD registry are light blue, and those from TRAViATA are in gray.

4.2. Ethical approval

Ethical approval for the undertaking of the thesis was obtained from the Ethics Committee of the University Hospital Centre Zagreb and the Ethics Committee of the University of Zagreb School of Medicine (Approval of the Ethics Committee of the University Hospital Centre Zagreb, Croatia; Class: 8.1-16/164-2).

4.3. The PCHF-VAD registry

The PCHF-VAD registry is a retrospective, observational registry, currently including 13 European tertiary referral centres (Figure 2, Table 2), established and led by the mentor of this thesis, associate professor Maja Čikeš, MD, PhD, and coordinated by the PhD candidate, Nina Jakuš, MD, under the supervision of the co-mentor of the thesis, professor Frank Ruschitzka, MD. The registry is populated by the participants and alumni of the Postgraduate Course in Heart Failure (PCHF) of the Heart Failure Association of the ESC and the European Heart Academy. Currently, the registry includes 672 patients with durable VADs, but for the purpose of the analyses presented in the thesis, only cf-LVAD carriers have been included. We have excluded underaged patients (age at implantation < 18 years), as well as pulsatile LVAD, right VAD and biventricular assist devices carriers from further analyses. The first enrolled patient has been implanted in December 2006, and the last patient enrolled in the currently analysed dataset was implanted in January 2020. The registry has been updated on several occasions, due to which number of included patients varies between the publications. The list of participating centres is listed in Table 2, and graphically depicted in Figure 2.

Table 2. List of participating centres by country for the PCHF-VAD registry.

Country	LVAD Centre
The Netherlands	Erasmus MC, University Medical Center Rotterdam, Rotterdam
Belgium	University Hospital Leuven, Leuven
	Cliniques Universitaires St. Luc, Brussels
	Antwerp University Hospital, Antwerp

Croatia	University Hospital Center Zagreb, Zagreb
Poland	John Paul II Hospital, Krakow
Lithuania	Faculty of Medicine, Vilnius University, Vilnius
Spain	Complejo Hospitalario Universitario de A Coruña
Italy	Federico II University of Naples
	Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome
Germany	Heart Center Freiburg University
Sweden	Lund University and Skåne University Hospital
Greece	Onassis Cardiac Surgery Centre, Athens

Figure 2. The map of European VAD referral centres involved in the PCHF-VAD registry.

The variables collected in the registry include baseline demographic patient information (age at time of implantation, sex) and anthropomorphic data (weight, height), physical examination including vital signs and functional status (NYHA class, INTERMACS profile), relevant

comorbidities and relevant past surgical procedures, as well as information on pertinent medical therapy. Echocardiographic findings, laboratory findings and right heart catheterisation data were acquired. Information on CIEDs (i.e. ICD and CRT devices) was collected as well, along with pertinent CIED parameters. Data on LVAD type and other data regarding the surgical procedure (prior MCS and concomitant surgical procedures) were obtained, as well as relevant LVAD parameters. Except for baseline data, all other variables were collected at three time points: prior to LVAD implantation, at discharge from LVAD implantation, and 6 months after the last device implantation.
For all further analyses, baseline variables with more than 30% of missing data were excluded. Specifics of the methods section of each publication are discussed in the corresponding chapters.

4.4. The TRans-Atlantic registry on VAd and TrAnsplant (TRAViATA) registry

299 patients in 7 European and 225 patients in 3 US centres participated in the TRAViATA registry. The list of participating centres is shown in Table 3 and Figure 3. All the participating sites were required to meet the following criteria: 1) expertise in MCS and heart transplantation; 2) active heart transplantation and LVAD programmes during the study period; 3) willingness to volunteer, as no funding support for data collection was provided.

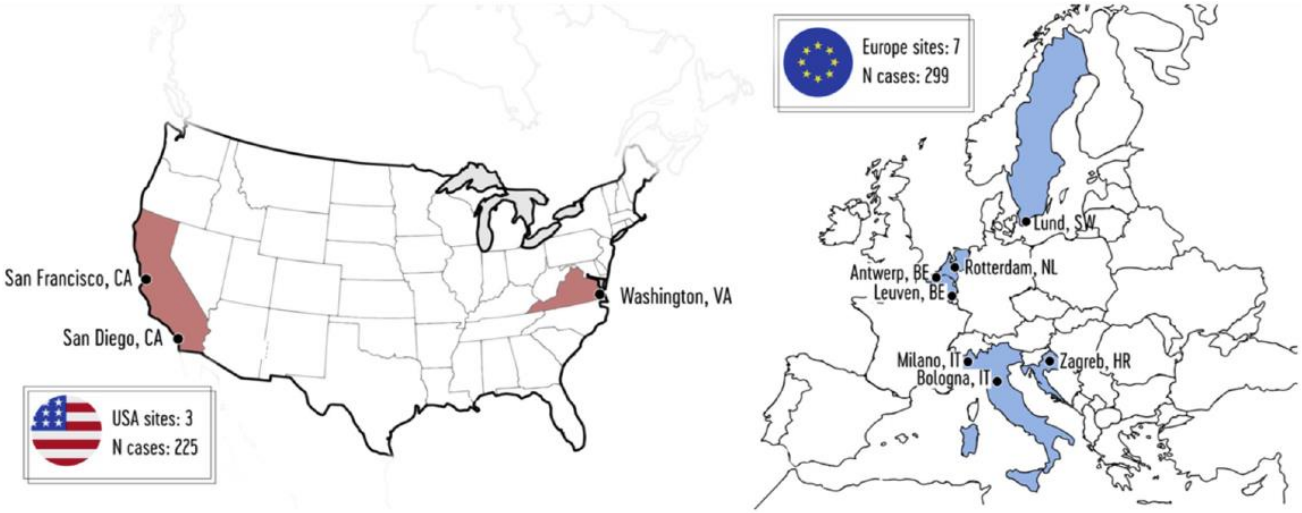

Figure 3. Map of centres participating in the TRAViATA registry.

Table 3. List of participating centres by country for the TRAViATA registry.

Country	LVAD Centre
EUROPE	
The Netherlands	Erasmus MC, University Medical Center Rotterdam, Rotterdam
Belgium	University Hospital Leuven, Leuven
	Antwerp University Hospital, Antwerp
Croatia	University Hospital Center Zagreb, Zagreb
Italy	Niguarda Hospital, Milan
	Sant' Orsola Malpighi Hospital, Bologna
Sweden	Skåne University Hospital, Lund
UNITED STATES OF AMERICA	
	University of California San Diego, La Jolla, California
	Inova Heart and Vascular Institute, Falls Church, Virginia
	University of California San Francisco, San Francisco, California

Consecutive patients that received a LVAD in accordance with the study protocol were included.

Inclusion criteria for TRAViATA consisted of:

(1) age ≥ 16 years; (2) LVAD implantation between January 2008 and April 2017;

(3) implantation of either HW (Minnesota, MN, US) or HM II (Abbott, Pleasanton, CA, US);

(4) listing at any point for heart transplantation or heart and kidney transplantation while supported with LVAD.

Exclusion criteria consisted of:

(1) patients implanted with HM 3 device (Abbott Pleasanton, CA, US) as it was still under investigation in the US during the study period; (2) patients treated with bi-ventricular VAD (BiVAD) or total artificial heart (TAH); (3) patients never listed for heart transplantation;

(4) prior heart transplantation before LVAD implantation.

Patient selection and post-operative management were left at the discretion of the local investigators. Last date of data collection in the follow up was March 31, 2018.

Baseline demographics, prior history of cardiovascular disease, comorbidities, NYHA classification and INTERMACS profile, laboratory values, hemodynamic and echocardiographic parameters were collected. LVAD-related adverse events (i.e. stroke, major bleeding, driveline infections, late RVF and pump thrombosis) were defined using the INTERMACS registry criteria (75). Survival after heart transplantation and donor characteristics were also collected from each centre.

4.5. Data collection

For both registries, the patient data were entered locally by participating investigators and collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools (108, 109). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. For the PCHF-VAD registry, the server was hosted at the University of Zagreb, School of Medicine, which also served as the data coordinating centre, while for the TRAViATA registry, this was set in Lund University in Lund, Sweden, with University of California, San Diego (US) as the coordinating centre. Since the data were not monitored on-site, dedicated investigators in both registries checked fidelity of the data and, when needed, contacted local investigators for clarifications. A data dictionary with a detailed description of each variable in the dataset was also provided to each participating centre.

4.6. Thesis outline – published manuscripts

4.6.1. LVAD population landscape and general outcomes

Publication I*: *Improved survival of left ventricular assist device carriers in Europe according to implantation eras: results from the PCHF-VAD registry

556 patients were involved, and for the purpose of this sub-analysis, the patient data were divided into two eras of similar duration, according to the date of LVAD implantation (Figure 4).

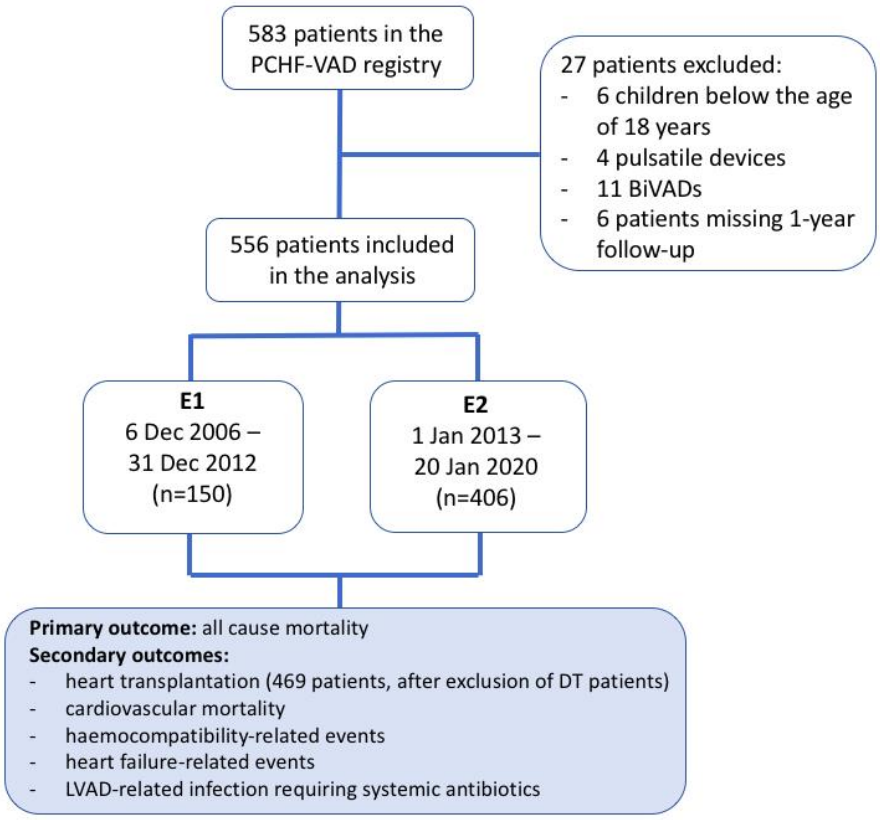

Figure 4. CONSORT diagram depicting the enrolment and grouping of patients according to time of LVAD implantation, as well as the examined outcomes.

The primary outcome was defined as all-cause mortality, while the secondary outcomes included: heart transplantation, cardiovascular death, haemocompatibility-related events (non-intracranial bleeding, intracranial bleeding, ischaemic stroke and pump thrombosis), HF-related events (RVF and hospitalization for HF), and LVAD-related infection requiring systemic antibiotics (110). All events were adjudicated by the attending physicians. For the analysis of the heart transplantation outcome, patients designated as DT LVAD candidates were excluded from the analysis, resulting in a population of 469 patients. The risk of the outcome events was analysed according to implantation era.

Publication II: Outcome of patients on heart transplant list treated with a continuous flow left ventricular assist device: Insights from the TRans-Atlantic registry on VAd and TrAnsplant (TRAViATA)

The manuscript addresses descriptive statistics of the entire TRAViATA population. The primary outcome was defined as all-cause mortality and was compared among the patients enrolled across both continents.

4.6.2. Association of patient characteristics with outcomes

Publication III: Sex-related differences in left ventricular assist device utilization and outcomes: results from the PCHF-VAD registry
&
Publication IV: How does age affect the clinical course after left ventricular assist device implantation: results from the PCHF-VAD registry

Both sub-analyses included 562 patients. For the analysis of the effect of age at LVAD implantation, patients were categorized into three categories: those younger than 50 years, patients between 50-64 years, and 65 years and older. In the analysis of the effect of sex, patient outcomes were compared according to female / male sex. The primary endpoint was all-cause mortality. Secondary outcomes comprised heart transplantation, weaning from LVAD support, HF hospitalization, RVF, device-related infection requiring systemic antibiotics, non-fatal thromboembolic events, intracranial bleeding, non-cerebral bleeding, LVAD exchange, and haemocompatibility score. In order to analyse the aggregate burden of haemocompatibility-related adverse events (HRAE), the haemocompatibility score (HCS) was calculated for all patients. Each HRAE received a point score, based on its clinical relevance (Publication Suppl. Table S1). The HCS was calculated for each patient by summing up all points associated with all HRAEs experienced by the patient during the follow-up period (111).

Publication V: Impact of Progressive Aortic Regurgitation on Outcomes after Left Ventricular Assist Device Implantation

This sub-analysis included patients with first-time cf-LVAD implantation, with documented dynamics of AR during follow up. Exclusion criteria were prior or concomitant aortic valve surgery and lack of paired echocardiographic data (Figure 5). Aortic regurgitation was quantitated into none, mild, moderate and severe, per centre-specific protocols, predominantly

assessed visually or by vena contracta (112). Patients were dichotomized into two groups based on AR progression during the course of follow-up. Patients in group AR_1 either developed *de-novo* AR or had evidence of AR progression by at least one grade, while patients in whom aortic valve competence was preserved were assigned to the AR_0 group.

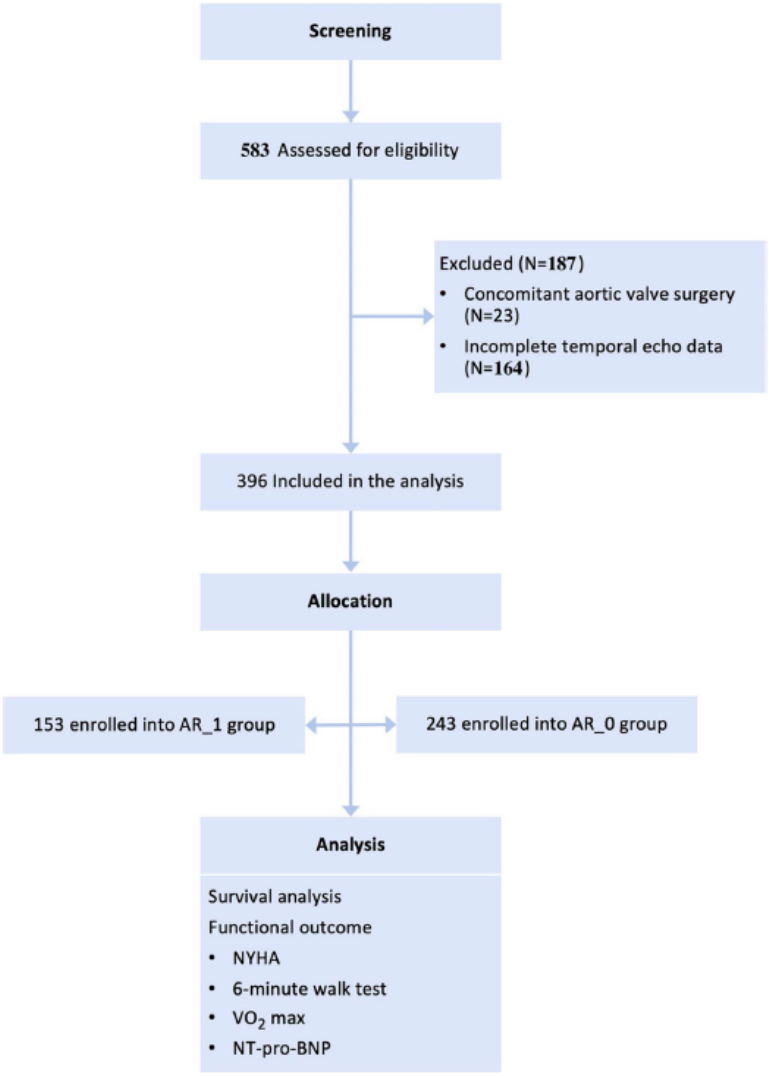

Figure 5. CONSORT diagram depicting the enrolment and grouping of patients according to presence of aortic regurgitation. AR, aortic regurgitation; AR_0, no AR group; AR_1, AR group.

The main outcome was all-cause mortality. The secondary outcomes were cardiovascular death, heart failure hospitalization, RVF, life- threatening ventricular arrhythmias, intracranial and non-cerebral bleeding events after LVAD implantation (113). We performed an intergroup comparison of N-terminal fragment of B-type natriuretic peptide (NT-proBNP) at three time points: baseline, discharge from index hospitalization and at 6 months post LVAD implantation. Follow up assessments of functional, haemodynamic, echocardiographic and

electrocardiographic data were performed. Where available, additional information on the functional status was provided by an intergroup comparison of 6-minute walk tests (6MWT) and NYHA class.

4.6.3. Combined device therapy

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

448 patients with all relevant CIED data available (time of CIED implantation, any deactivation periods, generator replacements) were included into this sub-analysis (patient selection and cross-over depicted in Figure 6). 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.

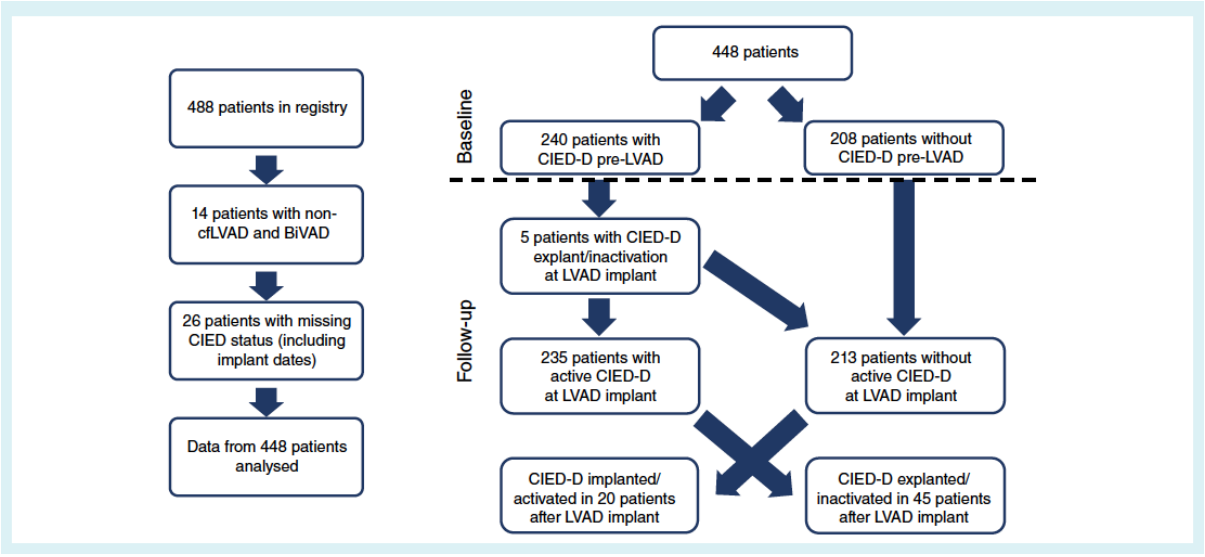

Figure 6. (Left) CONSORT diagram depicting patient selection from the PCHF-VAD registry. (Right) Patient flow during the follow-up period regarding a cardiac implantable electronic device with a defibrillator component (CIED-D). BiVAD, biventricular assist device; cf-LVAD, continuous flow left ventricular assist device; LVAD, left ventricular assist device.

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

This analysis included cf-LVAD carriers stratified by the presence or absence of CIED prior to LVAD implant: none, ICD, CRT-P, and CRT-D. Primary endpoints assessed were survival to transplant and late RVF. Secondary endpoints included early RVF, symptomatic VA 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 (clinical findings of peripheral oedema, 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 (need for post-implant intravenous 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.

4.7. Statistics

4.7.1. Descriptive statistics

Baseline characteristics are reported as counts and percentages for categorical variables and continuous variables as mean±standard deviation (or median and 25th–75th percentile for non-normally distributed variables). Baseline patient data in Publication I were compared according to era of LVAD implantation, in Publication II the baseline characteristics were compared between EU and US patients, in Publication III according to sex, in Publication IV according to age groups, in Publication V patient outcomes were compared based on aortic valve competence (groups AR_0 and AR_1), in Publication VI based on the presence of a CIED with an active defibrillator component, while in Publication VII, patients were grouped according to presence of CIED into multiple groups (none, ICD, CRT-P, and CRT-D). In

Publications I, III, IV, V, VI the inter-group differences based on the compared characteristic were assessed using the chi-square test for categorical variables or ANOVA (or Kruskal–Wallis test for non-normally distributed variables) for continuous variables. In Publication II, two-sample t-tests and two-sample Mann Whitney tests were used to compare continuous variables depending on normality, and Fisher's exact tests were used to compare categorical variables. Continuous data were evaluated for normality using the Shapiro-Wilk test.

4.7.2 Outcome analysis

4.7.2.1. Survival analysis / Regression models

For survival analyses, the time of LVAD implantation was considered as the index date, while the duration of follow-up was defined as time to last contact, weaning from LVAD, heart transplantation or death (whichever came first). In Publication I, the analysis time was limited to the first year after LVAD implantation, in order to equalise the time at risk among the two studied groups.

The primary outcome for all publications was all-cause death, while the main secondary outcomes included cardiovascular death, heart transplantation, device related infection, occurrence of VA, hemocompatibility related events (ischemic events, bleeding, pump thrombosis), HF related events (RVF and HF hospitalization), ICD activations, indicators of functional capacity, and other. Crude incidence rates for the studied outcomes were reported per 100 patient-years. The hazard ratio (HR) for the examined outcomes was estimated using the Cox proportional hazards model and presented with a corresponding 95% confidence interval (CI). In Publication IV, the HR were calculated for a 10-year increase in age. The Kaplan-Meier method and log-rank test were used to compare the primary and key secondary outcomes across groups.

Multivariate regression analysis differed between the papers, according to the specific hypotheses. In Publication I, multivariable models were adjusted for clinically relevant, patient-related baseline covariates, which were selected for each individual outcome (listed in detail in the article). In Publication II, multivariate analyses included several models: Model 1 was based on data with less than 5% missing data, while models 2 and 3 included variables with more missing data (up to 55%), and covariates with a p value <0.2 were used to fit multivariate models, while the region variable (US vs. EU) was forced into the model (listed

in greater detail in the article). In Publication III, the associations between gender and outcomes were adjusted for age, INTERMACS class, baseline creatinine serum levels, need for mechanical circulatory support prior to LVAD implantation, need for vasopressor use prior to LVAD implantation and the LVAD implantation date quartile. In Publication IV, the associations between age and outcomes were adjusted for gender, INTERMACS profile, baseline serum creatinine level, quartiles of LVAD implantation date, the need for mechanical circulatory support prior to LVAD surgery and pre-LVAD vasopressor use. In Publications III and IV additional sensitivity analyses for all-cause mortality were performed, adjusted for variables selected through the forward stepwise Cox proportional hazards model. Covariates with less than 30% of missing data were assessed in a forward stepwise selection process with a significance level of 0.05 and 0.10 for entry and removal thresholds respectively. The same statistical approach with the selection of covariates for multivariate analysis was used in Publications V and VI. In Publication VII, covariates in the adjusted models were chosen *a priori* based on prior literature, clinical knowledge, and availability.

4.7.2.2. Competing outcomes

In Publications I, III and IV, a competing outcomes analysis was performed accounting for heart transplantation and weaning from LVAD. The analysis was performed based on Fine and Gray's proportional subhazards model and depicted graphically with competing outcome curves.

4.7.2.3. Time-updated analysis

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 in Publication VI 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.

4.7.2.4. Propensity score analysis

In order to additionally adjust for the differences between the patient groups in Publication VI, a propensity score was created, 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 profile, LVAD implantation 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.

4.7.2.5. Missing data

For Publications III, IV, and VI, variables with less than 30% missing data were imputed using multiple imputation, while those with a larger proportion of missing data were not included in these analyses. The imputed data were only used for the multivariable analysis. Variables with missing data were reported to be minimal in the TRAViATA dataset, similarly distributed between the compared groups, and were thus omitted.

4.7.3. Utilised statistical tools and programmes

In all analyses, a two-sided P value of 0.05 or lower was considered statistically significant. In Publication I, statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA). In Publication II, statistical analyses were done using R programming language and environment (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (version 6, GraphPad Software Inc., CA, US). In Publication III and IV, statistical analyses were performed using Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). In Publication V and VI, data were processed using the Stata version 14 (StataCorp, College Station, TX, USA). For Publication VII, statistical analyses were performed using statistical package for social science (SPSS) version 26 (IBM Corp).

5. Results

This section outlines the most important findings of the thesis manuscripts, while the full results are presented in the corresponding publications, included in the thesis.

5.1. LVAD population landscape and key outcomes

5.1.1. Publication I

Baseline characteristics

556 patients included into the PCHF-VAD registry between December 2006 and January 2020 were divided into two eras by date of LVAD implantation, first era (E1: December 2006-December 2012) and the second era (E2: January 2013-January 2020), including 150 and 406 patients, respectively. All baseline data are presented in Table 1 in the article. The patients implanted in E2 were significantly older (50±12 vs. 54±12 years, $p<0.001$), with a significantly greater burden of nearly all registered comorbidities. There was a significant difference regarding the type of LVAD implanted, with HM 3 dominating in E2, and the implantation strategy: 86% of those implanted in E1 were BTT candidates, while in E2 a prominent DT population (21%) emerged. INTERMACS profiles 1 and 2 dominated E1, and accordingly a significantly higher proportion of patients required temporary mechanical circulatory support (MCS) prior to LVAD in E1 (39.6% vs. 21.5%, $p<0.001$).

The influence of implantation era on overall survival at 1 year

During the 1-year follow-up period, the primary outcome of all-cause death occurred in 107 patients (19%). In unadjusted analysis, there was a trend towards lower all-cause mortality in E2 compared to E1, although not reaching statistical significance (HR 0.75, 95% CI 0.50–1.13, $p = 0.17$) (Figure 7A, Publication Table 2 and Figure 1B), while in the multivariable analysis, receiving an LVAD during E2 was associated with a statistically significant 42% reduction in the risk of the primary outcome (HR 0.58, 95% CI 0.35–0.98, $p = 0.043$, Publication Table 3 and Table S2). The competing outcomes analysis resulted in a similar trend of reduction of the risk of all-cause mortality in E2 (subdistribution hazard ratio [SHR] 0.80, 95% CI 0.53–1.20, $p = 0.28$).

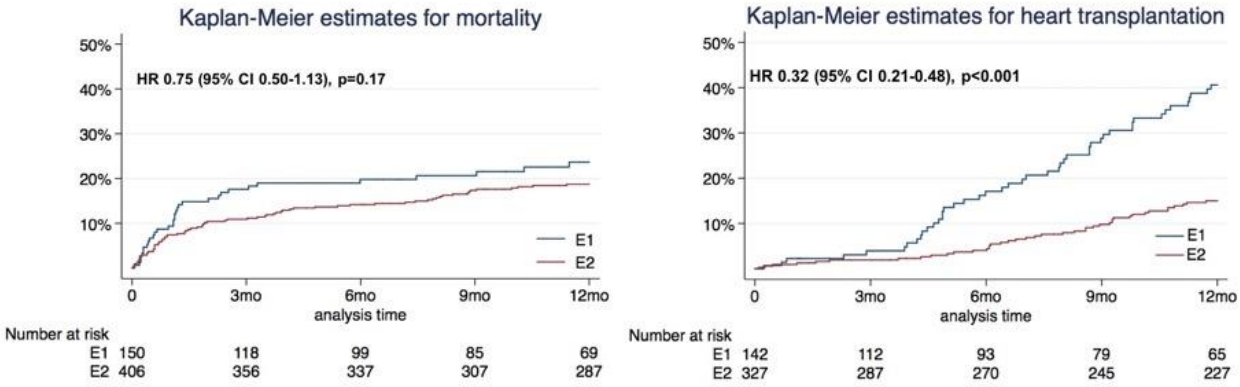

Figure 7. a) Kaplan Meier curves for a) all-cause mortality; and b) heart transplantation in 1-year follow up according to implantation eras. E1, Era 1; E2, Era 2.

The influence of implantation era on heart transplantation during 1-year follow-up

After excluding 87 DT patients, heart transplantation occurred in 88 patients (19%) during the 1-year follow-up period. In unadjusted analysis, there was a significant, 68% lower likelihood of undergoing heart transplantation in E2, compared to E1 (HR 0.32, 95% CI 0.21–0.48, p<0.001) (Figure 7B, Publication Table 4 and Figure 2B), which remained significant after adjusting for clinically relevant covariates (HR 0.40, 95% CI 0.23–0.67, p = 0.001) (Publication Table 4). When heart transplantation was considered a main event in the competing outcomes analysis (with death and weaning as competing events), receiving an LVAD in E2 was associated with a statistically significant, 65% reduction in chance of receiving a heart transplantation (SHR 0.35, 95% CI 0.23–0.53, p<0.001) (Publication Figure 3, Publication Figure S2).

The influence of implantation era on other secondary outcomes during 1-year follow-up

The incidence rate of haemocompatibility-related events was lower in E2 (E1: 44.5, 95% CI 32.8–60.4 vs. E2: 33.8, 95% CI 27.7–41.2 per 100 patient-years), and in multivariate analysis, LVAD implantation during E2 was associated with a significant, 40% reduction in the risk of developing a haemocompatibility-related outcome (HR 0.60, 95% CI 0.39–0.91, p = 0.016) (Publication Table 5 and Table S6). The crude incidence rate of HF-related events increased over time (E1: 23.0, 95% CI 15.0–35.2 vs. E2: 42.1, 95% CI 34.9–50.9 per 100 patient-years (p-y)), and E2 was associated with a significant increase in the risk of HF-related events, in unadjusted and adjusted analyses (Publication Table 5 and Table S7). LVAD-related infections requiring systemic antibiotics occurred in 138 patients (25%), with a 42% reduction in risk of infection in E2 compared to E1 (E2 vs. E1: HR 0.58, 95% CI 0.41–0.83, p = 0.003),

which remained significant in adjusted analysis (HR 0.64, 95% CI 0.43–0.95, p = 0.027 (Publication Table 5 and Table S9). Patient age was the only remaining covariate that modified the risk of infections, being lower in older patients.

5.1.2. Publication II

Baseline patient characteristics at the time of LVAD implantation

A total of 524 patients (225 from US and 299 from EU) were included in the TRAViATA registry, predominantly male (84.4%) with a median age of 55 years [IQR 45–61]. Notable differences included a more racially diverse and significantly older cohort in the US compared with EU cohort, with a significantly higher prevalence of comorbidities. Prevalence of INTERMACS class 1 or 2 and the need for temporary MCS were similar between the cohorts. The HM II device was implanted more frequently in the EU (71.9%), and the HW device in the US (56.0%; p < 0.001).

Outcomes and predictors of mortality

Overall patient survival was 83.1% at 1 year and 66.5% at 5 years and similar between the two cohorts (US 63.1% vs. EU 68.4% at 5 years, Figure 8).

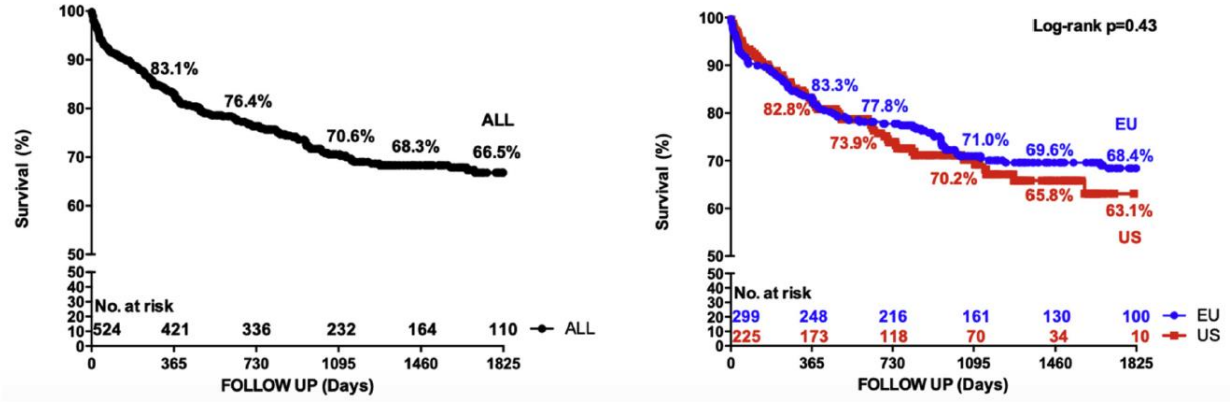

Figure 8 Left panel: Kaplan-Meier curve of the overall 5-year survival of BTT LVAD patients. Right panel: Kaplan-Meier curves of the overall 5-year survival of BTT LVAD patients in EU and US (differences in survival tested with the Mantel log-rank test). Follow-up began at LVAD implant, up to death or lost-to-follow-up, without censoring for transplantation.

The overall proportion of patients alive, on at 1, 2, and 3 years was 50.2%, 28.1% and 13.8%, respectively (Figure 9), without differences between the US and EU, but a larger proportion of death was observed in the US group, among patients completing 3 year follow up (47.0% vs. 34.0% respectively, p = 0.013). At 1-year, 46.0% and 33.8% were transplanted in the US and EU, respectively (p = 0.11), and none underwent LVAD explant. Cerebrovascular accidents were the main cause of death during LVAD support in the US and EU cohort.

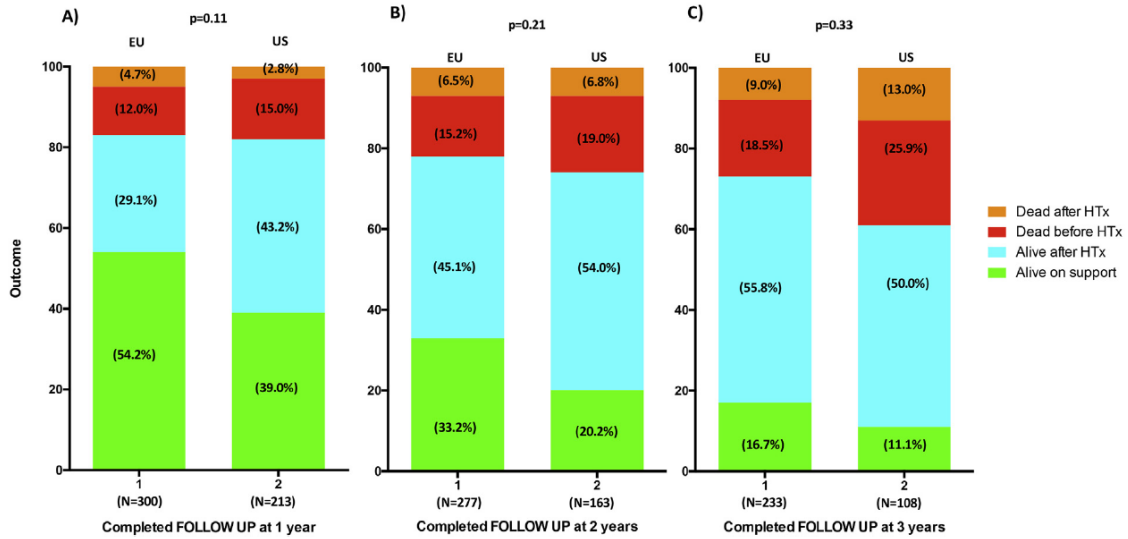

Figure 9. The status of patients that reached a complete follow up at 1, 2, and 3 years.

In Publication II, univariate and multivariate Cox regression analyses were utilised to evaluate predictors of mortality in the overall cohort (Publication Table 2). In the main adjusted model, independent predictors of overall mortality were older age, higher body mass index (BMI), higher creatinine, temporary MCS before LVAD and use of HW, while origin (US vs. EU) was not associated with survival. Heart transplantation, when added to the model as a time-dependent covariate, was independently associated with an improved survival rate (HR 0.46, 95% CI 0.31–0.68), as was US origin (HR 0.71, 95% CI 0.51–0.98) (Publication Table 2). Two other multivariate models presented in Publication II have not detected origin as a variable associated with survival.

Heart transplantation and donor characteristics

There was a similar proportion of BTT patients in the US and the EU cohort, with patients on average listed for heart transplantation the same day they received an LVAD (Publication Figure 3A). Median time to heart transplantation was shorter in the US vs. EU cohort (238 vs. 342 days, respectively; p = 0.0003), donors were significantly younger (median age: US 29

years; [IQR 23–39]; EU: 48 years [IQR 38–54], p < 0.0001), more likely to have been resuscitated from cardiac arrest (p < 0.0001), and the utilization of undersized donors (donor-to-recipient weight ratio≤0.80) was more common in the US (p= 0.011). Post-transplantation survival was similar between the two cohorts (US 82.0% vs. EU 84.7% at 4 years, unadjusted Mantel log-rank test p = 0.99; Publication Figure 3D). Higher age and HW implantation were independently associated with post-transplant mortality. Graft failure and sepsis were the main causes of death after heart transplantation in both groups.

Adverse events on LVAD support

Poisson regression analysis showed a significant difference in the incidence rates of overall stroke, ischemic stroke, gastrointestinal bleedings (GIBs), late RVF, and driveline infection in the US and EU cohort, while the incidence rates of haemorrhagic stroke and pump thrombosis did not differ. The results of the multivariate analysis are reported in Publication II.

5.2. Association of patient characteristics with outcomes

5.2.1. Publication III

A total of 562 patients, mean age 53.1±12.0 years, were included, 457 (81.3%) male and 105 (18.7%) female. The baseline characteristics are shown in Table 1 in the article. A higher proportion of women were critically ill at the time of LVAD implantation, more often in INTERMACS profile 1 or 2 (55.3% vs. 41.2%, p=0.009), and needing mechanical circulatory support pre-LVAD implantation (39.2% vs. 23.0%, p=0.001), but with less comorbidities.

Survival

Patients were followed for a median of 344 [IQR 147-823] and 435 [IQR 190-816] days respectively (p=0.40), with no differences in crude all-cause mortality between genders (Figure 10).

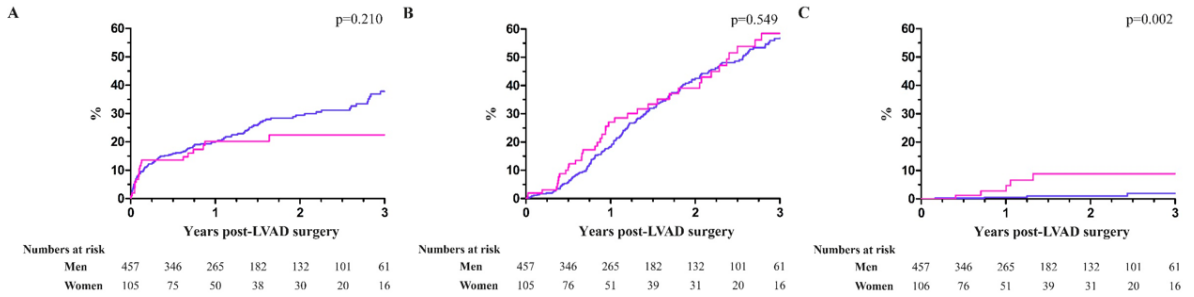

Figure 10. Kaplan-Meier plots of time to A) all-cause mortality, B) heart transplantation (censored for death) and C) weaning from LVAD (censored for death) according to sex. Men (blue line), women (pink line).

During the entire follow-up period, 29% male and 21% female patients died (p=0.08). Female patients were numerically less likely to die during follow-up, but not significantly after adjustment (HR 0.79, 95% CI 0.50-1.27), (Publication Table 2). Causes of death did not differ.

Secondary endpoints

Similar proportion of men and women underwent heart transplantation (Publication Figure 1), while women were more often weaned from LVAD support (Publication Table 2), most frequently those with peripartum and dilated cardiomyopathy. The results of the competing outcome analysis are shown in Figure 11.

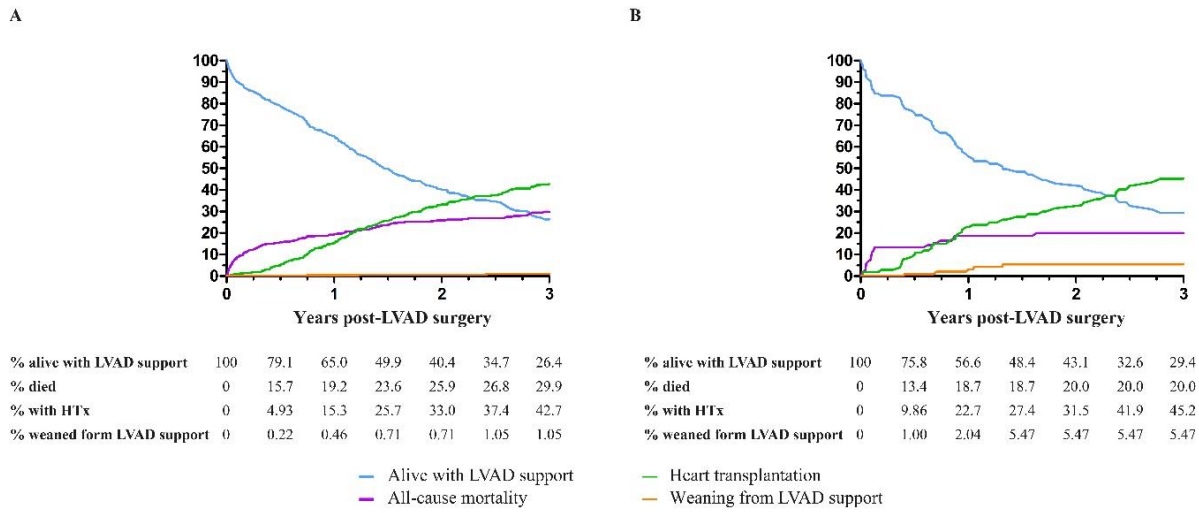

Figure 11. Competing event analysis presented for men (panel A) and women (panel B).

Female sex was associated with a lower chance of VA post-LVAD (HR 0.56, 95% CI 0.33-0.95) (Publication Table 2), and a non-significantly higher risk of RVF (HR 1.57, 95% CI 1.00-2.49, p=0.053).

5.2.2. Publication IV

Of the 562 patients, 184 (32.7%) were younger than 50 years, 305 (54.3%) were aged 50-64 years, and 73 (13.0%) were ≥65 years. The baseline characteristics of the patients stratified by age are shown in Table 1 in the Article. Older patients more often had a HM3 device and more often received LVAD as DT. Additionally, older patients had more advanced comorbidities and were less often implanted in an acute setting, indicated by a higher (less severe) mean INTERMACS profile.

Survival

Median follow-up time on LVAD support was 1.1 [IQR 0.5–2.2] years. Patients ≥65 years had a significantly higher all-cause mortality than those aged 50–64 and <50 years (46.3% vs. 37.5% and 25.0%, respectively, P = 0.03), with pairwise comparison showing no significant survival differences between the 50–64 and ≥65 age groups. One-year mortality was notably higher in the oldest patient group, but survival was more comparable 12 months post-LVAD implantation (Publication Figure 1B and C). Furthermore, patients aged ≥65 years were significantly less often transplanted (14.3% vs. 55.9% and 70.5%, respectively, P < 0.001) and weaned from LVAD support (0% vs. 1.0% and 7.7%, respectively, P = 0.021) than those aged 50–64 and <50 years. A 10-year increase in age was significantly associated with a higher mortality risk (HR 1.34, 95% CI 1.15–1.57) and lower chance of heart transplantation (HR 0.90, 95% CI 0.80–1.01) or weaning from LVAD (HR 0.63, 95% CI 0.35–1.16) after adjustment (Publication Table 2).

Secondary endpoints

LVAD-related infections that required systemic antibiotics occurred less often in older patients, with a 10-year age increase associated with significantly lower risk of infection in multivariate analysis (HR 0.88, 95% CI 0.77–0.99; Publication Table 2). A 10-year increase in age was associated with a higher risk of intracranial (HR 1.49, 95% CI 1.10–2.02) and non-intracranial bleedings (HR 1.30, 95% CI 1.09–1.56; Publication Table 2). The risk of incident

atrial fibrillation or flutter was higher in older patients (HR 1.38, 95% CI 1.11–1.73). The risk of non-fatal thromboembolic events was numerically, but not significantly higher with increasing age. There were no significant differences in other secondary outcomes (Publication Table 2).

5.2.3. Publication V

Study population

396 patients were included in the analysis; notable findings include a lower BMI (24 [IQR 22-28] vs. 26 [IQR 23-29], P<0.01), lower prevalence of diabetes (14% vs. 26%, p=0.01), and higher NT-proBNP (5181 [IQR 3004, 10098] vs. 3820 [IQR 2345, 7440] pg/ml, p<0.01) in AR_1 group, who more often received a HM II; and were more likely implanted with a BTT strategy than the control group. Baseline demographic data are shown in Table 1 in the article.

Primary and secondary outcomes

The median time on LVAD support was 1.4 [IQR 0.8, 2.6] years. All-cause death occurred in 62 (26%) patients in the AR_0 group and in 39 (26%) patients in the AR_1 group (Publication Table 2). The unadjusted analysis demonstrated a trend towards lower risk of all-cause mortality in the AR_1 group (HR 0.91, 95% CI 0.61-1.36, p=0.65) (Publication Figure 2), which remained insignificant after adjusting for LVAD type, detected as an independent predictor of mortality in stepwise regression (HR 0.95, 95% CI 0.63-1.43, p=0.82). There were no significant differences in other adverse events between the groups.

Follow-up assessments - NT-proBNP values and metrics of functional outcome

There were no differences in NT-proBNP values, NYHA class or 6MWT (Publication Table 4) at discharge from index hospitalization between the groups, but there was a lower proportion of patients in NYHA class III in the AR_0 group than in AR_1 (10% vs. 18%, respectively, p=0.03). Variables associated with NYHA class at 6-month follow-up on univariate analysis were then entered into a multiple linear regression model (AR progression, age, hypertension and chronic obstructive pulmonary disease (COPD)). Progression of AR was significantly associated with NYHA class at later follow-up in the multiple regression analysis (p=0.03), as was the presence of COPD (p=0.01).

Hemodynamic and echocardiographic data

Patients in the AR_1 group at 6-month follow-up were significantly more likely to have permanently closed AoV on echocardiography (55% vs. 38%, p<0.01, Publication Figure 3). In multivariate regression analysis, absence of AoV opening at 6-month was related to worsening AR (p<0.001), irrespective of systolic blood pressure value (p=0.67). Patients with progressive AR had less efficient LV unloading at 6-month follow-up, albeit not statistically significant (Publication Table 4). RV function, quantified by TAPSE, deteriorated in the AR_1 group at 6-month follow-up (Publication Table 4). In a multivariate logistic regression model, an increase in log-transformed NTproBNP increased the odds of developing *de-novo* or worsening AR (OR 1.50, 95% CI 1.12-2.02, p=0.008), while diabetes at baseline and LVAD as BTD (vs. LVAD as BTT) were associated with its lower odds (OR 0.40, 95% CI 0.21-0.78, p=0.007 and OR 0.39, 95% CI 0.17-0.88, p=0.023).

5.3. Combined device therapy

5.3.1. Publication VI

Baseline characteristics

Data from 448 patients were analysed, grouped according to CIED-D status before LVAD implantation: 240 patients (54%) carried a CIED-D pre-LVAD, while 208 patients (46%) did not (Figure 6). Baseline characteristics according to CIED-D status pre-LVAD are provided in Table 1 in the article. CIED-D carriers were older and more frequently male, predominantly with dilated cardiomyopathy and chronic kidney disease, while the other group more often had ischaemic cardiomyopathy. Known atrial fibrillation and previous VAs (requiring therapy) were more frequent in the CIED-D pre-LVAD group. Patients with CIED-D were more frequently carriers of HW and HM 3 devices, while HM II was more common in the control group. The proportion with an LVAD as a BTD was higher in those without a CIED-D, and these patients were also more frequently in INTERMACS profiles 1 and 2. The proportion of patients receiving 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 required vasopressor medications, life support, had prior cardiac surgery or a concomitant surgical procedure. 44% of the patients without a CIED-D and 34% of those with were transplanted (39% of the entire cohort). 20 patients received a

CIED-D post-LVAD (9.6% of those without a CIED-D pre-VAD) (median time to CIED-D implant of 57 [IQR 29.5–243.5] days), and 45 patients (19% of those with a CIED-D pre-VAD) had their CIED-D deactivated post-LVAD (median time of deactivation of 252 [IQR 77–379] days). Of these deactivations, 11 occurred during active LVAD support (median time 40 [IQR 0–368] days), while the rest was deactivated at transplantation.

All-cause mortality and active CIED-D carrier status following LVAD implantation

The median time on LVAD support was 1.1 [IQR 0.5–2.0] years, similar in both groups. At the time of LVAD implantation, 213 patients (48%) did not have a CIED-D and 235 (52%) did (Figure 6). All-cause death occurred in 134 patients (30% of the overall study population). 68 patients remained in the non-CIED-D group and 55 remained in the CIED-D group and suffered all-cause death, while 5 patients had the CIED-D deactivated and 6 entered the CIED-D group before death. The incidence rates for all-cause death were 28 events per 100 patient-years (95% 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 (Article 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 an unadjusted time-varying analysis, there was a 36% reduction in the risk of all-cause mortality in patients with an active CIED-D post-LVAD implantation (HR 0.64; 95% CI 0.46–0.91, p = 0.012) (Figure 12 and Publication Table 2).

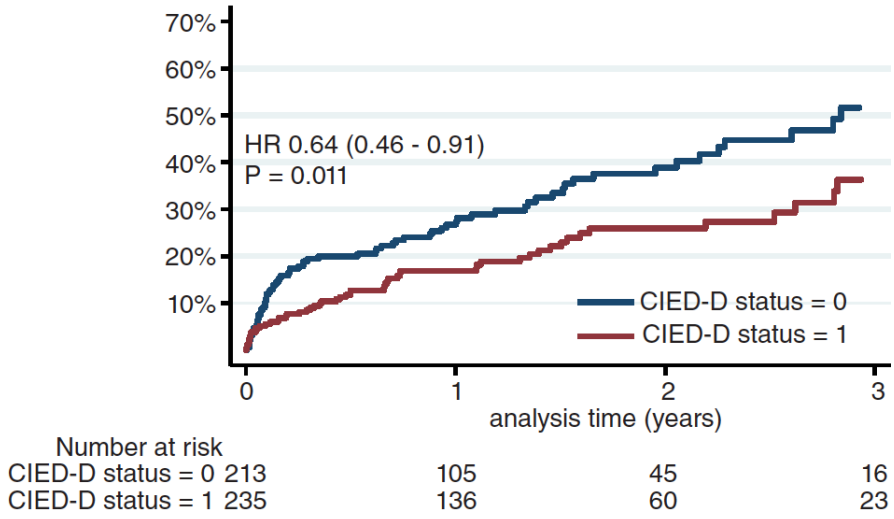

Figure 12. Kaplan–Meier plot of time to all-cause mortality, according to CIED-D status following LVAD implantation. CIED-D status 0 = no CIED-D post-LVAD, CIED-D status 1 = CIED-D present post-LVAD.

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). After adjustment for variables independently significant in stepwise regression, the HR for CIED-D post-LVAD status remained significant (0.59, 95% CI 0.40–0.87; p=0.008), while age, prior cardiac surgery, number of VA episodes pre-LVAD and vasopressor use were the remaining significant predictors of the primary outcome (Publication Table 3). Active post-LVAD CIED-D carrier status remained significant after adjusting for active CRT-P post-LVAD implant (HR 0.57, 95% CI 0.38–0.84; p=0.005) (Publication Table 3). Furthermore, this finding was consistent even after excluding patients with a CIED-D placed or deactivated following LVAD implantation, both in unadjusted and adjusted analysis. In a subgroup analysis, the treatment effect of a CIED-D post-LVAD was consistent across various categorical subgroups (Publication Figure 3).

Secondary outcomes and active ICD/CRT-D carrier status following LVAD implantation
The occurrence of symptomatic VAs or those requiring intervention was noted in 24% of the entire cohort (107 patients). In patients with a CIED-D, a VA episode requiring anti-tachycardia pacing (ATP) occurred in 25 patients, while 42 received a shock; 29% of the CIED-D cohort received at least one of these therapies, but none died on the day of therapy delivery. Patients with a CIED-D post-LVAD had a significantly increased crude risk of post-LVAD VAs, no longer significant after adjusting for the relevant baseline characteristics (HR 1.57, 95% CI 0.98–2.52, p=0.06). An additional analysis of incident VAs post-LVAD as a time-varying covariate demonstrated that the occurrence of VA 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. Prior cardiac surgery, baseline vasopressor use 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 (Publication Table S4).

Sensitivity analyses

Given the significant differences in the baseline characteristics between the patient groups, a propensity score adjustment was performed, following which the relative risk of all-cause death remained significantly reduced in the CIED-D carriers, while the propensity score itself was not significantly related to all-cause death. Strong predictors of CIED-D carrier status were a history of atrial fibrillation or VAs, while having a prior myocardial infarction and a concomitant procedure with LVAD implantation reduced the odds of carrying a CIED-D. In order to account for missing data, additional sensitivity analyses were performed by multiple imputation of missing values, yielding results consistent with the original analyses.

5.3.2. Publication VII

Baseline characteristics

Baseline characteristics of the 524 patients are shown in Table 1 in the article. The mean age was 52±12 years, 84.4% were men, and 59.9% were implanted with HM II. 74% patients had a pre-existing CIED prior to LVAD implantation: ICD (N = 239), CRT-P (N = 28), and CRT-D (N = 111). Those with no device were more likely to be anaemic, have a lower INTERMACS profile and require temporary mechanical circulatory support. Those with an ICD were more likely to have a history of ischaemic cardiomyopathy and tricuspid valve repair. Patients with CRT-D were older and more likely to be implanted with a HM II.

Primary endpoints

Overall median follow-up was 354 days [IQR 166–701]. 113 deaths occurred prior to heart transplantation: 19.9% in those with no device, 24.3% in ICD, 10.7% in CRT-P, and 20.7% in CRT-D carriers. 312 transplantations occurred during follow-up: 63.7% in those with no device, 54.4% in ICD, 67.9% in CRT-P, and 63.1% in CRT-D carriers. Kaplan-Meier analysis showed no significant difference across the groups (log-rank $p = 0.83$) (Figure 13). Adjusted Cox regression survival analysis similarly showed that type of CIED vs. no device was not associated with death prior to heart transplantation (Publication Figure 2A).

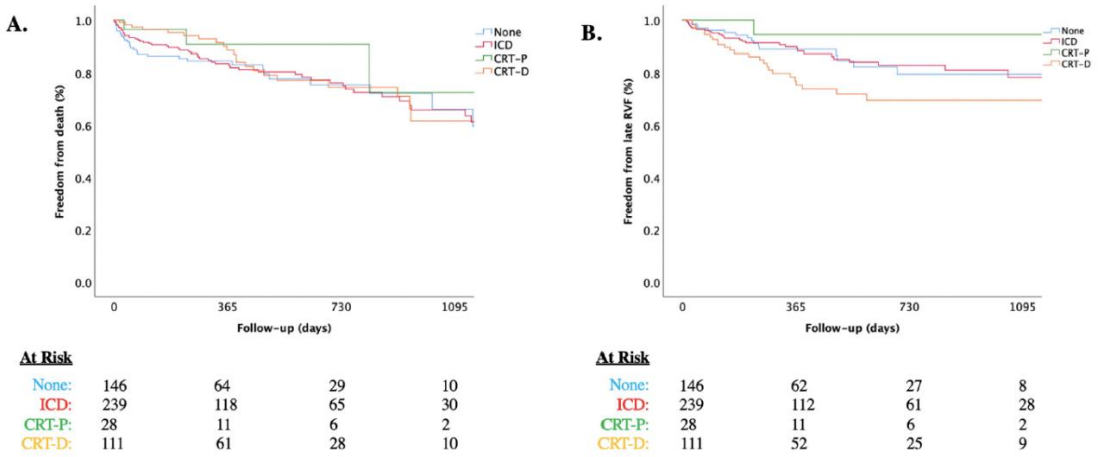

Figure 13. Kaplan-Meier estimates for the cumulative incidence of **A.)** mortality and **B.)** late right ventricular failure as stratified by CIED**.** Log-rank *p* value: 0.83 for mortality and 0.02 for late RVF.

72 patients developed late RVF at a median of 189 days (Q1-Q3: 72–364): 11.0% in those with no device, 12.1% in ICD, 3.6% in CRT-P, and 23.4% in CRT-D carriers. Kaplan-Meier analysis showed a higher incidence of late RVF in CRT-D compared to other groups (log-rank = 0.02) (Figure 13). Compared to no CIED, CRT-D was associated with nearly a three-fold adjusted increase in late RVF (HR 2.85, 95% CI 1.42–5.72, p=0.003), which was not noted in ICD and CRT-P groups (Figure 14).

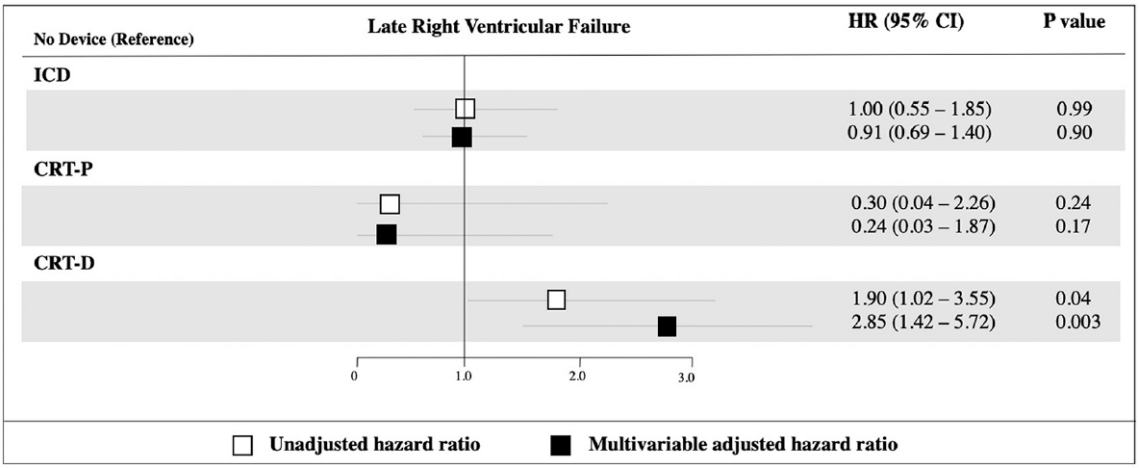

Figure 14. Unadjusted and adjusted Cox regression models for late right ventricular failure stratified by cardiac implantable electronic device, compared to patients with no device.

CRT-D in HW patients was associated with nearly a 5-fold adjusted increase in late RVF (HR 4.73, 95% CI 1.71–13.1, p=0.003), while no significant association was observed with HM II.

Furthermore, when stratified by continent, a nonsignificant trend was observed with increased risk of late RVF in the US in CRT-D carriers.

Secondary endpoints

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, but no difference in experiencing ICD shocks (Publication Table 2).

6. Discussion

Given the lack of prospective, randomised, multicentric studies on the growing population of LVAD patients, the retrospective registry data is increasingly more relevant. The data presented in this thesis stem from two large multicentric, retrospective registries, dedicated to accumulating data on cf-LVAD carriers, resulting in several important findings. Improved overall survival was noted in European LVAD carriers implanted in the more recent years, despite older, more comorbid patients being implanted. A comparison of the EU and US BTT patient populations yielded similar overall survival, despite significant differences in baseline characteristics (US patients were older and with more comorbidities, whereas the EU patients had lower BMI and lower incidence of diabetes).

Further subgroup analyses showed that higher patient age was associated with an increased risk of all-cause mortality after LVAD implantation, with more bleeding complications; fewer women than men underwent LVAD implantation, with women receiving the LVAD at a more advanced stage of HF and more critically ill, but nevertheless, without significant survival differences. In regard to LVAD-associated adverse events, we have shown that the *de-novo* occurrence or worsening of aortic regurgitation post-LVAD implantation did not affect survival.

Finally, analyses of combined device therapy demonstrated that carrying a CIED with an active defibrillator component (an ICD or CRT-D device) during the course of LVAD support was associated with a reduced crude and adjusted risk of all-cause mortality, compared to the patients without an active defibrillator component in the European PCHF-VAD registry, while the aforementioned benefit was not noted in the EU-US TRAViATA cohort.

6.1. Baseline population characteristics in the registries (PCHF-VAD vs. TRAViATA)

Baseline characteristics of the PCHF-VAD population

Baseline characteristics of the PCHF-VAD population implanted with an LVAD throughout the years are presented in Publication I, where patient characteristics of LVAD carriers are compared according to date of LVAD implantation, separating the patients into Era 1 and 2. By positioning the PCHF-VAD population in the context of global trends of LVAD carriers, we have noted several important points. Publication I demonstrated that significantly older patients with an increasing comorbidity burden, higher INTERMACS profile and a higher

proportion of CIEDs were implanted more recently. This somewhat differs from the 12th INTERMACS report (US LVAD carriers), which also compared two time eras of LVAD implantation, concluding that the recently implanted patients were less haemodynamically stable, requiring more temporary MCS and inotropes, were less often ICD carriers, but still noting an increasing DT population, attributable to shifts in device approvals and HTx allocation regulation (114). Interestingly, despite these differences, both registries suggested improved survival in the most recent era, what we postulate may be due to improved experience of the LVAD centres (Figure 15).

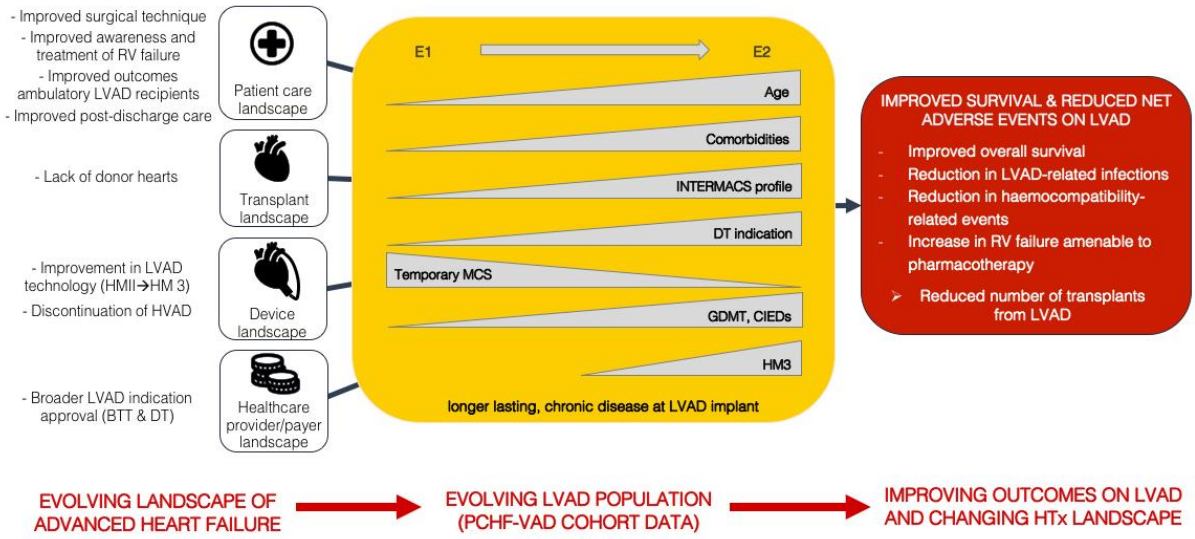

Figure 15. Multiple factors influencing the outcomes of the LVAD patients.

E1, era 1; E2, era 2; RV, right ventricle; LVAD, left ventricular assist device; HMII, HeartMate II; HM3, HeartMate 3; HVAD, HeartWare; BTT, Bridge to transplantation; DT, destination therapy; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; MCS, mechanical circulatory support.

Significant evolution in the devices implanted and the implantation indication is seen in the PCHF-VAD registry throughout the observed period, especially between the implantation eras. This requires to be interpreted in the light of the period of availability and approval of indication for use for each device in Europe: the HMII received the CE mark in 2005, followed by the CE mark for the HeartWare HVAD in 2009, and the HM3 in 2015. The HM3 device represented 38% of LVADs in E2 in PCHF-VAD (2013-2020), which seems to be a large proportion, given the later approval, while the proportion of HVAD carriers (28%) in E2 is smaller, despite its CE approval already during Era 1. The INTERMACS registry only

started enrolling HM3 patients in 2017, prior to which the patients have been enrolled in the MOMENTUM 3 trial, creating a decrease in the total number of LVAD patients enrolled in the INTERMACS registry during that period. This enrolment bias in devices between the EU and the US is important to bear in mind when interpreting data from these populations.
When comparing the differences in implantation indication between European and US centres, the EU DT indication somewhat increased in E2 to 21% of all LVAD recipients, which is still far less than the 56% reported in the second era of the INTERMACS report (114). However, it is important to note that in Europe, healthcare payers of each country determine local reimbursement policies which govern the possible indications for LVAD implantation (mostly, BTT approval was followed by DT in several years), typically more stringent than those in the US, as reflected in the overall European landscape.
When comparing the LVAD indications between the continents, it is important to bear in mind that the increase in DT indication in the US centres could be due to the revision of the allocation criteria for heart transplantation published by the United Network for Organ Sharing (UNOS), as emphasised in the STS INTERMACS report, according to which stable LVAD carriers had a much lower level of urgency when listed for HTx, and in return, received less heart transplants in the more recent years (114). The categorisation of indication for implantation can be considered fluid, with changes during the course of LVAD support, bringing into question the relevance of such classifications, especially given the impact of parameters other than clinical characteristics of the patient. On the other hand, in the PCHF-VAD registry, only 1 patient in the DT population ultimately underwent HTx. Recently published work (115) stresses the importance of occasional reassessment the LVAD implantation indication, since certain circumstances can change during the course of LVAD support, also having in mind that a subanalysis of the MOMENTUM 3 trial did not demonstrate any difference in outcomes between the indication groups (115).
Publication IV, which examined the effect of age on survival and other outcomes in the PCHF-VAD population, confirmed an increasing number of patients aged ≥65 years implanted with an LVAD over recent years, in line with the findings in Publication I. This was partially explained by the expanded indications for DT in Europe as well as the emergence of the HM3 device, ushered by the successful MOMENTUM 3 trial, which demonstrated similar favourable effects of the HM3 device for patients aged ≥65 years (65). The HM3 has been approved for DT for several years and is being increasingly used in this indication for older patients. This is reflected in Publication IV by a large presence of HM3

devices in the oldest patient category, where this device was the most prevalent. The use of BTT LVAD has also increased in older patients in the recent years, suggesting that general acceptance of older patients for both DT and BTT indications is increasing (66).

The influence of recipients' sex on outcomes was examined in Publication III, which confirmed a low prevalence of female recipients compared to male in Europe (19% vs. 81%, respectively), as noted in multiple previously published papers (67, 113), and clinical trials concerning LVAD carriers (116). There have been publications investigating differences in the utilization and outcomes of LVAD therapy between male and female recipients; however, most of these studies were performed in the US, reflected an earlier time period, and included almost exclusively HW or HM II devices (52, 53, 60-62). Given the current LVAD device landscape with the HM3 as the only approved LVAD device, new insights into this issue are warranted and provided by Publication III stemming from an LVAD population rich with HM3 carriers (116). Based on these findings, an issue of LVAD underutilization in female patients with advanced HF was raised in Publication III, examining several possible explanations for this. Firstly, the lower inclusion rate of women in LVAD trials has led to a gap of evidence in the effectiveness of LVAD support in women, which might have caused a difference in the utilization of LVAD therapy. Secondly, women are more frequently diagnosed with HFpEF, in which LVAD support is typically not indicated (5). Furthermore, it has been suggested that women are more likely to decline LVAD support than men (117, 118). In a multinational European screening study, women were somewhat less likely to be eligible for LVAD and/or HTx, but considerably less likely to accept LVAD and/or HTx if indicated (119). This potential reluctance could result in delayed decision-making by both physicians and patients to proceed towards LVAD implantation, as reflected by the strikingly high proportion of women in the worst INTERMACS profile and the higher need for MCS in women (61). The worse INTERMACS profile and high need for mechanical life support seen in women referred for LVAD therapy in the PCHF-VAD database could be a result of a higher incidence of acute disease, possibly indicated by better renal function and lower prevalence of atrial fibrillation. Finally, the inconsistencies in current literature on sex-related differences in LVAD outcomes could have influenced LVAD implantation rates in women, as well (52,53,60-62). It is clear that the issue of utilization of LVAD therapy in women requires further clarification, and action towards removal of any undue reluctance in cases where LVAD therapy is needed.

Differences in medical therapies prior to LVAD implantation between the eras noted in Publication I seem to resemble trends in current literature: in the INTERMACS sub-analysis Khazanie et al. (120) reported that 38% patients received an ACEi/ARB prior to LVAD implantation, 55% received beta-blockers and 40% received an MRA. This is not surprising as the inability to tolerate HF medications is often an indication for LVAD referral. The low utilization of HF medications in the PCHF-VAD registry could be attributed to their interruption prior to LVAD implantation, possibly due to haemodynamic instability. We observed a somewhat greater utilization of beta-blockers in E2, which is in line with the general findings of the publication (Publication I), that the LVAD candidates in E2 were more often chronic HF patients. Low utilization of ACEi/ARB in E2 could, to some extent, be attributed to the introduction of sacubitril/valsartan.

Baseline characteristics of the TRAViATA population

The TRAViATA registry provided a valuable overview of the baseline characteristics of the BTT populations of LVAD carriers in European and US centres. Significant differences in baseline characteristics and practice patterns between the US and EU were observed: patients in the US cohort were older and with more comorbidities, whereas those in the EU cohort had a lower average BMI and lower incidence of diabetes. The age distribution was comparable to the previously published results, considering the STS INTERMACS (114) and PCHF-VAD (67) populations to be representative of the US and EU landscape, respectively.

As defined by the study protocol, the TRAViATA population only consisted of HM II and HW carriers, given that only these devices were approved by the FDA at the time, and therefore available for the participating US centres, making the findings of this registry more comparable to the INTERMACS cohort. This limitation has been incorporated in further comparisons of the outcomes among PCHF-VAD and TRAViATA datasets.

The preimplantation medications in the TRAViATA registry were presented in Publication VII, where the utilisation of GDMT was compared between the groups regarding the presence of CIED. It was found that the utilisation of ACEi/ARB, beta blockers and mineralocorticoid receptor antagonists differed significantly between the groups, with CRT-D patients treated with these medication the most (65.8%, 80%, 73%, respectively), while the patients with no CIED had GDMT in the lowest percentage (37%, 35.6%, 26%, respectively). This is consistent with the current HF Guidelines (1) which recommend ICD and CRT implantation in HF patients who remain symptomatic despite maximal GDMT, and possibly suggests that

the patients without CIED on LVAD implant presented in a more acute setting, therefore unable to tolerate GDMT.

A key point regarding baseline data in the TRAViATA population is the prevalence of CIED in the EU and the US populations. Publication II reports that of the 524 patients included in the analysis, 69% of the European patients and 77% of the US patients had a CIED at the time of LVAD implantation. The prevalence of the CIED in the US cohort was comparable with the INTERMACS population, where 79% patients had an ICD, with a greater presence of ICD in the earlier era (2011-2015). On the other hand, the European population, as presented by the PCHF-VAD population in Publication I, reported a notable difference in the presence of CIEDs between the two eras (ICD: E1 32.9% vs. E2 50.9%, $p<0.001$; CRT: E1 16.2% vs. E2 28.7%, $p=0.003$). This finding is in line with the conclusions of Publication I, regarding the shift of the characteristics of LVAD candidates in this population, with Era 2 candidates resembling the US population more closely in this regard. We believe these results clearly underscore important differences in the real-world practices of the US and EU centres, which ultimately have to be taken into account when interpreting data from these populations.

6.2. All-cause mortality according to examined patient characteristics

The association of all-cause mortality as the primary outcome with examined patient characteristics has been in the focus of all publications included in this thesis. The most important findings from each publication are discussed below. One-year survival of LVAD carriers included in the registries presented in this thesis was 81% in the PCHF-VAD population and 83% in the TRAViATA population, which is comparable to the INTERMACS registry (82%) (114) and notably higher than survival reported in the EUROMACS registry (69%) (77).

All-cause mortality and implantation era

Publication I of the PCHF-VAD registry reports a significant reduction in the adjusted risk of all-cause mortality in patients receiving an LVAD in the more recent era, i.e., patients implanted in the period 2013-2020. This is an important finding highlighting the improvement in survival in the more recently implanted LVAD carriers, indicating a favourable general direction of the durable LVAD treatment strategy in Europe. This could be attributed to several factors, some of which, such as the learning curve of LVAD centres, are more difficult

to quantify, while others include technological advancements in the field of cf-LVADs. In the light of the reports of the MOMENTUM trial (116) and several recent analyses reporting favourable outcomes for patients treated with the HM3 device (110, 121, 122), this likely accounts for some of the survival differences between the eras.

All-cause mortality differences between EU and US

All-cause mortality was examined in the TRAViATA registry, by investigating the association of patient origin (EU vs. US) with mortality, concluding that no significant survival difference in the two patient cohorts was seen. This is an important point underscoring the findings from Publication I, where the comparison of the PCHF-VAD and the INTERMACS population yielded comparable survival, despite the heterogeneity noted between the patient characteristics and the practices of the EU and US centres.

Some patient characteristics were associated with mortality in the TRAViATA population, such as older age, renal insufficiency and higher BMI (123). The association of older age with inferior outcomes has been established and is further discussed in the section regarding Publication IV. Prior analyses of the UNOS database established that impaired renal function prior to implantation predicted waitlist mortality (124). Patients with reduced renal function pose a therapeutic challenge for all aspects of HF treatment, potential LVAD candidates likewise. As worsening renal function can signal progression of cardiac disfunction, thus accelerating implementation of advanced HF treatment options, renal failure has been associated with early mortality after MCS (39, 69, 125). A small proportion may be suitable for multi-organ transplantation, i.e. heart-kidney transplantation, as seen in the TRAViATA registry, where 4.1 and 0.5% patients underwent combined transplantation in the US and EU cohorts, respectively. Increased BMI was also associated with worse outcomes in both geographical cohorts. Possible explanations include longer waiting time on the transplantation list, and a described association of higher BMI with pump thrombosis (older generation LVADs), but the causality has not been elucidated. Subgroup analysis in this study also suggested a higher risk of death in patients implanted with HVAD compared with patients implanted with HMII, which is similar to finding from the PCHF-VAD registry, but since these were not randomized studies of the two devices, conclusions are limited to observation of association. Finally, temporary MCS before LVAD implantation was a strong predictor of mortality, which is consistent with multiple other studies demonstrating worse outcomes with INTERMACS 1 patients that undergo LVAD implantation (72, 126). All the variables

identified in the TRAViATA study as independently associated with early or late mortality in patients treated with cf-LVAD confirm prior results from the 2019 INTERMACS annual report (increasing recipient age, critical cardiogenic shock at time of cf-LVAD implantation, renal dysfunction and higher BMI), with the exception of the type of device (73).

All-cause mortality according to sex

Patients of female sex are significantly and consistently underrepresented throughout all of the publications from both investigated registries presented in this thesis, similar to most other publications investigating the LVAD population (67, 113), suggesting a worldwide occurrence. Survival differences between male and female LVAD patients have previously been investigated with inconsistent results (52, 53, 60-62). The two largest US databases, the UNOS and INTERMACS registry, with a combined total of 32,173 LVAD patients, both demonstrated a higher adjusted mortality risk for women (52, 53), similar to the smaller European Registry for Patients with Mechanical Circulatory Support (EUROMACS) which also demonstrated worse survival in women (61). Conversely, a sub-analysis from the Mechanical Circulatory Support Research Network as well as a recently published meta-analysis did not show survival differences between male and female LVAD recipients (60, 62). In contrast to earlier analyses, survival for women in Publication III was at least as good as for men, despite a more critically ill state prior to LVAD implantation, reflected by lower INTERMACS profile and higher need for MCS, both of which have been associated with worse outcomes (127, 128). The observed discrepancy regarding survival differences may partially be attributed to differences in the devices studied. Earlier studies including pulsatile-flow LVADs predominantly demonstrated worse survival in women, possibly related to the size of the devices in relation to female patients (54). Later studies on sex differences in the cf-LVAD era mainly incorporated older devices, whereas 28% of the overall PCHF-VAD population had a HM3 device implanted. This is a relatively large proportion compared to the HM3 presence in UNOS and EUROMACS studies (2.7% and 0.1%, respectively), whilst the INTERMACS study did not incorporate any data from HM3 LVADs (52, 53, 61). This is important as the MOMENTUM 3 trial demonstrated more favourable outcomes of the HM3 LVAD, making it the most contemporary LVAD in Europe (116). An additional subgroup analysis of the MOMENTUM 3 trial showed comparably favourable outcomes for men and women (129). Given the current world-wide LVAD landscape, we consider the PCHF-VAD

and MOMENTUM 3 data relating to survival differences between sexes to be the most relevant.

All-cause mortality and age at LVAD implantation

Publication IV reported an association of increasing age at LVAD implantation with worse survival. On the other hand, the analysis of outcomes per implantation era indicated improved survival in patients implanted in the more recent years, despite being somewhat older than the population in the earlier years (Publication I). It is important to stress that the mean ages of patients in E1 and E2 were 50.1±12.3 and 54.2±11.7 years, respectively, thus not corresponding to the oldest group in Publication IV, where the survival difference was most prominent. Despite the statistically significant difference in the age at LVAD implantation, still, the oldest tertile of patients is represented by a small sample. Ultimately, we can conclude that there is a trend towards selecting slightly older patients with a higher comorbidity burden for LVAD implantation, yet the patients on the older side of the age spectrum still have worse survival than their younger counterparts. This finding was corroborated by the TRAViATA registry findings, presented in Publication II, where an association with worse survival was noted in both cohorts (EU and US) with older age. Based on the TRAViATA dataset, we suggested that selecting a more straightforward and permanent treatment option would be preferable in older patients (cf-LVAD as DT or HTx as the final treatment strategy), citing additional contemporary studies that suggested comparable outcomes (130).

Interestingly, in the PCHF-VAD registry, this difference dissipated after the first year post-LVAD implantation, suggesting that carefully selected elderly candidates could benefit greatly from LVAD therapy. Future research should help determine the predictors of better outcomes in older candidates, thus improving the selection process.

All-cause mortality and valvular disease

Publication V examined the association of valvular disease with survival, i.e. *de-novo* or worsening aortic regurgitation during LVAD support. The occurrence of significant AR in previous reports ranged around 25-34% of LVAD patients, which compares well with the 39% incidence among the 396 patients in the PCHF-VAD registry (82-84). Despite the haemodynamic consequences of such valvular disease, worsening or *de-novo* AR was not significantly associated with survival in our dataset, yet an adverse association with NYHA

status at 6-month follow-up was seen. Aortic regurgitation in a continuous flow system, such as with LVAD, is mostly pancyclic, which makes comparison with diastolic AR seen in natural pulsatile flow patterns inherently flawed. The definition of AR in most published studies on patients with cf-LVADs is not based on quantifiable parameters and therefore lacks both uniformity and reproducibility (82). Visual estimation of AR severity is limited in continuous flow settings, as well as in eccentric jets, which are both seen in LVAD recipients (84). Recently, a novel Doppler echocardiographic approach obtained at the LVAD outflow cannula has been suggested for the quantification of AR in LVAD carriers (84, 131). The authors demonstrated a better correlation with measured cardiac loading and have further shown that conventional visual estimation may underestimate AR severity. Imamura et al. have shown that 98% of patients in their series were initially found to have mild or less AR on visual estimation (84). This was contrasted by the results of their reevaluation based on novel echocardiographic parameters for quantifying AR, which identified 34% of patients as having at least moderate AR (84). After reclassification, survival free from hemocompatibility-related events was significantly lower in those with significant AR which was also an independent predictor of death or hemocompatibility-related adverse events (84). In Publication V, all patients with worsening AR were grouped into the AR_1 group, irrespective of the absolute degrees of AR. Only 15 patients in the entire cohort had moderate AR by conventional semiquantitative evaluation. It is believed that this relatively low number of cases in the PCHF-VAD registry quantified as having significant AR may be a shortcoming of the definition rather than a reflection of the rarity of these observations - the current practice of quantifying AR which equalizes haemodynamic conditions of pulsatile systems with continuous flow systems may be erroneous. This could explain why, in our study, more patients with AR progression were found to be in NYHA III class and had worsening RV function. The current strategy of AR quantification may be especially unsuitable for LVAD patients with permanently closed aortic valves, in whom AR is completely pancyclic. This could provide the motivation to promote management algorithms that allow for intermittent AoV opening in patients with continuous flow systems, as well stimulate physicians involved in imaging LVAD patients to re-evaluate current practices.

6.3. Secondary outcomes according to examined patient characteristics

In addition to all-cause mortality, a multitude of other outcomes have been examined in the PCHF-VAD and TRAViATA registries. Such outcomes are gaining importance with the increasing duration of LVAD support in some patients (most importantly, those determined as DT candidates), as well as the growing number of supported patients, emphasizing the importance of reduction in the number of adverse events and complications, which can significantly affect quality of life for patients and their families, as well as the cost of treatment.

Secondary outcomes and era of LVAD implantation

Haemocompatibilty-related outcomes have been detected as a significant shortcoming of the otherwise satisfactory results of the LVAD programmes, and important technological advances have been made with the aim of minimizing this challenge (110, 116). In Publication I, intracranial bleeding, non-intracranial bleeding, cerebrovascular ischaemia and pump thrombosis were unified as a single haemocompatibility-related outcome, as recently proposed by Mehra et al. (110). This PCHF-VAD subanalysis indicated a significant, 40% reduction in the adjusted risk of HRAEs in patients implanted with an LVAD in E2. A similar decrease in HRAEs has indeed been documented in the MOMENTUM 3 publications, (110, 116) indicating a lesser incidence of these events in HM3 carriers, which could explain the results seen in E2 of the PCHF-VAD, since this was the leading device of the second era. Conversely, an increase in the adjusted risk of HF-related events (encompassing HF hospitalizations and RVF) was noted in E2: the incidence rate of HF-related events was 23 and 42 events per 100 person-years in E1 and E2, respectively. We postulate that these events may have been underreported in the E1 of the PCHF-VAD registry: when looking at recent reports, such as publications from the MOMENTUM 3 trial, RVF solely occurred with the rate of 27 events per 100 patient-years (110). We suspect that the lower RVF and HF hospitalization rates in E1 could be attributable to several factors, some of which are discussed below:

(i) a higher competing risk of all-cause mortality in E1,

(ii) patient selection, i.e. implanting patients with less favourable RV function prior to LVAD implantation in the more recent era (which were previously, perhaps, more frequently rejected from LVAD candidacy);

(iii) raised awareness of RVF leading to earlier and better recognition of post-implantation RVF in E2, which is also more clearly defined in recent publications (132);

(iv) the latter most likely resulting in a larger proportion of patients in E2 treated only with inotropes, and a smaller proportion requiring MCS for acute RVF (online supplementary Table S8 of the Publication I).

These data in fact support the hypothesis that increasing experience of European LVAD centres results in a trend towards more favourable overall outcomes, i.e. better survival; however, caution in the interpretation of the results is needed due to a fairly low number of these events.

The highest event rate in the PCHF-VAD cohort has been reported for LVAD-related infections requiring systemic antibiotics, occurring in one quarter of the entire cohort. This is comparable to the MOMENTUM 3 data (23.3% and 19.4%, in HM3 and HMII, respectively), but notably lower than the proportion of affected patients in the INTERMACS registry (only 59% of patients are free from infection at 1 year) and the EUROMACS registry (35% of patients) (36, 116, 133). Most importantly, we have noted a significant, 42% reduction in risk of infection in E2 compared to E1, which remained significant after adjustment, signalling an important improvement in the morbidity of the LVAD population. Previous publications have noted less driveline infections in the older LVAD patients, which can translate to the decrease of infections in E2, where the population was somewhat older (134, 135). There have been improvements in the incidence of driveline infections, attributable to alternative surgical techniques (136), or improved post-implantation care (137). Increasing awareness of the importance of driveline exit site care and other efforts towards reduced risk of chronic infections is highly relevant, as this frequent adverse event will remain unresolved until the advent of new modalities of energy transfer, thus impacting the quality of life and otherwise favourable outcomes of LVAD carriers.

Given the effect of repeated hospitalizations for device related complications on the quality of life of LVAD patients, it is reassuring that some of the most frequently occurring complication – device-related infections, as well as haemocompatibility-related events decreased over time, which should further improve with the currently exclusive utilization of the HM3 device.

Difference in secondary outcomes between EU and US

In the TRAViATA dataset, we showed that cf-LVAD-related adverse events differed significantly between the US and EU cohorts. The incidence of RVF and GIB were higher in the US, while rates of driveline infection were higher in the EU. The higher rates of RVF and

GIB observed in the US cohort may be explained by the differences in baseline comorbidities, primarily older age and higher prevalence of diabetes. It is uncertain whether differences in prescribing patterns between the US and Europe may explain these differences as well. It is also unclear why driveline infections were observed more frequently in the EU; further study of these findings is indicated. A higher rate of cerebrovascular accident (CVA) and late RVF, as well as higher risk of death, were observed with HVAD patients, which is consistent with previous studies (138, 139), as well as to the PCHF-VAD registry, regarding RVF. It should be noted that most of the patients in the registry were implanted before the publication of papers demonstrating the importance of blood pressure control in HW patients to limit complications (140). The adverse events profile of HM II appears more favourable since higher rates of GIB typically lead to higher probability to undergo heart transplantation. Consistently, in the TRAViATA registry, HMII carriers were more likely to undergo heart transplantation compared with those carrying a HW. Since this was not a randomized study of the two devices, confounding limits further conclusions.

Secondary outcomes and LVAD recipient sex

Publication III examined the association of LVAD recipient sex with secondary outcomes, mostly hemocompatibility related outcomes. As opposed to earlier studies reporting an increased risk of major bleeding events, the risk of bleeding and thromboembolic events between men and women was similar in the PCHF-VAD cohort, possibly related to a higher proportion of HM3 devices (53, 61), as opposed to the HW and HM II devices which dominated previous publications and have been linked to higher rates of stroke, pump thrombosis and major bleeding (39, 61, 116, 126). Several studies did not find a difference in bleeding risk, and inconsistent results have been reported whether women are at an increased risk for thromboembolic events (42, 53, 61, 62, 141). In very carefully selected patients with cardiac recovery after LVAD surgery, weaning from LVAD support can be a viable option (142). Similar to a recent INTERMACS registry analysis, the PCHF-VAD results demonstrate that women were more likely to recover from LVAD support (53). This might be explained by the observed difference in the aetiology of HF, especially due to the (partial) reversibility of peripartum cardiomyopathy (139). Additionally, it has been demonstrated that women have more favourable reverse remodelling on LVAD support compared to men (58). Thus, some sex-related specifics exist regarding the potential for LVAD weaning, but, more importantly, there was no difference in major adverse events between men and women, which should

reassure practitioners caring for women with advanced HF when considering referral for LVAD surgery.

Secondary outcomes and age at LVAD implantation

In the PCHF-VAD registry, a 10-year increase in age was associated with a higher risk of both intracranial and non-intracranial bleedings (HR 1.49 and HR 1.30 respectively). The risk of non-fatal thromboembolic events was slightly higher in older patients, although not significantly, despite a higher prevalence and risk of incident atrial fibrillation in older patients. No differences were found with respect to the occurrence of pump thrombosis. The clinical HCS (111) was found to be significantly higher in older patients (1.37 vs. 0.77, p=0.033). With the detrimental effects of a stroke especially at older age during LVAD support, this is an important finding that warrants further research in the methodology of overall bleeding risk assessment in elderly LVAD patients. One could imagine a cut-off point above which bleeding risk is deemed too high in order to prevent disabling events during LVAD support. Analyses from the INTERMACS and IMACS database reported higher risks of gastrointestinal bleeding for patients aged ≥70 years and ≥75 years (143-145). These results suggest more vigilant monitoring for bleeding risk in elderly LVAD recipients. Reports on age-related stroke risk, on the other hand, are conflicting, (72, 143, 144), but given the timepoints at which the studies were undertaken, it is likely that, compared to our study, very few patients in the previous studies received the HM3 LVAD with superior haemocompatibility. The MOMENTUM 3 trial showed a lower risk of bleeding, stroke and pump thrombosis for the HM3 as compared to the HMII, underscoring the importance of studying age-related effects in the present era (65). Furthermore, differences in study populations are important as one study only investigated DT patients, whereas another study only found age to be associated with higher stroke risk in the DT, but not the BTT patients (72, 145).

Beside neurologic complications, device-related infections are a major cause of morbidity and mortality, often requiring hospitalization for long courses of intravenous antibiotics (146). We found a significantly lower risk of LVAD-related infections among older patients (HR 0.88, 95% CI 0.78-0.99) which underscores earlier work (72, 111, 143, 145). A possible explanation might be that younger patients exhibit a more (pro)active lifestyle that includes more exercise and can easily lead to manipulation or irritation of the driveline causing

infection, or that younger patients may be less careful in their driveline and general post-LVAD care, a pattern also observed after HTx (147). Furthermore, based on the INTERMACS profile and proportion of patients on life support prior to LVAD implantation, it seems plausible that younger patients more often had the LVAD implanted in an acute setting and were therefore at higher risk of developing a driveline infection. Lastly, elderly LVAD patients had a lower BMI than the middle age group, which has also been associated with a lower risk of driveline infections (135, 145).

Secondary outcomes and valvular disease

Notable findings in Publication V include worse RV function in the AR_1 group, with slightly larger LV dimensions, possibly indicating lesser unloading by the LVAD. Incomplete LV unloading has been shown to increase RV afterload, and subsequently, impair RV function (148). The PCHF-VAD data substantiates this link, as patients with progression of AR also had a reduction in RV function. Previous publications have associated such complications with an increased risk of HRAEs (GIB and stroke), explained by the stimulation of a systemic inflammatory and angiogenesis cascade (84). Less efficient LV unloading, coupled with the fact that the AoV was persistently closed in 55% of patients in the investigated group (AR_1), is likely to have a cumulative impact with increasing duration of LVAD support. Data on RV function in LVAD recipients in relation to AR progression has thus far been scarce and requires further attention.

Since the association of permanent closure of the AoV and the progression of AR has been established in this publication, attempts at optimizing cf-LVAD speeds, that have previously been proposed in order to allow for intermittent AoV opening (82, 88), may be warranted. Jorde et al. proposed a staged approach to symptomatic AR which initially included optimization of LVAD parameters under echocardiographic guidance, followed by haemodynamic studies in the absence of clinical improvement (149). Interventional approaches were reserved for symptomatic patients in whom less invasive management failed to improve symptoms.

6.4. Heart transplantation in LVAD registries

Heart transplantation is a prominent moment in the journey of a patient supported by an LVAD, indicating successful bridging. Providing adequate support by the LVAD and

avoiding all major adverse events is an important task for the physicians caring for the LVAD population. There are many factors affecting the likelihood of undergoing heart transplantation for the LVAD patient, and the identification of such factors could improve care for these patients.

Publication I of the PCHF-VAD registry examined the likelihood of undergoing HTx in association with the era of LVAD implantation. This sub-analysis noted a significantly lower chance of receiving a heart transplantation during 1-year follow-up for patients receiving an LVAD in E2, including a longer median time to heart transplantation in E2 compared to E1. A similar finding has been described in the ELEVATE registry, a real-world study of patients receiving a HM3 LVAD between March 2015 and February 2017, where only 8.2% patients underwent heart transplantation within the first 2 years after LVAD implantation (150). Several factors could possibly contribute to this finding. Availability of donor organs is a well-known limiting factor, stifling the expansion of heart transplantation as a treatment option for advanced HF (151). With the improvements in MCS therapy, more patients survive until heart transplantation candidacy, thereby increasing the demand for donor hearts. When listed, these patients are usually categorized as elective, only to be 'upgraded' to high urgent status in case of serious complications, thus typically having a longer waiting time for the donor organ (152). The absolute numbers of heart transplantation have decreased over the last 10 years, according to the recent Eurotransplant report (33), which has to be additionally interpreted in the light of the growing population of candidates, partially due to improved overall survival of LVAD carriers. Finally, improved outcomes with an LVAD in the more recent years may potentially divert both the patients and physicians from proceeding to heart transplantation, even in BTT candidates.

Publication III showed no sex-related differences in the proportion of patients undergoing heart transplantation in the PCHF-VAD registry. Similar findings have been described in current literature (61, 153).

Publication IV examined the association of age with heart transplantation and found that patients aged ≥65 years were significantly less often transplanted, than those aged 50-64 and <50 years (14.3% vs. 55.9% and 70.5% respectively, $p<0.001$). A 10-year increase in age was significantly associated with a lower chance of undergoing heart transplantation (HR 0.90, 0.80-1.01) after adjustment for sex, INTERMACS profile, baseline serum creatinine level, quartiles of LVAD implantation date, the need for MCS prior to LVAD surgery and pre-

LVAD vasopressor use. This finding is not unexpected given that some transplant centres limit the age of potential transplant recipients at 65 years of age. On the other hand, analysis by Emerson et al. (134), demonstrated that even in the age group 65-75 years, 17.7% of LVAD carriers underwent heart transplantation, and even some in the >75-year group, but the outcomes after transplant are not reported. Although advanced age *per se* is not a contraindication for heart transplantation, per the ISHLT listing criteria for heart transplantation (154), as well as the position statement of the Heart Failure Association (HFA) of the ESC (16), given the limited number of donor organs available, it is expected that this resource would be mostly utilized in the younger population.

The TRAViATA registry focused on the regional differences of the likelihood of undergoing heart transplantation between the investigated populations. It is important to note that heart transplantation is coordinated by UNOS in the US, and Eurotransplant in the EU, with the caveat that some of the EU countries are not Eurotransplant members. These two organisations differ in some respects, and the listing priority of LVAD patients may not be completely similar, but all these differences would be difficult to objectify and require further clarification. Some additional changes in the UNOS listing criteria occurred in 2018, providing more heterogeneity.
At 1-year follow-up, 46% of the US patients and 33.8% of the EU patients underwent heart transplantation ($p = 0.11$). Furthermore, EU patients waited longer for transplantation and received organs from older donors. When the heart transplantation variable was added to the multivariate analysis, US origin emerged as a variable associated with better survival, possibly related to the abovementioned points. The probability of undergoing heart transplantation is partially dictated by local availability of donor organs, allocation policies, and healthcare service organizations; hence, wide geographic variability in practice exists between the US and EU. Differences in donor organ availability and their clinical characteristics, including older age in EU than in the US, also impact outcomes in those who undergo LVAD placement as a BTT.

6.5. Comparison of the outcomes of combined device therapy between the two registries: (PCHF-VAD vs. TRAViATA)

The survival benefit of CIED therapy in LVAD recipients, investigated in Publication VI and VII, is the focal point of this thesis. The hypothesis of the thesis stated that CIED improved survival in LVAD carriers. Several previous publications have addressed this issue, providing opposing conclusions (95-102). Publications VI and VII both analysed data from multicentric LVAD registries, with PCHF-VAD registry focusing on the European landscape of LVAD support, while the TRAViATA registry provided comparative insight into the LVAD populations of several European and US centers, excluding DT patients and HM3 carriers. In addition to several differences in inclusion criteria, the statistical approach carries additional distinctions. Seemingly opposing conclusions can be drawn from the two registries regarding the utility of combination device therapy in advanced HF. The registries share some similarities, regarding the general design (both are multicentric, retrospective registries of cf-LVAD carriers) – but some crucial differences exist, which could help elucidate the dissimilarities in the association of CIED with survival and other outcomes.

Firstly, the PCHF-VAD registry included all LVAD patients, implanted in the participating centres, regardless of implant strategies, while the TRAViATA registry focused solely on heart transplantation candidates, i.e. BTT candidates. We have discussed previously that the implantation strategy stratification of patients is sometimes fluid and can change during the course of LVAD support, but in most cases, it is indicative of some intrinsic patient properties, and it is a well-established mode of patient stratification, present in the Guidelines (1). This would imply some significant baseline dissimilarities between the patient populations of the two registries, suggesting that the PCHF-VAD population is more comprehensive, and thus more applicable to the general LVAD population.

Secondly, the PCHF-VAD registry included a larger variety of continuous flow devices, with HM II, HW and HM3 dominating the registry. On the other hand, the TRAViATA registry included only HM II and HW devices, in order to make the European cohort more comparable to the US cohort, where the HM3 device was not approved at the time of registry initiation, and therefore, these patients were not included. Both HM II and HW device have since faded out of clinical focus, with the proportion of HM II devices decreasing after the publication of the MOMENTUM 3 study results, which demonstrated the superiority of the HM3 device regarding survival free of stroke and the need for device replacement. On the other hand, the HW device was discontinued by the manufacturer in 2021, due to an increased risk of

neurological adverse events and mortality associated with the internal pump, as well as reports of failure to restart once stopped (155). In summary, that the conclusions stemming from the PCHF-VAD registry are more relatable to the modern cf-LVAD population, which currently consists mostly of HM3 carriers, especially the more recently implanted patient populations.

Thirdly, it is important to note that the TRAViATA cohort differs from the European PCHF-VAD registry based on the inclusion of US centres. It is well known, and corroborated by our data, that US centres have a higher prevalence of CIED-D use prior to LVAD: in TRAViATA, 68% carried a CIED-D, as opposed to 54% carrying a CIED-D in the PCHF-VAD cohort. These proportions suggest a different profile of CIED-D carriers in the European LVAD cohort, with likely more stringent selection criteria, which may have impacted the preferable outcomes of patients with combined device therapy in Europe.

Fourthly, the statistical approaches utilised to analyse the association of CIED-D with outcomes differed significantly between the registries. The PCHF-VAD database survival analysis was conducted using a time-varying analysis, including the periods of time where the CIED-D was active during LVAD support, accounting for postoperative periods where the devices might have been deactivated, as well as any timepoints, where the device was shut off or explanted. Likewise, the analysis accounted for CIED-Ds implanted or reactivated during LVAD support. Methodologically, this is the most correct way to address the issue of the association of CIED-D with outcomes, by accounting for the times these devices were active (most of the data were lacking in TRAViATA for which reason such an analysis could not be undertaken). On the other hand, the TRAViATA registry segregated patients by the presence of CIED, without additional consideration. Thus, the results brought forward by the PCHF-VAD registry and Publication VI address the issue of CIED-D in a general LVAD population, particularly regarding EU carriers, with more granularity. Based on these results, the relevance of the implantation / activation of CIED-Ds following LVAD implantation has been underscored by the most recent European Guidelines on the prevention of sudden cardiac death (106).

6.6. Limitations

This thesis is based on data from two retrospective, observational registries, with the inherent limitations of such studies. As it is not uncommon in registries, there was some amount of missing data, especially in the echocardiography and haemodynamic section, which was accounted for in some analyses by using the multiple imputation method. The endpoint adjudication was performed by the clinical teams of each centre individually, which may have led to a misclassification or underreporting of events, particularly those more challenging to define. In respect to the outcome analyses, this type of study design does not enable optimal accounting for multiple potential confounders, yet careful adjusted analyses were performed accounting for the available confounding variables, as well as additional sensitivity analyses. To account for the lack of randomisation, in some of the analyses propensity score matching was utilised. There was also a difference in enrolment between the participating centres, and some heterogeneity between practices in different centres, that is more difficult to analyse, but this again is a feature of registry data.

Although observational data offers a weaker level of evidence and causation cannot be inferred, large randomised trials involving LVAD patients are difficult to execute, and at this point, registries provide a highly relevant and welcome source of information for the everyday management of patients with an LVAD. We believe that this information conveys a wide overview of the progress made in the field of long-term MCS, particularly in Europe, but also in the US.

7. Conclusion

This PhD thesis explores the field of LVAD recipients with granular insights commencing from a data-driven overview of the changing European LVAD landscape and comparisons between European and US LVAD recipients, across subanalyses addressing outcomes related to patient sex, age, and ensuing aortic regurgitation and ultimately outcomes of patients with advanced HF treated with combined (LVAD and CEID) device therapy. It is based on analyses from two retrospective, observational registries, focused on different aspects of the cf-LVAD population – the PCHF-VAD registry and TRAViATA, both with prominent involvement of the PhD candidate and mentor, particularly the PCHF-VAD registry that has been founded by the candidate's mentors and coordinated by doctor Jakuš.

Analyses from the PCHF-VAD registry demonstrated more favourable outcomes in the patients receiving an LVAD more recently, with improved survival despite implanting older, more comorbid patients. This registry also demonstrated worse early survival in the oldest recipients but stressed that the survival equalises after the first year. Importantly, it detected a severe underutilisation of this treatment strategy in women, albeit confirming comparable survival in male and female candidates, despite women receiving LVADs in a more acute setting. No difference in survival was found with developing aortic regurgitation during LVAD support, but it did translate to worse functional capacity. The TRAViATA registry concluded that the key outcomes following LVAD implantation did not differ significantly between the US and EU cohorts, despite significant differences between the cohorts, as well as variances in transplantation policies. Finally, some discrepancies were found between the PCHF-VAD and TRAViATA populations in respect to outcomes with combined device therapy. However, taking into account the contemporaneity and other methodological merits of the PCHF-VAD analysis, the presence of a CIED-D has been proven to be associated with significantly better survival in the LVAD population , as evidenced by the inclusion of our findings to the most recent Guidelines on the prevention of sudden cardiac death (106).

8. Sažetak

Kombinacija uređaja u liječenju uznapredovaloga zatajenja srca
Nina Jakuš, 2023.

Disertacija detaljno opisuje područje primjene uređaja za mehaničku potporu lijevoj klijetci (engl. left ventricular assist device, LVAD), uključujući usporedbu općih karakteristika i ishoda bolesnika s LVAD-om u Sjedinjenim Američkim Državama (SAD) i u Europi (EU) te pomniju analizu mijene karakteristika i ishoda europskih bolesnika s LVAD-om tijekom posljednjih gotovo 15 godina. Nadalje, istražuje se utjecaj različitih obilježja bolesnika, poput spola, dobi i prisutnosti aortne regurgitacije (AR) na promatrane ishode. Zbog kroničnog tijeka zatajivanja srca (ZS), bolesnici nosioci LVAD uređaja nerijetko imaju ranije implantiran elektronički implantabilni srčani uređaj (engl. cardiac implantable electronic device, CIED), od kojih neki mogu imati i defibrilacijsku elektrodu (CIED-D). U svakodnevnoj kliničkoj praksi postavlja se pitanje optimalne skrbi za bolesnike nosioce oba uređaja, s posebnim zanimanjem za utjecaj CIED na preživljenje nosioca LVAD uređaja. Istraživanje je temeljeno na podatcima iz dva multicentrična, opservacijska, retrospektivna registra bolesnika s LVAD, Postgraduate Course on Heart Failure – Ventricular Assist Device (PCHF-VAD) i TRans-Atlantic registry on VAd and TrAnsplant (TRAViATA), pri čemu većina publiciranih podataka proizlazi iz PCHF-VAD registra, utemeljenog i vođenog od strane mentora i kandidatkinje Jakuš. Uključeni su bolesnici stariji od 18 godina, kojima je LVAD ugrađen u sklopu liječenja uznapredovalog ZS, a za potrebe ove analize isključeni su nosioci desnostrane ili biventrikulske potpore, te pumpi s pulsatilnim protokom. Prikupljani su antropometrijski i podatci o vitalnim parametrima, komorbiditetima, ranijim operativnim zahvatima, te o potrebi za privremenom mehaničkom cirkulacijskom potporom prije implantacije LVAD. Također, prikupljeni su podatci o ugrađenim CIED uređajima (u PCHF-VAD registru i informacije o aktivacijama i deaktivacijama CIED-a), ehokardiografski i hemodinamski podatci. U konačnici, prikupljani su ishodi poput ukupnog i kardiovaskularnog mortaliteta, transplantacije srca, ishemijskih ili krvarećih komplikacija, tromboze pumpe, desnostranog srčanog zatajivanja, te poremećaja srčanog ritma. Podatci bolesnika su uneseni putem sigurne mrežne platforme „REDCap“. Sva istraživanja provedena su sukladno s etičkim načelima. Rezultati istraživanja provedenih u sklopu ove disertacije objavljeni su u 7 publikacija, većinom u vodećim svjetskim časopisima u području zatajivanja srca.

Za potrebe prve publikacije, bolesnici PCHF-VAD registra su podijeljeni u dvije ere prema vremenu implantacije LVAD uređaja (era 1 (E1) i era 2 (E2)) te su ishodi uspoređivani prema eri implantacije. U druge dvije publikacije PCHF-VAD registra ishodi su uspoređivani prema spolu i dobi bolesnika (stratificirani su u tri grupe prema dobi: mlađi od 50 godina, 50-64 i 65 godina i stariji). Sljedeća PCHF-VAD publikacija ispitivala je povezanost ishoda s pojavom AR tijekom LVAD potpore. Posljednja PCHF-VAD publikacija fokusirala se na utjecaj aktivnih CIED-D na preživljenje LVAD bolesnika. Prva publikacija TRAViATA registra uspoređivala je ishode između LVAD nosioca-kandidata za transplantaciju srca implantiranima u Europi (EU) i Sjedinjenim Američkim Državama (SAD), dok je druga publikacija istraživala utjecaj CIED na ishode LVAD nosioca.

Navedene publikacije prikazale su sljedeće rezultate:

1. Bolesnici uključeni u PCHF-VAD registar implantirani u E2 bili su signifikantno stariji uz više komorbiditeta, ali rjeđe u akutnom ZS. Također, imali su značajno bolje 1-godišnje preživljenje u prilagođenoj analizi (HR 0.58, 95% CI 0.35–0.98; p = 0.043), uz manju šansu upućivanja na transplantaciju srca, te niži rizik od infekcija povezanih s LVAD-om.
2. Registar TRAViATA fokusirao se na razlike u ishodima LVAD nosioca, uvrštenih u listu kandidata za transplantaciju srca, implantiranih u EU i SAD. Nije nađeno značajne razlike u preživljenju (SAD 63.1%, EU 68.4%; p=0.43), iako su zabilježene značajne razlike između populacija (SAD populacija je bila signifikantno starija uz veću zastupljenost komorbiditieta).
3. Analizom LVAD nosioca uključenih u PCHF-VAD registar prema spolu, detektirano je kako su žene značajno manje zastupljene (19% ukupne populacije), te su u trenutku implantacije češće bile u fazi akutnog ZS i zahtijevale privremenu mehaničku cirkulacijsku potporu. Unatoč tome, nisu zabilježene značajne razlike u smrtnosti (HR 0.79, 95% CI 0.50–1.27), uz nešto viši rizik od razvoja postimplantacijskog zatajivanja desne klijetke u žena.
4. U PCHF-VAD registru utvrđeno je da je 10-godišni porast dobi pri implantaciji povezan sa značajnim porastom smrtnosti (HR 1.34, 95% CI 1.15–1.57) te rizika od intrakranijskog i neintrakranijskog krvarenja. Međutim, nakon prve godine dana, rizik smrtnosti izjednačava se u starijih nosioca LVAD-a s onima mlađe dobi.
5. Analizom LVAD nosioca uključenih u PCHF-VAD registar prema razvoju AR tijekom LVAD potpore, utvrđeno je da AR nije značajno utjecala na mortalitet (HR 0.91, 95% CI 0.61-1.36; p=0.65), ali je bila povezana s lošijim funkcijskim kapacitetom.
6. Analizom bolesnika uključenih u PCHF-VAD registar ovisno o prisutnosti aktivnog CIED-D tijekom LVAD potpore, nađeno je da su LVAD bolesnici s aktivnim CIED-D imali

statistički značajno bolje preživljenje (HR 0.64, 95% CI 0.46–0.91; p = 0.012), signifikantno i poslije prilagodbe.
7. U registru TRAViATA, u užoj populaciji nosioca LVAD uređaja, koji su bili uvršteni u listu kandidata za transplantaciju srca, nije nađena razlika u preživljenju između bolesnika s CIED i onih bez.
Zaključno, registri su pokazali bolje ishode LVAD nosioca implantiranih u posljednjim godinama, te kako je viša dob pri implantaciji bila povezana s lošijim preživljenjem, dok nije nađena razlika u preživljenju između spolova, kao niti razlika u preživljenju povezana s pojavom AR. U PCHF-VAD registru prisutnost aktivnog CIED-D tijekom LVAD potpore bila je povezana s boljim preživljenjem, a vrijednost ovih zaključaka potvrđuje i činjenica da je ova PCHF-VAD publikacija uvrštena i u posljednje smjernice Europskog kardiološkog društva za prevenciju nagle srčane smrti (106).

Ključne riječi: uređaj za lijevostranu srčanu potporu, srčani implantabilni elektronički uređaj, preživljenje, registar.

9. Abstract

Combined device therapy for advanced heart failure
Nina Jakuš, 2023.

This PhD thesis explores the field of left ventricular assist device (LVAD) recipients with granular insights commencing from a data-driven overview of the changing European LVAD landscape and comparisons between European and US LVAD recipients, across subanalyses addressing outcomes related to patient sex, age, and ensuing aortic regurgitation (AR) and ultimately outcomes of patients with advanced HF treated with combined (LVAD and cardiac implantable electronic device (CEID)) device therapy. It is based on analyses from two retrospective, observational registries, focused on different aspects of the LVAD population – the PCHF-VAD and TRAViATA registry, both with prominent involvement of the PhD candidate and mentor, particularly the PCHF-VAD registry that has been founded by the candidate's mentors and coordinated by doctor Jakuš.

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Keywords: left ventricular assist device, cardiac implantable electronic device, survival, registry.

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11. List of scientific publications

PUBLICATION 1

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The candidate, Nina Jakuš, contributed to this publication by:

- Having a substantial contribution to the conception and design of the publication; as well as the acquisition, analysis, and interpretation of data for the work; AND
- She drafted the work with additional critical revision for important intellectual content; AND
- She gave final approval of the version to be published; AND
- Agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contribution of other co-authors:

- Having a substantial contribution to the acquisition, analysis, and interpretation of data for the work; AND
- Critically revised the manuscript for important intellectual content; AND
- Gave final approval of the version to be published; AND
- Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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RESEARCH ARTICLE

Improved survival of left ventricular assist device carriers in Europe according to implantation eras: results from the PCHF-VAD registry

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Aims Temporal changes in patient selection and major technological developments have occurred in the field of left ventricular assist devices (LVADs), yet analyses depicting this trend are lacking for Europe. We describe the advances of European LVAD programmes from the PCHF-VAD registry across device implantation eras.

Methods and results Of 583 patients from 13 European centres in the registry, 556 patients (mean age 53 ± 12 years, 82% male) were eligible for this analysis. Patients were divided into eras (E) by date of LVAD implantation: E1 from December 2006 to December 2012 (6 years), E2 from January 2013 to January 2020 (7 years). Patients implanted more recently were older with more comorbidities, but less acutely ill. Receiving an LVAD in E2 was associated with improved 1-year survival in adjusted analysis (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.35–0.98; $p = 0.043$). LVAD implantation in E2 was associated with a significantly lower chance of heart transplantation (adjusted HR 0.40, 95% CI 0.23–0.67; $p = 0.001$), and lower risk of LVAD-related infections (adjusted HR 0.64, 95% CI 0.43–0.95; $p = 0.027$),

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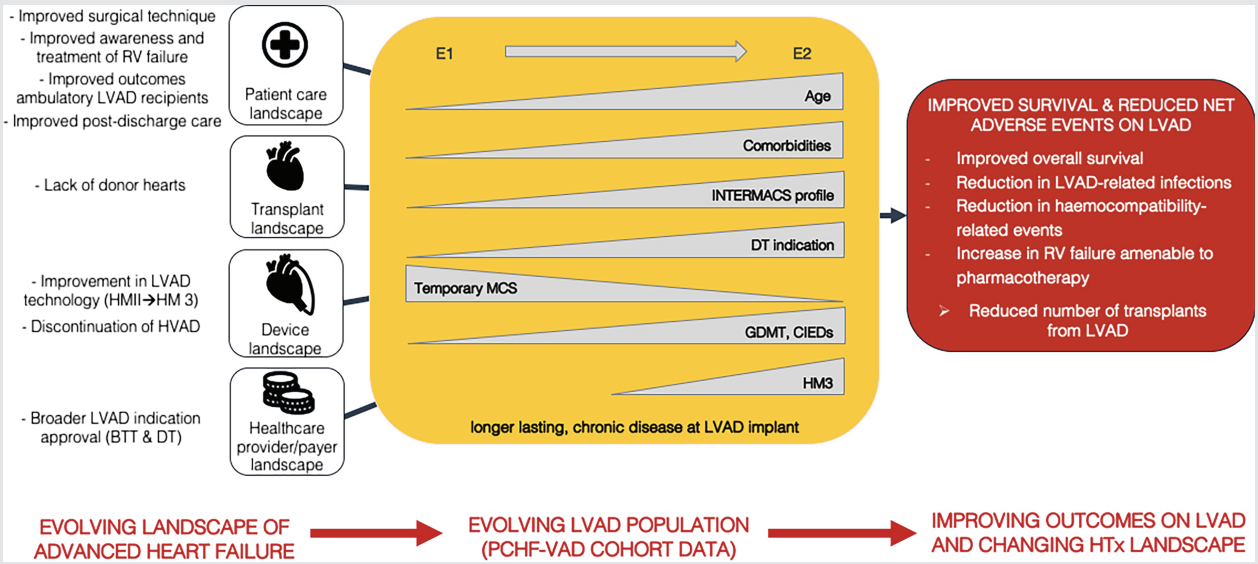
both in unadjusted and adjusted analyses. The adjusted risk of haemocompatibility-related events decreased (HR 0.60, 95% CI 0.39–0.91; $p = 0.016$), while heart failure-related events increased in E2 (HR 1.67, 95% CI 1.02–2.75; $p = 0.043$).

Conclusion In an analysis depicting the evolving landscape of continuous-flow LVAD carriers in Europe over 13 years, a trend towards better survival was seen in recent years, despite older recipients with more comorbidities, potentially attributable to increasing expertise of LVAD centres, improved patient selection and pump technology. However, a smaller chance of undergoing heart transplantation was noted in the second era, underscoring the relevance of improved outcomes on LVAD support.

Graphical Abstract



Multiple factors influencing the outcomes of left ventricular assist device (LVAD) patients. BTT, bridge to transplantation; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; DT, destination therapy; GDMT, guideline-directed medical therapy; HMII, HeartMate II; HM3, HeartMate 3; HTx, heart transplantation; HVAD, HeartWare; ICD, implantable cardioverter-defibrillator; MCS, mechanical circulatory support; RV, right ventricle.

Keywords Advanced heart failure • Left ventricular assist device • Survival • Comorbidities • Heart transplantation

Background

Left ventricular assist devices (LVADs) have been in use for several decades[1]; with the introduction of smaller, continuous-flow devices, LVADs havebecome an established method of treating advanced heart failure (HF),[2,3] with survival rates approaching those of the current 'gold standard' – heart transplantation. Throughout the evolution of LVAD use from early implementation to routine clinical practice, improvement in survival and outcomes was achieved, attributable to the inevitable learning curve,[4,5] development of surgical techniques with lower rates of surgical complications,[6] technical advances in pump architecture,[7] as well as the evolution of treatment indications[8,9] and improved patient selection.[10]

A shift of utilization of LVADs from treating acutely ill patients, towards including the more 'stable' chronic HF patients has occurred over the past decade(s),[7,11] powered by the early data suggesting worse outcomes in INTERMACS profile 1 patients.[12] The clinical introduction of continuous-flow LVADs (cf-LVADs) resulted in improved reliability and superior outcomes

in comparison to first generation pulsatile-flow LVADs.[13] The most recent advancements include a fully magnetically levitated centrifugal cf-LVAD, the HeartMate 3 (HM3) LVAD, for which short- and long-term follow-up data show favourable results regarding multiple outcomes, mainly linked to improved haemocompatibility.[14,15] Currently, the HM3 is the only LVAD approved for clinical use by regulatory agencies in the EU and USA.

An 'era effect' that amalgamates such progress in LVAD therapies was described in the latest INTERMACS registry report, with the improvement of outcomes in patients implanted in the more recent years[16]; however, similar analyses are lacking for Europe.

In order to more granularly describe the advances of European LVAD programmes since their implementation to the most recent advances in pump technology, we aimed to describe the LVAD landscape in a European cohort of LVAD carriers as a function of implantation date and to investigate the relevance of the era of LVAD implantation on outcomes in Europe.

Methods

This observational study is based on data from a multicentre registry of LVAD carriers, which consisted of 13 European tertiary HF centres from 10 countries (list of participating centres is in online supplementary *Table S1*), led by expert HF investigators of the Postgraduate Course in Heart Failure (PCHF) of the Heart Failure Association of the European Society of Cardiology and the European Heart Academy, as recently described.[17] Each of the centres acquired the approval of their local ethics review board (predominantly, a waiver of informed consent was obtained).

This registry includes 583 patients who underwent the implantation of a durable ventricular assist device during the course of treatment of advanced HF and were in regular follow-up of the participating centres. The implantations took place between December 2006 and January 2020. Of the initial number of patients, children below the age of 18 years and those implanted with pulsatile devices, right ventricular (RV) and biventricular assist devices, and patients alive at last contact, but without completed 1-year follow-up, were excluded from further analysis, which resulted in 556 patients included in this analysis (online supplementary *Figure S1*).

Baseline patient data were collected prior to LVAD implantation and included demographic (age at time of implantation, sex) and anthropomorphic data (weight, height), physical examination including vital signs and functional status (New York Heart Association class, INTERMACS profile), relevant comorbidities and past relevant surgical procedures, echocardiographic findings, laboratory findings, as well as information on pertinent medical therapy. Information on cardiac implantable electronic devices (CIED) (i.e. implantable cardioverter defibrillator [ICD], cardiac resynchronization therapy) was gathered as well. Information on LVAD type and other data regarding the surgical procedure (prior life support and concomitant surgical procedures) were acquired.[17] Baseline variables with more than 30% of missing data were excluded from further analysis.

For the purpose of this sub-analysis, the patient data were divided into two eras of similar duration, according to the date of LVAD implantation. The primary outcome was defined as all-cause mortality. Similarly to the publication stemming from the MOMENTUM trials,[15] secondary outcomes were compartmentalized as follows: heart transplantation, cardiovascular death, haemocompatibility-related events (non-intracranial bleeding, intracranial bleeding, ischaemic stroke and pump thrombosis), HF-related events (HF events; RV failure and hospitalization for HF), and LVAD- related infection requiring systemic antibiotics. All events were adjudicated by the attending physicians. For the analysis of the heart transplantation outcome, patients designated as destination therapy (DT) candidates were excluded from the analysis, resulting in a population of 469 patients. The risk of the outcome events was analysed according to implantation era. As previously described, 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.[17]

Statistical analysis

Baseline characteristics are reported as counts and percentages for categorical variables and continuous variables as mean ± standard deviation (or median and 25th–75th percentile for non-normally distributed variables). At baseline, patients were distributed into two eras, according to the date of implantation. The inter-group differences based on date of implantation eras were assessed using the chi-square test for categorical variables or ANOVA (or Kruskal–Wallis test for non-normally distributed variables) for continuous variables.

The hazard ratio (HR) for the outcomes was estimated using the Cox proportional hazards model with the first era serving as the referent group. For survival analyses, the time of LVAD implantation was considered as the index date, while the duration of follow-up was defined as time to last contact, weaning from LVAD, heart transplantation or death (whichever came first). Outcome analyses were performed for both eras over the first year after implantation in order to equalise the time at risk. There were no patients lost to follow-up. Multivariable models were adjusted for clinically relevant, patient-related baseline covariates, which were selected for each individual outcome. Overall survival and occurrence of heart transplantation were assessed using the Kaplan–Meier method and compared between eras using the log-rank test. The association between the incidence rate of all-cause mortality/heart transplantation and date of LVAD implantation was graphically depicted using restricted cubic spline curves with three knots. A competing outcomes analysis accounting for heart transplantation and weaning from LVAD was performed based on Fine and Gray's proportional subhazards model and depicted graphically with competing outcome curves.

A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

This analysis was performed on a population of 556 patients, included into the registry between December 2006 and January 2020. The patients were divided according to date of LVAD implantation into two eras of comparable duration, first era (E1) extending from December 2006 up to and including December 2012 (first 6 years), and the second era (E2) from January 2013 to January 2020 (later 7 years), resulting in 150 patients in E1, and 406 in E2.

The baseline, pre-implantation data of patients stratified into two eras are shown in *Table 1*. The patients implanted in E2 were significantly older (50 ± 12 vs. 54 ± 12 years, $p < 0.001$), with a

Table 1 Baseline data of the patients according to left ventricular assist device implantation eras

	E1 Dec 2006–Dec 2012 (n = 150)	E2 Jan 2013–Jan 2020 (n = 406)	p-value
Age at implantation (years), mean ± SD	50.1 ± 12.3	54.2 ± 11.7	<0.001
Female sex, *n* (%)	36 (24.0)	66 (16.3)	0.036
BMI (kg/m^2), mean ± SD	24.6 ± 3.8	26.3 ± 4.8	0.002
Obese (BMI >30 kg/m^2), *n* (%)	7 (4.7)	83 (20.4)	0.002
Systolic blood pressure (mmHg), mean ± SD	96.5 ± 14.4	100.4 ± 13.7	0.01
Heart rate (bpm), mean ± SD	91.3 ± 20.1	82.0 ± 18.6	<0.001
Arterial hypertension, *n* (%)	28 (18.7)	99 (24.4)	0.15
Diabetes mellitus, *n* (%)	19 (12.7)	94 (23.2)	0.006
Chronic kidney disease[a], *n* (%)	14 (9.3)	89 (21.9)	0.001
Coronary artery disease, *n* (%)	63 (42.0)	192 (47.3)	0.27
Chronic obstructive pulmonary disease, *n* (%)	4 (2.7)	38 (9.4)	0.008
Atrial fibrillation or flutter, *n* (%)	27 (18.0)	143 (35.2)	<0.001
Ventricular arrhythmia, *n* (%)	28 (18.7)	124 (30.5)	0.005
Prior cardiac surgery, *n* (%)	28 (18.7)	45 (11.1)	0.019
Aetiology of heart failure, *n* (%)			0.005
Dilated cardiomyopathy	56 (37.3)	187 (46.1)	
Ischaemic cardiomyopathy	68 (45.3)	186 (45.8)	
Other aetiology	26 (17.3)	33 (8.1)	
INTERMACS profile, *n* (%)			<0.001
1	34 (23.9)	55 (13.8)	
2	55 (38.7)	91 (22.8)	
3	30 (21.1)	145 (36.3)	
4–7	23 (16.2)	108 (27.1)	
NYHA class, *n* (%)			0.18
II	3 (2.8)	12 (3.1)	
IIIa	25 (22.9)	123 (31.4)	
IIIb	27 (24.8)	107 (27.3)	
IV	54 (49.5)	150 (38.3)	
LVAD type, *n* (%)			<0.001
HeartMate II	140 (93.3)	125 (30.8)	
HeartWare HVAD	3 (2.0)	114 (28.1)	
HeartMate 3	0 (0.0)	153 (37.7)	
Other	7 (4.7)	14 (3.4)	
LVAD strategy, *n* (%)			<0.001
Bridge to transplantation	121 (85.8)	230 (59.6)	
Bridge to decision/candidacy	12 (8.5)	77 (19.9)	
Destination therapy	8 (5.7)	79 (20.5)	
Life support prior to LVAD implantation, *n* (%)			<0.001
None	84 (60.4)	313 (78.4)	
ECMO	14 (10.1)	26 (6.5)	
Temporary LVAD	1 (0.7)	4 (1.0)	
Temporary RVAD	1 (0.7)	0 (0.0)	
Temporary BiVAD	0 (0.0)	2 (0.5)	
IABP	31 (22.3)	42 (10.5)	
Other	8 (5.8)	12 (3.0)	
LVIDd (mm), mean ± SD	67.3 ± 13.7	71.7 ± 12.1	0.002
Creatinine (μmol/L), mean ± SD	118.4 ± 51.1	129.2 ± 57.4	0.07
Bilirubin (μmol/L), mean ± SD	27.1 ± 25.9	23.6 ± 18.9	0.15
ICD, *n* (%)	48 (32.9)	202 (50.9)	<0.001
CRT, *n* (%)	23 (16.2)	114 (28.7)	0.003
Beta-blockers, *n* (%)	44 (50.6)	250 (67.2)	0.004
ACEi or ARB, *n* (%)	54 (58.7)	156 (41.2)	0.002
Sacubitril/valsartan, *n* (%)	0 (0.0)	15 (4.6)	0.06
MRA, *n* (%)	53 (65.4)	261 (73.5)	0.14

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BiVAD, biventricular assist device; BMI, body mass index; CRT, cardiac resynchronization therapy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; LVIDd, left ventricular intracavitary diameter in diastole; MRA, mineralocorticoid receptor antagonist; RVAD, right ventricular assist device; NYHA, New York Heart Association; SD, standard deviation.

[a]Chronic kidney disease is defined as estimated glomerular filtration rate ≤60 ml/min/1.73 m^2.

significantly greater burden of nearly all registered comorbidities. Significantly more women were implanted in E1 versus E2 (24% vs. 16%, $p = 0.036$). There was a significant difference regarding the type of LVAD implanted: in E1 93% of patients received a HeartMate II (HMII), while in E2 all three major device types were represented, with a predominance of the HM3 (38% of patients). A significant difference was also present between LVAD implantation strategies: most of those implanted in E1 were bridge to transplantation (BTT) candidates (86%); in E2 a prominent population of DT patients (21%) emerged, while BTT intention still dominated (60%). There was a significant shift in haemodynamic stability of patients at implantation: in E1 most patients were in INTERMACS profiles 1 and 2, while profiles 3 and higher dominated in E2. This was paralleled with a significantly higher proportion of patients requiring temporary mechanical circulatory support (MCS) prior to LVAD in E1 (39.6% vs. 21.5%, $p < 0.001$). More patients in E1 were subject to cardiac surgery prior to LVAD implantation.

Patients in E2 had higher mean systolic blood pressure and lower average heart rate at implantation, compared to E1; E2 patients also had significantly larger left ventricles. Beta-blockers were prescribed in 50.6% of patients in E1, versus 67.2% in E2. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) were more often present in E1 (58.7%) than in E2 (41.2%), with the noted introduction of sacubitril/valsartan in the last years of E2. The prescription of mineralocorticoid receptor antagonists (MRA) was comparable between the eras. More patients were treated with CIED in E2 – the proportion of those with an ICD rose from 33% in E1 to 50.9% in E2.

The influence of implantation era on overall survival at 1 year

During the 1-year follow-up period, the primary outcome of all-cause death occurred in 107 patients (19%). The incidence rate of all-cause death per 100 patient-years was notably lower in E2 (E1: 32.3, 95% confidence interval [CI] 23.0–45.4 vs. E2: 22.2, 95% CI 17.7–27.9) (*Table 2*). In unadjusted analysis, there was a trend towards lower all-cause mortality in E2 compared to E1, although not reaching statistical significance (HR 0.75, 95% CI 0.50–1.13, $p = 0.17$) (*Table 2*, *Figures 1A* and *2A*). In multivariable analysis, receiving an LVAD during E2 was associated with a statistically significant 42% reduction in the risk of the primary outcome, compared to E1 (HR 0.58, 95% CI 0.35–0.98, $p = 0.043$, *Table 3*, online supplementary *Table S2*). The competing outcomes analysis resulted in a similar trend of reduction of the risk of all-cause mortality in E2 (subdistribution hazard ratio [SHR] 0.80, 95% CI 0.53–1.20, $p = 0.28$) (*Figure 3*, online supplementary *Figure S2*).

The influence of implantation era on heart transplantation during 1-year follow-up

After excluding 87 DT patients (of which only one ultimately underwent heart transplantation), heart transplantation occurred in 88 patients (19%) during the 1-year follow-up period. In E2, there was a notably lower incidence rate of heart transplantation per 100 patient-years (E1: 47.8, 95% CI 35.8–63.8 vs. E2: 15.7, 95% CI 11.6–21.3) (*Table 4*). In those transplanted during the first year of follow-up, the median time to transplantation in E1 was 213 days (interquartile range [IQR] 141–280), and 224 days in E2 (IQR 157–283). In unadjusted analysis, there was a significant, 68% lower likelihood of undergoing heart transplantation in E2, compared to E1 (HR 0.32, 95% CI 0.21–0.48, $p < 0.001$) (*Table 4*, *Figures 1B* and *2B*), which remained significant after adjusting for clinically relevant covariates (HR 0.40, 95% CI 0.23–0.67, $p = 0.001$) (*Table 4*, online supplementary *Tables S3* and *S4*). When heart transplantation was considered a main event in the competing outcomes analysis (with death and weaning as competing events), receiving an LVAD in E2 was associated with a statistically significant, 65% reduction in chance of receiving a heart transplant (SHR 0.35, 95% CI 0.23–0.53, $p < 0.001$) (*Figure 3*, online supplementary *Figure S2*).

Table 2 Incidence rates and hazard ratios for all-cause mortality by left ventricular assist device implantation eras during 1-year follow-up

	E1 Dec 2006–Dec 2012 ($n = 150$)	E2 Jan 2013–Jan 2020 ($n = 406$)
Incidence rate per 100 person-years	32.3 (95% CI 23.0–45.4)	22.2 (95% CI 17.7–27.9)
HR (unadjusted)	Referent	HR 0.75 (95% CI 0.50–1.13) $p = 0.17$
HR (adjusted[a])	Referent	HR 0.58 (95% CI 0.35–0.98) **$p = 0.043$**

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, comorbidities prior to left ventricular assist device implantation (atrial fibrillation, ventricular arrhythmia, arterial hypertension, chronic kidney disease), prior cardiac surgery, body mass index, and systolic blood pressure prior to left ventricular assist device implantation.

The influence of implantation era on other secondary outcomes during 1-year follow-up

The incidence rates of cardiovascular death decreased over time translating to a trend towards lower, yet non-significantly reduced risk of cardiovascular death in E2 (HR 0.78, 95% CI 0.47–1.29, $p = 0.34$) (*Table 5*, online supplementary *Table S5*).

The incidence rate of haemocompatibility-related events was lower in E2 (E1: 44.5, 95% CI 32.8–60.4 vs. E2: 33.8, 95% CI 27.7–41.2 per 100 patient-years). In unadjusted analysis, there was a trend towards less haemocompatibility-related events in E2 compared to E1, while in multivariable analysis, implantation of an LVAD during E2 was associated with a significant, 40% reduction in the risk of developing a haemocompatibility-related outcome (HR 0.60, 95% CI 0.39–0.91, $p = 0.016$) (*Table 5*, online supplementary *Table S6*).

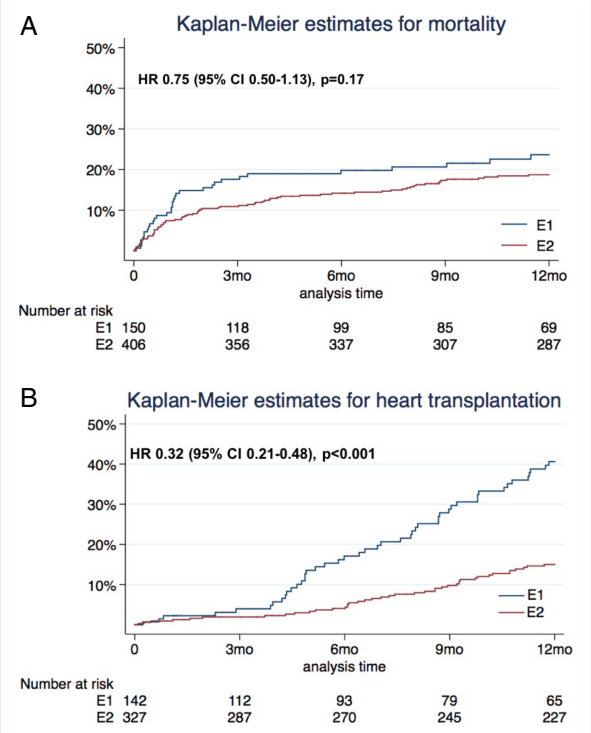


Figure 1 Kaplan–Meier curves for (*A*) all-cause mortality and (*B*) heart transplantation in 1-year follow-up according to implantation eras. CI, confidence interval; HR, hazard ratio.

The crude incidence rate of HF-related events increased over time (E1: 23.0, 95% CI 15.0–35.2 vs. E2: 42.1, 95% CI 34.9–50.9 per 100 patient-years). E2 was associated with a significant increase in the risk of HF-related events, compared to E1 in unadjusted and adjusted analyses (HR 1.78, 95% CI 1.11–2.83, $p = 0.016$, and HR 1.67, 95% CI 1.02–2.75, $p = 0.043$, respectively) (*Table 5*, online supplementary *Table S7*). Additional information on the treatment modalities used for acute and chronic RV failure is given in online supplementary *Table S8*.

LVAD-related infections requiring systemic antibiotics occurred in 138 patients (25%), with a decreasing incidence rate over time (55.4, 95% CI 41.7–73.8 vs. 31.8, 95% CI 25.9–39.0 per 100-patient years) (*Table 5*). In unadjusted analysis, E2 was associated with a significant, 42% reduction in risk of infection (E2 vs. E1: HR 0.58, 95% CI 0.41–0.83, $p = 0.003$), which remained significant in adjusted analysis (HR 0.64, 95% CI 0.43–0.95, $p = 0.027$ (*Table 5*, online supplementary *Table S9*). Patient age was the only remaining covariate that modified the risk of infections, being lower in older patients. Results of individual outcomes are presented in online supplementary *Tables S10–S14*).

Discussion

Our principal findings include the description of the evolving landscape of patients implanted with cf-LVADs in Europe over a course of 13 years: more recently, patients receiving an LVAD were significantly older with a higher comorbidity burden, with a transition to higher INTERMACS profiles and reduced use of MCS prior to LVAD implantation. Patients implanted in the more recent era had a trend towards a lower risk of all-cause mortality over a 1-year follow-up period, while having a significantly lesser chance of undergoing heart transplantation, but with a lower risk of device-related infections and haemocompatibility-related events.

General findings

Significantly older patients with an increasing comorbidity burden, and a higher proportion of CIEDs were implanted more recently, suggesting more chronically ill patients with longer standing or later onset HF received LVADs over time in our European cohort. This seems to be the opposite from the USA population presented in the latest INTERMACS report, also comparing two time eras of LVAD implantation, yet concluding that the recently implanted patients were less haemodynamically stable, requiring more temporary MCS and inotropes, less often ICD carriers, but still noting an increasing DT population, attributable to shifts in device approvals and heart transplant allocation regulation.[16] Interestingly, despite these differences, both registries suggested improved survival in the most recent era, what we postulate is due to improved experience of the LVAD centres.

Furthermore, we noted a significant difference in the devices implanted between the eras, as well as the indication for implantation. While interpreting these findings, we have to keep in mind the period of availability and approval of indication for use in Europe: the HMII received the CE mark in 2005, followed by the CE mark for the HeartWare HVAD in 2009, and the HM3 in 2015. The HM3 device represented 38% of LVADs in E2 (spanning from 2013 to 2020), which we find to be a large proportion, given the later approval. The proportion of HVAD carriers (28%) in E2 is smaller, despite its CE approval already during the E1 time span. Although the DT indication did increase in E2 to 21% of all LVAD recipients, this is still far less than the 56% reported in the second era of the INTERMACS report.[16] However, in Europe, healthcare payers of each country determine local reimbursement policies which governed the possible indications for LVAD implantation (mostly, BTT approval was followed by DT in several years), yet still more stringent than those in the USA, as reflected in the overall European landscape.

Differences in medical therapies prior to LVAD implantation between the eras were noted as well. The proportion of patients receiving HF therapy prior to LVAD implantation presented in our population was quite similar to the INTERMACS sub-analysis by Khazanie *et al.*[19] which reported that 38% patients received an ACEi/ARB prior to LVAD implantation, 55% received beta-blockers and 40% received an MRA. This is not surprising as the inability to tolerate HF medications is often an indication for LVAD referral. The low utilization of HF medications in both eras could be attributed to their interruption prior to LVAD implantation, possibly due to haemodynamic instability. We observed a somewhat greater utilization of beta-blockers in E2, which is in line with our general findings. Low utilization of ACEi/ARB in E2 could, to some extent, be attributed to the introduction of sacubitril/valsartan.

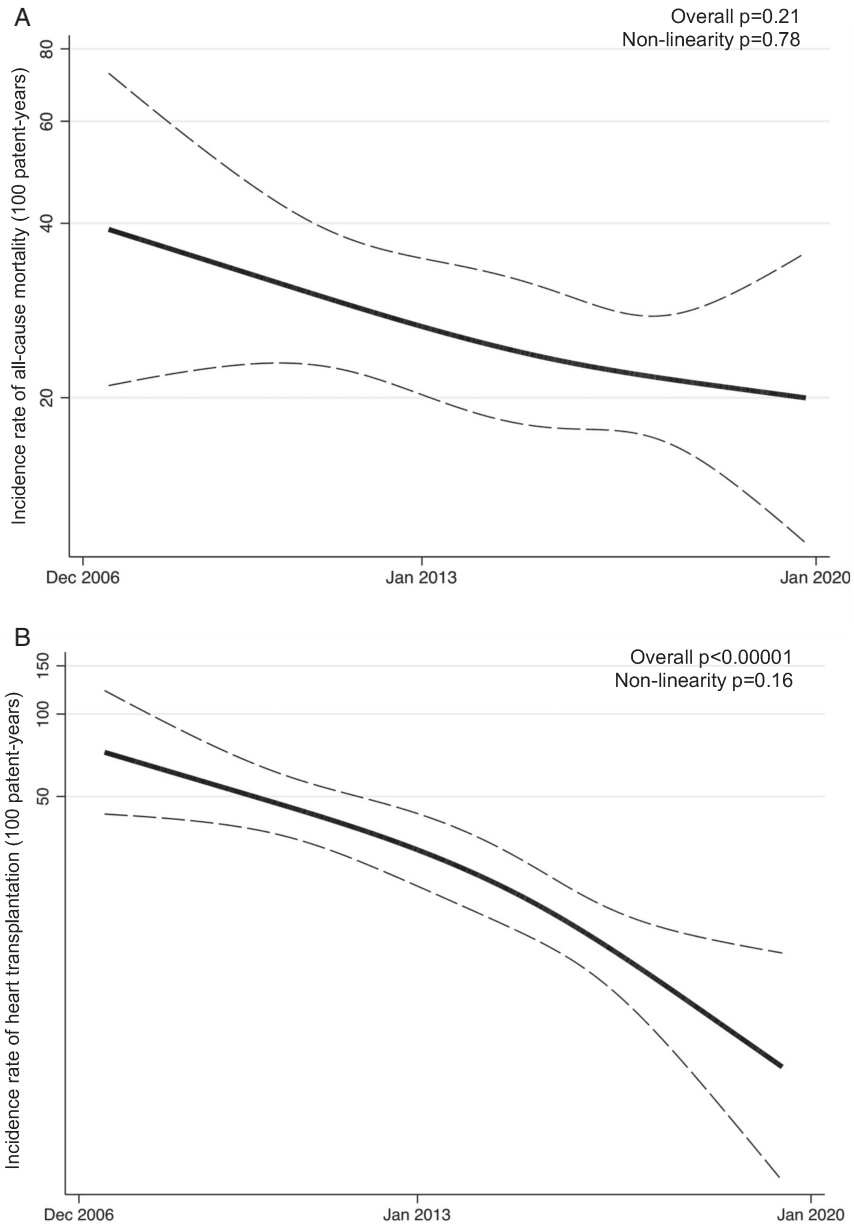


Figure 2 (*A*) Spline curve for the association between all-cause mortality and the date of left ventricular assist device implantation. (*B*) Spline curve for the association between heart transplantation and the date of left ventricular assist device implantation.

Era effect on all-cause mortality

One-year survival in our population was 81%, which is very similar to the 81.5% survival reported in the latest INTERMACS registry,[16] and higher than that reported from the EUROMACS registry (69%).[20] We report a reducing risk of all-cause mortality in patients receiving an LVAD in the more recent era, significant when adjusted for clinically relevant, patient-related variables. This finding could be attributed to several factors, some of which, such as the learning curve of LVAD centres, is more difficult to quantify, while others include technological advancements in the field of cf-LVADs. In the light of the reports of the MOMENTUM trial[14] and several recent analyses reporting favourable outcomes for patients treated with the HM3 device,[15,21,22] this likely accounts for some of the survival differences between the eras, where the HMII dominated E1 (93.3%) with a growing proportion (38%) of HM3 carriers in E2.

Era effect on the chance of undergoing heart transplantation

An important finding of this analysis is a significantly lower chance of receiving a heart transplantation during 1-year follow-up for patients receiving an LVAD in E2, including a longer median time to transplantation in E2 compared to E1. A similar finding has been

Table 3 Multivariable Cox regression model for all-cause mortality by left ventricular assist device implantation eras during 1-year follow-up

Variable	HR (95% CI)	*p*-value
LVAD implantation era	0.58 (0.35–0.98)	**0.043**
Age at implantation	1.04 (1.01–1.06)	**0.003**
Female sex	1.02 (0.57–1.83)	0.95
Arterial hypertension	1.16 (0.71–1.90)	0.55
Chronic kidney disease	0.95 (0.56–1.59)	0.84
Atrial fibrillation	1.24 (0.78–1.97)	0.37
Ventricular arrhythmia	1.25 (0.77–2.03)	0.37
Body mass index at implantation	1.01 (0.96–1.06)	0.82
Systolic blood pressure prior to implantation	1.00 (0.98–1.02)	1.00
Prior cardiac surgery	1.68 (0.95–2.96)	0.07

CI, confidence interval; HR, hazard ratio; LVAD, left ventricular assist device.

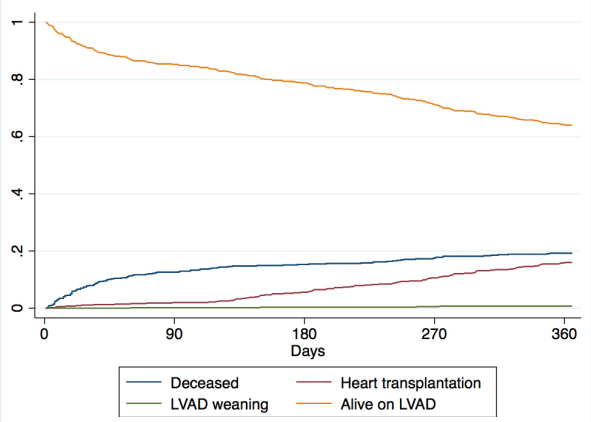


Figure 3 Kaplan–Meier curves for competing outcomes for the 1-year follow-up period (entire population). LVAD, left ventricular assist device.

Table 4 Incidence rates and hazard ratios for heart transplantation by left ventricular assist device implantation eras during 1-year follow-up

	E1 Dec 2006–Dec 2012 (*n* = 142)	E2 Jan 2013–Jan 2020 (*n* = 327)
Incidence rate per 100 person-years	47.8 (95% CI 35.8–63.8)	15.7 (95% CI 11.6–21.3)
HR (unadjusted)	Referent	HR 0.32 (95% CI 0.21–0.48) ***p* < 0.001**
HR (adjusted[a])	Referent	HR 0.40 (95% CI 0.23–0.67) ***p* = 0.001**

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, comorbidities prior to left ventricular assist device implantation (atrial fibrillation, chronic kidney disease, diabetes mellitus, chronic obstructive pulmonary disease), prior cardiac surgery, and body mass index prior to left ventricular assist device implantation.

described in the ELEVATE registry, a real-world study of patients receiving a HM3 LVAD between March 2015 and February 2017, where only 8.2% patients underwent heart transplantation within the first 2 years after implantation.[23] We speculate that several factors possibly contribute to this finding. Availability of donor organs is a well-known limiting factor, stifling the expansion of heart transplantation as a treatment option for advanced HF.[24] With the improvements in MCS therapy, more patients survive until heart transplantation candidacy, thereby increasing the demand for donor hearts. When listed, these patients are usually categorized as elective, only to be 'upgraded' to high urgent status in case of serious complications, thus typically having a longer waiting time for the donor organ.[25] The absolute numbers of heart transplantations have decreased over the last 10 years, according to the recent Eurotransplant report,[26] which has to be additionally interpreted in the light of the growing population of candidates, partially due to improved overall survival of LVAD carriers. Finally, improved outcomes with an LVAD in the more recent years may divert both the patients and physicians from proceeding to heart transplantation, even in BTT candidates.

Era effect on other secondary outcomes

During the course of the development of LVAD therapies, haemocompatibilty-related outcomes have been detected as a significant shortcoming of the otherwise satisfactory results of the LVAD programmes, and important technological advances have been made with the aim of minimizing this challenge.[14,15] We analysed this occurrence in our registry by examining a unified haemocompatibility-related outcome, encompassing intracranial bleeding, non-intracranial bleeding, cerebrovascular ischaemia and pump thrombosis, as recently proposed by Mehra *et al.*[15] Our results indicated a significant, 40% reduction in the adjusted risk of haemocompatibility-related events in patients implanted with an LVAD in E2. A decrease in haemocompatibility-related events has indeed been well documented in publications stemming from the MOMENTUM trial portfolio,[14,15] indicating a lesser incidence of these events in HM3 carriers. The HM3 became the leading device in E2 of our registry, which likely contributes to the reduction in risk of haemocompatibility-related outcomes.

Conversely, an increase in the adjusted risk of HF-related events (encompassing HF hospitalizations and RV failure) was noted in E2: the incidence rate of HF-related events was 23 and 42 events per 100 person-years in E1 and E2, respectively. We postulate that these events may have been underreported in the E1 of our registry: namely, only RV failure occurred with the rate of 27 events per 100 patient-years in a recent publication from the MOMENTUM investigators.[15] Both lower RV failure and HF hospitalization rates in E1 could also be attributable to several factors: (i) a higher competing risk of all-cause mortality in E1,

Table 5 Incidence rates and hazard ratios for other secondary endpoints by left ventricular assist device implantation eras during 1-year follow-up

	E1 Dec 2006–Dec 2012 (n = 150)	E2 Jan 2013–Jan 2020 (n = 406)
Cardiovascular mortality		
Incidence rate per 100 person-years (no. of events = 73)	21.5 (95% CI 14.2–32.7)	15.3 (95% CI 11.6–20.1)
HR unadjusted	Referent	HR 0.78 (95% CI 0.47–1.29) p = 0.34
HR adjusted[a]	Referent	HR 0.66 (95% CI 0.36–1.23) p = 0.19
Haemocompatibility-related events		
Incidence rate per 100 person-years (no. of events = 139)	44.5 (95% CI 32.8–60.4)	33.8 (95% CI 27.7–41.2)
HR unadjusted	Referent	HR 0.78 (95% CI 0.54–1.12) p = 0.18
HR adjusted[b]	Referent	HR 0.60 (95% CI 0.39–0.91) **p = 0.016**
Heart failure-related events		
Incidence rate per 100 person-years (no. of events = 129)	23.0 (95% CI 15.0–35.2)	42.1 (95% CI 34.9–50.9)
HR unadjusted	Referent	HR 1.78 (95% CI 1.11–2.83) **p = 0.016**
HR adjusted[c]	Referent	HR 1.67 (95% CI 1.02–2.75) **p = 0.043**
LVAD-related infection requiring systemic antibiotics		
Incidence rate per 100 person-years (no. of events = 138)	55.4 (95% CI 41.7–73.8)	31.8 (95% CI 25.9–39.0)
HR unadjusted	Referent	HR 0.58 (95% CI 0.41–0.83) **p = 0.003**
HR adjusted[d]	Referent	HR 0.64 (95% CI 0.43–0.95) **p = 0.027**

CI, confidence interval; HR, hazard ratio; LVAD, left ventricular assist device.
[a]Cardiovascular mortality analysis adjusted for: age, sex, body mass index at implantation, mechanical circulatory support prior to LVAD implantation, prior cardiac surgery, history of atrial fibrillation, and chronic kidney disease prior to LVAD implantation.
[b]Haemocompatibility-related events adjusted for: age, sex, history of atrial fibrillation and chronic kidney disease prior to LVAD implantation, systolic blood pressure prior to LVAD implantation, prior cardiac surgery, and mechanical circulatory support prior to LVAD implantation.
[c]Heart failure-related events analysis adjusted for: age, sex, history of atrial fibrillation, chronic kidney disease, diabetes mellitus and chronic obstructive pulmonary disease prior to LVAD implantation, prior cardiac surgery, and INTERMACS profile at implantation.
[d]LVAD-related infection analysis adjusted for: age, sex, history of diabetes mellitus and chronic kidney disease, prior cardiac surgery, INTERMACS profile at implantation, and mechanical circulatory support prior to LVAD implantation.

(ii) patient selection, i.e. implanting patients with less favourable RV function prior to LVAD implantation in the more recent era (previously, they were more frequently rejected from LVAD candidacy); (iii) raised awareness of RV failure leading to earlier and better recognition of post-implantation RV failure in E2, which is also more clearly defined in recent publications[27]; (iv) the latter most likely resulting in a larger proportion of patients in E2 treated only with inotropes, and a smaller proportion requiring MCS for acute RV failure (as seen in online supplementary *Table S8*). These data in fact support the hypothesis that increasing experience of European LVAD centres results in a trend towards more favourable overall outcomes, i.e. better survival; however, caution in the interpretation of the results is needed due to a fairly low number of these events.

The highest event rate in our cohort has been reported for LVAD-related infections requiring systemic antibiotics, occurring in one quarter of our entire cohort. This is comparable to the MOMENTUM data (23.3% and 19.4%, in HM3 and HMII, respectively), but notably lower than the proportion of affected patients in the INTERMACS registry (only 59% of patients are free from infection at 1 year) and the EUROMACS registry (35% of patients).[14,16,28] Most importantly, we have noted a significant, 42% reduction in risk of infection in E2 compared to E1, which remained significant after adjustment, signalling an important improvement in the morbidity of our LVAD population. We have also confirmed that older age, which has been linked to less driveline infections in previous publications, is associated with a decreased risk of infection.[29,30] Recent publications have also described improvements in the incidence of driveline infections, attributing this to alternative surgical techniques,[31] or improved post-implantation care.[32] Increasing awareness of the importance of driveline exit site care and other efforts towards reduced risk of chronic infections is highly relevant, as this frequent adverse event will remain unresolved until the advent of new modalities of energy transfer, thus impacting the quality of life and otherwise favourable outcomes of LVAD carriers.

While a trend towards better survival in the more recent years represents a major advance, many patients consider the

burden of complications and repeat post-implantation hospitalizations a greater drawback. It is reassuring that the most frequently occurring complication – device-related infections, as well as haemocompatibility-related events decreased over time, which should further improve with the currently exclusive utilization of the HM3 device. Ultimately, a trend towards better survival with LVAD devices, as evident in the recent era, should be appealing to patients, providers and payers alike, yet LVAD therapy remains underutilized. In real-world clinical practice, there is still a remaining presence of some of the complications of LVAD therapy, particularly in those remaining on LVAD support from earlier implantation eras. This may be at the root of the ongoing referral reluctance, despite clear benefits of the therapy and guideline recommendations. Therefore, proper and timely referral to advanced HF centres is imperative for patients to receive adequate and equal opportunities for LVAD and other advanced HF interventions.[3] Identification of proper candidates, before progression to irreversible contraindications such as severe renal or RV failure, by screening patients for advanced HF therapy may be a possibility.[33] Finally, due to the ongoing burden of device-related infections, further efforts are needed from the industry to open a new era with wireless LVADs.

Limitations

This is a retrospective, observational, registry-based analysis, with all the inherent flaws of such studies. The populations compared can be seen as quite heterogeneous, but this reflects the evolving LVAD landscape in Europe over the past 13 years and is a representation of real-world data. In respect to the outcome analyses, this type of study design does not enable optimal accounting for multiple potential confounders, yet careful adjusted analyses were performed accounting for the available confounding variables. The endpoint adjudication was performed by the clinical teams of each centre individually, which may have led to a misclassification or underreporting of events, particularly those more challenging to define. However, the changes noted in the occurrence of the most frequently reported endpoint, device-related infection, achieved a significant difference in the risk profile among eras – perhaps a higher number of other events would have provided more power for stronger inferences. As it is not uncommon in registries, there was some amount of missing data, especially in the echocardiography section, most likely due to the retrospective nature of data collection. Given the lacking data, some indicators, commonly used in risk predicting scores, were not assessed as potential covariates.

Although a direct comparison of survival between eras is burdened by many confounding factors, we believe this conveys a realistic view of the progress made in the field of long-term MCS in Europe. We have detected a trend towards lower mortality in E2, but we do not suggest causation nor detect a single protective factor.

Conclusion

Over a course of 13 years, we find that the overall survival and risk of some complications in patients implanted with a cf-LVAD in Europe improves with time while LVAD recipients are increasingly older, with more comorbidities, however more haemodynamically stable with a higher proportion of CIED and beta-blocker recipients prior to LVAD implantation. We also demonstrated a significant reduction in the chance of undergoing heart transplantation for BTT candidates in the later era. In light of this finding, a significant reduction in the risk of LVAD-related infections, a frequent cause of morbidity in this population, is particularly relevant.

Ultimately, we should consider the intricate interplay and the dynamics of the wider LVAD ecosystem, beyond the changing patient population or technological advances, involving also the changes in transplantation trends, healthcare funding and improved overall patient care that may lead to improved outcomes in this population (*Graphical Abstract*). This description of temporal trends in a multinational LVAD cohort could provide valuable information for future patient selection and a motivation for continuous development of European LVAD programmes.

Supplementary Information

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

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Improved survival of left ventricular assist device carriers in Europe according to implantation eras - results from the PCHF-VAD registry

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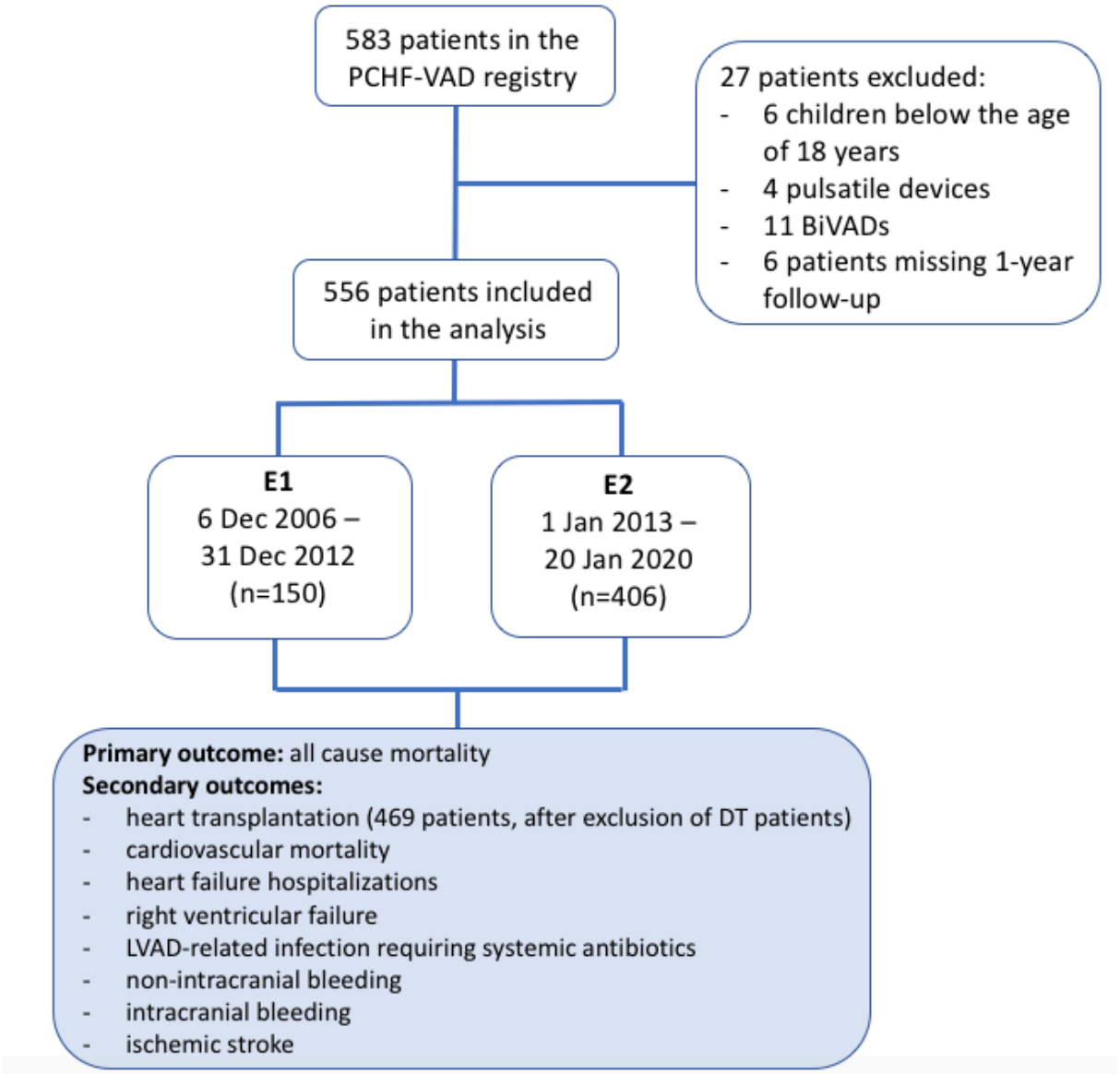
Supplemental material

Supplemental Figures

Supplemental figure 1. Selection of patients for the analysis.

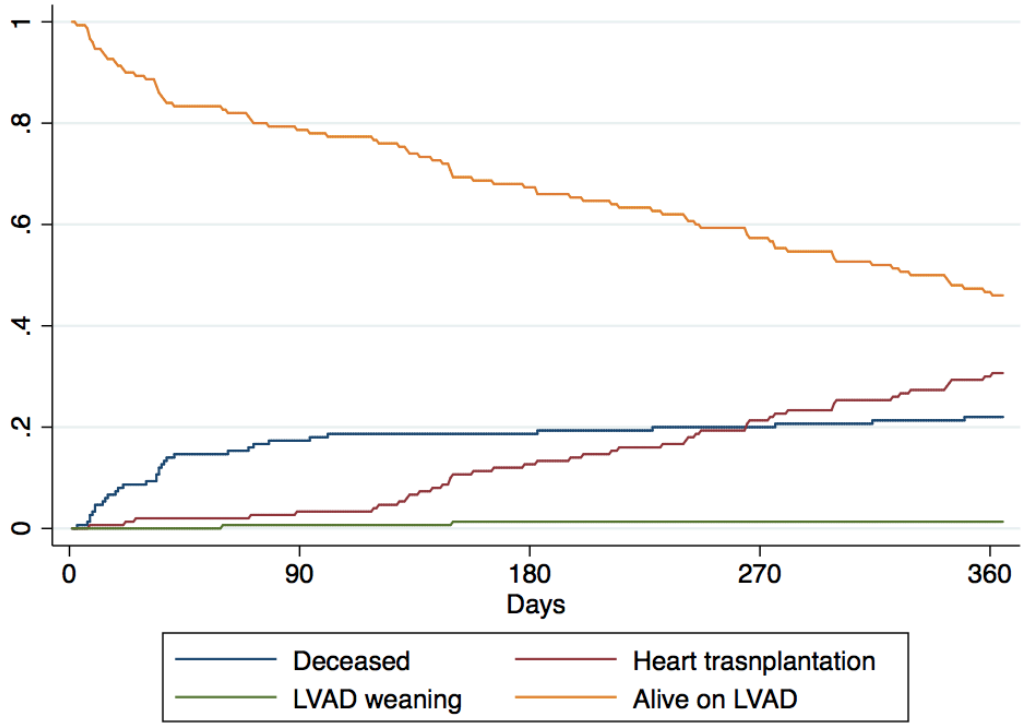
Supplemental Figure 2a & 2b. Kaplan Meier curves for competing outcomes for the 1-year follow-up period divided per LVAD implantation era: A) Era 1, B) Era 2.

Supplemental figure 1. Selection of patients for the analysis.

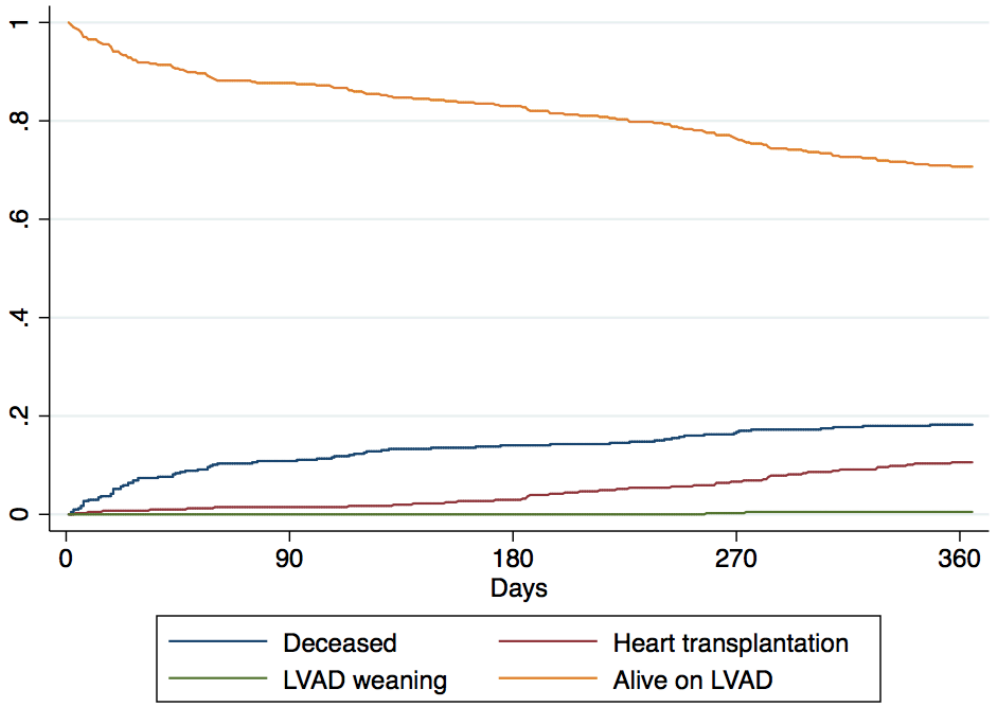


Supplemental Figure 2a & 2b. Kaplan Meier curves for competing outcomes for the 1-year follow-up period divided per LVAD implantation era: A) Era 1, B) Era 2.

2a. Era 1



2b. Era 2.


0
.2
.4
.6
.8
1
0
90
180
270
360
Days
Deceased
Heart transplantation
LVAD weaning
Alive on LVAD

Supplemental Tables

Supplemental Table 1. List of participating centres by country.

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Supplemental Table 7. Multivariable Cox regression model for **HF-related events** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

Supplemental Tables 8a & 8b. Treatment of acute and chronic right ventricular failure.

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Supplemental Table 10. Multivariable Cox regression model for **heart failure hospitalization** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

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Supplemental Table 12. Multivariable Cox regression model for **non-intracranial bleeding** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

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Supplemental Table 14. Multivariable Cox regression model for **ischaemic stroke** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

Supplemental Table 1. List of participating centres by country.

Country	LVAD Centre
The Netherlands	Erasmus MC, University Medical Center Rotterdam, Rotterdam
Belgium	University Hospital Leuven, Leuven
	Cliniques Universitaires St. Luc, Brussels
	Antwerp University Hospital, Antwerp
Croatia	University Hospital Center Zagreb, Zagreb
Poland	John Paul II Hospital, Krakow
Lithuania	Faculty of Medicine, Vilnius University, Vilnius
Spain	Complejo Hospitalario Universitario de A Coruña
Italy	Federico II University of Naples
	Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome
Germany	Heart Center Freiburg University
Sweden	Lund University and Skåne University Hospital
Greece	Onassis Cardiac Surgery Centre, Athens

Supplemental Table 2. Univariate analysis of the covariates used in the multivariate model for all-cause mortality.

	HR (CI 95%)	**p-value**
Age at implantation	1.03 (1.01-1.05)	**0.001**
Female gender	0.98 (0.60-1.61)	0.94
Arterial hypertension	1.27 (0.83-1.94)	0.28
Chronic kidney disease	1.12 (0.70-1.79)	0.63
Atrial fibrillation	1.31 (0.88-1.94)	0.18
Ventricular arrhythmia	1.17 (0.77-1.77)	0.45
Body mass index at implantation	1.00 (0.96-1.05)	0.93
Systolic blood pressure at implantation	1.01 (0.99-1.02)	0.28
Prior cardiac surgery	1.75 (1.08-2.81)	**0.022**

Supplemental Table 3. Multivariable Cox regression model for heart transplantation by LVAD implantation era for 1-year follow-up.

Variable	HR (95% CI)	p-value
LVAD implantation era	0.40 (CI 0.23-0.67)	**0.001**
Age at implantation	1.00 (CI 0.98-1.02)	0.89
Female gender	1.44 (CI 0.77-2.69)	0.26
Atrial fibrillation	1.17 (CI 0.64-2.13)	0.62
Chronic obstructive pulmonary disease	2.16 (CI 0.93-5.01)	0.07
Chronic kidney disease	0.68 (CI 0.30-1.55)	0.36
Diabetes mellitus	0.67 (CI 0.31-1.46)	0.31
Body mass index at implantation	1.01 (CI 0.95-1.08)	0.69
Prior cardiac surgery	1.54 (CI 0.76-3.10)	0.23

LVAD = left ventricular assist device.

Supplemental Table 4. Univariate analysis of the covariates used in the multivariate model for heart transplantation.

	HR (CI 95%)	p-value
Age at implantation	1.00 (0.98-1.02)	0.86
Female gender	1.45 (0.90-2.36)	0.13
Chronic obstructive pulmonary disease	1.68 (0.81-3.47)	0.16
Diabetes mellitus	0.71 (0.38-1.34)	0.29
Chronic kidney disease	0.45 (0.21-0.98)	**0.044**
Atrial fibrillation	1.08 (0.68-1.73)	0.75
Ventricular arrhythmia	0.72 (0.42-1.21)	0.22
Body mass index at implantation	1.00 (0.95-1.06)	1.00
Systolic blood pressure at implantation	0.99 (0.97-1.01)	0.52
Prior cardiac surgery	1.45 (0.83-2.52)	0.19

Supplemental Table 5. Multivariable Cox regression model for **cardiovascular death** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	0.66 (0.36-1.23)	0.19	0.78 (0.47-1.29)	0.34
Age at implantation	1.05 (1.02-1.08)	**0.002**	1.03 (1.01-1.06)	**0.004**
Female gender	0.78 (0.38-1.60)	0.49	0.98 (0.54-1.79)	0.96
Chronic kidney disease	1.15 (0.64-2.06)	0.64	1.42 (0.83-2.42)	0.20
Atrial fibrillation	1.12 (0.66-1.90)	0.69	1.33 (0.83-2.15)	0.23
Body mass index at implantation	0.99 (0.94-1.05)	0.76	1.00 (0.95-1.05)	0.99
MCS prior to LVAD implantation	1.07 (0.93-1.22)	0.35	1.04 (0.93-1.16)	0.53
Prior cardiac surgery	1.47 (0.76-2.84)	0.26	1.84 (1.04-3.24)	**0.036**

LVAD = left ventricular assist device; MCS = mechanical circulatory support.

Supplemental Table 6. Multivariable Cox regression model for **haemocompatibility-related events** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	0.60 (0.39-0.91)	**0.016**	2.03 (1.07-3.83)	**0.030**
Age at implantation	1.02 (1.00-1.03)	0.06	1.02 (1.01-1.04)	**0.01**
Female gender	0.85 (0.53-1.38)	0.52	0.87 (0.55-1.35)	0.53
Chronic kidney disease	1.29 (0.84-1.97)	0.24	1.28 (0.86-1.92)	0.23
Atrial fibrillation	0.90 (0.61-1.34)	0.61	1.09 (0.76-1.55)	0.64
Systolic blood pressure	1.01 (0.99-1.02)	0.42	1.01 (0.99-1.02)	0.42
MCS prior to LVAD implantation	1.01 (0.92-1.11)	0.80	1.02 (0.94-1.11)	0.56
Prior cardiac surgery	1.06 (0.61-1.84)	0.83	1.24 (0.76-2.00)	0.39

LVAD = left ventricular assist device.

Supplemental Table 7. Multivariable Cox regression model for **HF-related events** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	1.67 (1.02-2.75)	**0.043**	1.91 (1.00-3.64)	**0.049**
Age at implantation	1.01 (0.99-1.03)	0.35	1.01 (0.99-1.03)	0.15
Female gender	1.01 (0.62-1.62)	0.98	1.00 (0.63-1.58)	1.00
Chronic kidney disease	1.48 (0.97-2.25)	0.07	1.63 (1.11-2.42)	**0.014**
Atrial fibrillation	1.10 (0.75-1.62)	0.63	1.30 (0.91-1.86)	0.15
Diabetes mellitus	1.14 (0.75-1.75)	0.54	1.28 (0.86-1.91)	0.23
Chronic obstructive pulmonary disease	0.82 (0.43-1.56)	0.54	1.02 (0.55-1.89)	0.95
INTERMACS profile	0.87 (0.72-1.05)	0.15	0.95 (0.80-1.14)	0.58
Prior cardiac surgery	0.76 (0.41-1.42)	0.87	0.73 (0.40-1.32)	0.29

LVAD = left ventricular assist device.

Supplemental Tables 8a & 8b. Treatment of acute and chronic right ventricular failure.

8a. Treatment of acute right ventricular failure

	E1 **Dec 2006 – Dec 2012** **(n=150)**	**E2** **Jan 2013 – Jan 2020** **(n=406)**
Temporary RVAD	14 (51.9%)	25 (28.7%)
ECMO	4 (14.8%)	3 (3.5%)
Nitric oxide	0 (0.0%)	6 (6.9%)
Prostaglandins	1 (3.7%)	0 (0.0%)
PDE5 inhibitors	0 (0.0%)	9 (10.3%)
Inotropes	6 (22.2%)	39 (44.8%)
MCS + medication	1 (3.7%)	5 (5.8%)
Missing data	1 (3.7%)	0 (0.0%)

8b. Treatment of chronic right ventricular failure

	E1 **Dec 2006 – Dec 2012** **(n=150)**	**E2** **Jan 2013 – Jan 2020** **(n=406)**
Prostaglandins	1 (100%)	0 (0.0%)
PDE5 inhibitors	0 (0.0%)	4 (33.3%)
Inotropes	0 (0.0%)	6 (50.0%)
Missing data	0 (0.0%)	2 (16.7%)

RVAD = right ventricular assist device; ECMO = extracorporeal membrane oxygenation; PDE5 inhibitors= phosphodiesterase-5 inhibitors; MCS = mechanical circulatory support.

Supplemental Table 9. Multivariable Cox regression model for **LVAD-related infection requiring systemic antibiotics** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	0.64 (0.43-0.95)	**0.027**	0.58 (0.41-0.83)	**0.003**
Age at implantation	0.98 (0.97-1.00)	**0.036**	0.99 (0.97-1.00)	**0.043**
Female gender	0.70 (0.43-1.15)	0.16	0.80 (0.50-1.27)	0.35
Chronic kidney disease	0.90 (0.55-1.46)	0.67	0.75 (0.47-1.19)	0.22
Diabetes mellitus	1.16 (0.75-1.85)	0.47	0.99 (0.65-1.50)	0.96
INTERMACS profile	0.97 (0.79-1.20)	0.80	0.87 (0.74-1.03)	0.11
Prior cardiac surgery	1.21 (0.71-2.06)	0.49	1.48 (0.94-2.34)	0.09
MCS prior to LVAD implantation	1.01 (0.91-1.11)	0.91	1.04 (0.95-1.12)	0.40

LVAD = left ventricular assist device; MCS = mechanical circulatory support.

Supplemental Table 10. Multivariable Cox regression model for **heart failure hospitalization** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	1.78 (0.92-3.45)	0.09	2.03 (1.07-3.83)	**0.030**
Age at implantation	1.02 (1.00-1.04)	0.12	1.02 (1.00-1.04)	0.11
Female gender	1.11 (0.63-1.98)	0.71	1.07 (0.61-1.88)	0.81
Chronic kidney disease	1.20 (0.69-2.08)	0.52	1.42 (0.85-2.38)	0.19
Atrial fibrillation	0.99 (0.60-1.63)	0.97	1.14 (0.71-1.82)	0.58
Diabetes mellitus	0.97 (0.56-1.69)	0.92	1.15 (0.68-1.95)	0.60
INTERMACS profile	0.90 (0.71-1.15)	0.41	1.01 (0.81-1.27)	0.91
Prior cardiac surgery	0.52 (0.21-1.30)	0.17	0.49 (0.20-1.22)	0.12

Supplemental Table 11. Multivariable Cox regression model for **RV failure** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	1.77 (0.88-3.56)	0.11	1.94 (1.02-3.69)	**0.044**
Age at implantation	0.99 (0.97-1.02)	0.57	1.01 (0.98-1.03)	0.58
Female gender	0.87 (0.42-1.77)	0.69	0.81 (0.42-1.58)	0.53
Chronic kidney disease	1.63 (0.94-2.83)	0.08	1.82 (1.08-3.06)	**0.023**
Atrial fibrillation	1.73 (1.04-2.86)	**0.035**	2.05 (1.28-3.27)	**0.003**
Chronic obstructive pulmonary disease	1.00 (0.45-2.25)	1.00	1.27 (0.58-2.78)	0.54
INTERMACS profile	0.94 (0.73-1.21)	0.63	1.01 (0.80-1.28)	0.94
Prior cardiac surgery	1.08 (0.51-2.28)	0.84	1.06 (0.53-2.14)	0.87

Supplemental Table 12. Multivariable Cox regression model for **non-intracranial bleeding** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	0.89 (0.48-1.68)	0.73	0.85 (0.53-1.38)	0.52
Age at implantation	1.02 (1.00-1.04)	0.07	1.03 (1.00-1.05)	**0.015**
Female gender	0.61 (0.29-1.29)	0.20	0.90 (0.51-1.60)	0.72
Arterial hypertension	0.85 (0.48-1.51)	0.58	1.08 (0.65-1.78)	0.77
Chronic kidney disease	1.50 (0.88-2.53)	0.13	1.48 (0.90-2.42)	0.12
Atrial fibrillation	1.11 (0.66-1.85)	0.70	1.11 (0.70-1.75)	0.67
Ventricular arrhythmia	0.77 (0.43-1.35)	0.35	0.78 (0.46-1.31)	0.35
Body mass index at implantation	1.01 (0.96-1.07)	0.68	1.02 (0.97-1.07)	0.39
Prior cardiac surgery	1.24 (0.63-2.45)	0.53	1.40 (0.78-2.53)	0.26

LVAD = left ventricular assist device; MCS = mechanical circulatory support.

Supplemental Table 13. Multivariable Cox regression model for **intracranial bleeding** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	0.68 (0.29-1.57)	0.36	0.76 (0.33-1.74)	0.51
Age at implantation	1.07 (1.02-1.12)	**0.003**	1.06 (1.02-1.10)	**0.006**
Chronic kidney disease	0.25 (0.06-1.06)	0.06	0.34 (0.08-1.44)	0.14
Atrial fibrillation	1.43 (0.65-3.14)	0.37	1.58 (0.73-3.41)	0.24

LVAD = left ventricular assist device; MCS = mechanical circulatory support.

Supplemental Table 14. Multivariable Cox regression model for **ischaemic stroke** by LVAD implantation era for 1-year follow-up and the univariate analysis of each covariate used in the model.

	Multivariable model		**Univariate analysis of individual covariates**	
	HR (CI 95%)	**p-value**	**HR (CI 95%)**	**p-value**
LVAD implantation era	1.34 (0.50-3.61)	0.58	1.45 (0.55-3.83)	0.45
Age at implantation	1.02 (0.98-1.06)	0.27	1.02 (0.99-1.06)	0.21
Chronic kidney disease	1.08 (0.42-2.76)	0.87	1.26 (0.51-3.12)	0.62
Atrial fibrillation	0.97 (0.43-2.22)	0.95	1.13 (0.51-2.51)	0.77

LVAD = left ventricular assist device; MCS = mechanical circulatory support.

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- She critically revised the manuscript for important intellectual content; AND
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- Agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Outcome of patients on heart transplant list treated with a continuous-flow left ventricular assist device: Insights from the TRans-Atlantic registry on VAd and TrAnsplant (TRAViATA)

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ABSTRACT

Background: Geographic variations in management and outcomes of individuals supported by continuous-flow left ventricular assist devices (CF-LVAD) between the United States (US) and Europe (EU) is largely unknown.
Methods: We created a retrospective, multinational registry of 524 patients who received a CF-LVAD (either HVAD or Heartmate II) between January 2008 and April 2017. Follow up spanned from date of CF-LVAD implant to post-HTx period with a median follow up of 44.8 months.
Results: The cohort included 299 (57.1%) EU and 225 (42.9%) US patients. Although the US cohort was significantly older with a higher prevalence of comorbidities, survival was similar between the cohorts (US 63.1%, EU 68.4% at 5 years, unadjusted log-rank test $p = 0.43$).Multivariate analyses suggested that older age, higher body mass index, elevated creatinine, use of temporary mechanical circulatory support prior CF-LVAD, and implantation of HVAD were associated with increased mortality. Among CF-LVAD patients undergoing HTx, the median time on CF-LVAD support was shorter in the US, meanwhile US donors were younger. Finally, the pattern of adverse events (stroke, gastrointestinal bleedings, late right ventricular failure, and driveline infection) during support differed significantly between US and EU.
Conclusions: Although waitlisted patients in the US on CF-LVAD have higher risk comorbid conditions, the overall outcome is similar in US and EU. Geographic variations with regards to donor characteristics, duration of CF-LVAD support prior to transplant, and adverse events on support can explain the disparity in the utilization of mechanical bridge to transplant strategy between US and EU.

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1. Introduction

Continuous-flow left ventricular assist devices (CF-LVADs) are commonly used as a bridge therapy to heart transplantation (HTx) [1–3]. Despite the survival benefit, extended time on support increases the rates of CF-LVAD-related complications with a higher risk of delisting or worse post-HTx outcomes [4]. In addition, heart donor availability largely affects duration on support and the subsequent outcomes before and after HTx.

Current large registries (i.e. Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS], or International Society for Heart and Lung Transplantation [ISHLT] Mechanically Assisted Circulatory Support [IMACS] registries, or European Registry for Patients with Mechanical Circulatory Support [EUROMACS] evaluating CF-LVADs as bridge to HTx do not report survival after HTx [1,2,5]. Similarly, the United Network for Organ Sharing (UNOS) only collects data at the time of listing and at the time of HTx, without reporting baseline characteristic at the time of CF-LVAD implant [3]. Hence there is a critical knowledge gap regarding the impact of LVAD on the long term outcomes of patients bridged to transplant.

The United States (US) and Europe (EU) differ in a variety of factors related to CF-LVAD-strategy and HTx indications [6]. Relevant factors that may affect outcomes are numerous, the most obvious being the older age of transplant recipients in the US and older age of transplant donor hearts in the EU. Furthermore, there is a significant discrepancy in HTx and CF-LVAD volume between the US and EU, with the number of CF-LVAD implants being nearly 4 times greater in the US (1700/year in the US compared with 430/year in EU) [7], even though the EU has more than twice the population of the US (741 million compared to 328 million respectively). The extent to which geographic variations affect the management and outcomes of individuals who receive a CF-LVAD implantation while listed or eventually become listed for transplant is largely unknown.

To address the issues above, we created the TRans-Atlantic registry on VAd and TrAnsplant (TRAViATA), a retrospective, observational, multinational registry that includes CF-LVAD patients who are candidates for HTx or heart-kidney transplant. Herein, we performed an analysis of TRAViATA with the following objectives: (1) characterize overall outcomes from the time of CF-LVAD implant to the post-transplant period, focusing on survival and adverse events, while controlling for regional variations. (2) describe differences in preimplant patients' characteristics, as well as in donors' aspects, between US and EU.

2. Methods

2.1. Participant centers

Patients in 7 EU hospitals (Niguarda Hospital in Milan, Italy [n = 72]; Sant'Orsola Malpighi Hospital in Bologna, Italy [n = 7]; Skåne University Hospital in Lund, Sweden [n = 35]; Erasmus MC Thoraxcenter in Rotterdam, the Netherlands [n = 54]; Antwerp University Hospital in Antwerp, Belgium [n = 22]; University Hospitals Leuven in Leuven, Belgium [n = 99]; and University Hospital Centre in Zagreb, Croatia [n = 10]) and 3 US centers (University of California San Diego, La Jolla, California [n = 69]; Inova Heart and Vascular Institute, Falls Church, Virginia [n = 88]; and University of California San Francisco, San Francisco, California [n = 68]) participated in the TRAViATA registry (Fig. 1A). All the participating sites were required to meet the following criteria: 1) expertise in mechanical circulatory support (MCS) and HTx; 2) active HTx and CF-LVAD programs during the study period; 3) willingness to volunteer, as no funding support for data collection was provided. Institution review board at each respective institution approved the study and, included a waiver of informed consent due to the retrospective nature of the registry.

2.2. Patient population

Consecutive patients that received a CF-LVAD in accordance with the study protocol were included. Inclusion criteria for TRAViATA consisted of: (1) age ≥ 16 years; (2) CF-LVAD implantation between January 2008 and April 2017; (3) implantation of either HeartWare HVAD (HVAD, Minnesota, MN, US) or Heartmate II (HMII, Abbott, Pleasanton, CA, US); (4) listing at any point for HTx or heart and kidney transplantation while supported with CF-LVAD. Exclusion consisted of: (1) patients implanted with HeartMate 3 device (HM3,Abbott Pleasanton, CA, US) as it was still under investigation in the US during the study period; (2) patients treated with bi-ventricular VAD (BiVAD) or total artificial heart (TAH); (3) patients never listed for HTx; (4) prior HTx before CF-LVAD implantation. Patient selection and post-operative management were left at the discretion of the local investigators. Last date of data collection in the follow up was March 31, 2018. Median follow-up time on CF-LVAD support was 354 days (first to third quartiles [Q1-Q3]: 168–697) while overall median follow-up time, including both CF-LVAD and HTx was 979 days (Q1-Q3: 448–1669).

2.3. Data collection and management

Baseline demographics, prior history of cardiovascular disease, comorbidities, New York Heart Association (NYHA) classification and INTERMACS profile, laboratory values, hemodynamic and echocardiographic parameters were collected. CF-LVAD-related adverse events (i.e. stroke, major bleeding, driveline infections, late right ventricular failure [RVF] and pump thrombosis) were defined using the INTERMACS registry criteria [1]. Survival after HTx and donor characteristics were also collected from each center.

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, when needed, contacted local investigators for clarifications. A data dictionary with a detailed description of each variable in the dataset was also provided to each participating center.

2.4. Statistical analysis

Continuous variables were presented as either means with standard deviation (SD) or medians with first to third quartile (Q1-Q3). Categorical variables were presented as numbers and percentages. Continuous data were evaluated for normality using the Shapiro-Wilk test. Two-sample t-tests and two-sample Mann Whitney tests were used to compare continuous variables depending on normality, and Fisher's exact tests were used to compare categorical variables. Overall and post-transplant survival of patients receiving CF-LVAD support were estimated using the Kaplan-Meier method. Differences in survival between US and EU were tested using the Mantel log-rank test. Univariate Cox regression analyses were used to determine predictors of overall mortality. We first conducted a univariate an multivariate analysis based on variables for which more than 95% of values were available for each variables (model 1). Then, we performed a univariate and multivariate analyses also including baseline clinical and diagnostic variables with a larger number of missing data (up to 55% of missing data for some variables; models 2 and 3). In the model 1, 507 patients with 159 events were included in the multivariate analysis (variables included in the analysis were: age, body mass index [BMI], diabetes, previous sternotomy, history of atrial fibrillation [AF], type of CF-LVAD: HVAD, creatinine, need for temporary MCS, and region of origin: USA). In the model 2 were included baseline variables before CF-LVAD implant that significantly differed between EU and the US cohort (this model included 179 patients and 56 event; and the

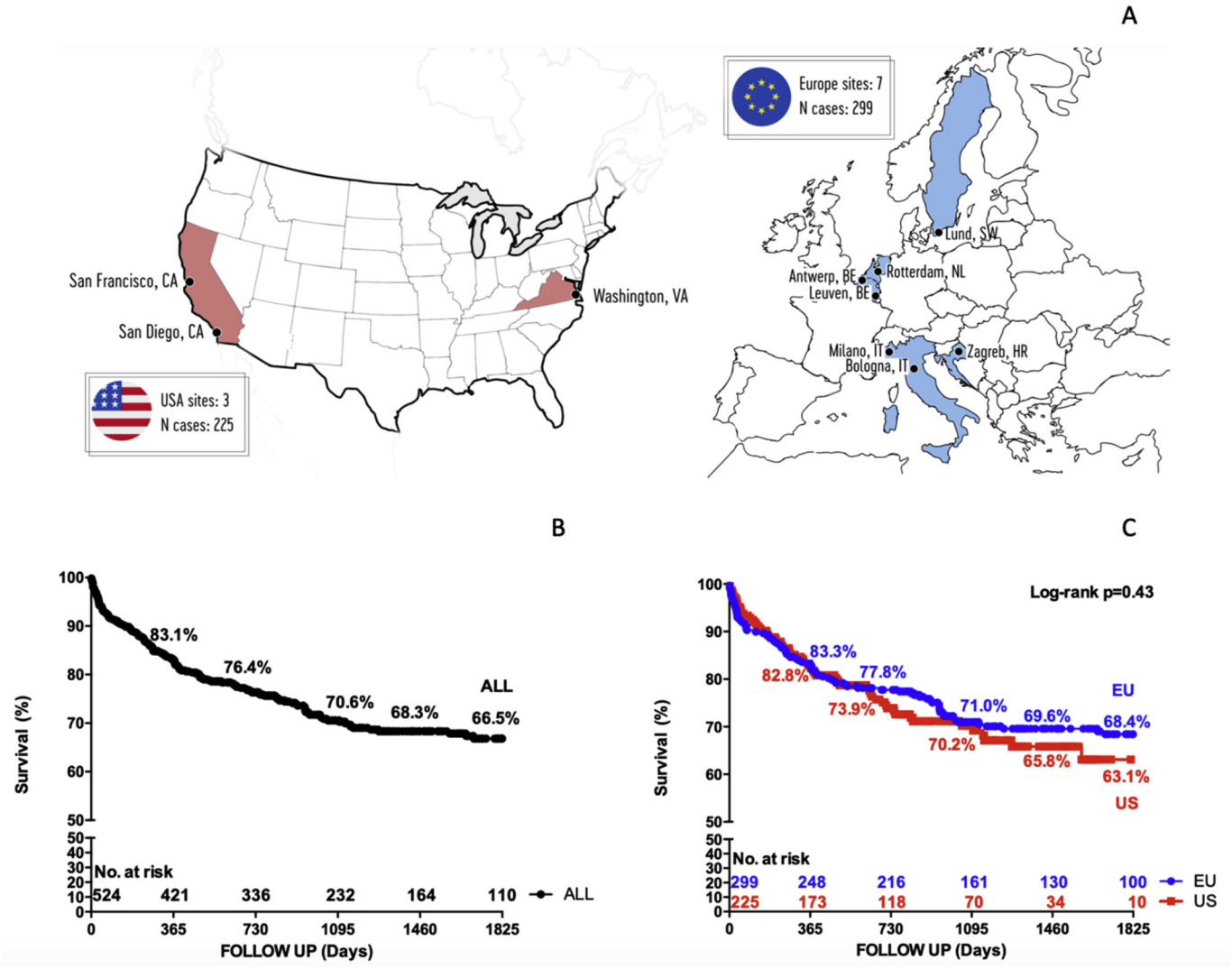

Fig. 1. US and EU participating centers and overall survival of patients on heart transplant list implanted with a left ventricular assist device (A) Map of the US and European sites participating in the TRans-Atlantic registry on VAd and TrAnsplant (TRAVIATA) registry (B) Kaplan-Meier curve showing the overall 5-year survival of patients who received an LVAD and were on HTx list. Follow-up started on the implant date and continued up to death or lost-to-follow-up. No censoring for transplantation was used. (C) Kaplan-Meier curves comparing the overall 5-year survival of EU and US patients who received an LVAD and were on HTx list. Follow-up started on the implant date and continued up to death or lost-to-follow-up. No censoring for transplantation was used. Differences in survival were evaluated with the Mantel log-rank test.

following variables: age, BMI, diabetes, history of AF, previous sternotomy, type of CF-LVAD: HVAD, need for temporary MCS, creatinine, right atrial pressure [RAP], mean pulmonary artery mean pressure [mPAP], pulmonary capillary wedge pressure [PCWP], left ventricular ejection fraction [LVEF], left ventricular end-diastolic diameter [LVEDD], tricuspid annular plane systolic excursion [TAPSE], alanine transaminase [ALT], aspartate transaminase [AST] and region of origin: USA. In the model 3 we included the variables included in the model 1 plus variables associated with right ventricular function: RAP and TAPSE (this model included 199 patients and 66 events). Covariates with a p-value <0.2 were used to fit multivariate models, while the region variable (US vs. EU) was forced into the model. Time dependent survival analysis was used to adjust for effect of HTx (treated as time-dependent variable) on the overall survival of the patients. Waiting time on CF-LVAD until HTx was calculated treating HTx as the event and censoring the patients who were lost to follow up or dead before the HTx. Adverse events while supported on CF-LVAD were reported as events/100 patient per month, which was calculated as the number of events divided by the cumulative support durations for all patients. Comparisons of adverse event rates between EU and US occurring in a 3-year follow up period following CF-LVAD implant were performed with a Poisson regression adjusted for differences at baseline (age, body mass index [BMI], diabetes, history of atrial fibrillation [AF], and type of CF-LVAD). Median follow-up time in month was calculated using reverse Kaplan-Meier estimate. All statistical comparisons were 2-sided, and the significance level was set at $p = 0.05$. Statistical analyses were done using R programming language and environment (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (version 6, GraphPad Software Inc., CA, US).

3. Results

3.1. Baseline patient characteristics at the time of CF-LVAD implantation

A total of 524 patients (225 from US and 299 from EU) were included in the TRAViATA registry. Patients were predominantly male (84.4%) with a median age of 55 years (Q1-Q3, 45–61). Table 1 shows the distribution of baseline characteristics from both US and EU cohorts. Notable differences include a more racially diverse and significantly older cohort in the US compared with EU cohort. The US cohort also had a

significantly higher prevalence of comorbidities, including obesity, diabetes and AF.

Severity of illness at the time of CF-LVAD implantation as determined by INTERMACS class 1 or 2 (43.9% vs. 47.3%, p = 0.48) and the need for temporary MCS (25.8% vs. 30.9%, p = 0.24) were similar between US and EU cohorts. However, the axial HMII device was implanted more frequently in the EU cohort (71.9%), while the centrifugal Heartware HVAD device was more common in the US cohort (56.0%; p < 0.001). The median follow-up in the EU cohort was longer compared with the US cohort (60.0 vs. 34.0 months) even if it was not statistically significant based on the log rank test (Table 1).

3.2. Outcomes and predictors of mortality

Overall patient survival at 1 year was 83.1% and at 5 years was 66.5% estimated by the Kaplan-Meier curves (Fig. 1B) and was similar between the two cohorts (US 63.1% vs. EU 68.4% at 5 years, unadjusted Mantel log-rank test p = 0.43; Fig. 1C). Fig. 2 shows the status of patients that reached a complete follow up at 1, 2, and 3 years. The overall proportion of patients alive and still on mechanical support at 1, 2, and 3 years was 50.2% (256/510), 28.1% (128/456) and 13.8% (52/378) respectively. There were no significant differences among US and EU cohorts in the proportion of this status. At 1-year patients that were transplanted in the US cohort was 46.0% vs. 33.8% in EU (p = 0.11). None of the patients in the registry recovered to the point where CF-LVAD was explanted. Supplemental Fig. 1 shows the status (alive or dead) of patients that reached a complete follow up at 1, 2, and 3 years. We observed a larger proportion of death in the US group compared the EU group among patients that complete at 3 year follow up (47.0% vs. 34.0% respectively, p = 0.013), even if this result must be affected by the fact that a larger proportion of US patients, that could survive beyond 3 years, did not reach a 3 years of follow-up compared with the EU cohort (40.4% vs. 18.4% respectively, p = 0.001).

Supplemental Table 1 shows univariate analysis of baseline factors before CF-LVAD associated with the occurrence of death. Table 2 shows the univariate and multivariate Cox regression analyses evaluating predictors of mortality in the overall cohort. In the adjusted model, independent predictors of overall mortality were older age (hazard ratio [HR] 1.038, 95%CI 1.020–1.057), higher BMI (HR 1.051, 95%CI 1.016–1.087), higher creatinine (HR 1.221, 95%CI 1.021–1.460), temporary MCS (HR 1.487, 95%CI 1.062–2.081) before CF-LVAD implantation and use of Heartware HVAD (vs. HMII; HR of 1.549; 95%CI 1.105–2.172). Origin (US vs. EU) did not emerge as a variable associated with survival. Both the interactions terms Region*HTx (HR 1.055; 95%CI 0.530–2.102, p value = 0.879) and Region*type of device (HR 0.664; 95%CI 0.371–1.188, p value = 0.168) were tested and both were not significant.

When HTx was added in the model as time dependent covariate, elder age, higher BMI, increased creatinine, pre-CF-LVAD use of a temporary MCS and implantation of HVAD (vs. HMII) remained independent factors associated with mortality. HTx was independently associated with an improved survival rate (HR 0.456, 95%CI 0.308–0.675), and US origin emerged as a variable independently associated with better survival (HR 0.708, 95%CI 0.510–0.983) (Table 2). Multivariate model analysis that included baseline variables before CF-LVAD implant that significantly differend between EU and the US cohort (model 2; Supplemental Table 2) shows in the adjusted model, independent predictors of overall mortality were older age (HR 1.047, 95%CI 1.010–1.084), higher BMI (HR 1.071, 95%CI 1.004–1.142), and previous sternotomy (HR 2.113, 95%CI 1.048–4.260), whereas borderline significance was observed for use of Heartware HVAD (vs. HMII; HR of 1.804; 95%CI 0.940–3.461, p = 0.076), and higher TAPSE (HR 0.528; 95%CI 0.270–1.034; p = 0.063). Multivariate model analysis that included variables in model 1 plus variables associated with right ventricular function (RAP and TAPSE; called model 3, Supplemental Table 3) shows in the adjusted model, independent predictors of overall mortality were older age (HR 1.041, 95%CI 1.009–1.073), and use of Heartware HVAD (vs. HMII; HR of 1.794; 95%CI 1.06–3.198), whereas borderline significance was observed for higher BMI (HR 1.051, 95%CI 0.991–1.115; p = 0.098), previous sternotomy (HR 1.869, 95%CI 0.975–3.198; p = 0.060), and higher TAPSE (HR 0.564; 95%CI 0.308–10.30; p = 0.062). Origin (US vs. EU) did not emerge as a variable associated with survival also in model 2 and 3 of multivariate analyses.

3.3. Time to HTx and donor characteristics

We analyzed time with CF-LVAD until HTx, and donor characteristics to further understand the effect of the origin in patients mechanically bridged to HTx in US vs. EU. The proportion of patients that were on HTx list at the time of CF-LVAD implantation (BTT indication) was similar in the US cohort and the EU cohort (52.9% vs. 55.2% respectively; p = 0.66). On average patients were listed for HTx the same day they received a CF-LVAD both in US and the EU (Fig. 3A). The cause-specific hazard of HTx within US patients was 13.3% higher compared with those in EU cohort, but the difference was not statistically significant (p = 0.29). Supplemental Table 4 compares the baseline characteristics of patients with CF-LVAD who received and who did not undergo HTx. Among patients who received HTx, the median time on CF-LVAD support was shorter among those in the US cohort compared to those in the EU cohort (238 vs. 342 days, respectively; p = 0.0003, Fig. 3B).

Supplemental Table 5 summarizes the donor characteristics in the US and EU cohorts. Donors were significantly younger in the US cohort compared with the EU cohort (median age of 29 years; Q1-Q3, 23–39 vs. 48 years; Q1-Q3, 38–54, respectively, p < 0.0001, Fig. 3C). Donors in the US cohort were more likely to have been resuscitated from cardiac arrest compared with EU donors (p < 0.0001). There were no significant differences in the use of sex-mismatched donors, while utilization of undersized donors (defined as a donor-to-recipient weight ratio of 0.80 or less) was more common in the US cohort compared with the EU cohort (p = 0.011). Ischemic time, donor LVEF, and donor inotrope requirement were not different between the two groups. Finally, the post-transplant survival was similar between the two cohorts (US 82.0% vs. EU 84.7% at 4 years, unadjusted Mantel log-rank test p = 0.99; Fig. 3D). Univariate and multivariate Cox regression analyses of factors associated with the occurrence of death in post-transplant patients are shown in Supplemental Table 6. Increased age (HR 1.06, 95% CI 1.03–1.10; p < 0.001) and Heartware HVAD implant (HR 2.08, 95% CI 1.06–4.09, p = 0.03) are the only variables independently associated with post-transplant mortality. On the other hand, origin from USA had a borderline protective effect on post transplant mortality (HR 0.43, 95% CI 0.18–1.02, p = 0.054). Supplemental Table 7 reports the causes of death during CF-LVAD in the US and EU cohort, where cerebrovascular accidents was the main cause of death; and Supplemental Table 8 reports the causes of death after HTx in the US and EU groups, where graft failure followed by sepsis were the main causes of death in both.

3.4. Adverse events on CF-LVAD support

Supplemental Table 9 shows the number of patients with CF-LVAD related adverse events within 3 years of implantation, and the incident rate of these events. Poisson regression analysis showed a significant difference in the incidence rates of overall stroke (both ischemic and hemorrhagic), ischemic stroke (including transient ischemic attack [TIA]), gastrointestinal bleedings (GIBs), late RVF, and driveline infection in the US and EU cohort. Incidence rates of hemorrhagic stroke and pump thrombosis were not significantly different between the US and EU cohorts. Supplemental Table 10 summarizes the factors associated with CF-LVAD adverse events in the multivariate analysis. The factors independently associated with stroke were the age at implant and implant of HVAD. Variables independently associated with GIB were US origin (incidence rate ratio [IRR] 2.604, 95%CI 1.793–3.810), elderly age, and the implantation of HMII. Development of late RVF was

Table 1
Clinical presentation and diagnostic findings in 524 patients on heart transplant list treated with continuous-flow left ventricular assist device (CF-LVAD).

Characteristics	Overall		Continents				p-value
			EU		US		
	Data (n.)	Value	Data (n.)	Value	Data (n.)	Value	
Demographics & comorbidities							
Age, years, median (Q1-Q3)	524	55 (45–61)	299	53 (44–59)	225	59 (50–64)	**<0.001**
Age ≥ 60 years, n (%)	524	173 (33.0)	299	69 (23.1)	225	104 (46.2)	**<0.001**
Male, n (%)	524	442 (84.4)	299	252 (84.3)	225	190 (84.4)	1
Race hispanic, n (%)	523	36 (6.9)	299	2 (0.7)	224	34 (15.2)	**<0.001**
Race, n (%)	521		299		222		**<0.001**
Asian		25 (4.8)		9 (3.0)		16 (7.2)	
Black		59 (11.3)		6 (2.0)		53 (23.9)	
Caucasian		393 (75.4)		282 (94.3)		111 (50.0)	
Others		44 (8.4)		2 (0.7)		42 (18.9)	
Blood type, n (%)	524		299		225		0.327
A		201 (38.4)		124 (41.5)		77 (34.2)	
AB		18 (3.4)		11 (3.7)		7 (3.1)	
B		70 (13.4)		36 (12.0)		34 (15.1)	
0		235 (44.8)		128 (42.8)		107 (47.6)	
BMI, kg/m^2, median (Q1-Q3)	521	25.4 (22.7–29.3)	296	24.6 (22.5–27.9)	225	26.9 (23.4–31.4)	**<0.001**
BMI ≥ 30 kg/m^2, n (%)	521	113 (21.7)	296	42 (14.2)	225	71 (31.6)	**<0.001**
Diabetes mellitus, n (%)	524	131 (25.0)	299	39 (13.0)	225	92 (40.9)	**<0.001**
Insulin dependent diabetes, n (%)	465	64 (13.8)	240	20 (8.3)	225	44 (19.6)	**<0.001**
History of atrial fibrillation, n (%)	522	162 (31.0)	297	76 (25.6)	225	86 (38.2)	**0.002**
INTERMACS class 1–2, n (%)	521	239 (45.9)	298	141 (47.3)	223	98 (43.9)	0.478
Ischemic cause of HF, n (%)	524	228 (43.5)	299	135 (45.2)	225	93 (41.3)	0.423
ICD, n (%)	524	239 (45.6)	299	119 (39.8)	225	120(53.3)	**0.002**
CRT, n (%)	524	139 (26.5)	299	86 (28.8)	225	53(23.5)	0.216
Hemodynamics							
RAP, mmHg, median (Q1-Q3)	382	10 (6–15)	168	9 (5–14)	214	11 (8–15)	**0.006**
mPAP, mmHg, median (Q1-Q3)	385	36 (28–42)	176	36 (28–42)	209	35 (30–42)	0.832
PCWP, mmHg, median (Q1-Q3)	379	25 (20−30)	170	25 (20−31)	209	25 (20–30)	0.328
CI, L/min/m^2, median (Q1-Q3)	351	1.8 (1.5–2.2)	142	1.7 (1.4–2.0)	209	1.9 (1.5–2.3)	**0.002**
PVR, WU, median (Q1-Q3)	322	2.9 (1.8–4.2)	138	3.1 (2.0–4.2)	184	2.7 (1.6–4.2)	0.140
Echocardiographic parameters							
LVEF %, median (Q1-Q3)	471	20 (15–25)	247	20 (15–25)	224	18 (14–23)	**<0.001**
LVEDD, cm, median (Q1-Q3)	457	6.9 (6.1–7.6)	262	6.9 (6.1–7.6)	195	6.9 (6.2–7.6)	0.761
TAPSE, cm, median (Q1-Q3)	239	1.5 (1.3–1.7)	152	1.5 (1.3–1.7)	87	1.5 (1.2–1.8)	0.623
Laboratory values							
Creatinine, mg/dL, median (Q1-Q3)	523	1.3 (1.0–1.6)	298	1.3 (1.0–1.6)	225	1.2 (1.0–1.7)	0.877
Bilirubin, mg/dL, median (Q1-Q3)	453	1.1 (0.7–1.7)	228	1.0 (0.6–1.6)	225	1.2 (0.7–1.8)	0.069
AST, UI/L, median (Q1-Q3)	451	28 (21–44)	226	25 (18–43)	225	30 (22–44)	**0.006**
ALT, UI/L, median (Q1-Q3)	454	28 (18–50)	229	26 (16–52)	225	29 (19–48)	0.120
Surgical aspects							
Previous sternotomy, n (%)	524	83 (15.8)	299	41 (13.7)	225	42 (18.7)	0.147
BTT at time of implant, n (%)	524	499 (95.2)	299	298 (99.7)	225	201 (89.3)	**<0.001**
Need for MCS pre-implant, n (%)	513	147 (28.7)	288	89 (30.9)	225	58 (25.8)	0.238
HeartMate II device, n (%)	524	314 (59.9)	299	215 (71.9)	225	99 (44.0)	**<0.001**
Heartware HVAD device n (%)	524	210 (40.1)	299	84 (28.1)	225	126 (56.0)	**<0.001**
Concurrent surgery, n (%)	517	127 (20.1)	292	29 (9.9)	225	75 (33.3)	**<0.001**
Minimal invasive surgery, n (%)	524	58 (11.1)	299	14 (4.7)	225	44 (19.6)	**<0.001**
OF cannula in descending aorta, n (%)	524	14 (2.7)	299	8 (2.7)	225	6 (2.7)	1
In-hospital antiplatelet therapy							
Use of aspirin, n (%)	443	377 (85.1)	269	219 (81.4)	174	158 (90.8)	**0.006**
Dosage of aspirin							
≤100 mg, n (%)	377	241 (63.9)	219	194 (88.6)	158	47 (29.7)	**<0.001**
≥200 mg, n (%)	377	136 (36.1)	219	25 (11.4)	158	111 (70.3)	**<0.001**
Use of dipyridamole, n (%)			266	70 (26.3)	214	68 (31.8)	0.22
Use of another antiplatelet, n (%)	479	36 (7.5)	265	21 (7.9)	214	15 (7.0)	0.73
Last in-hospital INR	452	2.4 (2.2–2.6)	246	2.4 (2.2–2.8)	206	2.3 (2.1–2.5)	**<0.001**
Last in-hospital LDH	385	303 (230–423)	184	320 (221–520)	201	294 (235–386)	0.21
Follow up Time, months, median (Q1-Q3)	524	44.8 (28.2–68.1)	299	60.0 (55.0–65.1)	225	34.0(29.6–39.2)	0.326*

P-values in bold report the statistically significant differences.
Abbreviations: BMI, body mass index; HF, heart failure; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; LVEF, left ventricle ejection fraction; LVEDD, left ventricle end diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; AST, aspartate transaminase; ALT, alanine transaminase; BTT, bridge to transplant; MCS, mechanical circulatory support; OF, outflow; INR, international normalized ratio; LDH, lactate dehydrogenase; WU, Woods Units.
* Median follow up time in month was calculated using Kaplan-Meier based method.

independently associated with US origin (IRR 4.509, 95%CI 2.971–7.011), diabetes and implantation with an HVAD. Driveline infection was associated with diabetes, and HVAD implant, whereas US origin (IRR 0.318, 95%CI 0.228–0.438) was associated with decreased risk in the multivariate analysis. Finally, pump thrombosis was independently associated with older age and elevated BMI at implant. Unexpectedly, diabetes was associated with a lower rate of pump thrombosis.

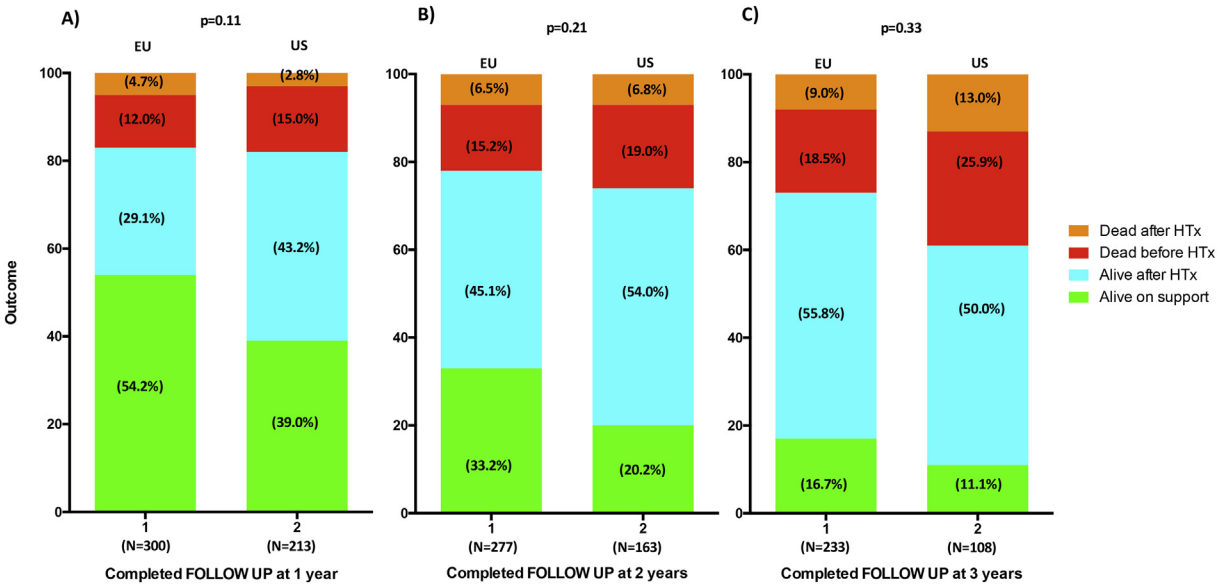

Fig. 2. Proportion of patients on CF-LVAD support or transplanted or dead with complete follow up at 1, 2 and 3 years. **(A)** Among patients who reached 1 year of follow up, in green is represented the proportion of patients still on LVAD, in light blue the proportion of patients undergoing HTx alive at 1 year, in red the patients that died on support and in orange the patients that died after HTx. **(B)** Proportions of outcomes among patients who reached 2 years of follow up. **(C)** Proportions of outcomes among patients who reached 3 years of follow up. Fisher's exact test was used to evaluate differences in the distribution of outcomes. Overall 14 (2.7%) patients had a follow up shorted than 1 year, of whom 3 were transplanted, 68 (13.0%) had a follow up shorter than 2 years, of whom 30 were transplanted, and 146 (27.9%) had a follow up shorter than 3 years, of whom 78 were transplanted.. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Univariate and multivariate Cox regression analysis of factors associated with the occurrence of death in patients with left ventricular assist devices including geographical origin.

Variables	US (n = 225) vs. EU (n = 299)			US (n = 225) vs. EU (n = 299)		
	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Age	1.037	1.021–1.053	**<0.001**	1.038	1.020–1.057	**<0.001**
BMI	1.043	1.012–1.075	**0.006**	1.051	1.016–1.087	**0.004**
Diabetes	1.650	1.190–2.289	**0.003**	1.323	0.909–1.926	0.144
Previous sternotomy	1.490	1.026–2.164	**0.036**	1.176	0.798–1.734	0.413
HeartWare HVAD device	1.500	1.089–2.065	**0.013**	1.549	1.105–2.172	**0.011**
Creatinine	1.233	1.048–1.450	**0.012**	1.221	1.021–1.460	**0.029**
Need for t-MCS	1.280	0.920–1.782	0.143	1.487	1.062–2.081	**0.021**
Region: USA	1.172	0.854–1.610	0.326	0.706	0.488–1.022	0.065

Adjusted for effect of HTx	Multivariate analysis		
Variables	HR	95%CI	p-value
Age	1.041	1.025–1.058	**<0.001**
BMI	1.042	1.012–1.074	**0.006**
Diabetes	1.171	0.841–1.631	0.350
Previous sternotomy	1.244	0.889–1.741	0.202
HeartWare HVAD device	1.467	1.090–1.975	**0.011**
Creatinine	1.244	1.064–1.454	**0.006**
Need for t-MCS	1.582	1.179–2.123	**0.002**
Region: USA	0.708	0.510–0.983	**0.039**
HTx	**0.456**	**0.308–0.675**	**<0.001**

P-values in bold report the statistically significant associations.
Abbreviations: HR, hazard ratio; CI, confidential interval; t-MCS, temporary mechanical circulatory support, HTx, heart transplantation.

4. Discussion

In summary, we present a comprehensive, multinational, contemporary registry aimed at the comparison of end-stage HF supported with CF-LVAD awaiting transplant in the US and EU. While other studies censored patients at the time of HTx, our study included post-HTx follow up to better evaluate the overall success of the intended therapeutic strategy, and to evaluate if, and how time on MCS affects post-transplant outcomes. Hence, this registry provides a holistic picture of CF-LVAD patients listed for HTx. Our principal finding is that the overall survival in CF-LVAD patients, whether or not they were transplanted, was similar between the US and EU cohorts. In addition, significant differences in baseline characteristics and practice patterns between the US and EU were observed. Patients in the US cohort were older and with more co-morbidities, whereas those in the EU cohort were younger, with lower BMI and less diabetes. In other two multivariate models that included also echocardiographic and hemodynamics data, still US vs. EU origin did not emerge as an independent factor associated with outcome. These models included only 34.2% (models 2) and 38.0% (model 3) of the patients of whole cohort, due to missing data. Based on these subanalysis older age consistenly emerged as associated with increased mortality. Patients from the US are 11.3% more likely to receive an HTx than EU patients, even if it was not statistically significant ($p = 0.29$). Furthermore, EU patients wait longer for transplantation and received older donors. When the variable HTx is added in the multivariate analysis, US origin emerged as a variable associated with a better survival, likely as a result of the abovementioned points.

End-stage HF is unique in that treatment is partially dictated by local availability of donor organs, allocation policies, and healthcare service organizations; hence, wide geographic variability in practice exists between the US and EU. Differences in donor organ availability and their clinical characteristics, including older age in EU than in the US, also impact outcomes in those who undergo CF-LVAD placement as a BTT. Ultimately, these factors may explain some of the differences we observed.

CF-LVAD related adverse events differed significantly between the US and EU cohorts. The incidence of RVF and GIB were higher in the US, while rates of driveline infection were higher in the EU. The higher rates of RVF and GIB observed in the US cohort may be explained by the differences in baseline co-morbidities, primarily older age and diabetes. It is uncertain whether differences in prescribing patterns between the US and Europe may explain these differences as well. It is also unclear why driveline infections were observed more frequently in the EU; further study of these findings is indicated.

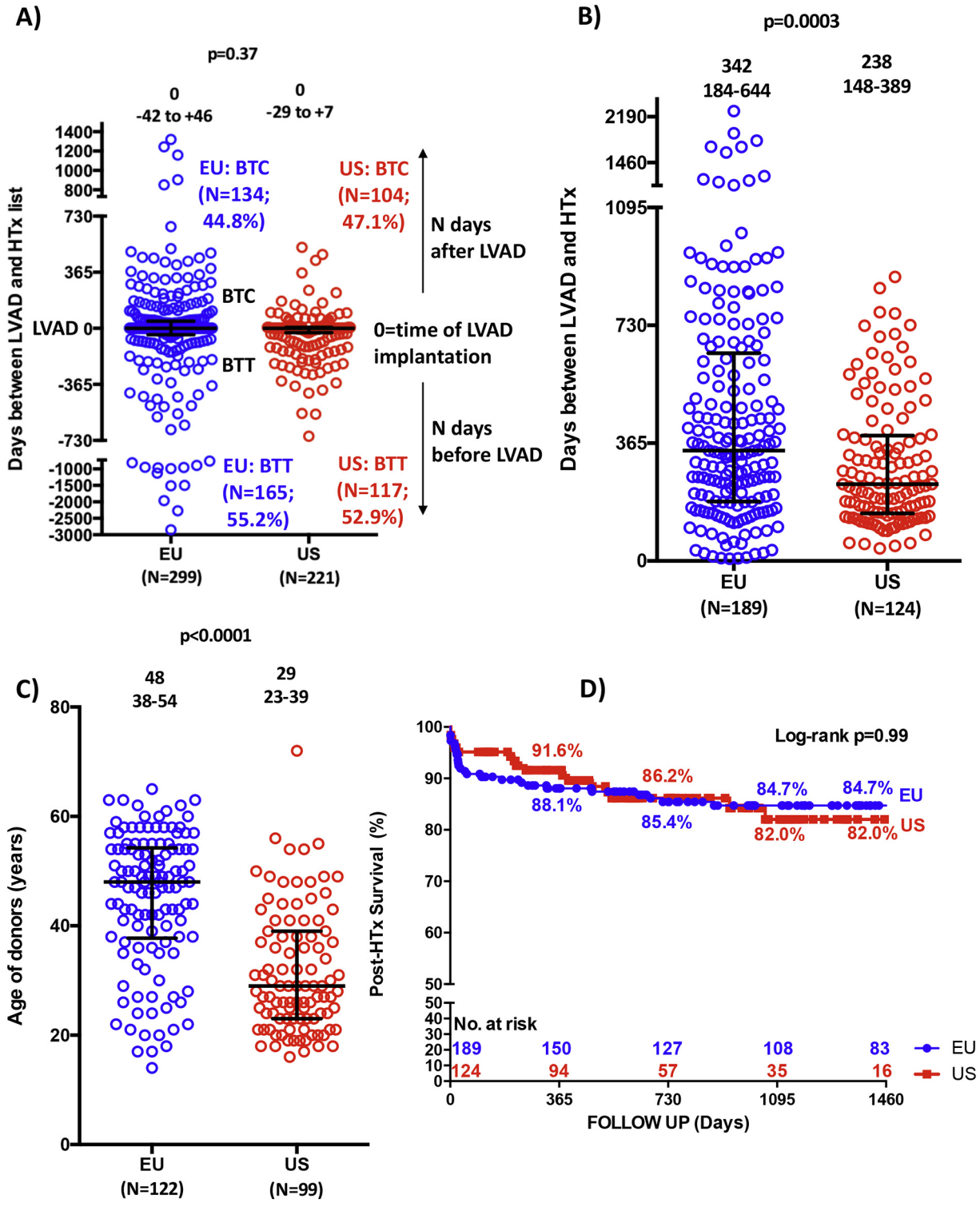

Fig. 3. Time to heart transplant, donor characteristics and post-transplantation outcome. (A) Scatter dot plot representing the median time (Q1-Q3) in days between LVAD implant and placement on a HTx list among EU and US patients. Mann Whitney test was used to compare medians. Percentages of patients implanted as bridge to candidacy (BTC) and as bridge to transplant (BTT) are shown. (B) Scatter dot plot representing the median time (Q1-Q3) in days between LVAD implant and HTx among EU and US patients. Mann Whitney test was used to compare medians. (C) Scatter dot plot representing the median age (Q1-Q3) in years of EU and US donors. Mann Whitney test was used to compare medians. (D) Kaplan-Meier curves comparing the 5-year post transplant survival of EU and US patients who received an LVAD. Follow-up started on the HTx day and continued up to death or lost-to-follow-up. Differences in survival were evaluated with the Mantel log-rank test.

Of note, specific subgroups of CF-LVAD patients did worse than others, regardless of geographic location, such as older-age. This suggests performing surgery once in these patients: CF-LVAD as destination therapy or direct to transplant. Though there is some trepidation in transplantation of elderly patients, contemporary studies suggest outcomes can be comparable [8].

Creatinine also emerged as a baseline variable associated with prognosis consistently with other studies, including an extensive analysis of

UNOS patients that showed impaired renal function predicted waitlist mortality [9]. It remains unclear how to select patients with considerable renal impairment for CF-LVAD, as opposed to listing directly for a multi-organ transplant. A small minority of patients in this registry underwent heart-kidney transplantation, predominantly in the US cohort compared with the EU cohort (4.1 vs. 0.5%, respectively). Increased BMI was also associated with worse outcomes in both the US and EU cohorts. This has historically been shown to be a risk factor for patients that undergo HTx as well [10,11]. This may be due to the fact that larger patients may have to wait a longer time to find a suitable donor. It also appears that patients with a high BMI were associated with pump thrombosis, though causation was not clearly established.

Our findings are consistent with a previous study of BTT patients demonstrating that patients over 60 years old, eGFR<40 mL/min/1.73m^2 and BMI >30 kg/m^2 have a significant higher 1-year mortality [11]. Subgroup analysis in this study also suggested a higher risk of death in patients implanted with HVAD compared with patients implanted with HMII. This was not a randomized study of the two devices; hence confounding limits the ability to make conclusions. Nonetheless, a higher rate of cerebrovascular accident (CVA) and late RVF were observed with HVAD patients, which is consistent with previous studies [12,13]. It should be noted that most of the patients in the registry were implanted before the publication of papers demonstrating the importance of blood pressure control in HVAD patients to limit complications [14]. The adverse events profile of HMII appears more favorable since higher rates of GIB typically lead to higher probability to be transplanted. Consistently, patients who received a HTx in our study were more frequently supported with an HMII compared with an HVAD. Finally, temporary MCS before CF-LVAD implantation was a strong predictor of mortality with a HR of 1.58, which is consistent with multiple other studies that demonstrate worse outcomes with INTERMACS 1 patients that undergo CF-LVAD [15,16]. All the variables identified in the current study as independently associated with early or late mortality in patients treated with CF-LVAD were also reported in the 2019 INTERMACS annual report (increasing recipient age, critical cardiogenic shock at time of CF-LVAD, renal dysfunction and higher BMI), with the exception of the type of device. It should be noted that in the INTERMACS analysis included both centrifugal flow devices (HVAD and HM3) while our analysis only included HVAD.

4.1. Study limitations

The retrospective nature of our work is the primary limitation of our study. We also acknowledge potential bias in site selection with some heterogeneity in the number of cases provided by each participating center. While only 3 US centers were included in the registry, 1-year survival was relatively similar between them and the most INTERMACS registry (83% vs. 87% respectively) [18], given we do not censure patients at the time of HTx. Similarly, the 1 year survival of European cohort is similar to the BTT cohort in EUROMACS (83% vs. 78% respectively) [5]. Also, prevalence of comorbidities at baseline between the two cohorts was consistent with previous published data [19]. Thus although residual selection bias may still persist, the above data suggest a representative study population in the TRAViATA registry. Centers may also vary for specific features such as volume, training and experience of personnel, availability of resources and characteristics of center organization. Furthermore, as the patients at risk after 4 years of follow-up becomes less than 15% of the initial cohort in the US group, statistical uncertainty of the esteem of survival is higher in the US cohort compared to EU group between 4 and 5 years of follow up [17].

We did not include the newest generation of CF-LVADs (HM3) as we wanted to include significant follow-up time in both cohorts. Further study will be required to validate our findings in HM3 patients. Furthermore, freedom from waitlist mortality or delisting at 1-year was 83.5% in patients mechanically supported in a UNOS analysis that considered 22,863 patients from 93 US HTx centers (period 2008–2015) [3]. Again, this figure was very close to the 1-year mortality reported in the 3 US centers in our study. Furthermore, another UNOS analysis on 5486 patients showed that patients with CF-LVAD at HTx spent a median of 191 days on the waitlist [11]. This figure is close to the time between CF-LVAD implant to HTx of 238 days observed in our US cohort.

In addition, some of laboratory tests which are related to RV failure (i.e. blood urea nitrogen) as well as medication regimens over time (i.e. anticoagulation and dressing protocol) that could explain differences in the adverse events rate in the two cohorts were not systematically obtained. Finally variables related to socio-economic status of patients, that could affect the outcome of LVAD patients were not collected in our registry. Similarly, we did not account for the impact on outcome of adverse events related or not with CF-LVAD that occurred in the follow up (for example occurrence of stroke or cancer).

In conclusion, in this large retrospective study of BTT CF-LVAD patients, outcomes are similar for US and EU patients. This is despite significant differences in the patient populations and organ availability. This suggests that MCS remains a a safe and effective tool for supporting patients waiting for HTx. Further prospective study is required to confirm these findings in more contemporary devices.

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Declaration of Competing interest

None.

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Appendix A. Supplementary data

Supplementary Table 1 to 10 and Supplementary Fig.1 to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.09.026.

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PUBLICATION 3

Radhoe SP*, Jakus N*, Veenis JF, Timmermans P, Pouleur AC, Rubís P, Van Craenenbroeck EM, Gaizauskas E, Barge-Caballero E, Paolillo S, Grundmann S, D'Amario D, Braun OÖ, Gkouziouta A, Planinc I, Macek JL, Meyns B, Droogne W, Wierzbicki K, Holcman K, Flammer AJ, Gasparovic H, Biocina B, Milicic D, Lund LH, Ruschitzka F, Brugts JJ*, Cikes M*.

Sex-related differences in left ventricular assist device utilization and outcomes: results from the PCHF-VAD registry.

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* S.P. Radhoe and Nina Jakuš, and Maja Čikeš and J.J. Brugts contributed equally.

The candidate, Nina Jakuš, contributed to this publication by:

- Having a substantial contribution to the conception and design of the publication; as well as the acquisition, analysis, and interpretation of data for the work; AND
- She drafted the work with additional critical revision for important intellectual content; AND
- She gave final approval of the version to be published; AND
- Agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contribution of other co-authors:

- Having a substantial contribution to the acquisition, analysis, and interpretation of data for the work; AND
- Critically revised the manuscript for important intellectual content; AND
- Gave final approval of the version to be published; AND
- Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The publisher’s approval for the inclusion of Publication 3 in the Thesis has been obtained.

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ORIGINAL ARTICLE

Sex-related differences in left ventricular assist device utilization and outcomes: results from the PCHF-VAD registry

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Abstract

Aims Data on sex and left ventricular assist device (LVAD) utilization and outcomes have been conflicting and mostly confined to US studies incorporating older devices. This study aimed to investigate sex-related differences in LVAD utilization and outcomes in a contemporary European LVAD cohort.

Methods and results This analysis is part of the multicentre PCHF-VAD registry studying continuous-flow LVAD patients. The primary outcome was all-cause mortality. Secondary outcomes included ventricular arrhythmias, right ventricular failure, bleeding, thromboembolism, and the haemocompatibility score. Multivariable Cox regression models were used to assess associations between sex and outcomes. Overall, 457 men (81%) and 105 women (19%) were analysed. At LVAD implant, women were more often in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 1 or 2 (55% vs. 41%, $P = 0.009$) and more often required temporary mechanical circulatory support (39% vs. 23%, $P = 0.001$). Mean age was comparable (52.1 vs. 53.4 years, $P = 0.33$), and median follow-up duration was 344 [range 147–823] days for women and 435 [range 190–816] days for men ($P = 0.40$). No significant sex-related differences were found in all-cause mortality (hazard ratio [HR] 0.79 for female vs. male sex, 95% confidence interval [CI] [0.50–1.27]). Female LVAD patients had a lower risk of ventricular arrhythmias (HR 0.56, 95% CI [0.33–0.95]) but more often experienced right ventricular failure. No significant sex-related differences were found in other outcomes.

Conclusions In this contemporary European cohort of LVAD patients, far fewer women than men underwent LVAD implantation despite similar clinical outcomes. This is important as the proportion of female LVAD patients (19%) was lower than the proportion of females with advanced HF as reported in previous studies, suggesting underutilization. Also, female patients were remarkably more often in INTERMACS profile 1 or 2, suggesting later referral for LVAD therapy. Additional research in female patients is warranted.

Keywords Advanced heart failure; Left ventricular assist device; Utilization; Sex; Survival

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Sumant P. Radhoe, Nina Jakus, Jasper J. Brugts and Maja Cikes contributed equally.

Introduction

Both men and women are frequently affected by heart failure (HF), and in both sexes, HF is strongly associated with morbidity and mortality.[1,2] However, several sex-related differences exist, such as the distribution of HF phenotypes and the aetiology of HF.[2–4] Although the overall lifetime risk of developing HF is comparable between men and women, women are underrepresented in HF trials.[1,5-7] Additionally, women are less likely to be treated with guideline-recommended drugs. Reports on potential underutilization of device therapies such as implantable cardioverter-defibrillator or cardiac resynchronization therapy in women have been inconsistent.[7-14] Even though it is suggested that women make up approximately one-third of the advanced HF population, several studies have shown lower utilization of left ventricular assist devices (LVADs) in women.[15-18] Furthermore, studies investigating sex-related differences in LVAD outcomes provided conflicting results. Analyses of large US and European LVAD registries demonstrated worse clinical outcomes in women, whereas a smaller study and a meta-analysis showed similar survival for women and men.[15,16,19-21] However, these previous studies contained only a very small proportion of the newest and currently predominant HeartMate 3 LVADs and primarily included data on US patients. Improving our understanding of sex differences in present-day European LVAD management is necessary to further enhance LVAD care. Therefore, this analysis aimed to assess sex-related differences in LVAD utilization and outcomes in a contemporary European cohort of LVAD patients.

Methods

The methods of the observational PCHF-VAD registry have been described previously.[22] Briefly, continuous-flow LVAD patients were included from 13 European HF tertiary referral centres by HF specialists—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. All participating centres acquired approval from the local ethics review boards (predominantly, a waiver of informed consent was obtained by the individual centres). The patient baseline (time of implantation) and outcome data were recorded and managed using REDCap (Research Electronic Data Capture) electronic data capture tools—a secure, web-based application,[23] hosted at the University of Zagreb School of Medicine, serving as the data-coordinating centre.

At the moment of this analysis, 583 patients implanted with a durable ventricular assist device between December 2006 and January 2020 were included in the registry. Patients with a pulsatile device (n = 4) or biventricular assist device (n = 11), as well as patients aged $<$18 years (n = 6), were excluded from this analysis. In total, 562 patients were included in this analysis.

The primary outcome was all-cause mortality. Secondary outcomes included heart transplantation, weaning from LVAD support, hospitalization for HF, right ventricular (RV) failure (acute and chronic), LVAD-related infection requiring systemic antibiotics, non-fatal thromboembolic events, intracranial bleeding, non-intracranial bleeding, LVAD exchange, and the haemocompatibility score (HCS).

Haemocompatibility score

To analyse the aggregate burden of haemocompatibility-related adverse events (HRAEs), the HCS was calculated for all patients. Each HRAE received a points score, based on its clinical relevance (*Table S1*). The HCS was calculated for each patient by summing up all points associated with all HRAEs experienced by the patient during the follow-up period.[24]

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median and interquartile range (IQR) for non-normally distributed data and were compared between men and women by the Student's t-test or the Mann–Whitney U test. Categorical data are expressed as counts and percentages and were compared by the Pearson's χ^2 test.

Cumulative survival was assessed using the Kaplan–Meier method and was compared between men and women using the log-rank test. Cox proportional hazards models were used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for female vs. male sex for the different outcomes. For the survival analyses, the time of LVAD implantation was considered as the index date. The follow-up duration was defined as time to last contact, heart transplantation, weaning from LVAD support, or death, whichever occurred first.

For the main analysis, a multivariable Cox regression model was used to test whether sex was associated with the outcomes. The association between sex and outcomes

was adjusted for age, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, baseline creatinine serum levels, need for mechanical circulatory support prior to LVAD implantation, need for vasopressor use prior to LVAD implantation, and the LVAD implant date quartile.

Additionally, a sensitivity analysis was performed to adjust the association between all-cause mortality and sex for baseline covariates that were selected in a forward stepwise Cox proportional hazards model. Age, cardiac implantable electronic devices (including implantable cardioverter-defibrillator or cardiac resynchronization therapy) status; heart rate, LVAD type, LVAD intention, INTERMACS profile, aetiology of HF, known history of chronic kidney disease, atrial fibrillation/flutter, or ventricular arrhythmias, significant ventricular arrhythmias pre-LVAD surgery, prior cardiac surgery, concomitant procedure with LVAD implant, life support pre-LVAD surgery, diuretic use, beta-blocker use, ivabradine use, mineralocorticoid receptor antagonist use, vasopressor use, ultrafiltration, mechanical ventilation, creatinine values, left ventricular (LV) internal dimension at end-diastole, and LVAD implant date quartile were assessed in a forward stepwise selection process with a significance level of 0.05 and 0.10 for entry and removal thresholds, respectively. Following this process, the baseline covariates that came out significant were used in a Cox proportional hazard model for the secondary outcomes.

The number of missing data in the variables mentioned above is shown in *Table S2*. Variables with <30% missing data were imputed using multiple imputation, whereas those with a larger proportion of missing data were not included in this analysis. If the missing variables showed a monotone pattern of missing values, the monotone method was used. Otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations was performed, and the pooled data were analysed. The imputed data were only used for the multivariable analysis. A two-sided *P*-value of 0.05 or lower was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences, Version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

In this analysis, a total of 562 patients with a mean age of 53.1 ± 12.0 years were included. The cohort included 457 (81.3%) male and 105 (18.7%) female patients. The baseline characteristics are shown in *Table 1*. A higher proportion of women were critically ill at the time of LVAD implantation as women were more often in INTERMACS profile 1 or 2 (55.3% vs. 41.2%, *P* = 0.009) and more often in need of mechanical circulatory support pre-LVAD implantation (39.2% vs. 23.0%, *P* = 0.001). Serum creatinine levels were lower and LV size was smaller in women. Additionally, women less often had diabetes mellitus or atrial fibrillation or flutter at baseline.

Survival

Women and men were followed for a median period of 344 [IQR 147–823] and 435 [IQR 190–816] days, respectively (*P* = 0.40). No differences were observed in the crude all-cause mortality between men and women, as shown in *Figure 1*. During the entire follow-up period, 29% of the male and 21% of the female patients died (*P* = 0.084). Female patients were numerically less likely to die during follow-up, but this difference was not statistically significant after adjustments for age, INTERMACS profile, creatinine serum levels, preoperative need for mechanical circulatory support or vasodilator use, and the quartiles of date of LVAD implantation (HR 0.79, 95% CI [0.50–1.27]; *Table 2*). The causes of death were not different between men and women and are presented in *Figure 2*.

Secondary endpoints

No sex-related differences were observed in the proportion of patients undergoing heart transplantation (HR 1.01, 95% CI [0.70–1.46]; *Figure 1*). Numerically, women were significantly more often weaned from LVAD support, but this was not statistically significant after multivariable adjustments (HR 3.10, 95% CI [0.68–14.1]; *Table 2*). Peripartum cardiomyopathy and dilated cardiomyopathy were the most frequent causes of HF in women who recovered from LVAD support (*Table S3*). The results from the competing outcome analysis are shown in *Figure 3*.

Female sex was associated with a significantly lower crude and adjusted risk of ventricular arrhythmias post-LVAD implant (adjusted HR 0.56, 95% CI [0.33–0.95]; *Table 2*). Female patients had a higher incidence of RV failure, although without statistically significant increase in risk thereof (HR 1.57, 95% CI [1.00–2.49], *P* = 0.053).

No significant differences between men and women were found in the occurrence of pump thrombosis, non-fatal thromboembolic events, or bleeding (*Table 2*). A small, non-significant difference between men and women was found in the median HCS, as shown in *Figure 4*. Furthermore, the risk of HF hospitalizations, new-onset atrial fibrillation or flutter, and LVAD-related infections requiring antibiotics was similar for men and women (*Table 2*).

Table 1 Baseline characteristics

	Overall population (n = 562)	Men (n = 457)	Women (n = 105)	P-value
Age, years	53 ± 12	53 ± 12	52 ± 12	0.33
Geographical area				
Northwest Europe (the Netherlands, Belgium, and Germany)	373 (66.4)	292 (63.9)	81 (77.1)	0.01
Southeast Europe (Croatia, Poland, Lithuania, Italy, Spain, and Greece)	189 (33.6)	165 (36.1)	24 (22.9)	
Quartiles of date of LVAD implant				
1st quartile (6 Dec 2006–29 Oct 2012)	143 (25.4)	110 (24.1)	33 (31.4)	0.41
2nd quartile (30 Oct 2012–4 Aug 2015)	143 (25.4)	121 (26.5)	22 (21.0)	
3rd quartile (5 Aug 2015–16 Apr 2017)	139 (24.7)	114 (24.9)	25 (23.8)	
4th quartile (17 Apr 2017–28 Jan 2020)	137 (24.4)	112 (24.5)	25 (23.8)	
ICD status				0.34
No ICD	294 (53.3)	235 (52.2)	59 (57.8)	
Primary prevention	180 (32.6)	147 (32.7)	33 (32.4)	
Secondary prevention	78 (14.1)	68 (15.1)	10 (9.8)	
CRT status				
No CRT	406 (74.1)	325 (72.9)	81 (79.4)	0.12
CRT-P carrier	14 (2.6)	14 (3.1)	0 (0.0)	
CRT-D carrier	128 (23.4)	107 (24.0)	21 (20.6)	
Heart rate, b.p.m.	83.3 ± 19.0	82.5 ± 17.8	87.1 ± 23.3	0.072
SBP, mmHg	99.5 ± 13.9	100.0 ± 14.1	97.7 ± 13.0	0.16
DBP, mmHg	64.2 ± 10.9	64.4 ± 10.5	63.2 ± 12.2	0.32
BMI, kg/m^2	25.9 ± 4.6	26.1 ± 4.5	24.9 ± 5.3	0.025
LVAD type				
HeartMate 2	265 (47.2)	215 (47.0)	50 (47.6)	0.82
HeartWare HVAD	119 (21.2)	94 (20.6)	25 (23.8)	
HeartMate 3	157 (27.9)	130 (28.4)	27 (25.7)	
Other	21 (3.7)	18 (3.9)	3 (2.9)	
LVAD destination				
BTT	356 (66.8)	292 (67.1)	64 (65.3)	0.081
BTD	90 (16.9)	67 (15.4)	23 (23.5)	
DT	87 (16.3)	76 (17.5)	11 (11.2)	
INTERMACS profile				
1	90 (16.5)	61 (13.7)	29 (28.2)	0.004
2	150 (27.4)	122 (27.5)	28 (27.2)	
3	176 (32.2)	149 (33.6)	27 (26.2)	
4–7	131 (23.9)	112 (25.2)	19 (18.4)	
Aetiology of heart failure				
Dilated cardiomyopathy	247 (44.0)	204 (44.6)	43 (41.0)	<0.001
Ischaemic cardiomyopathy	256 (45.6)	211 (46.2)	45 (42.9)	
Hypertrophic cardiomyopathy	9 (1.6)	7 (1.5)	2 (1.9)	
Toxic cardiomyopathy	15 (2.7)	6 (1.3)	9 (8.6)	
Non-compaction cardiomyopathy	3 (0.5)	3 (0.7)	0 (0.0)	
Valvular disease	6 (1.1)	6 (1.3)	0 (0.0)	
Myocarditis	12 (2.1)	9 (2.0)	3 (2.9)	
Peripartum cardiomyopathy	2 (0.4)	0 (0.0)	2 (1.9)	
Congenital/genetic	6 (1.1)	6 (1.3)	0 (0.0)	
Other	6 (1.1)	42 (9.2)	17 (16.2)	
Comorbidities				
Arterial hypertension	128 (22.8)	105 (23.0)	23 (21.9)	0.81
Diabetes mellitus	114 (20.3)	100 (21.9)	14 (13.3)	0.049
Chronic kidney disease	137 (24.4)	117 (25.6)	20 (19.0)	0.16
Coronary artery disease	139 (24.7)	120 (26.3)	19 (18.1)	0.080
Prior MI	211 (37.5)	178 (38.9)	33 (31.4)	0.15
Prior coronary revascularization	170 (30.2)	141 (30.9)	29 (27.6)	0.52
COPD	44 (7.8)	40 (8.8)	4 (3.8)	0.089
Atrial fibrillation/flutter	173 (30.8)	155 (33.9)	18 (17.1)	0.001
Ventricular arrhythmias	153 (27.2)	127 (27.8)	26 (24.8)	0.53
Cerebrovascular events	41 (7.3)	34 (7.4)	7 (6.7)	0.78
Significant ventricular arrhythmias pre-LVAD implant				
None	308 (65.5)	242 (63.2)	66 (75.9)	0.093
1 episode	78 (16.6)	64 (16.7)	14 (16.1)	
2 episodes	34 (7.2)	30 (7.8)	4 (4.6)	
3 episodes	18 (3.8)	17 (4.4)	1 (1.1)	
≥4 episodes	32 (6.8)	30 (7.8)	2 (2.3)	
Prior cardiac surgery	75 (13.3)	65 (14.2)	10 (9.5)	0.20

(*Continues*)

Table 1 (continued)

	Overall population (n = 562)	Men (n = 457)	Women (n = 105)	P-value
Concomitant procedure with LVAD implant	99 (17.6)	82 (17.9)	17 (16.2)	0.67
Mechanical circulatory support pre-LVAD implant				
None	401 (74.0)	339 (77.0)	62 (60.8)	0.007
ECMO	40 (7.4)	30 (6.8)	10 (9.8)	
Temporary LVAD	5 (0.9)	5 (1.1)	0 (0.0)	
Temporary RVAD	1 (0.2)	1 (0.2)	0 (0.0)	
Temporary BiVAD	2 (0.4)	2 (0.5)	0 (0.0)	
IABP	73 (13.5)	51 (11.6)	22 (21.6)	
Other	20 (3.7)	12 (2.7)	8 (7.8)	
Medications				
Diuretic	454 (91.0)	374 (91.7)	80 (87.9)	0.26
Beta-blocker	299 (64.4)	252 (65.5)	47 (59.5)	0.31
ACEi/ARB	213 (44.9)	176 (44.8)	37 (45.7)	0.88
MRA	315 (72.1)	265 (73.8)	50 (64.1)	0.08
Ivabradine	45 (10.9)	38 (11.1)	7 (9.7)	0.73
Inotrope	305 (66.6)	243 (65.1)	62 (72.9)	0.17
Laboratory values				
Creatinine, μmol/L	127.1 ± 56.0	131.4 ± 55.2	108.1 ± 55.8	<0.001
Bilirubin, μmol/L	24.3 ± 20.5	24.8 ± 21.0	22.2 ± 18.5	0.30
Echocardiographic data				
LVIDd, mm	70.7 ± 12.5	72.3 ± 12.3	63.9 ± 11.3	<0.001
LVIDd/BSA ratio	36.5 ± 6.8	36.4 ± 6.9	36.9 ± 6.6	0.61
LVEF, %	19.4 ± 7.5	19.2 ± 7.6	20.3 ± 6.8	0.24

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.p.m., beats per minute; BiVAD, biventricular assist device; BMI, body mass index; BSA, body surface area; BTD, bridge to decision; BTT, bridge to transplant; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacing; DBP, diastolic blood pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension at end-diastole; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; RVAD, right ventricular assist device; SBP, systolic blood pressure.

Sensitivity analysis

The results of the sensitivity analysis, in which the association between sex and the primary and secondary outcomes was adjusted using a forward stepwise Cox regression model, are shown in *Table S4*. Similar to the main analysis, there was no significant difference in all-cause mortality. However, female sex was significantly associated with RV failure post-LVAD implantation and weaning from LVAD support.

Discussion

In this contemporary European LVAD registry reflecting real-world clinical practice at multiple HF tertiary referral centres, we demonstrated that fewer women than men underwent LVAD implantation (19% vs. 81%, respectively). Also, women were implanted at a more advanced stage and were more critically ill pre-LVAD surgery; nevertheless, no significant survival differences were observed between men and women. Furthermore, only minor sex-related differences in LVAD-related outcomes were observed, with women less often at risk of ventricular arrhythmias, more often suffering from RV failure, and more often having explant for recovery (albeit rarely altogether).

Previous studies have investigated sex differences in the utilization and outcomes of LVAD therapy. However, most of these studies have been performed in the United States, reflected an earlier period, and included almost exclusively HeartWare HVAD or HeartMate 2 devices.[15,16,19-21] As opposed to these earlier studies, the current study included a relatively large number of patients with a HeartMate 3 device, and this registry therefore provides unique insights into the contemporary LVAD management at European tertiary referral centres using state-of-the-art LVADs.[25,26,27]

Potential left ventricular assist device underutilization

Women remain underrepresented in large pharmacological clinical HF trials, as well as in LVAD clinical trials.[7,25] Currently, less women than men receive an LVAD, as demonstrated in this registry as well as in other studies, with the proportion of female patients spanning from 20.8% to 23.2%.[15–17] Despite several large registries showing that women make up approximately one-third of the advanced and worsening HF populations, only 19% of our cohort were female, suggesting potential LVAD underutilization in female patients.[18,28] Several reasons might contribute to the lower utilization of LVADs in women. Firstly, women are more frequently diag-

Figure 1 Kaplan–Meier plots of time to (A) all-cause mortality, (B) heart transplantation (censored for death), and (C) weaning from left ventricular assist device (LVAD) (censored for death) according to sex.

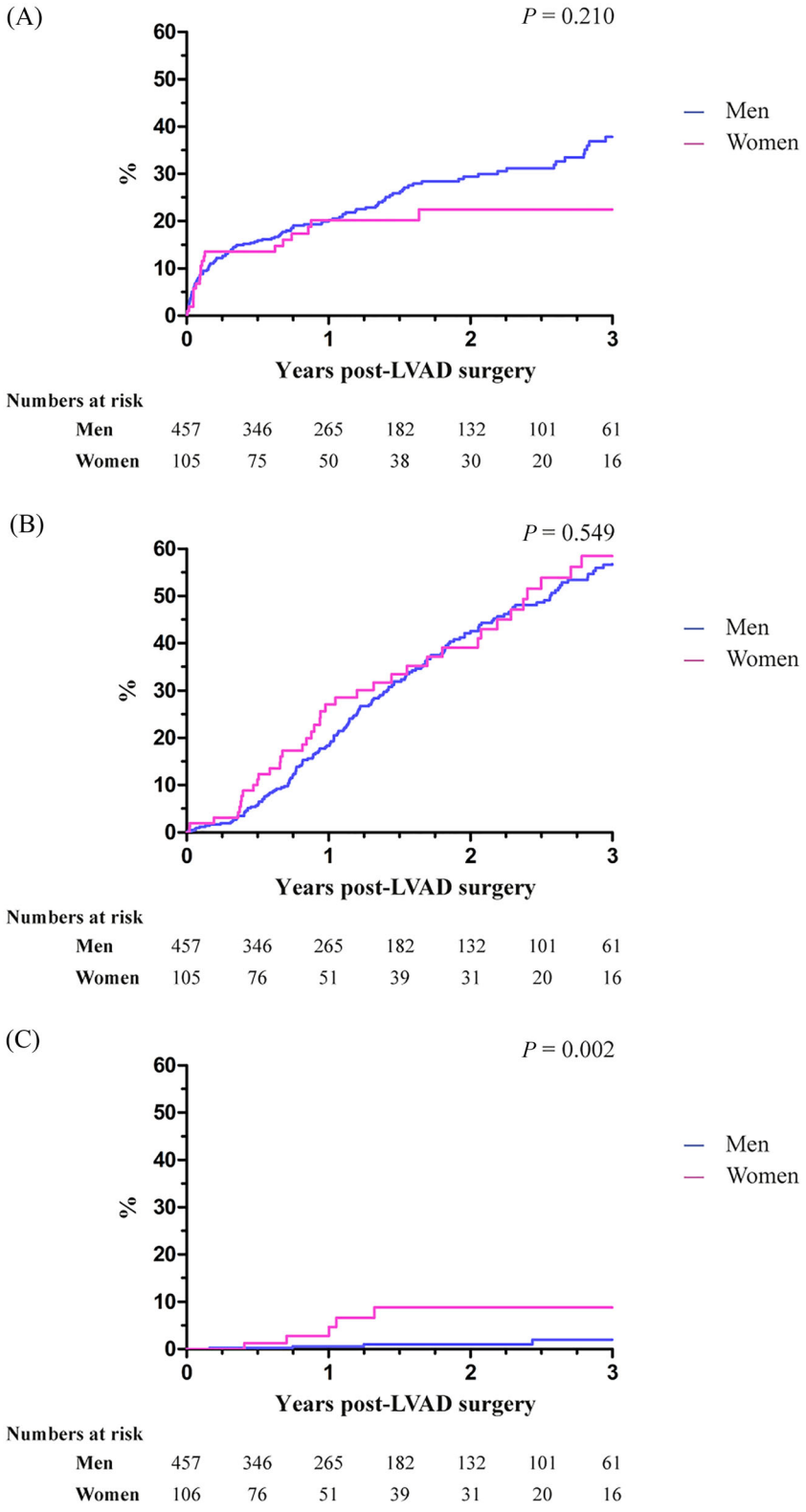

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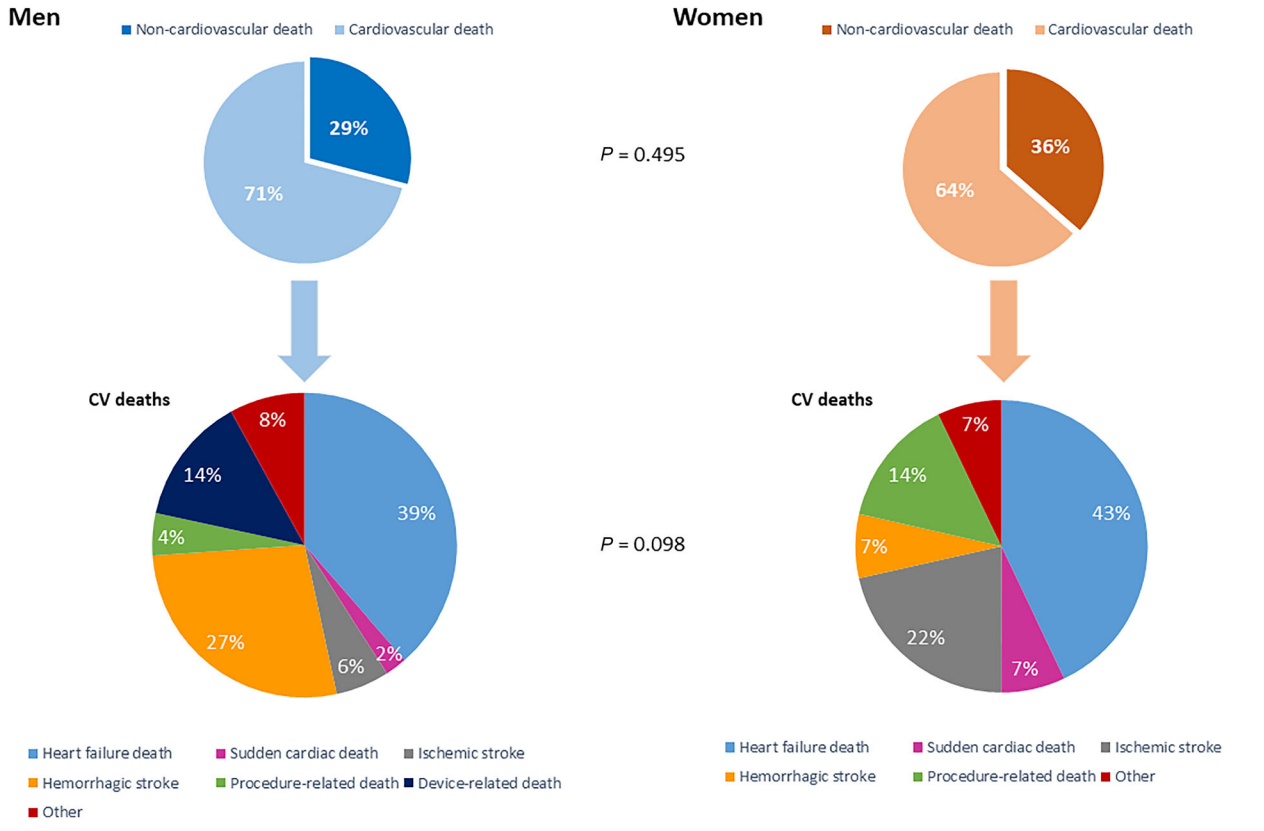
Table 2 Frequency (proportion) and hazard ratios for the studied endpoints

	Overall population (n = 562)	Men (n = 457)	Women (n = 105)	P-value	Unadjusted HR [95% CI]	Adjusted HR [95% CI][a]
All-cause mortality	156 (27.8)	134 (29.3)	22 (21.0)	0.084	0.75 [0.48–1.18]	0.79 [0.50–1.27]
HF hospitalization	108 (20.8)	85 (20.1)	23 (24.0)	0.41	1.16 [0.73–1.86]	1.27 [0.78–2.06]
RV failure	116 (21.4)	87 (19.7)	29 (29.0)	0.041	1.52 [0.98–2.35]	1.57 [1.00–2.49]
Atrial fibrillation/flutter	79 (14.8)	66 (15.2)	13 (13.0)	0.57	0.83 [0.45–1.54]	0.98 [0.52–1.86]
Ventricular arrhythmia	155 (28.4)	137 (30.9)	18 (17.6)	0.008	0.50 [0.30–0.85]	0.56 [0.33–0.95]
LVAD-related infections requiring AB	188 (34.6)	156 (35.4)	32 (31.4)	0.44	0.84 [0.56–1.25]	0.76 [0.50–1.14]
Non-intracranial bleeding	118 (22.1)	99 (22.7)	19 (19.6)	0.51	0.88 [0.54–1.45]	0.88 [0.53–1.46]
Intracranial bleeding	46 (8.6)	39 (8.9)	7 (7.1)	0.56	0.87 [0.39–1.94]	0.78 [0.32–1.89]
Pump thrombosis	41 (7.6)	38 (8.6)	3 (3.1)	0.06	0.35 [0.11–1.15]	0.38 [0.12–1.26]
Non-fatal thromboembolic events	56 (10.4)	44 (10.0)	12 (12.2)	0.51	1.21 [0.64–2.29]	1.31 [0.68–2.54]
Weaning from LVAD	9 (1.6)	4 (0.9)	5 (4.8)	0.004	6.07 [1.63–22.62]	3.10 [0.68–14.07]
LVAD exchange	22 (4.1)	18 (4.1)	4 (4.1)	0.98	0.93 [0.31–2.75]	0.85 [0.28–2.61]
Heart transplantation	218 (38.8)	175 (38.3)	43 (41.0)	0.61	1.11 [0.79–1.55]	1.01 [0.70–1.46]

AB, antibiotics; CI, confidence interval; HF, heart failure; HR, hazard ratio; LVAD, left ventricular assist device; RV, right ventricular.
[a]Adjusted for age, Interagency Registry for Mechanically Assisted Circulatory Support profile, creatinine serum levels at baseline, preoperative need for life support, preoperative vasodilator use, and quartiles of date of LVAD implantation.

Figure 2 Detailed causes of death stratified by sex. CV, cardiovascular.



nosed with HF with preserved ejection fraction, in whom LVAD support is not indicated.[29] Secondly, the lower inclusion rate of women in LVAD trials has led to a gap of evidence in the effectiveness of LVAD support in women, which might have caused a difference in the utilization of LVAD therapy. Additionally, in the pulsatile-flow device era, female patients were deemed less suited for implantation of the larger pumps due to their smaller intrathoracic volume.[15,20] Thus,

Figure 3 Competing event analysis in (A) men and (B) women. HTx, heart transplantation; LVAD, left ventricular assist device.

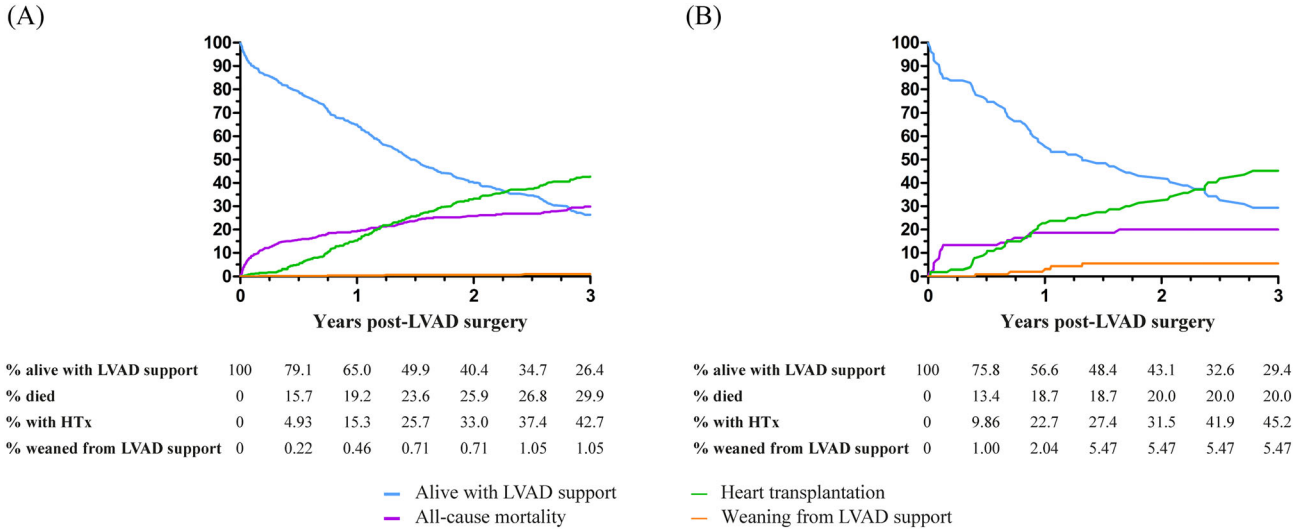
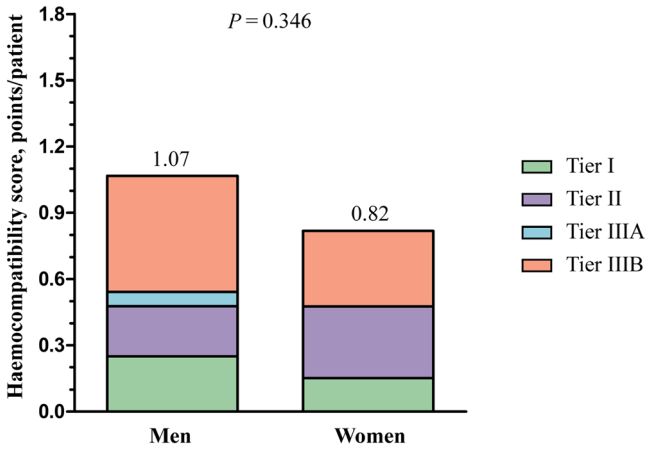


Figure 4 Haemocompatibility score according to sex.



for this and potentially other reasons, LVAD therapy may be less often utilized in women. Furthermore, it has been suggested that women are more likely to decline LVAD support than men.[30,31] In a multinational European screening study, women were somewhat less likely to be eligible for LVAD and/or heart transplantation but considerably less likely to accept LVAD and/or transplantation if indicated.[32] Additionally, it could be that physicians and patients wait too long with the decision to proceed towards LVAD implantation, as reflected by the strikingly high proportion of women in the worst INTERMACS profile and the higher need for mechanical circulatory support in women.[20] Another explanation for the worse INTERMACS profile and high need for mechanical circulatory support in women might be that they are more often affected by acute disease, which possibly explains their better renal function, lower prevalence of atrial fibrillation and ventricular arrhythmias prior to LVAD implantation, and smaller LV size, which possibly reflects less time for remodelling due to acuteness of disease. Finally, the inconsistencies in current literature on sex-related differences in LVAD outcomes might have influenced LVAD implantation rates in women.[15,16,19–21]

Outcomes after left ventricular assist device implantation

Survival differences between male and female LVAD patients have previously been investigated and inconsistent results

have been reported.[15,16,19–21] The two largest databases, the United Network for Organ Sharing (UNOS) and INTERMACS registry, included a combined total of 32 173 LVAD patients, and both studies demonstrated a higher adjusted mortality risk for women.[15,16] A smaller European sex-specific analysis from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) also demonstrated worse survival in women.[20] Conversely, a sub-analysis from the Mechanical Circulatory Support Research Network as well as a recently published meta-analysis did not show survival differences between male and female LVAD recipients.[19,21]

In contrast to most of the earlier studies, survival for women in our study was at least as good as for men despite a more critically ill state prior to LVAD implantation. This was reflected by lower INTERMACS profile and higher need for mechanical circulatory support, which have been associated with worse outcome.[33,34] The observed discrepancy regarding survival differences may partially be attributed to differences in the devices studied. Earlier studies including pulsatile-flow LVADs predominantly demonstrated worse survival in women.[17] Later studies on sex differences in the continuous-flow LVAD era mainly incorporated older devices, whereas 28% of our overall study population had a HeartMate 3 device implanted. This is a relatively large proportion compared with the UNOS and EUROMACS studies in which 2.7% and 0.1% of the overall population received a HeartMate 3, respectively, while the INTERMACS study did not incorporate any data from HeartMate 3 LVADs.[15,16,20] This is important as the MOMENTUM 3 trial demonstrated superiority of the HeartMate 3 LVAD in terms of a lower risk of disabling stroke or reoperation for replacement or removal due to malfunction and is considered the most contemporary LVAD in Europe.[25] An additional subgroup analysis of the MOMENTUM 3 trial showed comparably favourable outcomes for men and women, both on the short and long terms.[35,36] The higher proportion of HeartMate 3 devices in our study may further explain why the risk of bleeding and thromboembolic events was comparable for men and women in our study as opposed to earlier studies reporting an increased risk of major bleeding events.[16,20] The HVAD and HeartMate 2 have been associated with higher stroke, pump thrombosis, and major bleeding rates, which may translate into a higher mortality risk, as bleeding events and pump thrombosis have been associated with higher risk of mortality.[20,25,37,38] Several studies did not find a difference in bleeding risk, and inconsistent results have been reported on whether women are at an increased risk for thromboembolic events.[16,20,21,39,40] To the best of our knowledge, we are the first to investigate sex differences with regard to HRAE by using the HCS and found no significant differences between men and women in our cohort.

In very carefully selected patients with cardiac recovery after LVAD surgery, weaning from LVAD support can be a viable option.[41] Similar to a recent INTERMACS registry analysis, our results demonstrate that women were more likely to recover from LVAD support.[16] This might be explained by the observed difference in the aetiology of HF, especially due to the (partial) reversibility of peripartum cardiomyopathy.[42] Additionally, it has been demonstrated that women have more favourable reverse remodelling on LVAD support compared with men.[43]

In line with earlier studies, female LVAD patients showed a trend towards increased risk of RV failure.[19,20] It has been suggested that ventricular arrhythmias might explain the increased risk of RV failure in women, but in our study, women were less often affected by ventricular arrhythmias post-LVAD implant.[20,44] However, a higher proportion of women were in INTERMACS profile 1 (28.2% of female vs. 13.7% of male patients) and supported with extracorporeal membrane oxygenation (ECMO), which may explain the higher incidence of RV failure. Furthermore, the smaller LV size of women has been associated with RV failure through leftward shifting of the interventricular septum, which increases RV wall stress and reduces RV contractility, and may therefore also have contributed to the increased risk of RV failure.[45,46]

Limitations

This study has some limitations. Firstly, data missing not at random might have introduced bias to our results, although we have used the multiple imputation method to account for this in the multivariable Cox proportional hazard models. Secondly, due to its retrospective design, causality could not be investigated. Thirdly, due to the small number of patients weaned from LVAD support, our findings on recovery from LVAD support should be interpreted with caution. Finally, selection bias or misclassification of data might have occurred.

Conclusions

In this cohort of contemporary LVAD patients from multiple European HF tertiary referral centres, fewer women underwent LVAD implantation as compared to men. This is important as the proportion of female LVAD patients was lower than the proportion of females with advanced HF as reported in previous studies, suggesting underutilization. Furthermore, female patients were referred for LVAD implantation in an inferior INTERMACS profile, suggesting later referral for LVAD therapy. Despite a more critically ill state prior to implantation, LVAD therapy appears at least as beneficial in terms of survival and clinical outcomes in women as in men. This should reduce the hesitance of referring female patients for LVAD implantation, thus providing opportunities for improved outcome similar to male patients. Additional research is needed to investigate whether LVAD utilization in women is lower than required, why it occurs,

and whether this trend can be diverted to a more upstream use of LVAD therapy in women.

Conflict of interest

N.J. reports personal fees and non-financial support from Servier, personal fees from Teva Pharmaceutical Industries, Krka, Sanofi Genzyme, Boehringer Ingelheim, and Bayer, and non-financial support from Abbott, outside the submitted work. A.C.P. reports personal fees from Novartis, Bayer, Vifor, and AstraZeneca, outside the submitted work. I.P. reports grants and personal fees from Boehringer Ingelheim, personal fees from Teva Pharmaceutical Industries, Servier, Krka, and Corvia, and personal fees and non-financial support from Novartis, Pfizer, Bayer, Sandoz, Abbott, and Sanofi Aventis, outside the submitted work. A.J.F. reports personal fees from Alnylam, Bayer, Boehringer Ingelheim, Fresenius, Imedos Systems, Medtronic, MSD, Mundipharma, Pierre Fabre, Pfizer, Roche, Vifor, and ZOLL, and grants and personal fees from AstraZeneca and Novartis, outside the submitted work. L.H. L. reports personal fees from Merck, Bayer, Pharmacosmos, Abbott, Medscape, Myokardia, Sanofi, Lexicon, and Radcliffe Cardiology, grants and personal fees from Vifor-Fresenius, AstraZeneca, Boehringer Ingelheim, and Novartis, and grants from Boston Scientific, outside the submitted work. D.M. reports personal fees from Boehringer Ingelheim, Bayer, Pfizer, Novartis, AstraZeneca, Novo Nordisk, Teva, and Servier, outside the submitted work. F.R. has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years (remuneration for the time spent in activities, such as participation as steering committee member of clinical trials and member of the Pfizer Research Award selection committee in Switzerland, were made directly to the University of Zurich). The Department of Cardiology (University Hospital of Zurich/University of Zurich) reports research, educational, and/or travel grants from Abbott, Amgen, AstraZeneca, Bayer, Berlin Heart, B. Braun, Biosense Webster, Biosensors Europe AG, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Bracco, Cardinal Health Switzerland, Corteria, Daiichi, Diatools AG, Edwards Lifesciences, Guidant Europe NV (BS), Hamilton Health Sciences, Kaneka Corporation, Kantar, Labormedizinisches Zentrum, Medtronic, MSD, Mundipharma Medical Company, Novartis, Novo Nordisk, Orion, Pfizer, Quintiles Switzerland Sarl, Sahajanand IN, Sanofi, Sarstedt AG, Servier, SIS Medical, SSS International Clinical Research, Terumo Deutschland, Trama Solutions, V-Wave, Vascular Medical, Vifor, Wissens Plus, and ZOLL. The research and educational grants do not impact on F.R.'s personal remuneration. M.C. reports grants and personal fees from Novartis, grants from Abbott, personalfees from GE Healthcare, Bayer, Boehringer Ingelheim, AstraZeneca, Teva Pharmaceutical Industries, Sanofi, and LivaNova, non-financial support from Corvia, and personal fees and non-financial support from Pfizer, outside the submitted work. J.J.B. reports personal fees from Abbott, outside the submitted work. All other authors have no conflict of interest to disclose.

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Supporting information

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

Table S1. Classification of haemocompatibility score.
Table S2. Number (percentage) of missing data.
Table S3. Etiology of heart failure in patients who were weaned from LVAD support.
Table S4. Numbers and hazard ratios for the endpoints after a forward stepwise selection process.

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Sex-related differences in left ventricular assist device utilization and outcomes: results from the PCHF-VAD registry

Supplementary Tables

Contents

Table S1. Classification of haemocompatibility score

Intensity	Clinical components	Score
Tier I: *Mild*		
	≤2 gastrointestinal or other bleeding episodes (>30 days post-implant) requiring hospitalization	1 point each
	Suspected pump thrombosis episode that requires hospitalization, successfully medically treated	
	Non-stroke related neurological events	
	Arterial thromboembolism not resulting in organ loss	
Tier II: *Moderate*		
	>2 gastrointestinal or other bleeding episodes (>30 days post-implant) requiring hospitalization	2 points each
	Non-disabling stroke (hemorrhagic or ischemic)	
	Arterial thromboembolism resulting in organ loss	
Tier III A: *Moderately severe*		
	Pump malfunction due to pump thrombosis leading to reoperation for removal or replacement	3 points each
Tier III B: *Severe*		
	Disabling stroke	4 points each
	Death due to a haemocompatibility etiology or inconclusive (unknown or multiple causes)	

Table S2. Number (percentage) of missing data

Age	0 (0.0)
Men	0 (0.0)
Geographical area	0 (0.0)
Quartiles of date of LVAD implant	0 (0.0)
ICD status	10 (1.8)
CRT status	14 (2.5)
Heart rate	65 (11.6)
SBP	72 (12.8)
DBP	72 (12.8)
BMI	66 (11.7)
LVAD type	0 (0.0)
LVAD destination	29 (5.2)
INTERMACS class	15 (2.7)
Etiology of heart failure	0 (0.0)
Comorbidities	0 (0.0)
Prior cardiac surgery	0 (0.0)
Concomitant procedure with LVAD implant	0 (0.0)
Life support prior to LVAD implant	20 (3.6)
Medications	
Diuretic	63 (11.2)
Beta blocker	98 (17.4)
ACEi/ARB	88 (15.7)
MRA	125 (22.2)
Ivabradine	148 (26.3)
Inotrope	104 (18.5)
Laboratory values	
Creatinine	55 (9.8)
Bilirubin	115 (20.5)

Echocardiographic data	
LVIDd	76 (13.5)
LVEF	127 (22.6)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; CRT-P, CRT-pacing; CRT-D, CRT-defibrillator; DBP, diastolic blood pressure; ICD, implantable cardioverter defibrillator; INTERMACS, interagency registry for mechanically assisted circulatory support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension end-diastolic; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure

Table S3. Etiology of heart failure in patients who were weaned from LVAD support

	Overall population (n=9)	**Men** (n=4)	**Women** (n=5)
Dilated cardiomyopathy	3 (33.3)	1 (25.0)	2 (40.0)
Ischemic cardiomyopathy	2 (22.2)	1 (25.0)	1 (20.0)
Toxic cardiomyopathy	1 (11.1)	1 (25.0)	0 (0.0)
Myocardial necrosis	1 (11.1)	1 (25.0)	0 (0.0)
Peripartum cardiomyopathy	2 (22.2)	0 (0.0)	2 (40.0)

LVAD, left ventricular assist device

Table S4. Sensitivity analysis: numbers and hazard ratios for the endpoints assessed in a forward stepwise multivariable Cox proportional hazards model

	Overall population (n=562)	**Men** (n=457)	**Women** (n=105)	**p-value**	**HR [95% CI] unadjusted**	**HR [95% CI] adjusted***
All-cause mortality	156 (27.8)	134 (29.3)	22 (21.0)	0.084	0.75 [0.48-1.18]	0.86 [0.54-1.36]
HF hospitalization	108 (20.8)	85 (20.1)	23 (24.0)	0.41	1.16 [0.73-1.86]	1.30 [0.81-2.10]
RV-failure	116 (21.4)	87 (19.7)	29 (29.0)	0.041	1.52 [0.98-2.35]	1.68 [1.07-2.63]
Atrial fibrillation/ flutter	79 (14.8)	66 (15.2)	13 (13.0)	0.57	0.83 [0.45-1.54]	0.87 [0.46-1.63]
Ventricular arrhythmia	155 (28.4)	137 (30.9)	18 (17.6)	0.008	0.50 [0.30-0.85]	0.52 [0.31-0.88]
LVAD-related infections requiring AB	188 (34.6)	156 (35.4)	32 (31.4)	0.44	0.84 [0.56-1.25]	0.78 [0.52-1.17]
Non-intracranial bleeding	118 (22.1)	99 (22.7)	19 (19.6)	0.51	0.88 [0.54-1.45]	0.90 [0.55-1.49]
Intracranial bleeding	46 (8.6)	39 (8.9)	7 (7.1)	0.56	0.87 [0.39-1.94]	0.82 [0.34-1.96]
Pump thrombosis	41 (7.6)	38 (8.6)	3 (3.1)	0.06	0.35 [0.11-1.15]	0.35 [0.11-1.15]
Non-fatal thromboembolic events	56 (10.4)	44 (10.0)	12 (12.2)	0.51	1.21 [0.64-2.29]	1.31 [0.68-2.49]
Weaning from LVAD	9 (1.6)	4 (0.9)	5 (4.8)	0.004	6.07 [1.63-22.62]	4.53 [1.19-17.3]
LVAD exchange	22 (4.1)	18 (4.1)	4 (4.1)	0.98	0.93 [0.31-2.75]	0.73 [0.25-2.18]
Heart transplantation	218 (38.8)	175 (38.3)	43 (41.0)	0.61	1.11 [0.79-1.55]	1.01 [0.71-1.44]

* Adjusted for age, LVAD surgery as re-do surgery, preoperative need for life support, preoperative vasodilator use, quartiles of date of LVAD implantation

AB, antibiotics; CI, confidence interval; HF, heart failure; HR, hazard ratio; LVAD, left ventricular assist device; RV, right ventricle

PUBLICATION 4

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The candidate, Nina Jakuš, contributed to this publication by:

- Having a substantial contribution to the acquisition, analysis, and interpretation of data for the work; AND
- She critically revised the manuscript for important intellectual content; AND
- She gave final approval of the version to be published; AND
- Agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contribution of other co-authors:

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- Critically revised the manuscript for important intellectual content; AND
- Gave final approval of the version to be published; AND
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ORIGINAL ARTICLE

How does age affect outcomes after left ventricular assist device implantation: results from the PCHF-VAD registry

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Abstract

Aims Use of left ventricular assist devices (LVADs) in older patients has increased, and assessing outcomes in older LVAD recipients is important. Therefore, this study aimed to investigate associations between age and outcomes after continuous-flow LVAD (cf-LVAD) implantation.

Methods and results Cf-LVAD patients from the multicentre European PCHF-VAD registry were included and categorized into those <50, 50–64, and ≥65 years old. The primary endpoint was all-cause mortality. Among secondary outcomes were heart failure (HF) hospitalizations, right ventricular (RV) failure, haemocompatibility score, bleeding events, non-fatal thromboembolic events, and device-related infections. Of 562 patients, 184 (32.7%) were <50, 305 (54.3%) were aged 50–64, whereas 73 (13.0%) were ≥65 years old. Median follow-up was 1.1 years. Patients in the oldest age group were significantly more often designated as destination therapy (DT) candidates (61%). A 10 year increase in age was associated with a significantly higher risk of mortality (hazard ratio [HR] 1.34, 95% confidence interval [CI] [1.15–1.57]), intracranial bleeding (HR 1.49, 95% CI [1.10–2.02]), and non-intracranial bleeding (HR 1.30, 95% CI [1.09–1.56]), which was confirmed by a higher mean haemocompatibility score (1.37 vs. 0.77, oldest vs. youngest groups, respectively, $P = 0.033$). Older patients suffered from less device-related infections requiring systemic antibiotics. No age-related differences were observed in HF-related hospitalizations, ventricular arrhythmias, pump thrombosis, non-fatal thromboembolic events, or RV failure.

Conclusions In the PCHF-VAD registry, higher age was associated with increased risk of mortality, and especially with increased risk of major bleeding, which is particularly relevant for the DT population. The risks of HF hospitalizations, pump thrombosis, ventricular arrhythmia, or RV failure were comparable. Strikingly, older patients had less device-related infections.

Keywords Advanced heart failure; Left ventricular assist devices; Destination therapy; Survival; Age

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Introduction

Despite tremendous developments in heart failure (HF) therapy over the past decade, it is estimated that up to 10% of all HF patients have advanced HF.[1] Besides improvements in pharmacological therapy, mechanical options for advanced HF have become more readily available, with significant technological improvements.[2] The left ventricular assist device (LVAD) is an established treatment option for long-term mechanical circulatory support in advanced HF patients. This was to some extent facilitated by the growing mismatch between demand and availability of donor hearts, especially in Western Europe.[3] Additionally, more timely referral, improved patient selection, clinical experience, and technological advancement have improved outcomes after LVAD implantation, and LVADs are now more often used as destination therapy (DT) in older patients and those not deemed eligible or suited for heart transplantation.[4–10] Furthermore, the use of LVADs as bridge to transplant (BTT) has increased in older patients as well.[11] With the increasing use of LVADs and the expected number of patients who could benefit from LVAD support, risk stratification is essential for proper patient selection, especially in older patients. Several risk scores have been developed, but with improvements in LVAD technology and patient management, new insights into the impact of an aging LVAD population on the clinical management and outcomes are essential.[12,13] Moreover, outcomes other than mortality are particularly relevant for older recipients and DT, as they affect quality of life and costs. Therefore, this study aimed to assess the associations between age and cause-specific clinical outcomes after continuous-flow LVAD (cf-LVAD) implantation.

Methods

The methods and characteristics of the observational PCHF-VAD study have been described previously.[14] Briefly, cf-LVAD patients were included in 13 European HF tertiary referral centres, a collaborative of 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. All participating centres acquired approval from the local ethics review boards (predominantly, a waiver of informed consent was obtained by the individual centres). The patient data were recorded and managed using REDCap (Research Electronic Data Capture) electronic data capture tools—a secure, web-based application, hosted at the University of Zagreb School of Medicine, serving as the data-coordinating centre.[15]

At the time of analysis, 583 patients who were implanted with a durable ventricular assist device between December 2006 and January 2020 were included in this registry. Patients with a pulsatile device (n = 4) or biventricular assist device (n = 11), as well as patients aged $<$18 years (n = 6), were excluded from this analysis, leaving 562 patients.

Patients were categorized into those younger than 50 years, patients between 50 and 64 years, and patients aged 65 years and older. The primary endpoint was all-cause mortality. Secondary outcomes were rates of heart transplantation, weaning from LVAD support, HF hospitalization, right ventricular (RV) failure (acute and chronic), LVAD-related infection requiring systemic antibiotics, non-fatal thromboembolic events, intracranial bleeding, non-intracranial bleeding, LVAD exchange, and haemocompatibility score (HCS).

Haemocompatibility score

In order to analyse the aggregate burden of haemocompatibility-related adverse events (HRAEs), the HCS was calculated for all patients. Each HRAE received a points score, based on its clinical relevance (Supporting Information, *Table S1*). The HCS was calculated for each patient by summing up all points associated with all HRAEs experienced by the patient during the follow-up period.[16]

Statistical analysis

Continuous data are expressed as mean value ± standard deviation or median and interquartile range [IQR], depending on the distribution of the data, and were compared by the ANOVA or the Kruskal–Wallis test. Categorical data are expressed as counts and percentages and were compared by the Pearson's χ^2 test. The probability of survival was calculated using the Kaplan–Meier method and was compared between age groups using the log-rank test. The hazard ratios (HRs) for the outcomes were assessed using Cox proportional hazards models and were calculated for a 10 year increase in age. For the survival analyses, the date of LVAD implantation was considered the index date. Follow-up duration was defined as time to last contact, heart transplantation, weaning from LVAD support, or death whichever occurred first.

In order to test whether age was independently associated with the outcomes, multivariable Cox proportional hazards

models were constructed. The associations between age and outcomes were adjusted for gender, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile, baseline serum creatinine level, quartiles of LVAD implantation date, the need for mechanical circulatory support prior to LVAD surgery, and pre-LVAD vasopressor use.

Sensitivity analyses were performed to adjust the association between age and all-cause mortality for several baseline characteristics. The following baseline covariates, with <30% missing values, were tested in a forward stepwise Cox proportional hazards model: sex, cardiac implantable electronic device (CIED) status, heart rate, LVAD type, LVAD intention (BTT, bridge to decision [BTD], and DT), INTERMACS profile, aetiology of HF, known history of chronic kidney disease, atrial fibrillation/flutter, ventricular arrhythmias (VAs), significant VAs pre-LVAD, prior cardiac surgery, concomitant procedure with the 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. The significant baseline covariates were then used in the Cox regression model for the secondary outcomes. Furthermore, an additional forward stepwise Cox proportional hazards model was constructed using the baseline covariates that differed significantly between the age groups. For both analyses, a significance level of 0.05 and 0.10 for entry and removal thresholds was used, respectively.

The numbers of missing values of the variables mentioned above are shown in Supporting Information, *Table S2*. Variables with <30% missing data were imputed using multiple imputation, whereas those with a larger proportion of missing data were not included in this analysis. If the missing variables showed a monotone pattern of missing values, the monotone method was used. Otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations was performed, and the pooled data were analysed. The imputed data were only used for the multivariable analysis. An additional sensitivity analysis was performed to determine the consistency of the results. In this sensitivity analysis, patients were divided into tertiles according to their age at LVAD implantation. A two-sided *P*-value of 0.05 or lower was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences, Version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 562 patients, 184 (32.7%) were younger than 50 years, 305 (54.3%) were aged 50 to 64 years, whereas 73 (13.0%) were 65 years or older. The baseline characteristics of the patients stratified by age are shown in *Table 1*. Older patients more often had a HeartMate 3 (HM3) device and more often received their LVAD as DT (61.1% vs. 3.4% as DT, 20.8% vs. 79.9% as BTT, and 18.1% vs. 16.7% as BTD for the oldest vs. youngest patient groups, respectively). Additionally, older patients had more advanced comorbidities and were less often implanted in an acute setting, which was indicated by a higher (less severe) mean INTERMACS profile.

Survival

Of the overall population, the median follow-up time on LVAD support was 1.1 [IQR 0.5–2.2] years. Non-significant differences in follow-up time between the age groups were observed (patients younger than 50 years: 1.2 [0.7–2.3], patients between 50 and 64 years: 1.1 [0.5–2.2], and patients aged 65 years or older: 1.4 [0.3–2.8], $P = 0.464$).

The time to event analysis for all-cause mortality is shown in *Figure 1A*. Patients aged 65 years or older had a significantly higher all-cause mortality than those aged 50–64 and <50 years (46.3% vs. 37.5% and 25.0%, respectively, $P = 0.03$). Pairwise comparison showed no significant survival differences between the 50–64 and ≥65 age groups. One-year mortality was notably higher in the oldest patient group, whereas the survival after the initial 12 months post-LVAD implantation was more comparable (*Figure 1B,C*). Furthermore, patients aged ≥65 years were significantly less often transplanted (14.3% vs. 55.9% and 70.5%, respectively, $P < 0.001$) and weaned from LVAD support (0% vs. 1.0% and 7.7%, respectively, $P = 0.021$) than those aged 50–64 and <50 years. A 10 year increase in age was significantly associated with a higher mortality risk (HR 1.34, 95% confidence interval [CI] [1.15–1.57]) and lower chance of heart transplant or weaning from LVAD (HR 0.90, 95% CI [0.80–1.01] and HR 0.63, 95% CI [0.35–1.16], respectively) after adjustment for sex, INTERMACS profile, baseline serum creatinine level, quartiles of LVAD implantation date, the need for mechanical circulatory support prior to LVAD surgery, and pre-LVAD vasopressor use (*Table 2*). The majority of deaths in all age groups were due to cardiovascular-related causes (Supporting Information, *Table S3*).

Competing event analysis showed that patients younger than 50 years died less often (19.0%) and were more often transplanted (56.4%) or weaned from LVAD support (4.2%) than patients aged 50–64 years (29.9%, 43.3%, and 0.7%, respectively) and patients aged 65 years or older (43.8%, 10.1%, and 0.0%, respectively) (*Figure 2*).

Secondary endpoints

LVAD-related infections that required systemic antibiotics occurred less often in older patients. As shown in the multivar-

Table 1 Baseline characteristics

	Overall population (n = 562)	Patients aged <50 years (n = 184)	Patients aged 50–64 years (n = 305)	Patients aged ≥65 years (n = 73)	P-value
Age, years	53 ± 12	39 ± 9	58 ± 4	68 ± 3	<0.001
Men	457 (81.3)	148 (80.4)	247 (81.0)	62 (84.9)	0.69
Geographical area					
North and West Europe (the Netherlands, Belgium, Germany, and Sweden)	373 (66.4)	138 (75.0)	204 (66.9)	31 (42.5)	<0.001
South and East Europe (Croatia, Poland, Lithuania, Italy, Spain, and Greece)	189 (33.6)	46 (25.0)	101 (33.1)	42 (57.5)	
Quartiles of date of LVAD implant					
1st quartile (6 Dec 2006 to 29 Oct 2012)	143 (25.4)	65 (35.3)	68 (22.3)	10 (13.7)	0.001
2nd quartile (30 Oct 2012 to 4 Aug 2015)	143 (25.4)	46 (25.0)	79 (25.9)	18 (24.7)	
3rd quartile (5 Aug 2015 to 16 Apr 2017)	139 (24.7)	43 (23.4)	77 (25.2)	19 (26.0)	
4th quartile (17 Apr 2017 to 28 Jan 2020)	137(24.4)	30 (16.3)	81 (26.6)	26 (35.6)	
ICD status					
No ICD	294 (53.3)	106 (58.2)	154 (51.5)	34 (47.9)	0.43
Primary prevention	180 (32.6)	53 (29.1)	99 (33.1)	28 (39.4)	
Secondary prevention	78 (14.1)	23 (12.6)	46 (15.4)	9 (12.7)	
CRT status					
No CRT	406 (74.1)	146 (83.4)	215 (71.7)	45 (61.6)	0.004
CRT-P carrier	14 (2.6)	4 (2.3)	7 (2.3)	3 (4.1)	
CRT-D carrier	128 (23.4)	25 (14.3)	78 (26.0)	25 (34.2)	
Heart rate, b.p.m.	83.3 ± 19.0	89.9 ± 21.7	81.3 ± 17.4	77.5 ± 15.1	<0.001
SBP, mmHg	99.5 ± 13.9	96.7 ± 13.5	100.5 ± 14.0	101.9 ± 13.8	0.009
DBP, mmHg	64.2 ± 10.9	64.4 ± 10.9	64.0 ± 11.0	64.2 ± 10.2	0.95
BMI, kg/m^2	25.9 ± 4.6	25.0 ± 5.0	26.5 ± 4.4	25.4 ± 4.6	0.003
LVAD type					
HeartMate II	265 (47.2)	104 (56.5)	135 (44.3)	26 (35.6)	<0.001
HeartWare HVAD	119 (21.2)	34 (18.5)	70 (23.0)	15 (20.5)	
HeartMate 3	157 (27.9)	44 (23.9)	90 (29.5)	23 (31.5)	
Other	21 (3.7)	2 (1.1)	10 (3.3)	9 (12.3)	
LVAD destination					
BTT	356 (66.8)	139 (79.9)	202 (70.4)	15 (20.8)	<0.001
BTD	90 (16.9)	29 (16.7)	48 (16.7)	13 (18.1)	
DT	87 (16.3)	6 (3.4)	37 (12.9)	44 (61.1)	
INTERMACS profile					
1	90 (16.5)	40 (22.7)	46 (15.4)	4 (5.6)	<0.001
2	150 (27.4)	57 (32.4)	82 (27.4)	11 (15.3)	
3	176 (32.2)	52 (29.5)	90 (30.1)	34 (47.2)	
4–7	131 (23.9)	27 (15.3)	81 (27.1)	23 (31.9)	
Aetiology of heart failure					
Dilated cardiomyopathy	247 (44.0)	110 (59.8)	107 (35.1)	30 (41.1)	<0.001
Ischaemic cardiomyopathy	256 (45.6)	44 (23.9)	176 (57.7)	36 (49.3)	
Other	59 (10.5)	30 (16.3)	22 (7.2)	7 (9.6)	
Comorbidities					
Arterial hypertension	128 (22.8)	21 (11.4)	82 (26.9)	25 (34.2)	<0.001
Diabetes mellitus	114 (20.3)	18 (9.8)	75 (24.6)	21 (28.8)	<0.001
Chronic kidney disease	137 (24.4)	19 (10.3)	91 (29.8)	27 (37.0)	<0.001
Coronary artery disease	139 (24.7)	26 (14.1)	91 (29.8)	22 (30.1)	<0.001
Prior MI	211 (37.5)	38 (20.7)	144 (47.2)	29 (39.7)	<0.001
Prior coronary revascularization	170 (30.2)	29 (15.8)	118 (38.7)	23 (31.5)	<0.001
COPD	44 (7.8)	3 (1.6)	30 (9.8)	11 (15.1)	<0.001
Atrial fibrillation/flutter	173 (30.8)	41 (22.3)	103 (33.8)	29 (39.7)	0.006
Ventricular arrhythmias	153 (27.2)	52 (28.3)	81 (26.6)	20 (27.4)	0.92
Cerebrovascular events	41 (7.3)	10 (5.4)	26 (8.5)	5 (6.8)	0.44
Prior cardiac surgery	75 (13.3)	19 (10.3)	45 (14.8)	11 (15.1)	0.34
Concomitant procedure with LVAD implant	99 (17.6)	27 (14.7)	56 (18.4)	16 (21.9)	0.34
MCS prior to LVAD implant					
None	401 (74.0)	120 (68.6)	219 (74.2)	62 (86.1)	0.33
ECMO	40 (7.4)	14 (8.0)	24 (8.1)	2 (2.8)	
Temporary LVAD	5 (0.9)	3 (1.7)	1 (0.3)	1 (1.4)	
Temporary RVAD	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	
Temporary BiVAD	2 (0.4)	1 (0.6)	1 (0.3)	0 (0.0)	
IABP	73 (13.5)	27 (15.4)	40 (13.6)	6 (8.3)	
Other	20 (3.7)	9 (5.1)	10 (3.4)	1 (1.4)	

(*Continues*)

Table 1 (continued)

	Overall population (n = 562)	Patients aged <50 years (n = 184)	Patients aged 50–64 years (n = 305)	Patients aged ≥65 years (n = 73)	P-value
Medications					
Diuretic	454 (91.0)	130 (86.1)	254 (91.4)	70 (100.0)	0.003
Beta-blocker	299 (64.4)	85 (63.0)	171 (65.8)	43 (62.3)	0.79
ACEi/ARB	213 (44.9)	67 (47.5)	120 (45.6)	26 (37.1)	0.34
MRA	315 (72.1)	78 (62.9)	180 (73.2)	57 (85.1)	0.004
Ivabradine	45 (10.9)	13 (10.9)	24 (10.3)	8 (12.7)	0.87
Inotrope	305 (66.6)	99 (72.8)	166 (65.4)	40 (58.8)	0.11
Laboratory values					
Creatinine, μmol/L	127.1 ± 56.0	123.9 ± 68.1	127.4 ± 50.9	132.5 ± 45.5	0.56
Bilirubin, μmol/L	24.3 ± 20.5	27.8 ± 21.1	23.7 ± 21.8	19.4 ± 11.3	0.02
Echocardiographic data					
LVIDd, mm	70.7 ± 12.5	69.1 ± 12.4	71.3 ± 13.1	72.0 ± 10.2	0.14
LVEF, %	19.4 ± 7.5	19.0 ± 8.7	19.3 ± 7.1	20.4 ± 6.0	0.42

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BiVAD, biventricular assist device; BMI, body mass index; BTD, bridge to decision; BTT, bridge to transplant; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacing; DBP, diastolic blood pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; HVAD, HeartWare Ventricular Assist Device; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension at end-diastole; MCS, mechanical circulatory support; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; RVAD, right ventricular assist device; SBP, systolic blood pressure.

iable analysis, an increase of 10 years was associated with a significantly lower risk of infection (HR 0.88, 95% CI [0.77–0.99]; *Table 2*).

A 10 year increase in age was associated with a higher risk of intracranial (HR 1.49, 95% CI [1.10–2.02]) and non-intracranial bleedings (HR 1.30, 95% CI [1.09–1.56]; *Table 2*). The risk of incident atrial fibrillation or flutter was higher in older patients (HR 1.38, 95% CI [1.11–1.73]). The risk of non-fatal thromboembolic events was numerically but not significantly higher with increasing age. No significant differences in the rates of HF-related hospitalizations, VAs, pump thrombosis, or RV failure were observed between the age groups (*Table 2*).

Haemocompatibility score

The mean HCS was significantly higher in older LVAD patients (patients younger than 50 years: 0.77 ± 1.46, patients between 50 and 64 years: 1.09 ± 1.91, and patients aged 65 years or older: 1.37 ± 1.93, P = 0.033; *Figure 3*). The differences between the three groups were most prominent in Tier I and Tier IIIB.

Sensitivity analysis

In addition to categorizing patients into the pre-specified age groups, the study population was stratified into tertiles by age. In the first tertile (T1), patients aged 50 years or younger were included, the second tertile (T2) included patients between 50.1 and 60.1 years, whereas the third tertile (T3) consisted of patients aged 60.2 years or older. The baseline characteristics are shown in Supporting Information, *Table S4*, and differences between the age groups were similar to those observed in the main analysis. As reported in the main analysis, older LVAD patients had a higher risk of all-cause mortality, atrial fibrillation/flutter, and non-intracranial bleedings and lower chance of heart transplantation, weaning from LVAD support, and device-related infections (Supporting Information, *Table S5*). The mean HCS was significantly higher in Tier III compared with Tier I and Tier II (Supporting Information, *Figure S1*).

Figure 1 Kaplan–Meier plots of time to all-cause mortality for (A) the complete follow-up period, (B) the first year post-LVAD implantation, and (C) the period starting 1 year post-LVAD implantation. LVAD, left ventricular assist device.

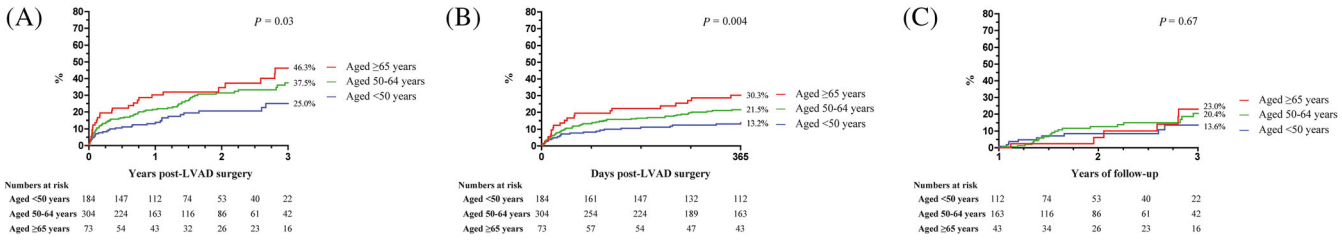


Table 2 Numbers and hazard ratios for the endpoints

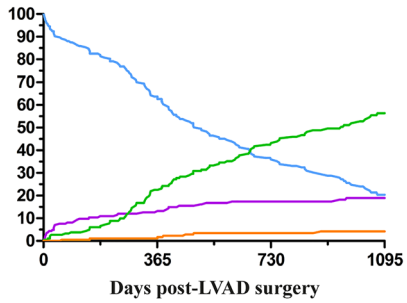
	Number of patients with an event (total n = 562)	Patients aged <50 years with an event (n = 184)	Patients aged 50–64 years with an event (n = 305)	Patients aged ≥65 years with an event (n = 73)	P-value	Hazard ratios	
						HR [95% CI] Unadjusted (per 10 years)	HR [95% CI] Adjusted[a] (per 10 years)
All-cause mortality	156 (27.8)	36 (19.6)	91 (29.8)	29 (39.7)	0.002	1.29 [1.11–1.50]	1.39 [1.12–1.72]
HF hospitalization	108 (20.8)	33 (19.9)	63 (22.3)	12 (17.4)	0.63	1.07 [0.91–1.26]	1.06 [0.89–1.25]
RV failure	116 (21.4)	33 (19.1)	73 (24.7)	10 (13.9)	0.089	1.05 [0.89–1.24]	1.07 [0.90–1.27]
Atrial fibrillation/flutter	79 (14.8)	16 (9.4)	47 (16.1)	16 (22.5)	0.022	1.38 [1.11–1.73]	1.35 [1.07–1.71]
Ventricular arrhythmia	155 (28.4)	45 (25.9)	95 (31.8)	15 (20.5)	0.11	1.03 [0.90–1.19]	1.00 [0.87–1.16]
LVAD-related infections requiring AB	188 (34.6)	76 (44.2)	96 (32.2)	16 (21.9)	0.002	0.86 [0.77–0.97]	0.88 [0.77–0.99]
Non-intracranial bleeding	118 (22.1)	29 (17.1)	68 (23.2)	21 (29.6)	0.081	1.30 [1.09–1.53]	1.30 [1.09–1.56]
Intracranial bleeding	46 (8.6)	9 (5.2)	31 (10.5)	6 (8.5)	0.14	1.46 [1.08–1.96]	1.49 [1.10–2.02]
Pump thrombosis	41 (7.6)	11 (6.4)	25 (8.5)	5 (7.0)	0.70	1.07 [0.82–1.40]	0.98 [0.75–1.29]
Non-fatal thromboembolic events	56 (10.4)	13 (7.6)	33 (11.2)	10 (13.9)	0.27	1.19 [0.94–1.51]	1.19 [0.93–1.53]
Weaning from LVAD	9 (1.6)	7 (3.8)	2 (0.7)	0 (0.0)	0.014	0.50 [0.30–0.81]	0.63 [0.35–1.16]
LVAD exchange	22 (4.1)	12 (7.0)	10 (3.4)	0 (0.0)	0.03	0.70 [0.51–0.95]	0.69 [0.49–0.98]
Heart transplantation	218 (38.8)	97 (52.7)	115 (37.7)	6 (8.2)	<0.001	0.83 [0.75–0.93]	0.90 [0.80–1.01]

AB, antibiotics; CI, confidence interval; HF, heart failure; HR, hazard ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; RV, right ventricular.

[a]Adjusted for gender, INTERMACS profile, serum creatinine level, quartiles of date of LVAD implantation, mechanical circulatory support prior to LVAD surgery, and pre-LVAD vasopressor use.

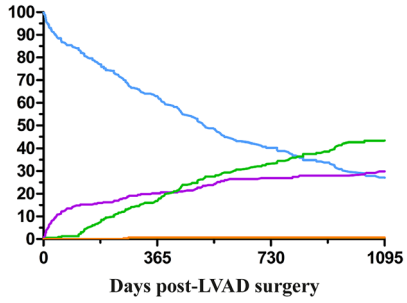
Figure 2 Competing event analysis for (A) patients aged <50 years, (B) patients aged 50–64 years, and (C) patients aged ≥65 years. HTx, heart transplantation; LVAD, left ventricular assist device.

(A)



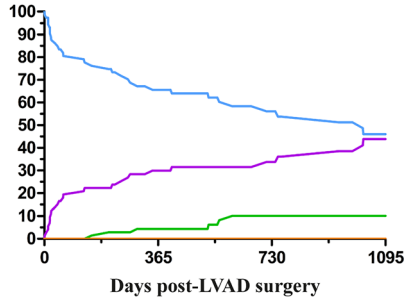
% alive with LVAD support	100	82.0	63.7	46.4	35.9	28.8	20.4
% died	0	10.9	12.6	16.8	17.4	17.4	19.0
% with HTx	0	6.03	22.5	33.3	43.2	49.6	56.4
% weaned from LVAD support	0	1.10	1.10	3.48	3.48	4.21	4.21

(B)



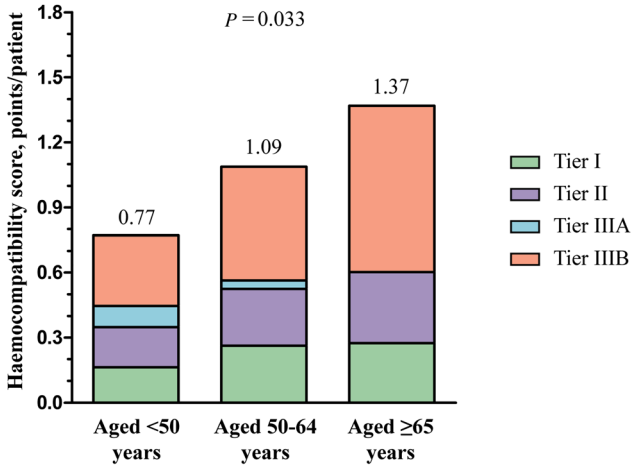
% alive with LVAD support	100	76.9	62.9	48.8	40.3	33.8	27.2
% died	0	15.9	20.2	23.9	27.0	28.0	29.9
% with HTx	0	7.47	16.8	27.7	33.1	38.6	43.3
% weaned from LVAD support	0	0	0.72	0.72	0.72	0.72	0.72

(C)



% alive with LVAD support	100	76.2	65.7	62.2	56.1	53.8	46.0
% died	0	22.3	29.9	31.5	33.8	36.1	43.8
% with HTx	0	1.44	4.41	6.24	10.1	10.1	10.1
% weaned from LVAD support	0	0	0	0	0	0	0

Figure 3 Haemocompatibility score according to age.



Additional assessment of the associations between age and outcomes adjusted for the covariates that were selected in a forward stepwise Cox regression model provided results comparable with the fixed model (Supporting Information, *Tables S6* and *S7*).

Discussion

In this large European multicentre study of cf-LVAD recipients, higher age was associated with an increased risk of all-cause mortality after LVAD implantation. Older LVAD patients more often suffered from intracranial and non-intracranial bleedings, which was also consistent with a higher mean HCS in comparison with younger patients. This is an important consideration for patient selection at higher age, especially in the case of DT. Strikingly, older patients less often suffered from device-related infections requiring systemic antibiotics. We provided numerous additional analyses of associations between age and cause-specific outcomes.

Several studies have previously investigated the effects of age on LVAD survival, but our results provide insights into a contemporary LVAD cohort in the European setting.[17–22] Earlier INTERMACS and IMACS analyses also found higher age to be associated with an increased mortality risk.[18,19,22,23] Similar findings were observed by several other studies[18,21] although some smaller single-centre studies reported no significant survival differences.[17,20] However, these earlier studies mainly included patients from the United States and consisted mostly of older types of LVADs. In our study, the mortality risk was highest in the oldest patient group, but the risk appeared to be upfront with similar risk of mortality

beyond 12 months. Interestingly, older patients were in less severe INTERMACS profile prior to LVAD implantation, yet had a higher mortality. This may be partially explained by other factors such as higher rates of comorbidities and frailty. However, despite the increased mortality risk, the overall survival of older patients on LVAD support was still acceptable, in particular after the first year. Therefore, LVAD implantation could be considered in carefully selected elderly patients.

Interestingly, the number of patients aged ≥65 years implanted with an LVAD increased over recent years. This may partially be explained by the expanded indications for DT in Europe as well as the advent of the HM3 after the successful MOMENTUM 3 trial, which showed similar favourable effects of the HM3 for patients aged ≥65 years.[6] The HM3 has been approved for DT for several years and is increasingly being used for said indication in older patients, which is also reflected in our study as the proportion of implanted HM3 devices was largest in the oldest patient category. The use of BTT LVAD has also increased in older patients in the recent years, suggesting that general acceptance of older patients for both DT and BTT indications is increasing.[10,11]

Bleeding and pump thrombosis are among the most common adverse events post-LVAD implantation. These are especially disabling in the DT setting, with the potential long-term risk of repeated hospitalizations and reduced quality of life. The MOMENTUM 3 trial showed a lower risk of bleeding, stroke, and pump thrombosis for the HM3 as compared with the HeartMate II (HMII), underscoring the importance of studying age-related effects in the present era.[6] In our study, a 10 year increase in age was associated with a higher risk of both intracranial and non-intracranial bleedings (HR 1.49 and HR 1.30, respectively). The risk of non-fatal thromboembolic events was slightly higher, although not significant, in older patients, despite a higher prevalence and higher risk of incident atrial fibrillation in older patients. No differences were found with respect to the occurrence of pump thrombosis. The clinical HCS was developed to analyse the burden of haemocompatibility-related LVAD events.[16] We found that the mean HCS was significantly higher in older patients (1.37 vs. 0.77, $P = 0.033$). With the detrimental effects of a stroke especially at older age during LVAD support, we believe this is an important finding that warrants further research in methods to assess overall bleeding risk in elderly LVAD patients. One could imagine a cutoff point above which bleeding risk is deemed too high in order to prevent disabling events during LVAD support. Analyses from the INTERMACS and IMACS database reported higher risks of gastrointestinal bleeding for patients aged ≥70 and ≥75 years.[18,22,23] These results suggest more vigilant monitoring for bleeding risk of elderly LVAD recipients. Reports on age-related stroke risk, on the other hand, are conflicting.[18,20,22] Given the time points at which the studies were undertaken, it is likely that, compared with our study, very few patients in the previous studies received an HM3 LVAD. Furthermore, differences in study populations are important as one study only investigated DT patients, whereas another study only found age to be associated with higher stroke risk in the DT, but not the BTT, patients.[20,23]

Besides haemocompatibility-related complications, device-related infections are a major cause of morbidity and mortality, often requiring hospitalization for long courses of intravenous antibiotics.[24] We found a significantly lower risk of LVAD-related infections among older patients (HR 0.88, 95% CI [0.78–0.99]), which underscores earlier work.[17,18,20,25] This finding is rather interesting because the immune system of older people is often impaired compared with younger people. A possible explanation might be that younger patients exhibit a more (pro)active lifestyle that includes more exercise and can easily lead to manipulation or irritation of the driveline causing infection or that younger patients may be less careful in their driveline and general post-LVAD care, a potential pattern also observed after heart transplantation.[26] Furthermore, based on the INTERMACS profiles and proportion of patients on mechanical circulatory support prior to LVAD implant, it seems plausible that younger patients more often had their LVAD implanted in an acute setting and were therefore at higher risk of developing a driveline infection. Lastly, elderly LVAD patients had a lower body mass index (BMI) than the middle age group, which has also been associated with a lower risk of driveline infections.[25,27]

Perspectives

To the best of our knowledge, this is the first study to investigate associations between age and detailed cause-specific clinical outcomes in a large multinational European population of contemporary cf-LVAD patients. LVAD DT is becoming more important and is expected to increase to similar numbers as BTT in Europe, especially with aging populations with otherwise high life expectancies in wealthy countries. Several studies have reported on age-related risks post-LVAD implantation. However, these studies almost exclusively incorporated data on US patients. The differences in HF and LVAD management between the United States and Europe make it difficult to extrapolate earlier findings to the current European setting. Furthermore, most studies were conducted in an earlier era in which the older HMII (axial-flow) and HeartWare Ventricular Assist Device (HVAD) were mostly used. The current study contains a significant number of patients with an HM3, which is the predominant and contemporary ventricular assist device in Europe after the successful MOMENTUM 3 trial, and particularly since the recent withdrawal of HVAD from the market. Our study therefore adds significantly to current literature and provides valuable in-

sights into contemporary European LVAD management in older recipients.

Limitations

Our analysis was limited by several factors mostly inherent to the study design. First of all, due to the non-randomized design, confounding might have biased our results. Even after adjusting for possible confounders, residual confounding cannot be excluded. Furthermore, selection bias and missing data, which we tried to limit by using multiple imputation methods, may have affected our results. Furthermore, the proportion of patients older than 65 years was relatively small, which may have influenced analysis of the secondary outcomes. Lastly, additional data on anticoagulation use, such as time in therapeutic range, were not available.

Conclusions

Although age was associated with increased risk of mortality and bleeding events, the clinical outcomes of older patients after cf-LVAD implantation were acceptable. Reflecting on the poor prognosis of end-stage HF patients and the fact that survival of elderly patients is by definition impaired due to advanced comorbidities and frailty, we suggest that age alone should not be a contra-indication for LVAD DT, which is consistent with European consensus recommendations. However, one should be aware of the increased risk of bleeding with a complicated clinical course post-LVAD implantation when selecting older patients. Future studies of anticoagulation regimens might also aid in better tailoring of these therapies in the elderly population, possibly allowing for less aggressive anticoagulation, particularly in the setting of a very low thrombosis rate in the newest generation HM3 LVAD.

Conflict of interest

N.J. reports personal fees and non-financial support from Servier, personal fees from Teva Pharmaceutical Industries, Krka, Sanofi Genzyme, Boehringer Ingelheim, Bayer, non-financial support from Abbott, outside the submitted work. A.C.P. reports personal fees from Novartis, Bayer, Vifor, Astra-Zeneca, outside the submitted work. I.P. reports grants and personal fees from Boehringer Ingelheim, personal fees from Teva Pharmaceutical Industries, Servier, Krka, Corvia, personal fees and non-financial support from Novartis, Pfizer, Bayer, Sandoz, Abbott, Sanofi Aventis, outside the submitted work. A.J.F. reports personal fees from Alnylam, Bayer, Boehringer Ingelheim, Fresenius, Imedos Systems, Medtronic, MSD, Mundipharma, Pierre Fabre, Pfizer, Roche, Vifor, Zoll, grants and personal fees from AstraZeneca, Novartis, outside the submitted work. L.H.L. reports personal fees from Merck, Bayer, Pharmacosmos, Abbott, Medscape, Myokardia, Sanofi, Lexicon, Radcliffe cardiology, grants and personal fees from Vifor-Fresenius, AstraZeneca, Boehringer Ingelheim, Novartis, grants from Boston Scientific, outside the submitted work. D. M. reports personal fees from Boehringer Ingelheim, Bayer, Pfizer, Novartis, AstraZeneca, Novo Nordisk, Teva, Servier, outside the submitted work. F.R. has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years (remuneration for the time spent in activities, such as participation as steering committee member of clinical trials and member of the Pfizer Research Award selection committee in Switzerland, were made directly to the University of Zurich). The Department of Cardiology (University Hospital of Zurich/University of Zurich) reports research-, educational- and/or travel grants from Abbott, Amgen, Astra Zeneca, Bayer, Berlin Heart, B. Braun, Biosense Webster, Biosensors Europe AG, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Bracco, Cardinal Health Switzerland, Corteria, Daiichi, Diatools AG, Edwards Lifesciences, Guidant Europe NV (BS), Hamilton Health Sciences, Kaneka Corporation, Kantar, Labormedizinisches Zentrum, Medtronic, MSD, Mundipharma Medical Company, Novartis, Novo Nordisk, Orion, Pfizer, Quintiles Switzerland Sarl, Sahajanand IN, Sanofi, Sarstedt AG, Servier, SIS Medical, SSS International Clinical Research, Terumo Deutschland, Trama Solutions, V-Wave, Vascular Medical, Vifor, Wissens Plus, ZOLL. The research and educational grants do not impact on F.R.'s personal remuneration. M.C. reports grants and personal fees from Novartis, grants from Abbott, personal fees from GE Healthcare, Bayer, Boehringer-Ingelheim, AstraZeneca, Teva Pharmaceutical Industries, Sanofi, LivaNova, non-financial support from Corvia, personal fees and non-financial support from Pfizer, outside the submitted work. J.J.B. reports personal fees from Abbott, outside the submitted work. All other authors have no conflict of interest to disclose.

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Supporting information

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

Figure S1. Haemocompatibility score according to age tertile.
Table S1. Classification of haemocompatibility score.
Table S2. Number (percentage) of missing data.

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Table S7. Sensitivity analysis: numbers and hazard ratios for the endpoints assessed in a forward stepwise multivariable Cox proportional hazards model with baseline covariates that differed significantly between the age groups.

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How does age affect the clinical course after left ventricular assist device implantation: results from the PCHF-VAD registry

Supplementary Tables

Contents

Table S1. Classification of haemocompatibility score

Intensity	Clinical components	Score
Tier I: *Mild*		
	≤2 gastrointestinal or other bleeding episodes (>30 days post implant) requiring hospitalization	1 point each
	Suspected pump thrombosis episode that requires hospitalization, successfully medically treated	
	Non-stroke related neurological events	
	Arterial thromboembolism not resulting in organ loss	
Tier II: *Moderate*		
	>2 gastrointestinal or other bleeding episodes (>30 days post implant) requiring hospitalization	2 points each
	Non-disabling stroke (hemorrhagic or ischemic)	
	Arterial thromboembolism resulting in organ loss	
Tier III A: *Moderately severe*		
	Pump malfunction due to pump thrombosis leading to reoperation for removal or replacement	3 points each
Tier III B: *Severe*		
	Disabling stroke	4 points each
	Death due to a haemocompatibility etiology or inconclusive (unknown or multiple causes)	

Table S2. Number (percentage) of missing data

Age	0 (0.0)
Men	0 (0.0)
Geographical area	0 (0.0)
Quartiles of date of LVAD implant	0 (0.0)
ICD status	10 (1.8)
CRT status	14 (2.5)
Heart rate	65 (11.6)
SBP	72 (12.8)
DBP	72 (12.8)
BMI	66 (11.7)
LVAD type	0 (0.0)
LVAD destination	29 (5.2)
INTERMACS class	15 (2.7)
Etiology of heart failure	0 (0.0)
Comorbidities	0 (0.0)
Prior cardiac surgery	0 (0.0)
Concomitant procedure with LVAD implant	0 (0.0)
Life support prior to LVAD implant	20 (3.6)
Medications	
Diuretic	63 (11.2)
Beta blocker	98 (17.4)
ACEi/ARB	88 (15.7)
MRA	125 (22.2)
Ivabradine	148 (26.3)
Inotrope	104 (18.5)
Laboratory values	
Creatinine	55 (9.8)
Bilirubin	115 (20.5)
Echocardiographic data	
LVIDd	76 (13.5)
LVEF	127 (22.6)
RVIDd	451 (80.2)
TAPSE	314 (55.9)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; CRT-P, CRT-pacing; CRT-D, CRT-defibrillator; DBP, diastolic blood pressure; ICD, implantable cardioverter defibrillator; INTERMACS, interagency registry for mechanically assisted circulatory support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension end-diastolic; MRA, mineralocorticoid receptor antagonist; RVIDd, right ventricular internal dimension end-diastolic; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion

Table S3. Causes of death

	Overall population (n=156)	**Patients aged < 50 years** (n=36)	**Patients aged 50-64 years** (n=91)	**Patients aged ≥65 years** (n=29)	**p-value**
Non-cardiovascular death	45 (30.2)	11 (32.4)	27 (31.0)	7 (25.0)	0.79
Cardiovascular death	104 (69.8)	23 (67.6)	60 (69.0)	21 (75.0)	
Heart failure death	40 (39.2)	11 (47.8)	25 (43.1)	4 (19.0)	
Sudden cardiac death	3 (2.9)	1 (4.3)	2 (3.4)	0 (0.0)	
Ischemic stroke	8 (7.8)	2 (8.7)	3 (5.2)	3 (14.3)	
Hemorrhagic stroke	25 (24.5)	3 (13.0)	18 (31.0)	4 (19.0)	0.075
Procedure related death	6 (5.9)	1 (4.3	2 (3.4)	3 (14.3)	
Device related death	12 (11.8)	1 (4.3)	7 (12.1)	4 (19.0)	
Other	8 (7.8)	4 (17.4)	1 (1.7)	3 (14.3)	

Table S4. Baseline characteristics according to age tertiles

	Overall population (n=562)	**Patients aged ≤50.0 years** (n=186)	**Patients aged 50.1-60.1 years** (n=188)	**Patients aged ≥60.2 years** (n=188)	**p-value**
Age, year	53±12	39±9	56±3	65±3	<0.001
Men	457 (81.3)	149 (80.1)	149 (79.3)	159 (84.6)	0.37
Geographical area					
North and West Europe (The Netherlands, Belgium, Germany, Sweden)	373 (66.4)	138 (74.2)	130 (69.1)	105 (55.9)	0.001
South and East Europe (Croatia, Poland, Lithuania, Italy, Spain, Greece)	189 (33.6)	48 (25.8)	58 (30.9)	83 (44.1)	
Quartiles of date of LVAD implant					
1st quartile (6 Dec 2006 - 29 Oct 2012)	143 (25.4)	65 (34.9)	43 (22.9)	35 (18.6)	0.001
2nd quartile (30 Oct 2012 - 4 Aug 2015)	143 (25.4)	46 (24.7)	50 (26.6)	47 (25.0)	
3rd quartile (5 Aug 2015 - 16 Apr 2017)	139 (24.7)	45 (24.2)	38 (20.2)	56 (29.8)	
4th quartile (17 Apr 2017 - 28 Jan 2020)	137(24.4)	30 (16.1)	57 (30.3)	50 (26.6)	
ICD status					
No ICD	294 (53.3)	108 (58.7)	101 (55.2)	85 (45.9)	0.14
Primary prevention	180 (32.6)	53 (28.8)	55 (30.1)	72 (38.9)	
Secondary prevention	78 (14.1)	23 (12.5)	27 (14.8)	28 (15.1)	
CRT status					
No CRT	406 (74.1)	146 (82.5)	135 (73.0)	125 (67.2)	0.015
CRT-P carrier	14 (2.6)	4 (2.3)	5 (2.7)	5 (2.7)	
CRT-D carrier	128 (23.4)	27 (15.3)	45 (24.3)	56 (30.1)	
Heart rate, b.p.m.	83.3±19.0	89.6±21.7	83.3±17.9	78.0±15.7	<0.001
SBP, mmHg	99.5±13.9	96.6±13.5	100.0±13.7	101.7±14.1	0.004
DBP, mmHg	64.2±10.9	64.3±11.0	65.0±11.5	63.3±10.0	0.32
BMI, kg/m2	25.9±4.6	25.1±5.2	26.4±4.3	26.0±4.4	0.031
NYHA class					
II	15 (3.0)	6 (3.8)	4 (2.3)	5 (2.8)	0.56
IIIa	152 (30.0)	48 (30.6)	46 (26.7)	58 (32.6)	
IIIb	134 (26.4)	34 (21.7)	50 (29.1)	50 (28.1)	
IV	206 (40.6)	69 (43.9)	72 (41.9)	65 (36.5)	
LVAD type					
HeartMate II	265 (47.2)	104 (55.9)	82 (43.6)	79 (42.0)	<0.001
HeartWare HVAD	119 (21.2)	36 (19.4)	47 (25.0)	36 (19.1)	
HeartMate 3	157 (27.9)	44 (23.7)	56 (29.8)	57 (30.3)	
Other	21 (3.7)	2 (1.1)	3 (1.6)	16 (8.5)	
LVAD destination					
BTT	356 (66.8)	140 (80.0)	130 (73.0)	86 (47.8)	<0.001
BTD	90 (16.9)	29 (16.6)	31 (17.4)	30 (16.7)	
DT	87 (16.3)	6 (3.4)	17 (9.6)	64 (35.6)	
INTERMACS profile					

1	90 (16.5)	41 (23.0)	37 (20.1)	12 (6.5)	
2	150 (27.4)	57 (32.0)	49 (26.6)	44 (23.8)	<0.001
3	176 (32.2)	53 (29.8)	53 (28.8)	70 (37.8)	
4-7	131 (23.9)	27 (15.2)	45 (24.5)	59 (31.9)	
Aetiology of heart failure					
Dilated cardiomyopathy	247 (44.0)	112 (60.2)	67 (35.6)	68 (36.2)	
Ischemic cardiomyopathy	256 (45.6)	44 (23.7)	112 (59.6)	100 (53.2)	<0.001
Other	59 (10.5)	30 (16.1)	9 (4.8)	20 (10.6)	
Comorbidities					
Arterial hypertension	128 (22.8)	22 (11.8)	43 (22.9)	63 (33.5)	<0.001
Diabetes mellitus	114 (20.3)	19 (10.2)	39 (20.7)	56 (29.8)	<0.001
Chronic kidney disease	137 (24.4)	20 (10.8)	53 (28.2)	64 (34.0)	<0.001
Coronary artery disease	139 (24.7)	26 (14.0)	56 (29.8)	57 (30.3)	<0.001
Prior MI	211 (37.5)	38 (20.4)	88 (46.8)	85 945.2)	<0.001
Prior coronary revascularization	170 (30.2)	29 (15.6)	73 (38.8)	68 (36.2)	<0.001
COPD	44 (7.8)	3 (1.6)	17 (9.0)	24 (12.8)	<0.001
Atrial fibrillation/flutter	173 (30.8)	41 (22.0)	52 (27.7)	80 (42.6)	<0.001
Ventricular arrhythmias	153 (27.2)	53 (28.5)	47 (25.0)	53 (28.2)	0.70
Cerebrovascular events	41 (7.3)	10 (5.4)	15 (8.0)	16 (8.5)	0.46
Significant ventricular arrhythmias prior to LVAD implant					
None	308 (65.5)	96 (70.1)	107 (65.2)	105 (62.1)	
1 episode	78 (16.6)	21 (15.3)	27 (16.5)	30 (17.8)	
2 episodes	34 (77.2)	10 (7.3)	12 (7.3)	12 (7.1)	0.51
3 episodes	18 (3.8)	3 (2.2)	4 (2.4)	11 (6.5)	
≥4 episodes	32 (6.8)	7 (5.1)	14 (8.5)	11 (6.5)	
Prior cardiac surgery	75 (13.3)	19 (10.2)	26 (13.8)	30 (16.0)	0.26
Concomitant procedure with LVAD implant	99 (17.6)	27 (14.5)	34 (18.1)	38 (20.2)	0.34
Life support prior to LVAD implant					
None	401 (74.0)	122 (68.9)	121 (66.9)	158 (85.9)	
ECMO	40 (7.4)	14 (7.9)	19 (10.5)	7 (3.8)	
Temporary LVAD	5 (0.9)	3 (1.7)	1 (06.)	1 (0.5)	
Temporary RVAD	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0.012
Temporary BiVAD	2 (0.4)	1 (0.6)	1 (0.6)	0 (0.0)	
IABP	73 (13.5)	27 (15.3)	30 (16.6)	16 (8.7)	
Other	20 (3.7)	9 (5.1)	9 (5.0)	2 (1.1)	
Medications					
Diuretic	454 (91.0)	132 (86.3)	151 (88.8)	171 (97.2)	0.001
Beta blocker	299 (64.4)	87 (63.5)	103 (64.0)	109 (65.7)	0.92
ACEi/ARB	213 (44.9)	68 (47.6)	77 (46.7)	68 (41.0)	0.44
MRA	315 (72.1)	80 (63.5)	109 (71.7)	126 (79.2)	0.013
Ivabradine	45 (10.9)	14 (11.6)	12 (8.2)	19 (12.9)	0.42
Inotrope	305 (66.6)	101 (73.2)	103 (66.9)	101 (60.8)	0.075
Vasopressor	53 (12.2)	18 (14.2)	26 (17.3)	9 (5.7)	0.006
Ultrafiltration	15 (3.5)	5 (4.0)	8 (5.3)	2 (1.3)	0.15
Mechanical ventilation					

None	403 (92.0)	115 (89.8)	134 (88.7)	154 (96.9)	
NIV/cPAP	5 (1.1)	1 (0.8)	3 (2.0)	1 (0.6)	0.062
Intubation	30 (6.8)	12 (9.4)	14 (9.3)	4 (2.5)	
Laboratory values					
Creatinine, umol/L	127.1±56.0	123.6±67.8	121.8±50.4	135.2±48.7	0.052
Bilirubin, umol/L	24.3±20.5	27.6±21.0	25.0±25.5	20.9±13.3	0.016
Echocardiographic data					
LVIDd, mm	70.7±12.5	69.3±12.4	71.4±13.5	71.5±11.6	0.21
LVEF, %	19.4±7.5	18.9±8.6	18.8±6.8	20.3±7.0	0.13

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BiVAD, biventricular assist device; BMI, body mass index; b.p.m, beats per minute; BTD, bridge to decision; BTT, bridge to transplant; COPD, chronic obstructive pulmonary disease; cPAP, continuous positive airway pressure; CRT, cardiac resynchronization therapy; CRT-P, CRT-pacing; CRT-D, CRT-defibrillator; DBP, diastolic blood pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; INTERMACS, interagency registry for mechanically assisted circulatory support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension end-diastolic; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NIV, non-invasive ventilation; NYHA, New-York Heart Association; RVAD, right ventricular assist device; SBP, systolic blood pressure

Table S5. Numbers of patients reaching the endpoints according to age tertiles

	Overall population (n=562)	**Patients aged < 50.0 years** (n=186)	**Patients aged 50.1-60.1 years** (n=188)	**Patients aged ≥60.2 years** (n=188)	**p-value**
All-cause mortality	156 (27.8)	37 (19.9)	53 (28.2)	66 (35.1)	0.004
Weaning from LVAD	9 (1.6)	7 (3.8)	1 (0.5)	1 (0.5)	0.016
Heart transplantation	218 (38.8)	97 (52.2)	73 (38.8)	48 (25.5)	<0.001
HF hospitalisation	108 (20.8)	35 (20.8)	40 (23.1)	33 (18.6)	0.59
Atrial fibrillation/ flutter	79 (14.8)	17 (9.9)	27 (15.1)	35 (19.2)	0.047
Ventricular arrhythmia	155 (28.4)	46 (26.1)	61 (33.2)	48 (25.8)	0.21
Device-related infections requiring AB	196 (36.1)	78 (44.8)	63 (34.8)	55 (29.3)	0.008
Pump thrombosis	41 (7.6)	11 (6.3)	18 (10.0)	12 (6.5)	0.34
Non-fatal thromboembolic events	56 (10.4)	13 (7.5)	18 (10.1)	25 (13.4)	0.18
Non-cerebral bleeding	118 (22.1)	30 (17.4)	34 (19.0)	54 (29.5)	0.011
Intracranial bleeding	46 (8.6)	10 (5.7)	18 (10.1)	18 (9.8)	0.26
RV-failure	116 (21.4)	33 (18.9)	43 (23.9)	40 (21.5)	0.51
LVAD exchange	22 (4.1)	12 (6.9)	8 (4.6)	2 (1.1)	0.02

AB, antibiotics; HF, heart failure; HR, hazard ratio; LVAD, left ventricular assist device; RV, right ventricle

Table S6. Sensitivity analysis: numbers and hazard ratios for the endpoints assessed in a forward stepwise multivariable Cox proportional hazards model

	Numbers of events					Hazard ratios	
	Overall population (n=562)	**Patients aged < 50 years** (n=184)	**Patients aged 50-64 years** (n=305)	**Patients aged ≥65 years** (n=73)	**p-value**	**HR (95% CI) Unadjusted (per 10 years)**	**HR (95% CI) Adjusted[a] (per 10 years)**
All-cause mortality	156 (27.8)	36 (19.6)	91 (29.8)	29 (39.7)	0.002	1.29 [1.11-1.50]	1.29 [1.11-1.51]
HF hospitalisation	108 (20.8)	33 (19.9)	63 (22.3)	12 (17.4)	0.63	1.07 [0.91-1.26]	1.04 [0.89-1.23]
RV-failure	116 (21.4)	33 (19.1)	73 (24.7)	10 (13.9)	0.089	1.05 [0.89-1.24]	1.01 [0.85-1.19]
Atrial fibrillation/ flutter	79 (14.8)	16 (9.4)	47 (16.1)	16 (22.5)	0.022	1.38 [1.11-1.73]	1.39 [1.11-1.76]
Ventricular arrhythmia	155 (28.4)	45 (25.9)	95 (31.8)	15 (20.5)	0.11	1.03 [0.90-1.19]	1.03 [0.89-1.18]
LVAD-related infections requiring AB	188 (34.6)	76 (44.2)	96 (32.2)	16 (21.9)	0.002	0.86 [0.77-0.97]	0.86 [0.76-0.97]
Non-intracranial bleeding	118 (22.1)	29 (17.1)	68 (23.2)	21 (29.6)	0.081	1.30 [1.09-1.53]	1.30 [1.09-1.54]
Intracranial bleeding	46 (8.6)	9 (5.2)	31 (10.5)	6 (8.5)	0.14	1.46 [1.08-1.96]	1.42 [1.05-1.92]
Pump thrombosis	41 (7.6)	11 (6.4)	25 (8.5)	5 (7.0)	0.70	1.07 [0.82-1.40]	1.04 [0.80-1.36]
Non-fatal thromboembolic events	56 (10.4)	13 (7.6)	33 (11.2)	10 (13.9)	0.27	1.19 [0.94-1.51]	1.20 [0.93-1.53]
Weaning from LVAD	9 (1.6)	7 (3.8)	2 (0.7)	0 (0.0)	0.014	0.50 [0.30-0.81]	0.51 [0.33-0.93]
LVAD exchange	22 (4.1)	12 (7.0)	10 (3.4)	0 (0.0)	0.03	0.70 [0.51-0.95]	0.75 [0.53-1.05]
Heart transplantation	218 (38.8)	97 (52.7)	115 (37.7)	6 (8.2)	<0.001	0.83 [0.75-0.93]	sss

[a]Adjusted for, mechanical circulatory support prior to LVAD surgery, LVAD surgery as re-do surgery, pre-LVAD vasopressor use and quartiles of date of LVAD implantation

AB, antibiotics; CI, confidence interval; HF, heart failure; HR, hazard ratio; LVAD, left ventricular assist device; RV, right ventricle

Table S7. Sensitivity analysis: numbers and hazard ratios for the endpoints assessed in a forward stepwise multivariable Cox proportional hazards model **with baseline covariates that differed significantly between the age groups**

	Numbers of events					**Hazard ratios**	
	Overall population (n=562)	**Patients aged < 50 years** (n=184)	**Patients aged 50-64 years** (n=305)	**Patients aged ≥65 years** (n=73)	**p-value**	**HR (95% CI) Unadjusted (per 10 years)**	**HR (95% CI) Adjusted[a] (per 10 years)**
All-cause mortality	156 (27.8)	36 (19.6)	91 (29.8)	29 (39.7)	0.002	1.29 [1.11-1.50]	1.32 [1.13-1.53]
HF hospitalisation	108 (20.8)	33 (19.9)	63 (22.3)	12 (17.4)	0.63	1.07 [0.91-1.26]	1.05 [0.89-1.24]
RV-failure	116 (21.4)	33 (19.1)	73 (24.7)	10 (13.9)	0.089	1.05 [0.89-1.24]	1.01 [0.86-1.19]
Atrial fibrillation/ flutter	79 (14.8)	16 (9.4)	47 (16.1)	16 (22.5)	0.022	1.38 [1.11-1.73]	1.37 [1.09-1.72]
Ventricular arrhythmia	155 (28.4)	45 (25.9)	95 (31.8)	15 (20.5)	0.11	1.03 [0.90-1.19]	1.01 [0.88-1.17]
LVAD-related infections requiring AB	188 (34.6)	76 (44.2)	96 (32.2)	16 (21.9)	0.002	0.86 [0.77-0.97]	0.88 [0.78-0.99]
Non-intracranial bleeding	118 (22.1)	29 (17.1)	68 (23.2)	21 (29.6)	0.081	1.30 [1.09-1.53]	1.30 [1.09-1.54]
Intracranial bleeding	46 (8.6)	9 (5.2)	31 (10.5)	6 (8.5)	0.14	1.46 [1.08-1.96]	1.45 [1.07-1.95]
Pump thrombosis	41 (7.6)	11 (6.4)	25 (8.5)	5 (7.0)	0.70	1.07 [0.82-1.40]	1.1 [0.84-1.43]
Non-fatal thromboembolic events	56 (10.4)	13 (7.6)	33 (11.2)	10 (13.9)	0.27	1.19 [0.94-1.51]	1.18 [0.93-1.50]
Weaning from LVAD	9 (1.6)	7 (3.8)	2 (0.7)	0 (0.0)	0.014	0.50 [0.30-0.81]	0.51 [0.31-0.84]
LVAD exchange	22 (4.1)	12 (7.0)	10 (3.4)	0 (0.0)	0.03	0.70 [0.51-0.95]	0.73 [0.53-1.00]
Heart transplantation	218 (38.8)	97 (52.7)	115 (37.7)	6 (8.2)	<0.001	0.83 [0.75-0.93]	0.87 [0.78-0.96]

[a]Adjusted for quartiles of date of LVAD implantation

AB, antibiotics; CI, confidence interval; HF, heart failure; HR, hazard ratio; LVAD, left ventricular assist device; RV, right ventricle

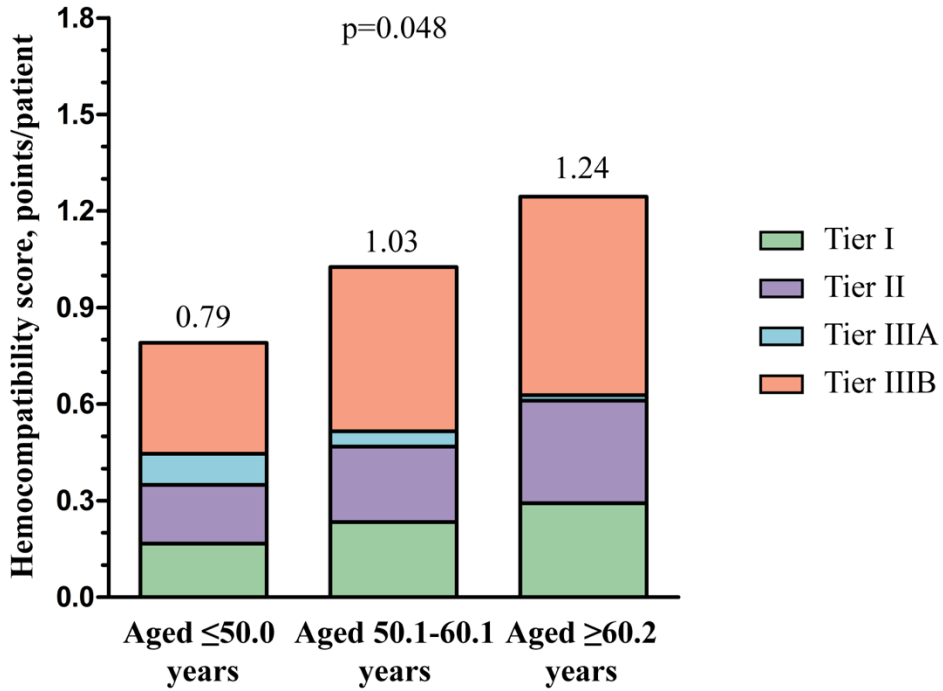

Figure S1. Haemocompatibility score according to age tertile.

PUBLICATION 5

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The candidate, Nina Jakuš, contributed to this publication by:

- Having a substantial contribution to the acquisition, analysis, and interpretation of data for the work; AND
- She critically revised the manuscript for important intellectual content; AND
- She gave final approval of the version to be published; AND
- Agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contribution of other co-authors:

- Having a substantial contribution to the design of the manuscript, acquisition, analysis, and interpretation of data for the work; AND
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ORIGINAL ARTICLE

Impact of progressive aortic regurgitation on outcomes after left ventricular assist device implantation

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Abstract
Aortic regurgitation (AR) following continuous flow left ventricular assist device implantation (cf-LVAD) may adversely impact outcomes. We aimed to assess the incidence and impact of progressive AR after cf-LVAD on prognosis, biomarkers, functional capacity and echocardiographic findings. In an analysis of the PCHF-VAD database encompassing 12 European heart failure centers, patients were dichotomized according to the progression of AR following LVAD implantation. Patients with de-novo AR or AR progression (AR_1) were compared to patients without worsening AR (AR_0). Among 396 patients (mean age 53 ± 12 years, 82% male), 153 (39%) experienced progression of AR over a median of 1.4 years on LVAD support. Before LVAD implantation, AR_1 patients were less frequently diabetic, had lower body mass indices and higher baseline NT-proBNP values. Progressive AR did not adversely impact mortality (26% in both groups, HR 0.91 [95% CI 0.61–1.36]; $P = 0.65$). No intergroup variability was observed in NT-proBNP values and 6-minute walk test results at index hospitalization discharge and at 6-month follow-up. However, AR_1 patients were more likely to remain in NYHA class III and had worse right ventricular function at 6-month follow-up. Lack of aortic valve opening was related to de-novo or worsening AR ($P < 0.001$), irrespective of systolic blood pressure ($P = 0.67$). Patients commonly experience de-novo or worsening AR when exposed to continuous flow of contemporary LVADs. While reducing effective forward flow, worsening AR did not influence survival. However, less complete functional recovery and worse RV performance among AR_1 patients were observed. Lack of aortic valve opening was associated with progressive AR.

Keywords Aortic regurgitation · Left ventricular assist device · Outcome

Introduction

The contemporary burden of advanced heart failure is extensive and is projected to escalate further [1]. Continuous-flow left ventricular assist devices (cf-LVAD) have fundamentally changed the management and prognosis of this syndrome. Notwithstanding their benefits, cf-LVADs are associated with complications arising from either the interaction between internal device components with blood elements, or rheological properties of non-pulsatile flow [2]. Aortic regurgitation (AR) develops and progresses insidiously in approximately a third of cf-LVAD recipients [3–5]. The pathological correlates of non-pulsatile flow at the level of the aortic valve (AoV) are commissural fusion and leaflet thinning [6]. These changes are accentuated in the absence of AoV opening and the ensuing continuous exposure to an increased transvalvular gradient [7]. The net result of alterations in AoV morphology is progressive valvular dysfunction [6]. Conventional semiquantitative echocardiography underestimates the severity of AR, as it does not take into account its pancyclic nature. Ostensibly small regurgitant orifices may therefore translate into significant AR, and potentially induce clinically relevant hemodynamic sequelae [4]. The importance of AR induced reduction of forward flow is proportional to the duration of support [3]. Other predictors of de-novo AR include absence of AoV opening,

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older age, female gender, systemic hypertension and suboptimal outflow graft anastomosis angles [3, 8]. The impact of de-novo AR on long-term LVAD survival is unknown, and there is an acute need for more data on the subject. An increase in LVAD output may counteract the adverse effects of inefficient flow, but this may come at the expense of reduced durability of older generation devices [9]. The clinical impact of AR after cf-LVAD support is subject to debate and remains a moving target, as does the appropriate management. The aims of the present study were to identify the mortality burden of progressive AR and its impact on the clinical and functional status in patients receiving cf-LVADs.

Patients and methods

Data acquisition and eligibility criteria

We reviewed the PCHF-VAD registry which accumulated data from 12 European heart failure centers and investigators of the Postgraduate Course in Heart Failure (PCHF) of the Heart Failure Association of the European Society of Cardiology and the European Heart Academy registry [10]. Institutional review boards of participating centers approved the study, with a waiver of informed consent in some instances. Inclusion criteria were met by patients with first-time cf-LVAD implantation in whom the temporal dynamics of echocardiographic AR descriptors were available for review. Exclusion criteria were prior or concomitant AoV surgery and lack of paired echocardiographic data. Aortic regurgitation was quantized into none, mild, moderate and severe per center-specific protocols, predominantly assessed visually or by vena contracta [11]. Patients were dichotomized into two groups based on echocardiographic evidence of AR progression during the course of follow-up. Patients in group AR_1 either developed de-novo AR or had evidence of AR progression by at least one grade. Patients in whom AoV competence was preserved were assigned to the AR_0 group. Data were recorded using REDCap (Research Electronic Data Capture) capture tools, hosted at the University of Zagreb School of Medicine [12]. Ethical standards were adhered to while conducting this research.

Outcome definitions

The main outcome was all-cause mortality. The secondary outcomes were cardiovascular death, heart failure hospitalization, right ventricular failure, life-threatening ventricular arrhythmias, intracranial and non-cerebral bleeding events after LVAD implantation [10]. We performed an intergroup comparison of N-terminal fragment of B-type natriuretic peptide (NT-proBNP) at three time points: baseline, discharge from index hospitalization and at 6 months post VAD implantation. Follow up assessments of functional, hemodynamic, echocardiographic and electrocardiographic data were performed. Where available, additional information on the functional status was provided by an intergroup comparison of 6-minute walk tests (6MWT) and NYHA class.

Statistical analysis

Continuous data are presented as means with standard deviations or medians with interquartile ranges for non-normally distributed variables. Categorical variables are presented as absolute numbers with percentages. Measures of association were derived from Fisher's exact or chi square tests. The Shapiro–Wilk test was used to determine whether a continuous outcome could be modeled by a normal distribution. ANOVA was used for analyzing normally distributed variables, while the Kruskal–Wallis or Mann–Whitney U tests were used for nonparametric variables.

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, weaning from LVAD, heart transplant, or death. Time-to-event estimates were calculated using the Kaplan–Meier method. Probability values were obtained from the log-rank test. The hazard ratios (HR) were estimated using the Cox proportional hazards model with the group of patients with no progression of aortic regurgitation 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, was used to test the association of progression of AR with 6 baseline covariates that significantly differed between the two patient groups at baseline (LVAD type, LVAD intention, diabetes mellitus, BMI, diastolic pulmonary artery pressure, and NT-proBNP value).

In patients in whom BNP values, but not NT-proBNP values, were available for review we used a previously validated formula to convert the former into the latter [13]. This method was used for 49 NT-proBNP datapoints pre-LVAD implantation, 27 datapoints at index hospitalization discharge and 26 NT-proBNP datapoints at 6-month follow-up. Logarithmic transformation was used to address the skewness of data. A two-tailed P value <0.05 was considered significant for all statistics. The data were processed using the Stata version 14 (StataCorp, College Station, TX, USA).

Results

Study population

Data from 583 patients were assessed for eligibility. Of these, 396 fulfilled the inclusion criteria. The study flow

diagram is detailed in Fig. 1. Baseline demographic and clinical profiles are shown in Table 1. In brief, patients in group AR_1 were comparable to group AR_0 with respect to age, gender, INTERMACS profile, prior stroke, renal function or atrial fibrillation. Pre-LVAD temporary mechanical circulatory support use did not differ between the groups. A lower body mass index (24 [22–28] vs. 26 [23–29], $P<0.01$), lower prevalence of diabetes (14% vs. 26%, $P=0.01$), and higher NT-proBNP (5181 [3004, 10098] vs. 3820 [2345, 7440] pg/ml, $P<0.01$) were observed in group AR_1. Patients in the AR_1 group were more likely to have received a HeartMate II device and less likely to have received a HeartWare device; they were more likely to have been bridged to transplantation than the control group (Table 1).

Primary outcome

The median time on LVAD support was 1.4 [0.8, 2.6] years. All-cause death occurred in 62 (26%) patients in the AR_0 group and in 39 (26%) patients in the AR_1 group (Table 2). The unadjusted HR demonstrated a nominally, but statistically non-significant, lower risk of all-cause mortality implantation in the AR_1 group (HR 0.91; 95% CI 0.61–1.36, $P=0.65$) (Fig. 2). Using stepwise regression, LVAD type was established as an independent predictor of all-cause death. After

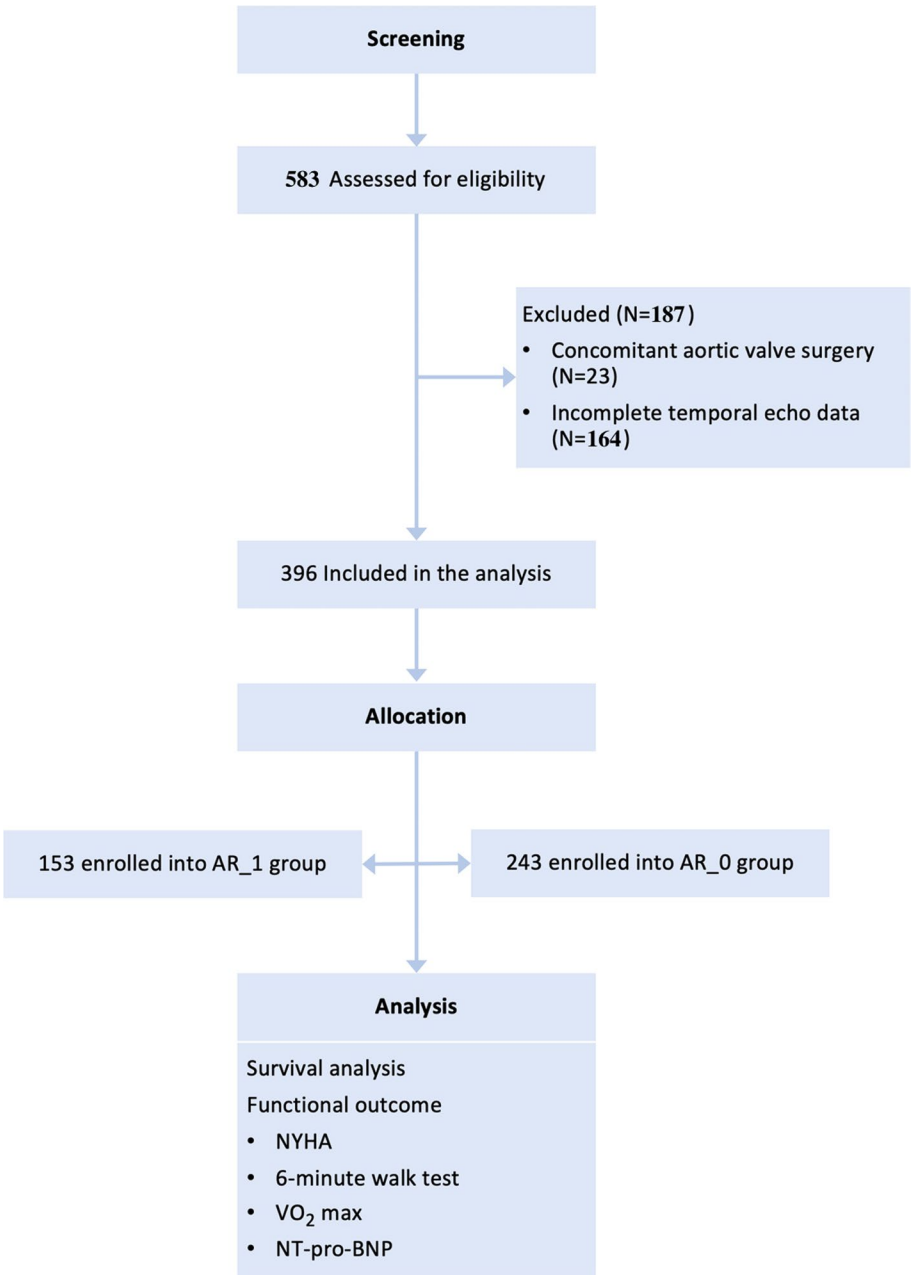

Fig. 1 Study flowchart summarizing patient eligibility, allocation and analysis. *RVAD* right ventricular assist device, *BiVAD* biventricular assist device

Table 1 Baseline demographic and clinical profiles of the study population

	Overall ($n=396$)	AR_0 group ($n=243$)	AR_1 group ($n=153$)	*P*-value
Age	53 ± 12	53 ± 12	54 ± 11	0.41
Male gender, *n* (%)	325(82)	203(84)	122(80)	0.34
Etiology of heart failure, *n* (%)				0.26
Dilated cardiomyopathy	184(47)	106(44)	78(51)	
Ischemic cardiomyopathy	181(46)	115(47)	66(43)	
Other	31(8)	22(9)	9(6)	
Arterial hypertension, *n* (%)	93(24)	58(24)	35(23)	0.82
Diabetes mellitus, *n* (%)	85(22)	63(26)	22(14)	0.01
Chronic kidney disease, *n* (%)	97(25)	59(24)	38(25)	0.90
Coronary artery disease, *n* (%)	100(25)	65(27)	35(23)	0.39
Chronic obstructive pulmonary disease, *n* (%)	36(9)	25(10)	11(7)	0.30
Atrial fibrillation/flutter, *n* (%)	122(31)	77(32)	45(29)	0.63
Ventricular arrhythmia, *n* (%)	102(26)	60(25)	42(28)	0.54
Cerebrovascular event, *n* (%)	31(8)	16(7)	15(10)	0.25
LVAD type, *n* (%)				0.04
HeartMate 3	124(31)	74(31)	50(33)	
HeartMate II	175(44)	98(40)	77(50)	
HeartWare	83(21)	62(26)	21(14)	
Other	14(4)	9(4)	5(3)	
LVAD intention, *n* (%)				0.02
Bridge to transplantation	254(68)	143(62)	111(76)	
Bridge to decision	56(15)	40(17)	16(11)	
Destination therapy	66(18)	47(20)	19(13)	
INTERMACS class, *n* (%)				0.63
Class 1	49(13)	33(14)	16(11)	
Class 2	102(26)	62(26)	40(27)	
Class 3	140(36)	82(34)	58(39)	
Class 4–7	100(26)	65(27)	35(24)	
Life support prior to LVAD implant, *n* (%)				0.17
None	301(78)	187(80)	114(76)	
ECMO	21(6)	15(6)	6(4)	
IABP	41(11)	19(8)	22(15)	
Temporary BiVAD	1(0.3)	1(0.4)	0(0)	
Temporary LVAD	3(1)	3(1)	0(0)	
Other	17(4)	9(4)	8(5)	
Prior cardiac surgery, *n* (%)	39(10)	22(9)	17(11)	0.50
Concomitant procedure with LVAD implant, *n* (%)	54(14)	38(16)	16(11)	0.14
Systolic blood pressure, mmHg	99 ± 14	99 ± 14	100 ± 14	0.64
Diastolic blood pressure, mmHg	64 ± 11	64 ± 10	65 ± 11	0.76
Heart rate, bpm	84 ± 19	84 ± 19	83 ± 21	0.58
Body mass index, kg/m2	26 [23–29]	26 [23–29]	24 [22–28]	< 0.01
NYHA class				0.52
II	11(3)	8(3)	3(2)	
III	226(58)	142(59)	84(56)	
IV	152(39)	89(37)	63(42)	
Creatinine, umol/L	116 [92–150]	112 [90–145]	122 [97–152]	0.55
Bilirubin, umol/L	24 ± 21	24 ± 22	23 ± 18	0.63
LVIDD, mm	71 [63–79]	71 [64–78]	72 [63–80]	0.28
LVEF, %	19 ± 7	19 ± 7	19 ± 7	0.82

Table 1 (continued)

	Overall ($n=396$)	AR_0 group ($n=243$)	AR_1 group ($n=153$)	*P*-value
Cardiac output, L/min	3.8 [3.1–4.5]	3.8 [3.1–4.5]	3.8 [3.0–4.3]	0.26
Prior concomitant therapy, *n* (%)				
Diuretic	350(92)	211(90)	139(94)	0.20
Beta blocker	240(67)	144(67)	96(67)	0.90
ACEi/ARB	163(45)	105(48)	58(41)	0.16
MRA	250(75)	149(75)	101(75)	0.86
ARNI	12(4)	7(4)	5(4)	0.90
Calcium channel blocker	1(0.3)	1(0.5)	0(0)	0.41
Ivabradine	37(12)	25(13)	12(10)	0.35
Inotrope	231(66)	137(63)	94(70)	0.23
Ultrafiltration	9(3)	7(4)	2(2)	0.26
NT-proBNP, pg/mL	4354 [2622, 8705]	3820 [2345, 7440]	5181 [3004, 10098]	< 0.01

LVAD Left ventricular assist device, *INTERMACS* Interagency registry for mechanically assisted circulatory support, *ECMO* Extracorporeal membrane oxygenation, I*ABP* Intra-aortic balloon pump, *NYHA* New York Heart Association, *LVIDD* Left ventricular internal diastolic diameter, *PA* Pulmonary artery, *ACEi/ARB* Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, *MRA* Mineralocorticoid receptor antagonists, *ARNI* Angiotensin receptor-neprilysin inhibitor, *NIV/cPAP* Non-Invasive ventilation/continuous positive airway pressure, *NT-proBNP* N-Terminal Pro B-Type Natriuretic Peptide

adjustment for this variable, AR progression or de-novo AR following LVAD was not significantly related to all-cause death (HR 0.95, 95% CI 0.63-1.43), *P*=0.82) (Table 3).

Secondary outcomes

Twenty-one patients in the AR_1 group (14%) and 36 patients in the AR_0 group (15%) suffered a cardiovascular death (HR 0.85; 95% CI 0.49-1.45, *P*=0.55). The incidence rates for cardiovascular mortality, heart failure hospitalization, right ventricular failure, ventricular arrhythmias, and bleeding events are presented in Table 2. Briefly, intergroup variations in non-fatal adverse events among patients with or without AR progression did not meet the prespecified thresholds of statistical significance.

Table 2 Incidence rates and hazard ratios for the primary and secondary endpoints by aortic regurgitation progression following LVAD implantation

	AR_0 group ($N=243$) Incidence Rate	AR_1 group ($N=153$) Incidence Rate	Hazard Ratio (95% CI), *P*-value	
			Unadjusted	Adjusted*
All-cause mortality (n of events = 101)	14.9 (11.6–19.1)	13.5 (9.9–18.5)	0.91 (0.61–1.36) $P=0.65$	0.95 (0.63–1.43) $P=0.82$
Cardiovascular mortality (n of events = 57)	8.7 (6.2–12.0)	7.3 (4.8–11.2)	0.85 (0.49–1.45) $P=0.55$	0.96 (0.55–1.67) $P=0.89$
Heart failure hospitalization (n of events = 91)	17.0 (13.2–21.9)	12.5 (8.8–17.8)	0.77 (0.50–1.18) $P=0.23$	0.88 (0.56–1.38) $P=0.58$
Right ventricular failure (n of events = 45)	8.1 (5.7–11.6)	6.1 (3.7–10.1)	0.78 (0.42–1.45) $P=0.43$	0.80 (0.43–1.51) $P=0.50$
Ventricular arrhythmias post-LVAD (n of events = 118)	19.8 (15.5–25.3)	26.1 (20.0–34.2)	1.35 (0.93–1.94) $P=0.11$	1.37 (0.94–1.98) $P=0.10$
Intracranial bleeding (n of events = 31)	3.9 (2.4–6.4)	5.3 (3.2–8.8)	1.38 (0.68–2.79) $P=0.37$	1.61 (0.78–3.32) $P=0.20$
Other bleeding (n of events = 81)	13.5 (10.2–17.9)	13.5 (9.5–19.1)	1.01 (0.65–1-58) $P=0.97$	1.03 (0.65–1.61) $P=0.91$

The incidence rates are presented as number of events per 100-patient years (95% confidence interval)

LVAD Left ventricular assist device

*Adjusted for LVAD type

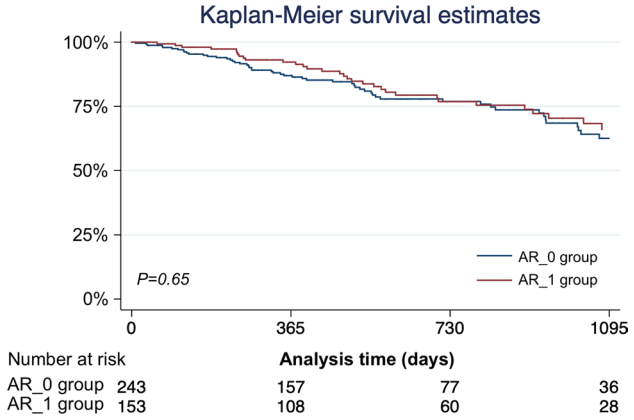

Fig. 2 Kaplan–Meier plot of time to all-cause survival, according to aortic regurgitation progression following left ventricular assist device LVAD implantation. The analysis begins at the time of LVAD implantation. *AR_0* no AR progression, *AR_1* de-novo AR or AR progression. *HR* hazard ratio

Table 3 Multivariate Cox regression model of risk factors for all-cause death following LVAD implantation

Variable	HR	95% CI	P value
Aortic regurgitation progression	0.95	0.63–1.43	0.82
LVAD type			0.03
Heart Mate 3	Referent		
Heart Mate II	2.04	1.14–3.64	
Heart Ware HVAD	2.65	1.40–5.00	
Other	1.62	0.54–4.90	

LVAD Left Ventricular Assist Device

Follow-up assessments-NT-proBNP values and metrics of functional outcome

There were no differences in the NT-proBNP values, NYHA class or 6MWT (Table 4) at the time of index hospitalization discharge between the AR_0 and AR_1 groups. Conversely, 15% of the patients in the AR_1 group were found to be in NYHA class I in comparison to 24% of patients in the AR_0 group, which was mirrored by a lower proportion of patients in NYHA class III among the AR_0 cohort than in the AR_1 cohort (10% vs. 18%, respectively, P=0.03). Variables associated with NYHA class at 6-month follow-up on univariate analysis were then entered into a multiple linear regression model. These included AR progression, age, hypertension and chronic obstructive pulmonary disease. Progression of AR was significantly associated with NYHA class at later follow-up in the multiple regression analysis (P=0.03), as was the presence of chronic obstructive pulmonary disease (P=0.01).

Table 4 Intergroup comparisons of follow-up assessments

	AR_0 group (N=243)	AR_1 group (N=153)	P
Assessments at index hospitalization discharge			
NYHA, *n* (%)			0.58
I	7(3)	1(1)	
II	144(64)	92(65)	
III	69(31)	49(35)	
IV	4(2)	0(0)	
LVIDD, mm	61 ± 13	61 ± 13	0.79
LVIDS, mm	53 ± 13	54 ± 13	0.83
TAPSE	12 [10, 16]	12 [10, 16]	1.0
6-min walk test, m[a]	383 ± 136	354 ± 132	0.39
NT-pro-BNP, pg/ml[b]	1962 [1302, 3272]	2275 [1300, 3662]	0.41
Assessments at 6-month follow-up			
NYHA, *n* (%)			0.03
I	49(24)	21(15)	
II	129(64)	91(66)	
III	21(10)	24(18)	
IV	4(2)	1(1)	
LVIDD, mm	63 ± 13	65 ± 12	0.26
LVIDS, mm	54 ± 14	58 ± 14	0.06
TAPSE	14 [12, 17]	10 [9, 14]	< 0.01
6-min walk test, m[d]	487 ± 158	415 ± 132	0.12
NT-pro-BNP, pg/ml[e]	1357 [770, 2207]	1483 [939, 2529]	0.30

NYHA New York Heart Association, NT-proBNP *N-Terminal pro B-type natriuretic peptide*; *LVIDD* Left ventricular internal diastolic diameter, *LVIDS* Left ventricular internal diameter end systole, *TAPSE* Tricuspid annular plane systolic excursion

[a]N = 71

[b]N = 208

[d]N = 49

[e]N = 243

Hemodynamic and echocardiographic data

Postoperative mean arterial blood pressure data were similar between the groups at 6-month follow-up. Patients in the AR_1 group at 6-month follow-up were significantly more likely to have their AoV permanently closed on echocardiographic evaluation (55% vs. 38%, P<0.01, Fig. 3). In multivariate regression analysis, lack of AoV opening at 6-month follow up was related to the occurrence of worsening AR (those with AR_1 had less frequent AoV opening, P<0.001), irrespective of SBP value (P=0.67). Patients with progressive AR had less efficient LV unloading at 6-month follow-up, albeit not reaching statistical significance (Table 4). RV

function, quantified with tricuspid annular plane systolic excursion, deteriorated in the AR_1 group at 6-month follow-up (Table 4).

In a multivariate logistic regression model, an increase in log-transformed NT-proBNP increased the odds of developing de-novo or worsening AR (OR 1.50, 95% CI 1.12-2.02, *P*=0.008), while the presence of diabetes at baseline and LVAD as bridge to decision (vs. LVAD as bridge to transplantation) were both associated with lower odds (OR 0.40, 95% CI 0.21-0.78, *P*=0.007 and OR 0.39, 95% CI 0.17-0.88, P=0.023).

Discussion

We have shown that patients commonly experience worsening incompetence of their native AoV when exposed to the continuous flow of contemporary LVADs. Previous reports placed the incidence of significant AR at 25–34% of LVAD patients, which compares well with the 39% incidence among our 396 patients from 12 European centers [3–5]. Notwithstanding the reduced effective forward flow by recycling the regurgitant volume, worsening or de-novo AR was not significantly associated with survival in our study. We did, however, demonstrate an adverse association of progressive AR with NYHA status at 6-month follow-up. This finding was not corroborated by other measures of functional status. A marginal decline in the capacity of LVADs to decompress the LV was seen in patients with progressive AR. Incomplete LV unloading has been shown to increase RV afterload, and subsequently, impair RV function [14]. Our data substantiates this link, as patients with progression of AR also had a reduction in RV function. Less efficient LV unloading, coupled with the fact that the AoV was persistently closed in 55% of patients in the investigated group (AR_1), is likely to have a cumulative impact with increasing duration of LVAD support. Our survival analysis captured the entire follow-up period, but the functional outcomes were accumulated only for the first 6 postoperative months. The impact of AR progression on functional outcomes beyond that period is not reflected by the present data and may therefore underestimate long-term outcomes. The mechanism of AR in cf-LVAD recipients is multifactorial. Size mismatches between the outflow graft and native aorta result in high velocity jets that create mosaics of high pressure and shear stress [15]. These flow patterns manifest as chaotic eddy currents which may lead to aortic root dilatation and shortening of AoV coaptation lengths [15, 16]. Greater angles between the outflow graft and the aorta have also been associated with greater regurgitant volumes [17]. We have established an association between non-opening of the AoV and the development of de-novo or worsening AR. Attempts at optimizing cf-LVAD speeds have previously been proposed to allow for intermittent AoV opening [3, 16]. There is, however, no consensus on the optimal line of management of de-novo AR among LVAD recipients. Jorde et al. proposed a staged approach to symptomatic AR which initially included optimization of LVAD parameters under echocardiographic guidance, followed by hemodynamic studies in the absence of clinical improvement [18]. Interventional approaches were reserved for symptomatic patients in whom less invasive management failed to improve symptoms. Aortic regurgitation in a continuous flow system is mostly pancyclic, which makes parallels with diastolic AR seen in natural pulsatile flow patterns inherently flawed. The definition of AR in most published studies on patients with cf-LVADs is not based on quantifiable parameters and therefore lacks both uniformity and reproducibility [3]. Visual estimation of AR severity is limited in continuous flow settings, as well as in eccentric jets, which are both seen in LVAD recipients [5]. Recently, a novel Doppler echocardiographic approach obtained at the LVAD outflow cannula has been suggested for the quantification of AR in LVAD carriers [5, 19]. The authors demonstrated a better correlation with measured cardiac loading and have further shown that conventional visual estimation may underestimate AR severity. Imamura et al. have shown that 98% of patients in their series were initially found to have mild or less AR on visual estimation. This was contrasted by the results of their reevaluation based on novel echocardiographic parameters for quantifying AR, which identified 34% of patients as having at least moderate AR [5]. After reclassification, survival free from hemocompatibility events was significantly lower in those with significant AR which was also an independent predictor of death or hemocompatibility-related adverse events [5]. We grouped all patients with worsening aortic regurgitation into the AR_1 group, irrespective of the absolute degrees

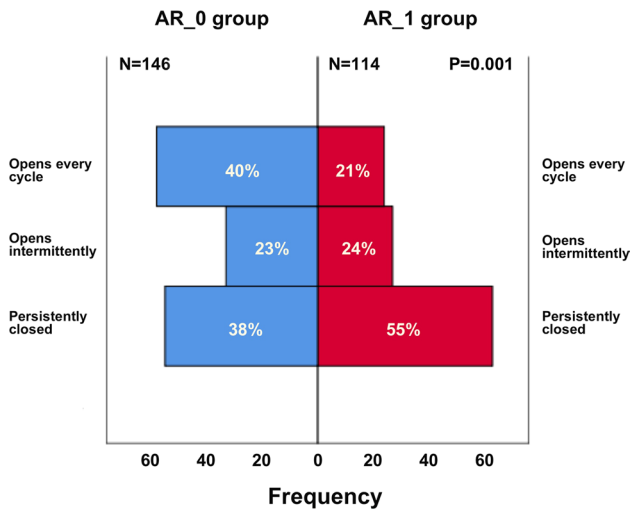

Fig. 3 Intergroup comparison of aortic valve mobility status. *AR_0* no progression of aortic regurgitation (AR), *AR_1* de-novo AR or AR progression

of AR. Only 15 patients in the entire cohort had moderate AR by conventional semiquantitative evaluation. We believe that the paucity of patients quantified as having significant AR may be a failure of definition rather than a reflection of the rarity of these observations. The current practice of quantifying AR which equalizes hemodynamic conditions of pulsatile systems with continuous flow systems may be erroneous. This may explain why, in our study, more patients with AR progression were found to be in NYHA III class and had worsening RV function. The current strategy of AR quantification may be especially unsuitable for LVAD patients with permanently closed aortic valves, in whom AR is completely pancyclic. We feel that our study may provide an additional impetus for promoting management algorithms that allow for intermittent aortic valve opening in patients with continuous flow systems. Data on RV function in LVAD recipients in relation to AR progression has thus far been scarce. Our observations to that effect should be explored in future studies in more detail.

Limitations

Our retrospective and observational design is limited by the comprehensiveness of data input. Furthermore, evaluation of AoV insufficiency was based on semiquantitative data from transthoracic echocardiograms, which leads to underestimation of the true AR burden with cf-LVADs. Finally, associations observed in our study may be subject to unmeasured confounding.

Conclusion

We found that the competence of the AoV in cf-LVAD recipients deteriorates in a significant proportion of patients. While this observation did not translate into worse survival in this large cohort of patients, we have shown that it results in a discrete negative effect on midterm functional outcomes of device therapy. Other manifestations of AR progression were reduction in longitudinal RV function and less complete LV unloading. A clear association between persistently closed AoVs and progressive AR was also confirmed in our LVAD recipients.

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Declarations

Conflict of interest Dr. Gasparovic has nothing to disclose. Dr. Jakus reports non-financial support from Servier, personal fees from Teva Pharmaceutical Industries, personal fees from Krka, non-financial support from Abbott, personal fees from Sanofi Genzyme, outside the submitted work. Dr. Brugts reports grants and personal fees from Abbott, outside the submitted work. Dr. Pouleur reports Advisory Board/ Speaker Fee for Astra-Zeneca, MSD, Bayer, Novartis, Actelion, Pfizer. Dr. Timmermans has nothing to disclose. Dr. Rubiś has nothing to disclose. Dr. Gaizauskas has nothing to disclose. Dr. Van Craenenbroeck has nothing to disclose. Dr. Barge-Caballero reports grants from ABBOT, personal fees from ABBOT, other from MEDTRONIC, outside the submitted work. Dr. Grundmann has nothing to disclose. Dr. Paolillo has nothing to disclose. Dr. D'Amario has nothing to disclose. Dr. Braun has nothing to disclose. Dr. Meyns has nothing to disclose. Dr. Droogne has nothing to disclose. Dr. Wierzbicki has nothing to disclose. Dr. Holcman has nothing to disclose. Dr. Planinc reports personal fees from Boehringer Ingelheim, personal fees from Teva Pharmaceutical Industries, personal fees and non-financial support from Novartis, personal fees and non-financial support from Pfizer, personal fees from Servier, personal fees and non-financial support from Krka, personal fees and non-financial support from Bayer, personal fees from Sandoz, personal fees from Corvia, personal fees and non-financial support from Abbott, non-financial support from Sanofi Aventis, outside the submitted work. Dr. Lovric reports personal fees and non-financial support from Astra Zeneca, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Novartis, personal fees from Pliva, personal fees from Servier, personal fees from Sandoz, personal fees from Krka Pharma, personal fees and non-financial support from PharmaS, non-financial support from Pfizer, personal fees from Bayer, personal fees from Pharma Swiss, personal fees from Berlin Chemie, non-financial support from Sanofi Genzyme, personal fees from Novo-Nordisc, personal fees from Mylan, personal fees from CSL Behring, personal fees from Belupo, personal fees from Amgen, personal fees from Alkaloid, outside the submitted work. Dr. Flammer reports personal fees from Alnylam, grants and personal fees from AstraZeneca, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Fresenius, personal fees from Imedos GmBH, personal fees from Medtronic, personal fees from MSD, personal fees from Mundipharma, grants and personal fees from Novartis, personal fees from Pierre Fabre, personal fees from Pfizer, personal fees from Roche, personal fees from Vifor, personal fees from Zoll, grants from Berlin Heart, outside the submitted work. Dr. Petricevic has nothing to disclose. Dr. Biocina has nothing to disclose. Dr. Lund reports personal fees from Merck, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, personal fees from Pharmacosmos, personal fees from Abbott, personal fees from Medscape, personal fees from Myokardia, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, personal fees from Sanofi, personal fees from Lexicon, outside the submitted work. Dr. Milicic reports personal fees from Boehringer Ingelheim, personal fees from Bayer, personal fees from Pfizer, personal fees from Novartis, personal fees from AstraZeneca, personal fees from Novo Nordisk, personal fees from Teva, personal fees from Servier, outside the submitted work. Dr. Ruschitzka has not received personal payments by pharmaceutical companies or device manufacturers in the last three years (remuneration for the time spent in activities, such as participation in steering committee member of clinical trials, were made directly to the University of Zurich). The Department of Cardiology (University Hospital of Zurich/University of Zurich) reports research-, educational- and/or travel grants from Abbott, Amgen, Astra Zeneca, Bayer, B. Braun, Biosense Webster, Biosensors Europe AG, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Bracco, Cardinal Health Switzerland, Daiichi, Diatools AG, Edwards Lifesciences, Guidant Europe NV (BS), Hamilton Health Sciences, Kaneka Corporation, Labormedizinisches Zentrum, Medtronic, MSD, Mundipharma Medical Company, Novartis, Novo Nordisk, Orion, Pfizer, Quintiles Switzerland Sarl, Sanofi, Sarstedt AG, Servier, SIS Medical, SSS In-

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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

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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

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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.

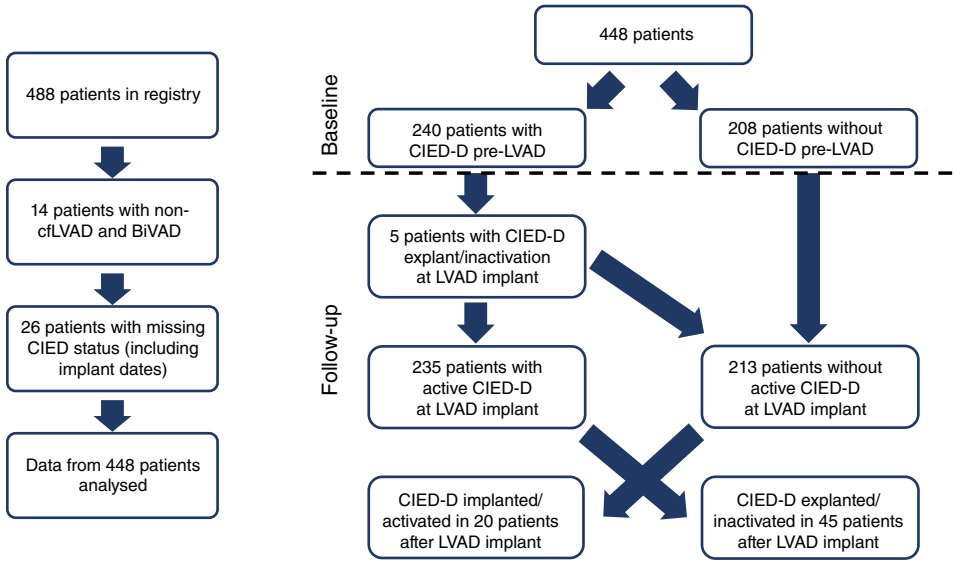

Figure 1 (*Left*) Selection of the study population from the PCHF-VAD registry. (*Right*) Patient flow during the follow-up period in respect to a cardiac implantable electronic device (CIED) with a defibrillator component (CIED-D). BiVAD, biventricular assist device; cfLVAD, continuous-flow left ventricular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

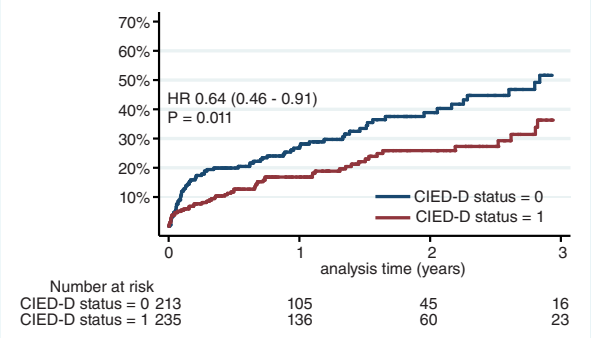

Figure 2 Kaplan–Meier plot of time to all-cause mortality, according to CIED-D carrier status following left ventricular assist device (LVAD) implantation. The analysis time begins at the time of LVAD implantation. CIED-D status 0 stands for no CIED-D present post-LVAD, CIED-D status 1 stands for CIED-D 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,

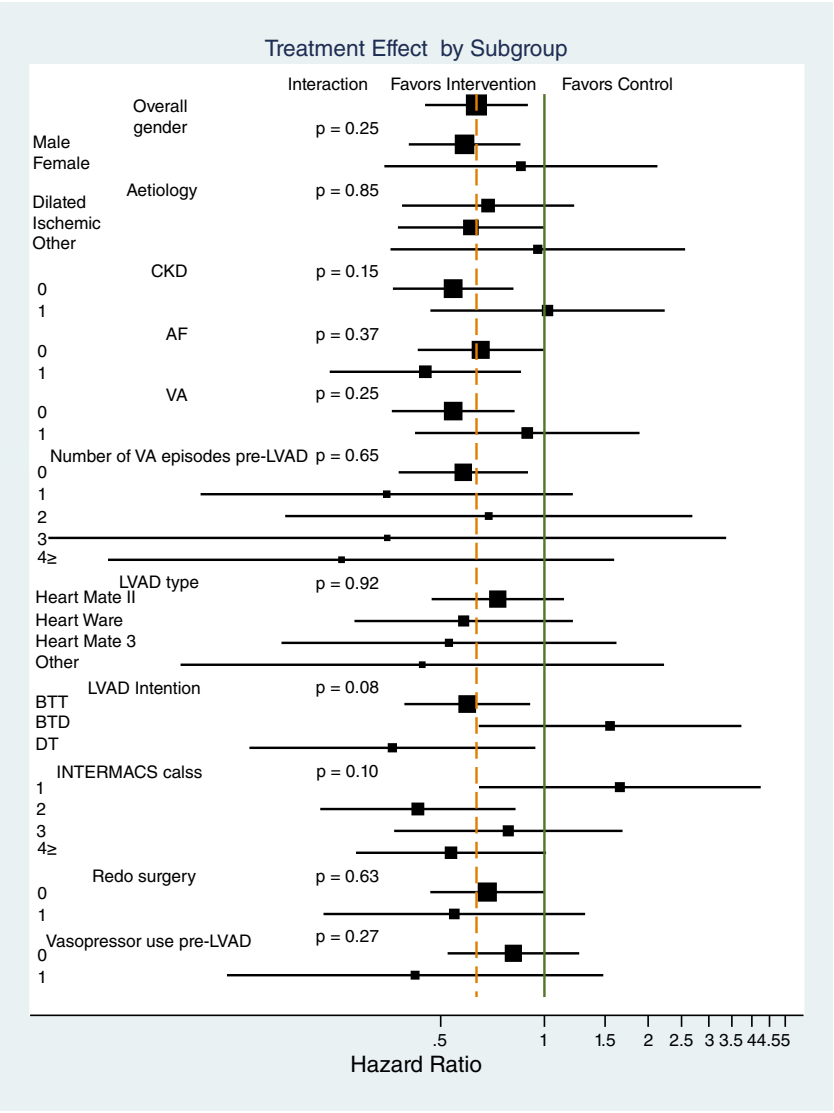

Figure 3 The effect of treatment with a cardiac implantable electronic device with a defibrillator component following left ventricular assist device (LVAD) implantation on all all-cause mortality for individual patient subgroups. 0 stands for absent, 1 for present. AF, atrial fibrillation; BTD, bridge 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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Cardiac implantable electronic devices with a defibrillator component and all-cause mortality in left ventricular assist device carriers – results from the PCHF VAD Registry

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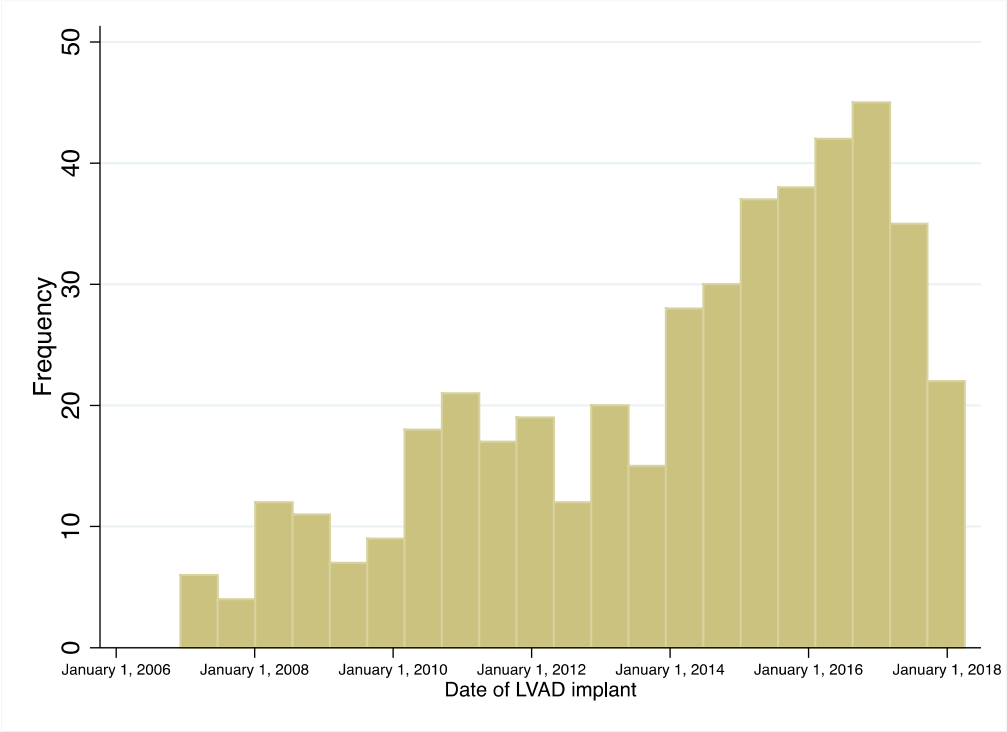
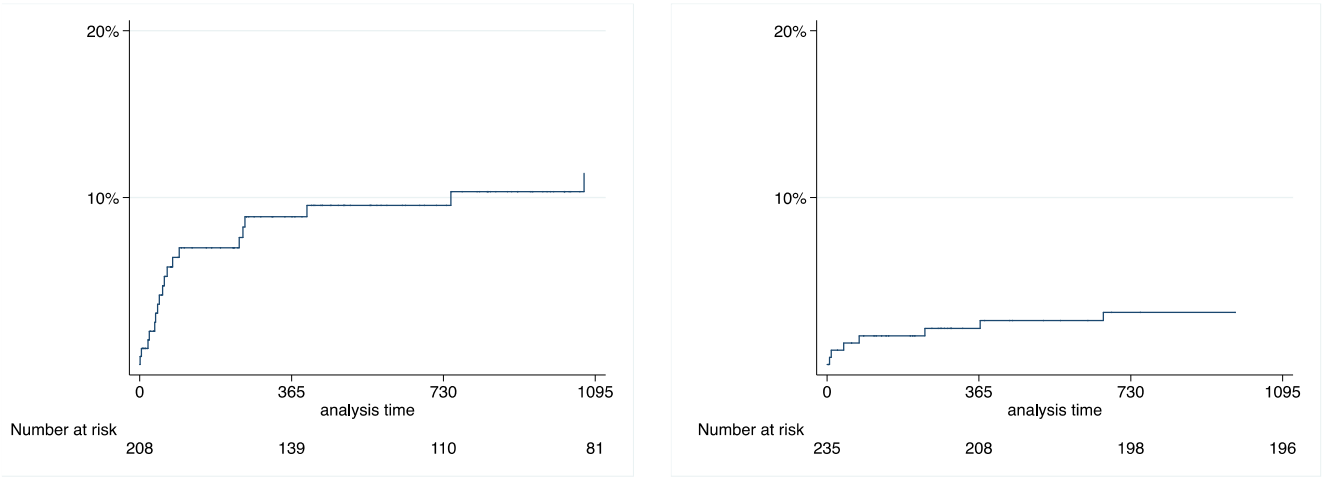
Supplemental material

Supplemental methods:

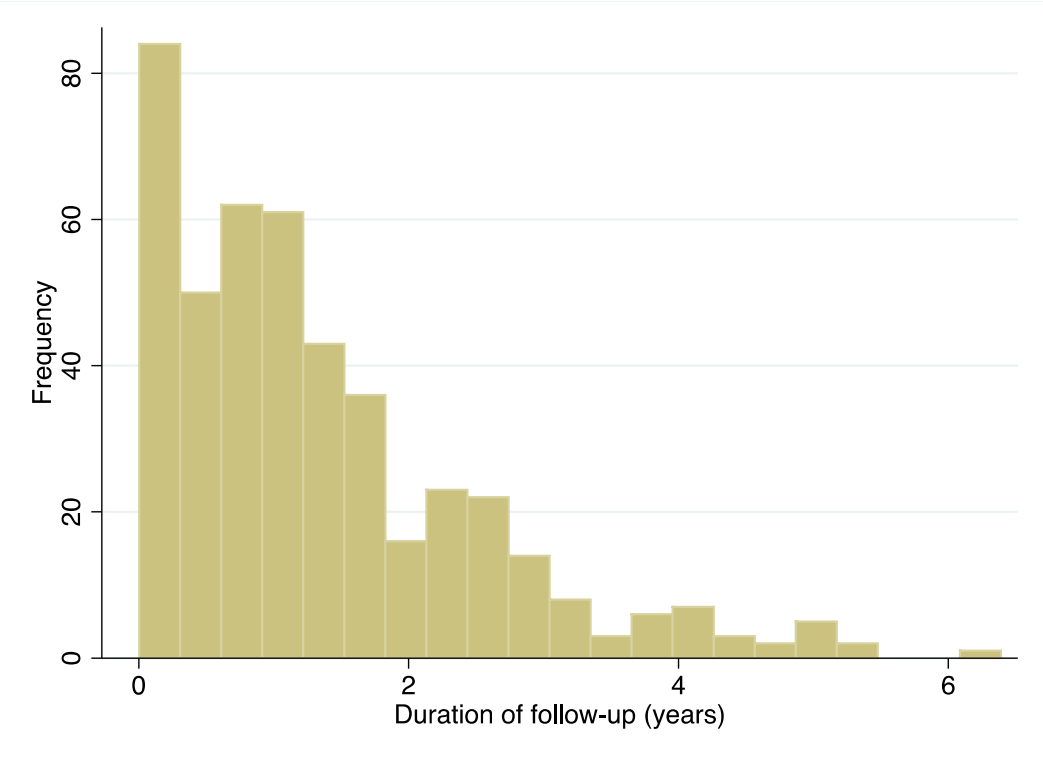
We have used 25 variables for the current stepwise selection process; the data were complete for 11 of these variables. The forward stepwise procedure considered only complete cases and was ultimately based on 333 subjects – for categorical variables with >5% of unreported values, we treated the unreported values as an additional category which increased the number of subjects from 249 to the final 333 subjects. In order to address the issue with missingness from an additional approach, we have also performed a multiple imputation analysis which has provided comparable results (adjusted analysis for the primary outcome: HR 0.59, 95% CI: 0.40-0.87; p=0.008, adjusted analysis for the primary outcome including multiple imputation: HR 0.63, 95% CI 0.43-0.93, p=0.019).



Supplemental Figure 1. The dates of LVAD implantation.



Supplemental Figure 2: Left panel: Kaplan-Meier plot of time to CIED-D implantation following LVAD implantation (during active LVAD support). Right panel: Kaplan-Meier plot of time to CIED-D deactivation following LVAD implantation (during active LVAD support).



Supplemental Figure 3. The duration of follow-up. The median time on LVAD support was 1.1 years (IQR 0.5-2.0 years) starting at the time of LVAD implantation.

Supplemental Table 1. Baseline characteristics of the studied patients by CIED-D carrier status prior to LVAD implantation – additional variables with more than 30% missing data

	Overall average	No CIED-D pre-LVAD (n=208)	CIED-D pre-LVAD (n=240)	P value
Medications, n (%)				
ARNI	3 (1.0)	1 (0.8)	2 (1.1)	0.80
Calcium channel blocker	1 (0.3)	1 (0.8)	0 (0.0)	0.23
Laboratory values				
Total cholesterol, mmol/L	3.6±1.2	3.5±1.1	3.7±1.2	0.25
NT-proBNP, pg/mL	4446 (2663- 8904)	3968 (2538- 8904)	4673 (2850-8950)	0.28
BNP, pg/mL	1750 (944-3174)	2219 (1335-4015)	1487 (682-2282)	0.05
Echocardiographic data				
RVIDd, mm	42.3±8.2	40.8±7.8	43.4±8.4	0.15
FAC, %	28±10	28±9	28±10	0.97
Right heart catheterization data				
sPAP, mmHg	51±17	52±17	51±18	0.41
mPAP, mmHg	34±12	35±11	34±13	0.38
dPAP, mmHg	27±11	29±10	27±11	0.13
CVP, mmHg	10 (6-14)	11 (7-15)	10 (5-14)	0.037
PCWP, mmHg	24.7±8.9	25.9±8.5	24.1±9.0	0.08
TPG, mmHg	11.7±6.7	11.2±7.1	12.1±6.4	0.40
PVR, Wood Units	3.0 (2.0-4.5)	3.0 (2.2-4.9)	3.0 (1.9-4.3)	0.32
CO, L/min	3.8±1.1	3.7±1.0	3.8±1.1	0.25
CI, L/min/m^2	1.9±0.5	1.9±0.5	2.0±0.6	0.22

Values expressed as mean ± standard deviation or median (interquartile range).

ARNI – angiotensin receptor-neprilysin inhibitor; BNP – B-type natriuretic peptide; NT-proBNP – N-terminal pro hormone BNP; RVIDd - right ventricular intraventricular dimension in end-diastole; FAC

– fractional area change; TAPSE - tricuspid annular plane systolic excursion; sPAP – systolic pulmonary artery pressure; mPAP – mean pulmonary artery pressure; dPAP – diastolic pulmonary artery pressure; CVP – central venous pressure; PCWP – pulmonary capillary wedge pressure; TPG – transpulmonary gradient; PVR – pulmonary vascular resistance; CO – cardiac output; CI – cardiac index.

Supplemental table 2a. 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 per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	1.57	0.98-2.52	0.06
Age	0.99	0.98-1.01	0.30
LVAD implant as redo surgery	0.74	0.35-1.54	0.42
LVAD type			0.80
Heart Mate II	Referent		
Heart Ware	0.90	0.54-1.50	
Heart Mate 3	1.03	0.61-1.74	
Other	0.64	0.24-1.69	
Number of VA episodes pre-VAD			<0.0001
Four or more	Referent		
None	0.45	0.19-1.08	
One	0.87	0.34-2.19	
Two	2.05	0.80-5.29	
Three	1.59	0.58-4.39	
Unknown	0.27	0.08-0.88	
Vasopressor use pre-LVAD			
Yes	Referent		0.12
No	0.54	0.28-1.02	
Unknown	0.45	0.19-1.04	

Supplemental table 2b. 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 outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	1.52	0.94-2.46	0.09
Female gender	0.38	0.18-0.80	0.011
Age	0.98	0.97-1.00	0.055
Aetiology			0.02
Nonischaemic cardiomyopathy	Referent		
Ischaemic cardiomyopathy	1.78	1.15-2.76	
Other	0.96	0.44-2.11	
Number of VA episodes pre-VAD			0.0001
Four or more	Referent		
None	0.62	0.26-1.49	
One	1.01	0.39-2.61	
Two	2.22	0.85-5.79	
Three	1.85	0.67-5.10	
Unknown	0.26	0.08-0.86	
Vasopressor use pre-LVAD			0.16
Yes	Referent		
No	0.50	0.25-1.03	
Unknown	0.44	0.05-3.81	
Beta blocker use pre-LVAD			0.009
Yes	Referent		
No	0.49	0.27-0.86	
Unknown	1.62	0.76-3.42	
Mechanical ventilation use pre-LVAD			0.64
Invasive ventilation	Referent		
None	0.66	0.25-1.76	
Non-invasive ventilation	0.00		
Unknown	0.47	0.05-4.47	

Supplemental Table 3. 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.

	Hazard Ratio 95% confidence interval p-value			
	Unadjusted	Adjusted by variable selection for the primary outcome	Adjusted by outcome-specific variable selection	Propensity score adjusted model
All-cause mortality (n=134)	0.64 0.46-0.91 p=0.012	0.59* 0.40-0.87 p=0.008	0.59* 0.40-0.87 p=0.008	0.60 0.39-0.94 p=0.024
Cardiovascular mortality (n=83)	0.72 0.46-1.11 p=0.13	0.65* 0.39-1.07 p=0.09	0.79† 0.50-1.24 p=0.30	0.73 0.42-1.28 p=0.27
Heart failure hospitalization (n=80)	1.50 0.96-2.38 p=0.08	0.92* 0.56-1.51 p=0.74	0.93‡ 0.57- 1.51 p=0.76	1.10 0.62-1.95 p=0.76
Ventricular arrhythmias post-LVAD (n=107)	2.20 1.46-3.34 p<0.0001	1.57* 0.98-2.52 p=0.06	1.52§ 0.94-2.46 p=0.09	1.68 1.00-2.81 P=0.049
Device-related infection requiring systemic antibiotics (n=149)	0.76 0.55-1.05 p=0.09	0.96* 0.66-1.40 p=0.84	0.96‖ 0.65-1.41 p=0.82	0.96 0.64-1.45 P=0.85
Non-cerebral bleeding (n=88)	0.79 0.52-1.20 p=0.27	0.64* 0.40-1.03 p=0.07	0.82¶ 0.52-1.28 p=0.37	0.67 0.39-1.17 p=0.16
Intracranial bleeding (n=32)	0.75 0.37-1.52 p=0.42	0.55* 0.24-1.26 p=0.16	0.70# 0.34-1.46 p=0.34	0.51 0.20-1.28 p=0.15

* 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.

† Adjusted for: LVAD type and LVAD implant as a redo surgical procedure.

‡ Adjusted for: LVAD type, number of VA episodes pre LVAD.

§ Adjusted for: gender, age, aetiology, number of VA episodes pre LVAD, use of vasopressors, beta-blockers and type of mechanical ventilation pre-LVAD.

‖ Adjusted for: age, LVAD type, number of VA episodes pre LVAD, use of ivabradine and beta-blockers and pre-LVAD.

¶ Adjusted for: aetiology, quartile of date of LVAD implant.

Adjusted for: LVAD type.

Supplemental table 4a. Multivariate Cox regression model of risk factors for the primary outcome of all-cause death, using post-LVAD VAs as a time-varying covariate.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.53	0.36-0.79	0.002
Incident VA post-LVAD	2.42	1.58-3.69	<0.0001
LVAD implant as redo surgery	1.75	1.12-2.73	0.013
Age	1.03	1.02-1.05	<0.0001
LVAD type			0.29
Heart Mate II	Referent		
Heart Ware	1.34	0.85-2.13	
Heart Mate 3	0.72	0.39-1.34	
Other	0.82	0.36-1.88	
Number of VA episodes pre-VAD			0.015
Four or more	Referent		
None	0.58	0.25-1.31	
One	0.28	0.10-0.76	
Two	0.64	0.24-1.70	
Three	0.43	0.14-1.34	
Unknown	0.24	0.09-0.68	
Vasopressor use			0.006
Yes	Referent		
No	0.49	0.28-0.86	
Unknown	0.90	0.47-1.73	

Supplemental table 4b. Multivariate Cox regression model of risk factors for the secondary outcome of cardiovascular death, using post-LVAD VAs as a time-varying covariate.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.57	0.34-0.95	0.031
Incident VA post-LVAD	2.60	1.53-4.43	<0.0001
LVAD implant as redo surgery	2.29	1.32-3.97	0.003
Age	1.03	1.01-1.05	0.01
LVAD type			0.23
Heart Mate II	Referent		
Heart Ware	1.41	0.80-2.49	
Heart Mate 3	0.74	0.35-1.58	
Other	0.47	0.13-1.62	
Number of VA episodes pre-VAD			0.19
Four or more	Referent		
None	0.75	0.26-2.21	
One	0.38	0.11-1.34	
Two	0.90	0.26-3.11	
Three	0.74	0.18-2.97	
Unknown	0.29	0.07-1.20	
Vasopressor use			0.022
Yes	Referent		
No	0.40	0.21-0.77	
Unknown	0.50	0.22-1.13	

Supplemental Table 5a. 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 per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.65	0.39-1.07	0.09
Age	1.03	1.00-1.05	0.018
LVAD as redo surgery	2.14	1.25-3.67	0.006
LVAD type			0.30
Heart Mate II	Referent		
Heart Ware	1.32	0.75-2.31	
Heart Mate 3	0.76	0.36-1.61	
Other	0.46	0.13-1.55	
Number of VA episodes pre-VAD			0.14
Four or more	Referent		
None	0.63	0.22-1.83	
One	0.38	0.11-1.34	
Two	1.03	0.30-3.49	
Three	0.72	0.18-2.87	
Unknown	0.25	0.06-0.98	
Vasopressor use pre-LVAD			0.024
Yes	Referent		
No	0.41	0.21-0.78	
Unknown	0.49	0.22-1.10	

Supplemental table 5b. 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 outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.79	0.50-1.24	0.30
LVAD implant as redo surgery	2.16	1.27-3.66	0.004
LVAD type			0.41
Heart Mate II	Referent		
Heart Ware	1.26	0.75-2.13	
Heart Mate 3	0.76	0.36-1.58	
Other	0.54	0.17-1.76	

Supplemental Table 6a. Multivariate Cox regression model of risk factors for secondary outcome of heart failure hospitalisation from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.92	0.56-1.51	0.74
Age	1.01	0.99-1.03	0.60
LVAD as redo surgery	0.88	0.40-1.96	0.76
LVAD type			0.0009
Heart Mate II	Referent		
Heart Ware	3.02	1.74-5.24	
Heart Mate 3	2.23	1.20-4.14	
Other	1.33	0.49-3.59	
Number of VA episodes pre-VAD			0.0177
Four or more	Referent		
None	0.33	0.13-0.81	
One	0.38	0.14-1.05	
Two	0.36	0.11-1.14	
Three	0.58	0.18-1.90	
Unknown	0.07	0.02-0.31	
Vasopressor use pre-LVAD			0.92
Yes	Referent		
No	0.85	0.37-1.92	
Unknown	0.84	0.28-2.48	

Supplemental table 6b. Multivariate Cox regression model of risk factors for secondary outcome of heart failure hospitalisation from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.93	0.57-1.51	0.76
LVAD type			0.0005
Heart Mate 2	Referent		
Heart Ware	3.05	1.79-5.21	
Heart Mate 3	2.25	1.23-4.13	
Other	1.39	0.53-3.62	
Number of VA episodes pre-VAD			0.0085
Four or more	Referent		
None	0.35	0.14-0.83	
One	0.40	0.15-1.08	
Two	0.38	0.12-1.18	
Three	0.63	0.20-2.01	
Unknown	0.07	0.02-0.28	

Supplemental Table 6c. Multivariate Cox regression model of risk factors for secondary outcome of device-related infection requiring systemic antibiotics from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.96	0.66-1.40	0.84
Age	1.00	0.98-1.01	0.64
LVAD as redo surgery	1.50	0.95-2.39	0.09
LVAD type			0.0008
Heart Mate II	Referent		
Heart Ware	1.72	1.16-2.55	
Heart Mate 3	0.57	0.32-1.03	
Other	0.47	0.17-1.33	
Number of VA episodes pre-VAD			0.49
Four or more	Referent		
None	0.63	0.28-1.42	
One	0.42	0.16-1.09	
Two	0.68	0.24-1.89	
Three	0.63	0.20-1.95	
Unknown	0.82	0.33-2.02	
Vasopressor use pre-LVAD			0.26
Yes	Referent		
No	1.33	0.61-2.92	
Unknown	1.81	0.78-4.19	

Supplemental table 6d. Multivariate Cox regression model of risk factors for secondary outcome of device-related infection requiring systemic antibiotics from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.96	0.65-1.41	0.82
Age	1.00	0.99-1.01	0.89
LVAD type			0.0005
Heart Mate II	Referent		
Heart Ware	1.88	1.25-2.83	
Heart Mate 3	0.59	0.33-1.07	
Other	0.57	0.20-1.62	
Number of VA episodes pre-VAD			0.39
Four or more	Referent		
None	0.54	0.24-1.21	
One	0.37	0.14-0.97	
Two	0.67	0.24-1.87	
Three	0.57	0.18-1.75	
Unknown	0.70	0.29-1.69	
Ivabradine use pre-LVAD			0.0016
Yes	Referent		
No	1.17	0.58-2.36	
Unknown	2.74	1.24-6.04	
Beta blocker use pre-LVAD			0.17
Yes	Referent		
No	1.11	0.73-1.69	
Unknown	0.65	0.37-1.11	

Supplemental Table 6e. Multivariate Cox regression model of risk factors for secondary outcome of non-cerebral bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.64	0.40-1.03	0.07
Age	1.02	1.00-1.04	0.07
LVAD as redo surgery	1.42	0.77-2.61	0.26
LVAD type			0.90
Heart Mate II	Referent		
Heart Ware	1.03	0.58-1.83	
Heart Mate 3	0.81	0.43-1.54	
Other	0.85	0.37-1.96	
Number of VA episodes pre-VAD			0.15
Four or more	Referent		
None	1.57	0.37-6.62	
One	1.69	0.38-7.55	
Two	0.51	0.07-3.65	
Three	1.86	0.36-9.63	
Unknown	0.50	0.09-2.77	
Vasopressor use pre-LVAD			0.43
Yes	Referent		
No	0.85	0.40-1.82	
Unknown	0.56	0.21-1.47	

Supplemental table 6f. Multivariate Cox regression model of risk factors for secondary outcome of non-cerebral bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.82	0.52-1.28	0.37
Aetiology			0.10
Nonischaemic cardiomyopathy	Referent		
Ischaemic cardiomyopathy	1.23	0.77-1.94	
Other	2.02	1.06-3.86	
LVAD implant date quartile			0.17
Q1	Referent		
Q2	0.55	0.30-1.03	
Q3	1.05	0.59-1.86	
Q4	0.94	0.50-1.77	

Supplemental Table 6g. Multivariate Cox regression model of risk factors for secondary outcome of intracranial bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.55	0.24-1.26	0.16
Age	1.05	1.01-1.09	0.01
LVAD as redo surgery	1.11	0.38-3.21	0.85
LVAD type			0.18
Heart Mate II	Referent		
Heart Ware	2.63	1.07-6.47	
Heart Mate 3	1.20	0.36-4.01	
Other	0.98	0.20-4.76	
Number of VA episodes pre-VAD			0.42
Four or more	Referent		
None	1.02	0.13-7.99	
One	0.20	0.01-3.35	
Two	1.83	0.20-16.64	
Three	1.15	0.10-13.70	
Unknown	0.50	0.04-5.66	
Vasopressor use pre-LVAD			0.65
Yes	Referent		
No	0.63	0.18-2.22	
Unknown	0.92	0.20-4.18	

Supplemental table 6h. Multivariate Cox regression model of risk factors for secondary outcome of intracranial bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.70	0.34-1.46	0.34
LVAD type			0.35
Heart Mate II	Referent		
Heart Ware	2.07	0.92-4.65	
Heart Mate 3	1.09	0.35-3.43	
Other	1.33	0.30-5.88	

Supplemental Table 7. 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.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.61	0.40-0.94	0.024
Age	1.04	1.02-1.06	<0.0001
Aetiology			0.73
Nonischaemic	Referent		
Ischaemic	1.01	0.68-1.51	
Other	1.25	0.70-2.24	
LVAD type			0.43
Heart Mate II	Referent		
Heart Ware	1.19	0.74-1.92	
Heart Mate 3	0.70	0.37-1.34	
Other	0.70	0.26-1.89	
LVAD intention			0.43
Bridge to transplantation (BTT)	Referent		
Bridge to decision (BTD)	1.13	0.66-1.92	
Destination therapy (DT)	0.70	0.38-1.30	
Beta blocker use			0.52
No	Referent		
Yes	0.86	0.55-1.34	
Unknown	0.67	0.33-1.38	
Vasopressor use			0.0007
No	Referent		
Yes	1.87	1.02-3.40	
Unknown	7.48	2.35-22.82	
Mechanical ventilation			0.025
Intubated	Referent		
None	0.69	0.34-1.40	
Non-invasive	1.80	0.17-19.30	

Unknown	0.18	0.05-0.68	
Number of VA episodes pre-VAD			0.028
Four or more	Referent		
None	0.43	0.19-0.99	
One	0.26	0.09-0.72	
Two	0.72	0.27-1.93	
Three	0.41	0.13-1.29	
Unknown	0.23	0.08-0.65	

Supplemental table 8. Results of the propensity score model assessing the possibility of having a CIED-D pre-LVAD.

Variable	OR	95% CI	P value
Age	1.02	1.00-1.04	0.07
Female gender	0.76	0.40-1.45	0.41
Arterial hypertension	1.12	0.62-2.02	0.72
Diabetes mellitus	0.94	0.50-1.77	0.85
Chronic kidney disease	1.62	0.89-2.96	0.12
Coronary artery disease	0.69	0.35-1.38	0.30
Prior MI	0.45	0.21-0.96	0.04
Prior coronary revascularization	1.56	0.72-3.37	0.26
Cerebrovascular events	1.68	0.68-4.15	0.26
Atrial fibrillation/flutter	2.90	1.63-5.15	<0.0001
Ventricular arrhythmias	2.03	1.12-3.68	0.020
LVAD as redo surgery	0.59	0.28-1.23	0.16
Concomitant procedure with LVAD implant	0.39	0.21-0.73	0.003
LVAD type			<0.0001
Heart Mate II	Referent		
Heart Ware	3.24	1.63-6.45	
Heart Mate 3	5.88	2.90-11.91	
Other	3.91	1.04-14.75	
LVAD intention			0.0008
Bridge to transplantation	Referent		
Bridge to decision	0.24	0.11-0.50	
Destination therapy	0.65	0.27-1.57	
INTERMACS class			0.002
1	Referent		
2	2.33	1.04-5.20	
3	4.25	1.86-9.72	
4 or higher	4.31	1.94-10.11	

Supplemental table 9. 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.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.63	0.43-0.93	0.019
Age	1.03	1.02-1.05	<0.0001
LVAD as redo surgery	1.72	1.11-2.66	0.015
LVAD type			0.36
Heart Mate II	Referent		
Heart Ware	1.13	0.73-1.76	
Heart Mate 3	0.66	0.36-1.22	
Other	0.68	0.30-1.52	
Number of VA episodes pre-VAD			0.13
None	Referent		
One	0.56	0.29-1.08	
Two	1.37	0.71-2.66	
Three	0.79	0.33-1.88	
Four or more	1.87	0.81-4.29	
Vasopressor use pre-LVAD			0.13
No	Referent		
Yes	1.52	0.88-2.63	

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.61	0.41-0.90	0.013
CRT-P post-LVAD	0.65	0.25-1.66	0.37
Age	1.03	1.02-1.05	<0.0001
LVAD as redo surgery	1.78	1.15-2.78	0.01
LVAD type			0.35
Heart Mate II	Referent		
Heart Ware	1.13	0.73-1.76	
Heart Mate 3	0.66	0.36-1.22	

Other	0.66	0.29-1.48	
Number of VA episodes pre-VAD			0.14
None	Referent		
One	0.56	0.29-1.07	
Two	1.35	0.70-2.63	
Three	0.82	0.34-1.97	
Four or more	1.84	0.80-4.25	
Vasopressor use pre-LVAD			0.11
No	Referent		
Yes	1.56	0.90-2.70	

Supplemental Table 10. 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.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.58	0.41-0.82	0.002
Age	1.03	1.01-1.05	<0.0001
LVAD as redo surgery	1.71	1.11-2.64	0.014

Supplemental Table 11a. 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

Variable	HR	95% CI	P value
ICD status	0.60	0.39-0.92	0.019
Age	1.03	1.01-1.05	0.001
LVAD implant as redo surgery	2.02	1.24-3.31	0.005
LVAD type			0.31
Heart Mate II	Referent		
Heart Ware	1.40	0.86-2.27	
Heart Mate 3	0.76	0.41-1.41	
Other	0.86	0.37-2.00	
Number of VA episodes pre-LVAD			0.0095
Four or more	Referent		
None	0.37	0.16-0.86	
One	0.21	0.07-0.59	
Two	0.56	0.21-1.50	
Three	0.31	0.10-1.02	
Unknown	0.13	0.04-0.44	
Vasopressor use pre-LVAD			0.01
Yes	Referent		
No	0.44	0.23-0.82	
Unknown	0.79	0.36-1.73	
LVIDd pre-LVAD	0.98	0.97-1.00	0.064

Supplemental Table 11b. 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.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.65	0.44-0.97	0.034
Age	1.03	1.02-1.05	<0.0001
LVAD as redo surgery	1.72	1.10-2.67	0.015
LVAD type			0.27
Heart Mate II	Referent		
Heart Ware	1.13	0.72-1.76	
Heart Mate 3	0.60	0.33-1.09	
Other	0.74	0.33-1.67	
Number of VA episodes pre-VAD			0.10
None	Referent		
One	0.56	0.29-1.08	
Two	1.42	0.73-2.78	
Three	0.72	0.30-1.74	
Four or more	1.97	0.84-4.62	
Vasopressor use pre-LVAD			0.16
No	Referent		
Yes	1.50	0.85-2.64	
LVIDd at LVAD implant	0.99	0.98-1.01	0.49

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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

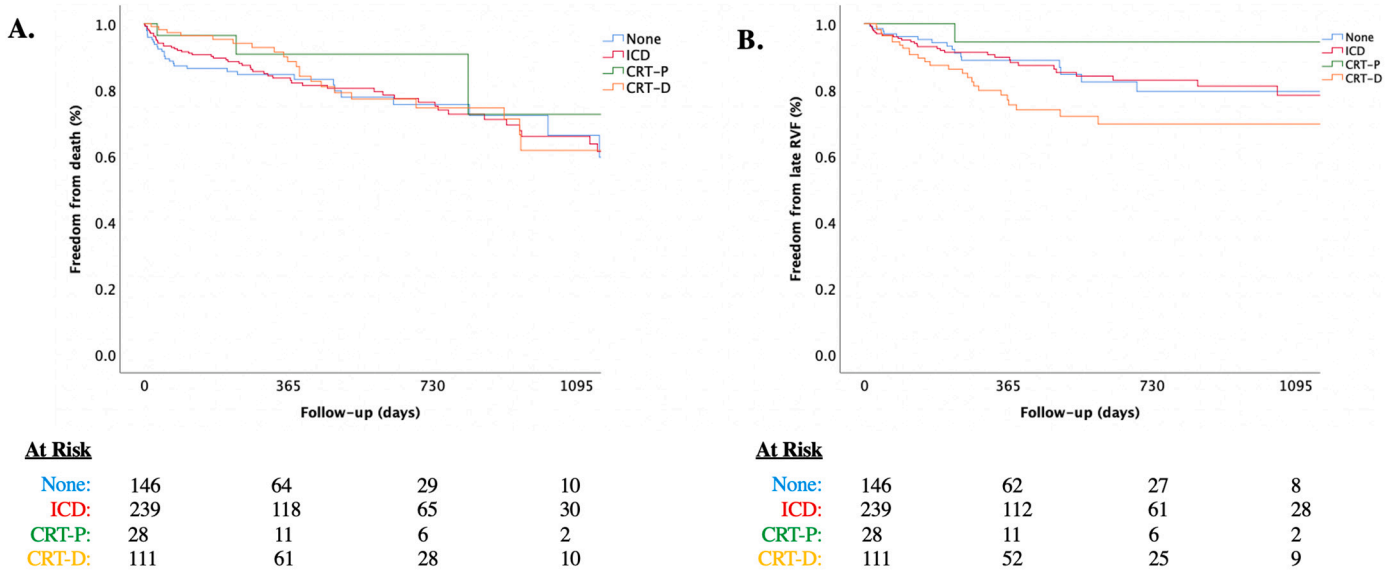

Fig. 1. Kaplan-Meier estimates for the cumulative incidence of **A.)** mortality and **B.)** late right ventricular failure as stratified by the presence or absence of cardiac implantable electronic device.
Captions: Log-rank *p* values; **A.)** 0.83 **B.)** 0.02.

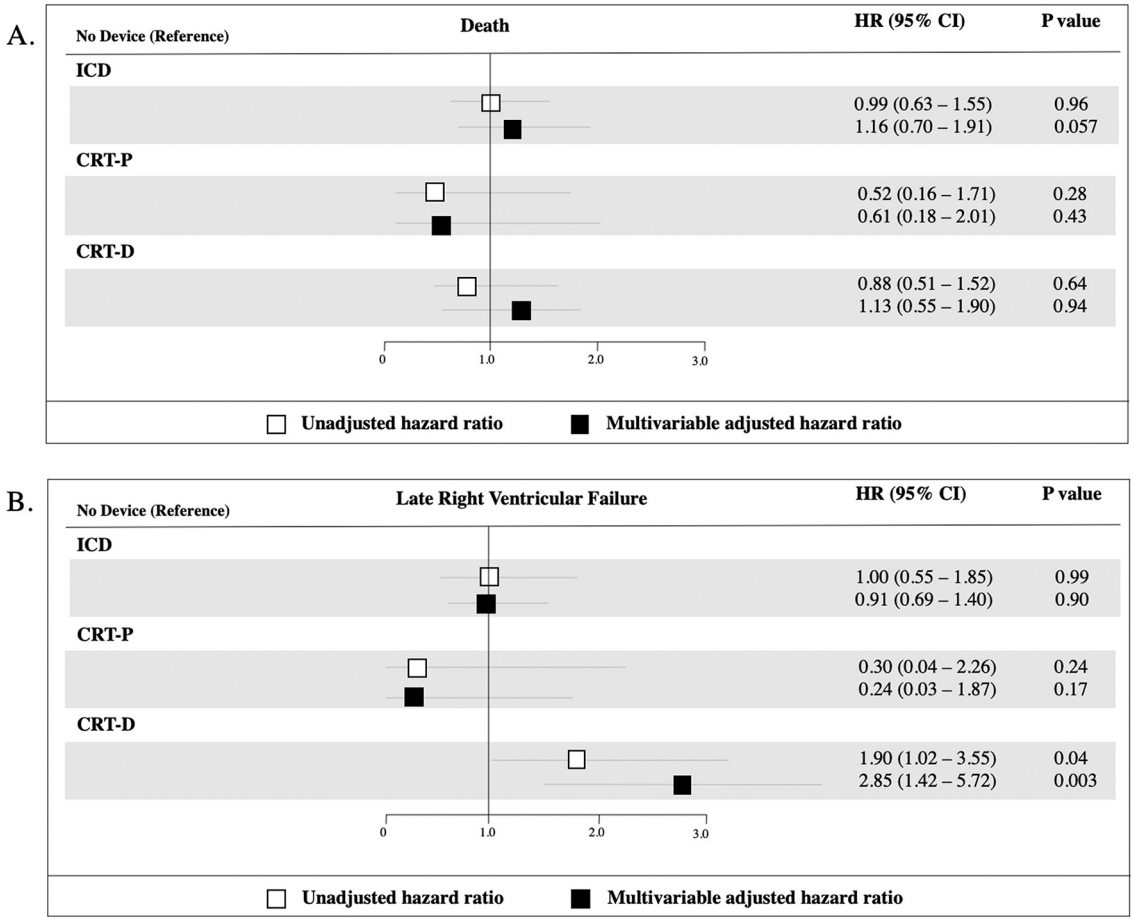

Fig. 2. Unadjusted and adjusted Cox regression models for primary endpoints as stratified by cardiac implantable electronic device, **A.)** Death and **B.)** late right ventricular failure.

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

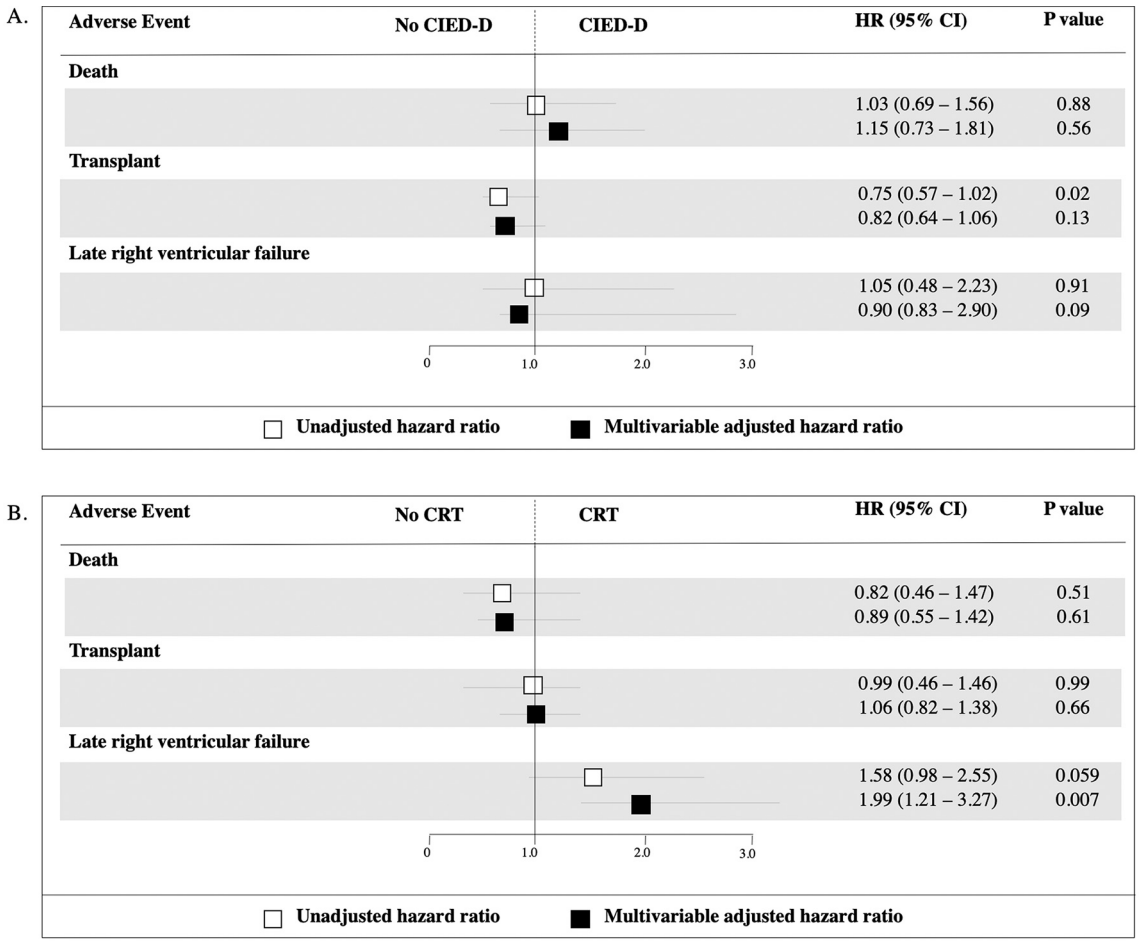

Fig. 3. Unadjusted and adjusted Cox regression models for primary endpoints as stratified by **A.)** Combined defibrillator vs no defibrillator **B.)** combined cardiac resynchronization vs no cardiac resynchronization therapy.

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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12. Biography

Nina Jakuš was born in 1987 in Zagreb, where she graduated at the University of Zagreb School of Medicine, and during her studies received the Dean's Award for best student. After graduation, she spent a year working as a research assistant in KU Leuven, Belgium, during which time she obtained a Master's degree in Advanced Medical Imaging (graduating magna cum laude). In 2015 she started her cardiology residency at the University Hospital Centre (UHC) Zagreb, working in the Intensive Cardiac Care Unit and the Advanced Heart Failure Unit, caring for heart transplantation and LVAD patients. The same year she enrolled in the Postgraduate studies at the School of Medicine Zagreb (Biomedicine and health). 2018-2019 she attended the Postgraduate Course in Heart Failure in Zurich, which she successfully completed. During this time, under the supervision of Prof. Čikeš and Prof. Ruschitzka, she coordinated the PCHF-VAD registry, which resulted in the publication of 5 articles, in some of the highest-ranking journals in the field. During this time, she actively participated in numerous European congresses, and was awarded several prizes for best presentation at Croatian congresses. She currently works as an attending cardiologist at UHC Zagreb, as well as a contributor at the School of Medicine at the University of Zagreb.

Biografija

Nina Jakuš rođena je 1987. godine u Zagrebu, gdje je uspješno diplomirala na Medicinskom fakultetu Sveučilišta u Zagrebu, a tijekom studija joj je dodijeljena Dekanova nagrada za uspjeh. Poslije studija provodi godinu dana radeći kao suradnik na istraživanju u KU Leuven u Belgiji**,** tijekom čega je stekla titulu Master's degree in Advanced Medical Imaging**.** 2015. godine započinje specijalizaciju iz kardiologije na Klinici za bolesti srca i krvnih žila, KBC Zagreb, gdje je uključena u rad Tima za uznapredovalo srčano zatajivanje i rad Intenzivne jedinice. Iste godine upisuje poslijediplomski studij Biomedicina i zdravstvo na Medicinskom fakultetu u Zagrebu. 2018.-2019. godine pohađa poslijediplomski studij o zatajivanju srca (PCHF) u Zurichu. Pod mentorstvom izv. prof. Čikeš i prof. Ruschitzke djeluje kao koordinator registra LVAD pacijenata, PCHF-VAD, koji je rezultirao objavom 5 članaka u visokorangirajućim časopisima iz područja kardiologije. Tijekom specijalizacije i daljnjeg rada redovito aktivno participira na europskim kongresima, a višekratno je nagrađena za

prezentacije na domaćim kongresima. Trenutačno radi kao specijalist kardiolog u KBC Zagreb, te kao vanjski suradnik Medicinskog fakulteta u Zagrebu.