Journal of the American Heart Association

ORIGINAL RESEARCH

Sex Differences in Recovery and Device Replacement After Left Ventricular Assist Device Implantation as Destination Therapy

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BACKGROUND: The relevance of sex and preimplant factors for clinical outcomes among patients with left ventricular assist devices intended for destination therapy is unclear.

METHODS AND RESULTS: INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) data (2006-2017) from 6771 men and 1690 women with left ventricular assist devices as destination therapy were analyzed to evaluate the contribution of preimplant clinical, demographic, and clinically judged psychosocial characteristics to time until death, heart transplant, device explant due to recovery, or complication-related device replacement. Associations of sex with time until each competing outcome were evaluated using cumulative incidence functions and event-specific Cox proportional hazards models. Women were younger, more likely to have nonischemic diagnoses, and reported less substance abuse but were more likely to be unmarried, not working for an income, overweight, and depressed than men. After 2 years, women had higher probabilities for recovery (3.7% versus 1.6%, $P<0.001$) and device replacement (12.1% versus 10%, $P=0.019$) than men but not for death and transplant ($P>0.12$). The sex differences remained after controlling for covariates (adjusted hazard ratio [HR_{adj}] recovery, 1.85; 95% CI, 1.30–2.70; $P<0.001$; HR_{adj} device replacement, 1.22; 95% CI, 1.04–1.33; $P=0.015$). Female-specific diagnoses (eg, postpartum heart failure) contributed to women's enhanced rate of recovery. Demographic and psychosocial factors were unrelated to women's increased event rates.

CONCLUSIONS: In destination therapy, women have higher rates of device replacement and recovery than men. The latter was partly explained by female-specific diagnoses. Standardized assessments of psychosocial characteristics are needed to elucidate their association with sex differences in outcomes.

Key Words: sex differences ■ INTERMACS ■ left ventricular assist device ■ outcomes

See Editorial by Rajapreyar and Le Jemtel

Continuous-flow left ventricular assist device (CF-LVAD) use has become standard therapy for patients with end-stage heart failure (HF). Originally intended as bridge-to-transplant therapy (BTT), today most of all CF-LVADs are implanted as destination therapy (DT).[1] This development highlights the need to focus on this growing subgroup of LVAD recipients and to identify clinical, demographic, and psychosocial patient characteristics that are associated with clinical outcomes in men and women.

Sex differences in clinical outcomes of DT patients have been examined previously but are difficult to

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Parts of the findings reported in this article were presented at the European Health Psychology Society (EHPS) annual conference, September 3–7, 2019, in Dubrovnik, Croatia and at the International Scientific Workshop "The Relevance of Registry Research for Clinical Practice: Gender Differences in Left Ventricular Assist Device Recipients with a Focus on Psychosocial and Behavioural Factors," October 10–12, 2019, in Trier, Germany.

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023294

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Among patients receiving a continuous-flow left ventricular assist device as long-term support, women were more likely than men to experience device explant due to cardiac recovery, especially women presenting with nonischemic and female-specific diagnoses, such as postpartum heart failure and adriamycin-induced heart failure.
- Women were more likely to experience complications that led to device replacement, independent of clinical characteristics (eg, diagnoses, INTERMACS [Interagency Registry for Mechanically Assisted Circulatory Support] profile, pump type).
- Clinically judged psychosocial patient characteristics did not contribute to sex differences in clinical outcomes.

What Are the Clinical Implications?

- In the modern continuous-flow left ventricular assist device era, women and men have similar probabilities to survive and women might even have higher probabilities for cardiac recovery.
- In addition, clinicians need to monitor women closely for complications.
- Preferring psychometrical questionnaires and standardized interviews above simple checklists might be useful to detect important psychosocial risk factors.

Nonstandard Abbreviations and Acronyms

BTT	bridge-to-transplant
CF-LVAD	continuous-flow left ventricular assist device
DT	destination therapy
IMACS	International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support

interpret, because many studies do not differentiate between device types (LVAD, bi-VAD, total artificial heart, pulsatile versus continuous) and device strategies. For example, a higher risk of death after LVAD implantation in women compared with men has been reported in 4 studies using INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support),[2,3] IMACS (International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support),[4] and EUROMACS (European Registry for Patients with Mechanical Circulatory Support) data,[5] whereas others could not confirm any sex differences in mortality.[6,7] All these studies combined devices and/or strategies. Considering device improvements over time, Joshi et al. found that only women in the pulsatile-flow era but not in the continuous-flow era have an increased risk of mortality.[8] DeFilippis and colleagues[9] reported in a United Network for Organ Sharing sample that among LVAD recipients in BTT only, women have an increased risk of waitlist mortality. They conclude that similar analyses of sex differences among patients intended for DT are clearly needed, as the observed mortality risk in women in BTT might be related to the fact that women are less likely to receive a heart transplant than their male counterparts.[10,11]

Furthermore, most studies focus solely on the outcome of death or adverse events. Evidence regarding other competing outcomes such as explantation due to recovery or device replacement due to complications are scarce. Some indication that female sex is involved in these outcomes comes from a recent study on myocardial recovery of patients with LVAD in general, which detected female sex as a predictor for partial recovery, independent of clinical parameters.[12] Other studies could not find independent sex effects regarding recovery[13] and evidence that women with LVADs suffer more complications is also mostly based on research neglecting device strategies.[6,14]

Sex differences in preimplant clinical characteristics have been investigated previously.[5,6,15] Therefore, focusing on demographic and psychosocial characteristics (eg, working for income, marital status, alcohol abuse) might help to further understand sex differences in outcomes. Findings from single-center studies suggest that high psychosocial risk (eg, substance abuse, depression) is associated with increased rates of complications[16,17] and mortality.[18] In 1 study using INTERMACS data patients with at least 1 psychosocial risk factor (eg, substance abuse) were at increased hazards for infection, bleeding, pump thrombosis, and readmission compared with patients without any psychosocial risk.[19] However, none of these studies considered recovery as an outcome. In the Waiting for a New Heart Study, a multicenter study of patients with advanced HF, depression and social isolation, standardly assessed, were associated with lower rates of delisting due to clinical improvement, with an increased requirement of LVAD implantation while on the heart transplant waiting list, and decreased survival after heart transplant.[20,21] Taken together, these studies indicate that psychosocial risk factors contribute to clinical outcomes. However, data on potential sex differences in these characteristics and their associations with clinical outcomes including recovery among male and female recipients of LVADs are still lacking.

Thus, the aims of this study are to (1) present sex differences in preimplant clinical, demographic, and psychosocial characteristics in patients with primary CF-LVADs as DT; (2) to examine sex differences in the competing outcomes death, transplant, explant due to recovery, and device replacement due to complications after LVAD implantation; and (3) to explore whether sex differences in preimplant characteristics can explain sex differences in outcomes.

METHODS

Database

The INTERMACS data were provided by the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center. Anonymized data and materials have been made publicly available at the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute and can be accessed at https://biolincc.nhlbi.nih.gov/studies/intermacs/.

Study Population

With Trier University Institutional Review Board approval (number 66/2018), study data were extracted from the INTERMACS, a North American prospective registry of VAD recipients. Clinical, demographic, and psychosocial patient characteristics were recorded before implantation. (For more information see[2] and https://www.uab.edu/medicine/intermacs). Analyses were based on de-identified data of adult patients (age >18 years at implant), whose informed consent was obtained. Patients who received pulsatile-flow LVADs, right ventricular assist devices, biventricular assist devices, or total artificial hearts were excluded. Data from 8471 patients (20% women), registered between June 2006 and December 2017, with primary CF-LVADs in the device strategy DT, were analyzed.

Preimplant Variables

Clinical variables are shown in Table 1. Demographics and psychosocial variables also included behavioral factors (body mass index [BMI] as a proxy of healthy lifestyle, smoking status, history of alcohol and substance abuse) (see Table 1). Of note, working for an income, history of alcohol abuse, history of drug abuse, smoking status, severe depression, and limited social support were extracted from *concerns and contraindications for transplant* within INTERMACS, coded as *not applicable* and *applicable*, recorded by clinical staff. We did not consider quality of life because the amount of missing data exceeded 50%.[22]

Clinical Outcomes

Death, heart transplantation, device explant due to heart recovery, and device replacement due to complications (ie, device malfunction, device thrombosis, and infection) were considered as competing outcomes. Time until the first occurrence of 1 of these events served as dependent variable, subject to censoring by the end of follow-up.

Statistical Analysis

To handle missing values (if <30%) in the covariates, the semiparametric multiple imputation procedure of van Buuren and Oudshoorn was applied.[23,24] According to the *missing at random* assumption, imputation models were built based on variables that were correlated with the missing variable in the original data set and with missingness (Pearson correlation ≥0.1). Multiple imputation was computed using the package MICE 3.3.0 for R 3.5.0.[23,25] We set the number of imputations to m=100, to increase statistical power. Each of the 100 imputed data sets was then analyzed and the results were pooled using Rubin's rule. Complete-case sensitivity analyses for univariable event-specific Cox regression were run.

Preimplant variables were evaluated as independent variables. Continuous variables were described as mean and SDs, and categorical variables were summarized as percentages. Sex differences in preimplant characteristics were examined using t tests for continuous variables and chi-square tests for categorical variables.

Outcomes were analyzed as competing risks. This approach allows for examining all clinically relevant outcomes, either favorable or unfavorable, instead of simply censoring certain outcomes. Thus, only patients with the original device in place at the end of follow-up were censored. Time to first event was calculated as the time from CF-LVAD implantation until 1 of these outcomes occurred or until the end of follow-up in patients who remained under primary CF-LVAD support. Cumulative incidence functions, showing cumulative event probabilities, were estimated using the Aalen-Johansen estimator[26] and compared using Gray's method.[27] Univariable event-specific Cox regression was used to investigate the impact of sex and preimplant characteristics on event-specific hazards.[28]

In a first multivariable model, additional to sex, all clinical variables significantly associated with at least 1 of the outcomes were entered stepwise to evaluate whether the effects of sex were accounted for by disease severity or other clinical parameters. For the second multivariable model, additional to sex and clinical variables all significant demographic and psychosocial factors from the univariable analyses were added to the model, to test whether these factors account for sex differences in outcomes, independent of clinical parameters.

Table 1. Preimplant Clinical, Demographic, and Psychosocial Characteristic for Men and Women With CF-LVAD in Destination Therapy

Variables*	Men (n=6771)	Women (n=1690)	Total (n=8471)	*P* value
Clinical variables				
Ejection fraction grade, n (%)				
<20%	4260 (67.8)	1080 (67.9)	5346 (67.8)	0.763
20%–29%	1753 (27.9)	436 (27.4)	2192 (27.8)	
>30%	272 (4.3)	75 (4.7)	348 (4.4)	
Left ventricular end-diastolic diameter	6.82 (1.08)	6.47 (1.06)	6.75 (1.08)	<0.001
Left ventricular assist device axial, n (%)	6536 (96.5)	1594 (94.3)	8136 (96.0)	<0.001
INTERMACS profiles, n (%)				
1	960 (14.2)	246 (14.6)	1207 (14.3)	0.405
2	2244 (33.3)	560 (33.3)	2806 (33.3)	
3	2331 (34.6)	609 (36.2)	2946 (34.9)	
4	969 (14.4)	216 (12.8)	1185 (14.0)	
5–7	239 (3.5)	53 (3.1)	292 (3.5)	
Primary diagnosis, n (%)				
Ischemic	3905 (58.2)	593 (35.3)	4503 (53.6)	<0.001
Idiopathic	1743 (26.0)	570 (33.9)	2317 (27.6)	
Other	1064 (15.9)	518 (30.8)	1583 (18.8)	
Time since diagnosis, n (%)				
<1 mo	256 (3.9)	67 (4.1)	323 (4.0)	<0.001
1 mo–1 y	565 (8.7)	197 (12.1)	762 (9.4)	
1–2 y	373 (5.7)	160 (9.8)	533 (6.5)	
>2 y	5312 (81.6)	1202 (73.9)	6523 (80.1)	
Current implantable cardioverter-defibrillator, n (%)	5553 (82.6)	1295 (77.2)	6856 (81.5)	<0.001
Severe diabetes, n (%)	645 (11.8)	177 (12.7)	822 (12.0)	0.380
Allosensitization, n (%)	16 (0.3)	39 (2.8)	56 (0.8)	<0.001
Diastolic blood pressure	64.84 (11.51)	64.13 (11.74)	64.69 (11.56)	0.028
Systolic blood pressure	106.47 (16.32)	107.30 (17.55)	106.63 (16.57)	0.083
Mean arterial pressure	78.74 (11.14)	78.52 (11.58)	78.69 (11.22)	0.496
Heart rate	86.17 (16.56)	90.81 (17.25)	87.10 (16.79)	<0.001
Pulmonary systolic artery pressure	50.48 (14.81)	48.82 (14.59)	50.15 (14.78)	<0.001
Preoperative blood values				
Albumin g/dl	3.36 (0.63)	3.32 (0.65)	3.35 (0.64)	0.029
Bilirubin total mg/dl	1.39 (1.87)	1.14 (1.58)	1.34 (1.82)	<0.001
Serum urea nitrogen, mg/dl	31.59 (18.67)	28.02 (18.31)	30.87 (18.65)	<0.001
Creatinine, mg/dl	1.48 (0.67)	1.28 (0.66)	1.44 (0.67)	<0.001
Hemoglobin, g/dl	11.30 (2.14)	10.62 (1.78)	11.16 (2.09)	<0.001
Platelets, ×1000/μl	188.69 (76.10)	204.86 (84.17)	191.90 (78.01)	<0.001
Potassium, mmol/l	4.08 (0.48)	4.04 (0.48)	4.07 (0.48)	0.002
Sodium, mmol/l	135.12 (4.67)	135.70 (4.61)	135.24 (4.67)	<0.001
Medication, *n* (%)				
Beta blocker	5230 (79.7)	1260 (77.3)	6497 (79.2)	0.036
Angiotensin-converting enzyme inhibitor	2891 (46.2)	735 (47.0)	3630 (46.3)	0.558
Angiotensin receptor blocker	1064 (17.5)	356 (23.1)	1420 (18.6)	<0.001

(*Continued*)

Table 1. Continued

Variables*	Men (n=6771)	Women (n=1690)	Total (n=8471)	*P* value
Aldosterone	3369 (52.8)	949 (59.6)	4324 (54.2)	<0.01
Demographic and psychosocial characteristics				
Age, y	62.22 (12.30)	58.51 (13.01)	61.48 (12.53)	<0.001
Educational attainment, n (%)				
Up to primary	210 (4.3)	46 (3.7)	256 (4.2)	0.133
Secondary	2323 (47.2)	615 (49.4)	2940 (47.7)	
Postsecondary	1252 (25.4)	330 (26.5)	1582 (25.7)	
Tertiary	1136 (23.1)	253 (20.3)	1389 (22.5)	
Marital status, n (%)				
Single	976 (14.6)	353 (21.4)	1329 (16.0)	<0.001
Married/domestic partners	4752 (71.3)	836 (50.6)	5590 (67.2)	
Divorced	716 (10.7)	291 (17.6)	1007 (12.1)	
Widowed	222 (3.3)	171 (10.4)	393 (4.7)	
Race White, n (%)	4924 (72.7)	916 (54.2)	5840 (68.9)	<0.001
Working for income, n (%)	823 (13.2)	164 (10.5)	987 (12.7)	0.005
Body mass index, n (%)				
Underweight	199 (3.0)	79 (4.7)	278 (3.3)	<0.001
Nonobese	4134 (61.6)	883 (52.5)	5021 (59.8)	
Obese	1974 (29.4)	535 (31.8)	2513 (29.9)	
Morbidly obese	403 (6.0)	186 (11.1)	591 (7.0)	
Smoking history, n (%)				
Currently	343 (6.3)	100 (7.2)	443 (6.5)	<0.001
Past	1639 (30.1)	297 (21.4)	1938 (28.3)	
Never	3466 (63.6)	992 (71.4)	4466 (65.2)	
History alcohol abuse, n (%)	529 (9.7)	54 (3.9)	583 (8.5)	<0.001
History drug abuse, n (%)	444 (8.1)	86 (6.2)	530 (7.7)	0.017
Limited social support, n (%)	341 (6.3)	99 (7.1)	440 (6.4)	0.264
Severe depression, n (%)	137 (2.5)	59 (4.2)	196 (2.9)	<0.001

Original unimputed data. History alcohol abuse, history drug abuse, limited social support, and severe depression assessed by clinical judgments (applicable/not applicable). In the category *other* of primary diagnosis are included: dilated myopathy–postpartum (4.5% of all women), dilated myopathy–adriamycin (4.7% of all women). CF-LVAD indicates continuous-flow left ventricular assist device; and INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

*Unless otherwise indicated, data are presented as mean (SD).

Additionally, potential moderating effects of sex on the association between demographic and psychosocial characteristics with outcomes were examined by adding the interaction of sex with each of the factors after the main effects. The proportional hazards assumption was checked by the global goodness-of-fit test proposed by Schoenfeld.[29] Significance level was set at $P<0.05$. Analyses were performed using R, version 3.5.0, including the packages *cpmrsk* and *survival*.[25]

RESULTS

Sex Differences Preimplant

In the device strategy DT, 8471 patients (20% women) received a CF-LVAD. Women were less likely to have an ischemic primary diagnosis but more likely to have "other" diagnoses compared with men. Fewer women had an axial device type and current implantable cardioverter-defibrillator than men. Women also had a shorter time since first cardiac diagnosis (Table 1). They were significantly younger and were less likely to have a history of substance use (tobacco, alcohol, drugs) than men, but women were more likely to be non-White, unmarried, not working for an income, morbidly obese, currently smoking, and were more often perceived as depressed than men. However, men and women were seen as similar regarding limited social support and did not differ in educational attainment (Table 1).

Clinical Outcomes

During a median follow-up of 15.1 months (range=0.02–96.43 months), there were 2878 deaths,

818 heart transplants, 178 device explants due to cardiac recovery, and 1139 device replacements due to complications. Sex-specific cumulative incidence functions are shown in Figures 1 and 2. The probabilities for mortality and transplant did not differ significantly between women and men (mortality: P=0.124, transplant: P=0.403). For example, after 1 year the probability for death was 19.4% in women and 19.3% in men, for transplant 4.4% and 4.9%, respectively. Women had a significant higher probability for explant due to recovery (P<0.001). At the 1-, 2-, and 3-year follow-up the cumulative incidences of recovery were 1.9%, 3.7%, and 4.9% for women and 0.9%, 1.6%, and 1.9% for men, respectively. Women also had a higher probability for device replacement (P=0.019), with a cumulative incidence (1-, 2-, and 3-year follow-up) of 8.3%, 12.1%, and 15.2% for women and 6.2%, 10%, and 13.6% for men. Sex differences in reasons for device replacement (ie, device malfunction, device thrombosis, and infection) were not significant in a chi-square test.

Associations of Sex and Preimplant Characteristics With Clinical Outcomes

Results from regression analyses confirmed the described effects: Female sex was associated with an increased rate for explant due to recovery (hazard ratio [HR], 2.50; 95% CI, 1.82–3.33; P<0.001) and device replacement (HR, 1.20; 95% CI, 1.04–1.37; P=0.011) (Table 2). Univariable event-specific proportional hazards for clinical, demographic, and psychosocial characteristics and the 4 outcomes are available in Table S1. Complete-case analyses supported the missing at random assumption. In the first multivariable model controlling for clinical variables, the adjusted HR for sex on recovery remained significant, but decreased to 1.82 (95% CI, 1.30–2.56; P<0.001) (Table 2). This was mainly owing to the variable primary cardiac diagnosis. The diagnosis categories "idiopathic" and "other" were each independently associated with recovery compared with an ischemic diagnosis (Table S2). The category "other" included diagnoses that are typical for women, such as postpartum HF and HF due to adriamycin medication (breast cancer). The HR for female sex and device replacement remained similar to the univariable analysis (HR, 1.22; 95% CI, 1.04–1.41; P=0.012), indicating an independent sex effect. A comprehensive overview of the first multivariable model can be found in Table S2.

When demographic and psychosocial characteristics were also added, the adjusted HR for sex on the outcome recovery changed marginally to 1.85 (95% CI,

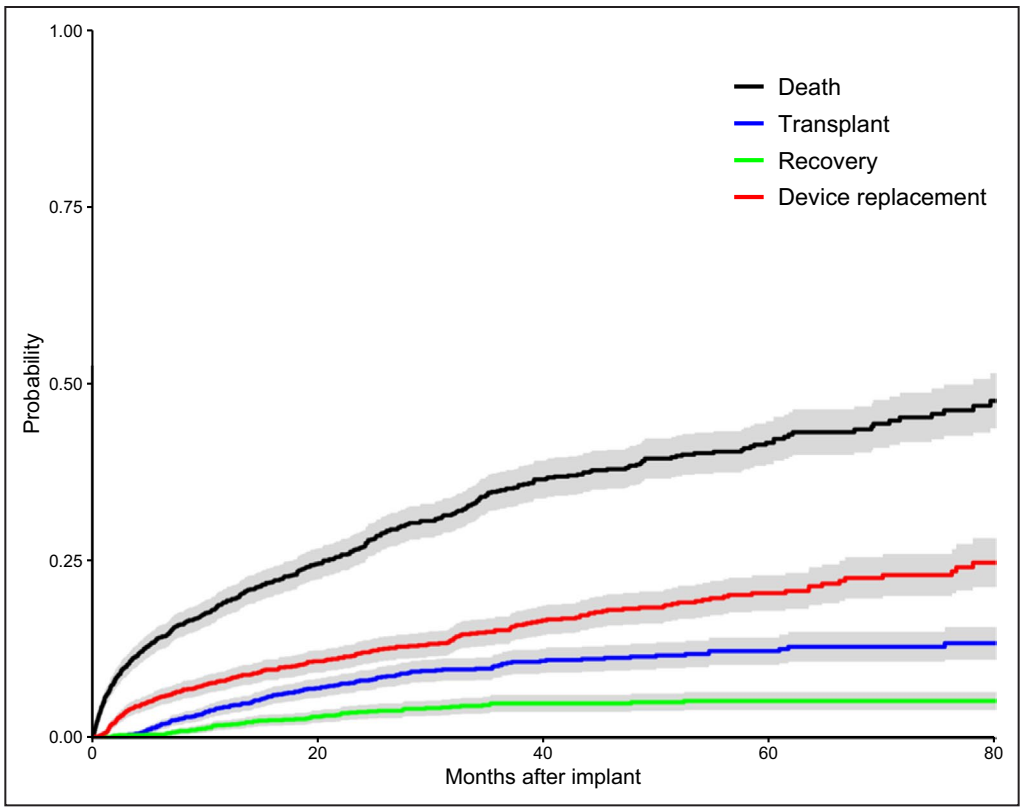

Figure 1. Women: Cumulative incidence functions with 95% CIs for outcomes death, transplant, explant due to recovery, and device replacement.

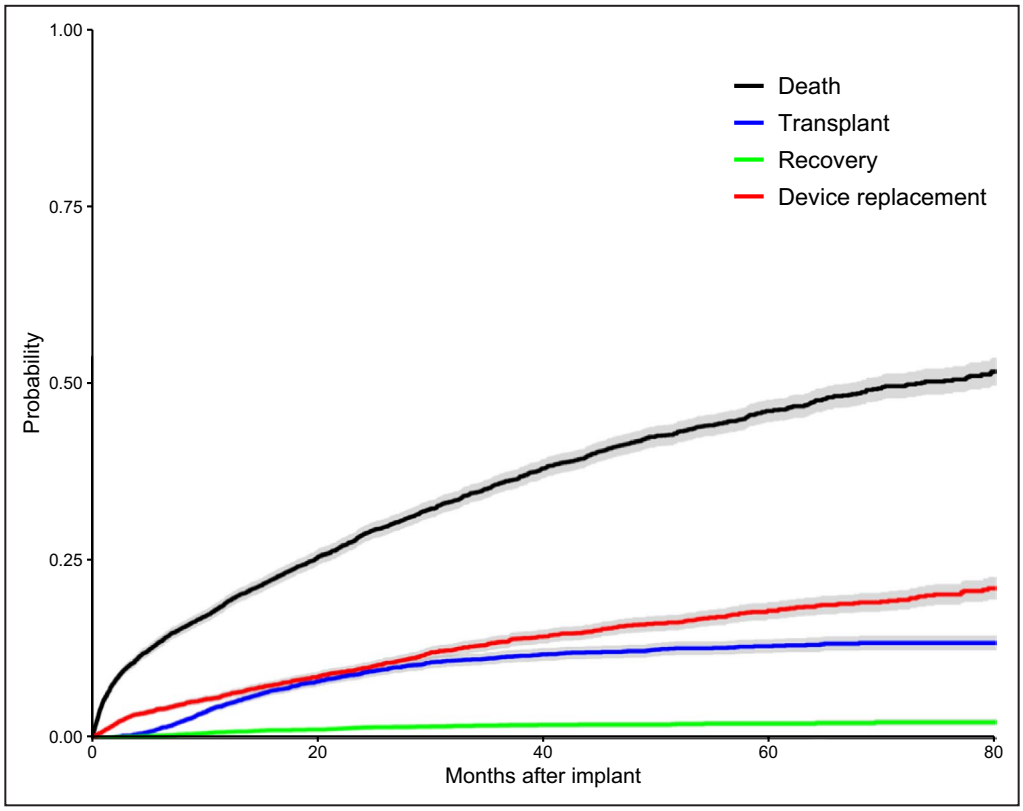

Figure 2. Men: Cumulative incidence functions with 95% CIs for outcomes death, transplant, explant due to recovery, and device replacement.

1.30–2.70; *P*<0.001) and to 1.22 (95% CI, 1.04–1.33; *P*=0.015) for device replacement (Table 2). Thus, there were no additional effects of demographic and psychosocial characteristics that accounted for the associations of sex with each of these outcomes.

The analyses of the second multivariable model (Table 2 and Table S3) also revealed that independent of sex, several demographic and psychosocial characteristics were associated with at least 1 of the 4 outcomes. For example, an advanced age, not working for an income, obesity, and currently smoking increased the rate for death.

A higher rate of transplantation was associated with younger age, working for an income, and nonobese BMI. Unexpectedly, only younger age predicted increased rates of explants due to recovery, independent of sex and clinical variables. An increased rate for device replacement was associated with advanced age and obese or morbidly obese BMI compared with nonobese BMI. After 6 and 12 months, the cumulative incidence for device replacement was 7% and 10.9% in patients who had morbid obesity and only 3.8% and 5.6% in patients who were not obese.

Testing whether sex moderated the associations of demographic and psychosocial variables with the outcomes explant due to recovery and device replacement yielded only 1 significant interaction. BMI was relevant for recovery only in men with men who had morbid obesity having an increased rate for recovery compared with men with a lower BMI.

DISCUSSION

Male and female patients with CF-LVAD intended for DT did not differ in the clinical outcomes death or transplant. However, women were significantly more likely than men to experience device explant due to cardiac recovery and device replacement over a median follow-up of 15.1 months since implant. The findings are based on competing risks analyses of all 4 outcomes, thereby avoiding overestimation of outcome probabilities[28] and contributing to a more detailed clinical outcome picture. For example, the finding that sex was associated with 1 favorable outcome (ie, recovery) as well as 1 unfavorable outcome (ie, device replacement) emerges only in the full competing risk analysis and would have been overlooked if device replacement and recovery had been censored, a common procedure in other investigations.

By restricting our analyses to the DT group with comparable cumulative incidences for transplant in

Table 2. Event-Specific Hazard Models for Sex and the Outcomes Death, Transplant, Explant Due to Recovery, and Device Replacement

Variable	Death (n=2878) HR (95% CI)	Transplant (n=818) HR (95% CI)	Recovery (n=178) HR (95% CI)	Device replacement (n=1139) HR (95% CI)
Univariable HR for female sex				
Female sex	0.97 (0.88–1.06)	0.97 (0.81–1.15)	2.50 (1.82–3.33)***	1.20 (1.04–1.37)*
Multivariable model 1: HR for female sex controlling for all clinical variables†				
Female sex	1.03 (0.93–1.14)	0.82 (0.68–0.99)*	1.82 (1.30–2.56)***	1.22 (1.04–1.41)*
Multivariable model 2: HR for female sex controlling for additional demographic and psychosocial characteristics†				
Female sex	1.02 (0.92–1.12)	0.88 (0.72–1.08)	1.85 (1.30–2.70)***	1.22 (1.04–1.33)*
Age, y	1.01 (1.01–1.02)***	0.96 (0.95–0.97)***	0.96 (0.95–0.97)***	0.99 (0.98–0.99)***
Marital status				
Married/domestic partners	[Ref]	[Ref]	[Ref]	[Ref]
Single	1.08 (0.96–1.22)	0.83 (0.68–1.02)	0.83 (0.55–1.26)	0.91 (0.76–1.08)
Divorced/separated	1.10 (0.98–1.25)	1.18 (0.95–1.45)	1.12 (0.72–1.75)	0.95 (0.79–1.15)
Widowed	1.14 (0.97–1.34)	0.75 (0.48–1.19)	1.25 (0.57–2.78)	0.74 (0.53–1.04)
Working for income	0.88 (0.77–1.00)*	1.79 (1.48–2.16)***	1.41 (0.94–2.12)	0.86 (0.70–1.06)
Body mass index				
Non obese	[Ref]	[Ref]	[Ref]	[Ref]
Underweight	1.08 (0.87–1.33)	0.79 (0.51–1.23)	0.69 (0.27–1.73)	0.86 (0.58–1.30)
Obese	1.11 (1.01–1.20)*	0.80 (0.68–0.95)**	1.04 (0.74–1.48)	1.26 (1.10–1.44)***
Morbidly obese	1.07 (0.90–1.27)	0.42 (0.30–0.58)***	1.12 (0.65–1.92)	1.38 (1.11–1.71)**
Smoking history				
Never	[Ref]	[Ref]	[Ref]	[Ref]
Past	1.07 (0.97–1.18)	0.90 (0.75–1.09)	0.77 (0.50–1.20)	1.10 (0.95–1.28)
Currently	1.22 (1.01–1.47)*	0.76 (0.55–1.05)	1.60 (0.94–2.73)	1.22 (0.94–1.59)
History of alcohol abuse	0.96 (0.79–1.16)	1.19 (0.92–1.55)	1.63 (0.97–2.72)	1.15 (0.90–1.47)
History of drug abuse	0.90 (0.72–1.12)	0.90 (0.68–1.20)	0.88 (0.50–1.55)	1.10 (0.86–1.41)
Limited social support	0.92 (0.75–1.14)	0.99 (0.73–1.35)	1.61 (0.94–2.74)	1.16 (0.90–1.50)
Severe depression	0.82 (0.60–1.13)	0.89 (0.56–1.42)	1.46 (0.68–3.17)	1.36 (0.98–1.88)

Imputed data (m=100). HR indicates hazard ratio. Each cell contains the HR adjusted for the other variables in the given hazard model.

†Clinical variables not depicted here, complete multivariable model 1 and 2 can be found in Tables S2–S3. Because of a suppressor effect of race on age, this variable was not used in the multivariable models. The results for death and transplant should be interpreted as time-averaged HRs, as the proportional hazard assumption was violated for these outcomes in the multivariable models.

***P<0.001

**P<0.01

*P<0.05

both sexs, we avoided a BTT-specific selection bias.[10,11] Some of the previous reports (mostly based on patients intended for BTT or combined strategies) suggest that female recipients of LVADs may have worse clinical outcomes compared with their male counterparts.[2,3,5,9] However, women intended for BTT are generally more medically disadvantaged (more severely ill, less ideal transplant candidates) when receiving a device than men.[30,31] Therefore, compared with men, they are less likely to be transplanted, resulting in longer waitlist time and time on device support, thereby increasing their risk for death with LVAD.[10] Focusing our analyses on DT patients helps to disentangle sex differences in death rates from this selection bias that may be responsible for the higher death rates observed in women intended for BTT.[9,10] Concentrating on the DT group resulted in equal probabilities for death in women and men. This supports the rational of considering device strategies separately and to differentiate between patients in short- and long-term support. This approach leads to a better understanding of sex-related differences in clinical outcomes, especially as more and more patients receive LVADs as long-term support today.[1]

Of the 4 outcomes evaluated in the present investigation, cardiac recovery has received the least attention in the literature. In the present DT sample, women had a better chance for explant due to recovery than men. This finding is in line with the report that women are generally overrepresented in the a priori bridge-to-recovery group (n=125, 37.6% women in INTERMACS until 2015), which is characterized by young age, shorter time since cardiac diagnosis, and nonischemic

diagnoses, compared with a non-bridge-to-recovery group.[13] Furthermore, female sex was found to be a predictor for partial recovery, as indicated by substantial improvement of LV function on CF-LVAD support, but without subsequent device explantation in a general LVAD cohort where all device strategies were combined.[12]

The increased rate for explant due to recovery in women compared with men was reduced after controlling for clinical variables. Specifically, sex differences in underlying diagnoses partially explained the higher recovery rates in women. Women were less likely than men to have coronary artery disease but were more likely to have sex-specific diagnoses: Adriamycin-induced HF represented 10.4% (and postpartum HF 7.5%) of all diagnoses in women who experienced recovery compared with 4.7% (and 3.6%) in those who died. HF induced by adriamycin, medication often used for breast cancer, or HF induced by pregnancy may be more easily reversed if detected early,[12,32] suggesting that female hearts may have the ability to recover in these instances. Clearly, more research on this matter is needed.

However, cardiac diagnosis did only partially account for the sex effect in recovery. After controlling for all clinical variables, the rate for women to experience a device explant due to recovery was still increased by 82% compared with men. Reasons for this sex difference need to be further examined. Keeping in mind that women with HF have been underrepresented in registries and clinical trials for decades, a shift to women-specific research to determine which women might benefit from receiving LVAD implantation is clearly needed.[33]

Interestingly, women in DT still had a significantly higher rate of device replacement compared with men, independent of clinical, demographic, and psychosocial covariates. Device-related factors (eg, specific pump types for women) were not associated with this outcome. Device replacement (eg, due to device malfunction, pump thrombosis, infection) can be seen as a proxy for complications and adverse events.[34,35] Therefore, our findings observed in women in DT are in line with prior studies in the general LVAD population,[3,6,14] emphasizing women's generally increased risk for complications after device implantation independent of competing outcomes.

It is noteworthy that sex differences in demographic and psychosocial variables (eg, unmarried, depressed) did not contribute to women's adverse events. It is conceivable that other factors (eg, device acceptance, mood, coping), not included in INTERMACS, could have influenced the occurrence of adverse events.[36,37] In line with this reasoning is the observation from a previous INTERMACS report indicating that women report more problems in quality of life dimensions (ie, usual activities, pain/discomfort, and anxiety/depression) than men before and at 3 and 6 months after LVAD implant.[38] These psychosocial problems might be associated with reduced adherence behaviors and thereby contribute to serious complications. Unfortunately, the poor quality of psychosocial data (quality of life data > 50% missing) limits their use in prediction models of sex-specific clinical outcomes. It is also conceivable that the devices implanted are not optimal for the female body, thereby increasing device replacement among women. However, as new device generations become more suitable for the female body, device-related causes for sex differences in adverse events may become less likely in the future.[8,39]

The increasing number of studies that report women to be disadvantaged regarding adverse events after LVAD implant[3,6,14] raises the question of adequate patient care for women. It is well known that women are underrepresented in clinical trials and referred to cardiac specialists later and in a more advanced status of disease than men.[33,40] More research regarding health status and psychosocial factors affecting women's and men's decisions to accept or decline LVAD therapy[41] might further elucidate sex differences in outcomes.

At the time point of a long-term LVAD implant, disease severity (eg, left ventricular ejection fraction, INTERMACS profile) appeared to be comparable between women and men. Apparently, the focus should shift to sex and gender differences in patient care *after* implant. Traditionally, women provide support to chronically ill male spouses.[40] Who is taking care of the women needing support after LVAD implant? Women seem to be less likely to have spouses as their primary support in advanced HF and rather choose parents and adult children.[42] The impact of traditional gender roles and the perceived social support on outcomes after LVAD implant needs to be further investigated.

Independent of sex, patients who had morbid obesity and obesity in this DT subgroup had an increased hazard to experience device replacement as well as higher death rates and reduced rates for transplantation. A similar finding of increased rates of infectious and device-related adverse events was reported in the IMACS registry, including all device strategies.[35] These findings highlight the need to clarify who might benefit from early weight reduction programs (eg, nutritional counseling, regular exercise) in this patient population.

Sex differences in preimplant demographic and psychosocial characteristics did neither contribute to women's increased rate of recovery nor to their increased rate of device replacement. Even when analyzing the influence of psychosocial characteristics on outcomes independent of sex, the variables of limited social support, substance abuse (drug and alcohol),

and severe depression were not associated with any of the 4 outcomes. This is unexpected considering that the 2018 International Society for Heart and Lung Transplantation Consensus recommendations[43] highlighted the role of these psychosocial domains for outcome prediction. A recent retrospective study, following these recommendations, found indicators of psychosocial risk, particularly mental health problem severity, nonadherence, and substance use as related to adverse events and device replacement.[44] It is noteworthy that in this single-center study, psychosocial data were systematically recorded and categorized, whereas the present study used clinical judgments intended to flag potential contraindications for implant.

A systematized process of psychosocial data collection and usage of psychometrically sound assessments may help to obtain complete data across INTERMACS sites. The training of the clinical staff assessing these characteristics may also play a key role in further improving data quality. Eventually, a focus on psychosocial data assessment might lead to a better description of patient selection criteria and patient care.

Limitations

Though INTERMACS represents a valuable data set, standardized psychological data are included only as quality of life questionnaires, which typically have a high amount of missing data in these registries (> 50%).[22] This was also the case in this DT sample. This led us to explore other, more frequently assessed aspects of psychosocial risk recorded in INTERMACS. These were based on clinical judgments from the category *concerns and contraindications*. These characteristics, although related to sex in the expected direction and possessing high face validity, did not contribute to sex differences in outcomes. The ways to capture these psychosocial aspects are not standardized in INTERMACS and, as a result, vary among participating sites,[45,46] reducing their usefulness for empirical analyses.

CONCLUSIONS

Of the 4 clinical outcomes considered, women with CF-LVAD as DT were more likely to experience device explant due to (1) recovery, particularly when presenting with female-specific diagnoses; and (2) need for device replacement, regardless of clinical, demographic, and psychosocial characteristics. These findings illustrate the importance of promoting sex-sensitive research, thereby considering multiple clinical outcomes and avoiding selection bias by differentiating between device strategies. Employing standardized assessments of psychosocial characteristics in lieu of subjective clinical impressions may further increase the understanding of sex differences in patients with LVAD.

ARTICLE INFORMATION

Received July 19, 2021; accepted January 19, 2022.

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Acknowledgments

This article was prepared using INTERMACS Research Materials obtained from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of INTERMACS or the National Heart, Lung, and Blood Institute. We thank all clinicians who contributed data to the INTERMACS database. Author Contributions: HS and GW were responsible for conception and design of the study. LM, HS, and GW were responsible for analyses, interpretation, drafting, and revising the article. JB provided the methodological approach and contributed to analyses, writing, and revising of the paper.

Sources of Funding

This work was supported by grants from the German Research Foundation (HS, GW; SP945/2-1), the Alexander von Humboldt Foundation (GW, HS, USA /1071425), and Trier University.

Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table of Contents

Table S1. Univariable event-specific hazard models for death, transplant, recovery, and device replacement

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Female gender	0.97 (0.88-1.06)	0.97 (0.81-1.15)	2.50 (1.85-3.33)***	1.20 (1.04-1.37)*
Ejection fraction				
>30	[Ref]	[Ref]	[Ref]	[Ref]
20-29	0.84 (0.71-1.00)	1.05 (0.68-1.61)	0.99 (0.42-2.36)	1.38 (0.97-1.96)
<20	0.73 (0.62-0.86)***	1.49 (0.99-2.23)	1.38 (0.61-3.13)	1.36 (0.97-1.91)
LVEDD	0.89 (0.86-0.92)***	1.08 (1.01-1.16)*	0.86 (0.74-1.00)	1.13 (1.07-1.20)***
LVAD axial	0.78 (0.63-0.97)*	0.56 (0.39-0.81)**	1.32 (0.42-4.17)	1.43 (0.88-2.33)
INTERMACS profile				
5-7	[Ref]	[Ref]	[Ref]	[Ref]
4	1.10 (0.89-1.36)	0.87 (0.57-1.33)	1.54 (0.45-5.24)	1.02 (0.75-1.40)

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
3	1.05 (0.86-1.28)	1.14 (0.77-1.68)	2.91 (0.92-9.24)	0.98 (0.72-1.31)
2	1.12 (0.92-1.37)	1.30 (0.88-1.92)	1.98 (0.62-6.36)	0.98 (0.72-1.32)
1	1.31 (1.06-1.62)*	1.96 (1.31-2.93)**	4.64 (1.43-15.04)*	1.11 (0.81-1.54)
Primary diagnosis				
Ischemic	[Ref]	[Ref]	[Ref]	[Ref]
Idiopathic	0.77 (0.71-0.84)***	1.40 (1.19-1.64)***	2.42 (1.69-3.46)***	1.17 (1.02-1.34)*
Other	0.82 (0.74-0.91)***	1.56 (1.30-1.86)***	2.98 (2.04-4.34)***	1.30 (1.11-1.51)***
Time since first diagnosis				
<1 month	[Ref]	[Ref]	[Ref]	[Ref]
1 month – 1 year	0.94 (0.72-1.22)	0.58 (0.41-0.84)**	1.20 (0.69-2.07)	1.09 (0.73-1.63)
1-2 years	1.21 (0.93-1.59)	0.71 (0.48-1.04)	0.78 (0.42-1.48)	1.08 (0.70-1.66)

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
>2 years	1.32 (1.05-1.65)*	0.55 (0.41-0.74)***	0.22 (0.13-0.37)***	1.24 (0.87-1.76)
Current ICD	1.13 (1.02-1.25)*	0.81 (0.68-0.96)*	0.25 (0.19-0.34)***	1.16 (0.99-1.37)
Severe diabetes	1.07 (0.95-1.22)	1.06 (0.85-1.34)	0.98 (0.58-1.63)	1.18 (0.97-1.43)
Mean arterial pressure	1.00 (0.99-1.00)*	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1.01 (1.00-1.01)*
Heart rate	1.00 (0.99-1.00)***	1.01 (1.01-1.02)***	1.02 (1.02-1.03)***	1.00 (1.00-1.01)**
Pul. systolic artery pressure	1.00 (1.00-1.00)	1.00 (1.00-1.01)	0.98 (0.97-0.99)***	1.00 (1.00-1.00)
Albumin g/dL	0.89 (0.84-0.94)***	0.94 (0.84-1.05)	0.75 (0.60-0.94)*	1.07 (0.98-1.18)
Bilirubin total mg/dL	1.02 (1.01-1.04)**	1.03 (1.00-1.06)*	0.93 (0.80-1.08)	1.02 (0.99-1.04)
BUN mg/dL	1.01 (1.01-1.01)***	0.99 (0.99-0.99)***	0.97 (0.96-0.99)***	1.00 (0.99-1.00)*
Creatinine mg/dL	1.07 (1.01-1.14)*	0.87 (0.74-1.01)	1.30 (1.05-1.61)*	1.07 (0.97-1.19)
Hemoglobin g/dL	0.94 (0.92-0.96)***	1.02 (0.98-1.05)	1.00 (0.93-1.07)	1.05 (1.02-1.08)***

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Platelets x1000/µL	1.00 (1.00-1.00)***	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)***
Beta blocker	1.02 (0.93-1.12)	0.78 (0.66-0.92)**	0.55 (0.40-0.76)***	1.02 (0.88-1.18)
ACE	0.91 (0.84-0.98)*	1.11 (0.97-1.28)	0.88 (0.65-1.20)	0.96 (0.85-1.08)
ARB	0.93 (0.84-1.03)	0.98 (0.81-1.18)	0.66 (0.41-1.06)	1.00 (0.85-1.18)
Aldosterone	0.91 (0.85-0.98)*	0.99 (0.86-1.14)	0.92 (0.68-1.24)	1.30 (1.15-1.46)***
Age in years	1.02 (1.02-1.02)***	0.97 (0.96-0.97)***	0.95 (0.94-0.95)***	0.98 (0.98-0.98)***
Educational attainment				
Up to primary	[Ref]	[Ref]	[Ref]	[Ref]
Secondary	0.95 (0.78-1.16)	1.23 (0.79-1.90)	0.99 (0.46-2.12)	1.13 (0.80-1.59)
Post secondary	0.90 (0.73-1.11)	1.34 (0.85-2.10)	0.87 (0.39-1.93)	1.16 (0.82-1.65)
Tertiary	0.95 (0.77-1.17)	1.17 (0.75-1.83)	0.71 (0.31-1.62)	0.99 (0.69-1.40)

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Marital status				
Married/domestic partners	[Ref]	[Ref]	[Ref]	[Ref]
Single	0.83 (0.74-0.93)**	1.54 (1.29-1.84)***	2.54 (1.79-3.60)***	1.26 (1.08-1.47)**
Divorced/separated	0.96 (0.85-1.08)	1.43 (1.17-1.74)***	1.95 (1.28-2.96)**	1.17 (0.98-1.40)
Widowed	1.19 (1.02-1.39)*	0.58 (0.37-0.90)*	1.11 (0.51-2.40)	0.69 (0.50-0.96)*
Race, white	1.30 (1.20-1.41)***	0.84 (0.73-0.97)*	0.95 (0.69-1.30)	1.00 (0.88-1.13)
Working for income	0.85 (0.75-0.97)*	2.02 (1.70-2.41)***	2.01 (1.38-2.92)***	0.86 (0.71-1.05)
BMI				
Non obese	[Ref]	[Ref]	[Ref]	[Ref]
Underweight	1.07 (0.87-1.32)	0.89 (0.58-1.38)	1.09 (0.44-2.69)	0.91 (0.61-1.36)
Obese	0.99 (0.91-1.07)	1.01 (0.86-1.17)	1.15 (0.83-1.61)	1.43 (1.26-1.63)***

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Morbidly obese	0.80 (0.68-0.94)**	0.74 (0.54-1.02)	1.74 (1.07-2.84)*	1.91 (1.58-2.33)***
Smoking history				
Never	[Ref]	[Ref]	[Ref]	[Ref]
Past	1.00 (0.91-1.10)	0.99 (0.84-1.18)	0.90 (0.61-1.34)	1.21 (1.05-1.39)**
Currently	1.03 (0.86-1.23)	1.13 (0.83-1.55)	2.43 (1.50-3.94)***	1.42 (1.10-1.83)**
History of alcohol abuse	0.84 (0.71-1.00)	1.48 (1.17-1.89)**	2.22 (1.41-3.48)***	1.36 (1.09-1.70)**
History of drug abuse	0.70 (0.58-0.86)***	1.49 (1.15-1.92)**	2.32 (1.45-3.70)***	1.52 (1.22-1.90)***
Limited social support	0.82 (0.68-1.00)	1.19 (0.89-1.60)	2.49 (1.54-4.00)***	1.37 (1.08-1.76)*
Severe depression	0.77 (0.57-1.05)	1.01 (0.63-1.61)	2.01 (0.97-4.19)	1.70 (1.23-2.33)**

Imputed data (*m* = 100). HR, hazard ratio; CI, confidence interval; BMI, body mass index; LVEDD, left ventricular end-diastolic diameter; ICD, implantable cardioverter-defibrillator; BUN, blood urea nitrogen; ACE, Angiotensin-converting-enzyme inhibitor; ARB, Angiotensin II receptor blocker. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

Table S2. Multivariable event-specific hazard models for gender and clinical variables for death, transplant, explant due to recovery, and device replacement

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Female gender	1.03 (0.93-1.14)	0.82 (0.68-0.99)*	1.82 (1.30-2.56)***	1.22 (1.04-1.41)*
Ejection fraction				
>30	[Ref]	[Ref]	[Ref]	[Ref]
20-29	0.92 (0.77-1.09)	1.05 (0.68-1.61)	0.91 (0.38-2.18)	1.29 (0.91-1.84)
<20	0.85 (0.72-1.01)	1.33 (0.88-2.01)	1.16 (0.50-2.69)	1.16 (0.82-1.64)
LVEDD	0.91 (0.87-0.95)***	1.03 (0.96-1.12)	1.00 (0.84-1.19)	1.11 (1.04-1.19)**
LVAD axial	0.80 (0.65-0.99)*	0.62 (0.43-0.89)*	1.52 (0.48-4.76)	1.45 (0.89-2.33)
INTERMACS profile				

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
5-7	[Ref]	[Ref]	[Ref]	[Ref]
4	1.06 (0.86-1.31)	0.91 (0.59-1.39)	1.74 (0.51-5.97)	1.04 (0.76-1.43)
3	1.06 (0.87-1.29)	1.10 (0.74-1.63)	2.78 (0.87-8.86)	0.98 (0.73-1.33)
2	1.09 (0.89-1.33)	1.22 (0.82-1.80)	1.81 (0.56-5.89)	1.00 (0.74-1.36)
1	1.20 (0.96-1.50)	1.78 (1.17-2.71)	3.07 (0.92-10.23)	1.33 (0.95-1.87)
Primary diagnosis				
Ischemic	[Ref]	[Ref]	[Ref]	[Ref]
Idiopathic	0.85 (0.77-0.93)***	1.30 (1.10-1.54)**	2.11 (1.44-3.11)***	1.01 (0.88-1.17)
Other	0.90 (0.80-1.00)*	1.42 (1.18-1.72)***	2.10 (1.39-3.18)***	1.14 (0.97-1.34)
Time since first diagnosis				

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
<1 month	[Ref]	[Ref]	[Ref]	[Ref]
1 month – 1 year	1.11 (0.85-1.46)	0.62 (0.43-0.91)*	1.43 (0.79-2.56)	1.00 (0.67-1.52)
1-2 years	1.44 (1.08-1.92)*	0.86 (0.57-1.30)	1.34 (0.67-2.70)	0.97 (0.62-1.52)
>2 years	1.54 (1.20-1.97)***	0.70 (0.50-0.99)*	0.52 (0.28-0.98)*	1.14 (0.77-1.67)
Current ICD	1.16 (1.03-1.30)*	0.94 (0.76-1.16)	0.44 (0.30-0.64)***	1.05 (0.87-1.27)
Mean arterial pressure	1.00 (0.99-1.00)	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1.00 (1.00-1.01)
Heart rate	1.00 (0.99-1.00)**	1.01 (1.00-1.01)**	1.01 (1.00-1.02)	1.00 (1.00-1.01)*
Pul. systolic artery pressure	1.00 (0.99-1.00)**	1.00 (1.00-1.01)	0.99 (0.98-1.00)	1.00 (0.99-1.00)
Albumin g/dl	0.94 (0.88-1.00)*	1.05 (0.92-1.19)	0.85 (0.65-1.10)	1.02 (0.92-1.13)
Bilirubin total mg/dl	1.02 (1.01-1.04)*	1.01 (0.98-1.05)	0.93 (0.79-1.09)	1.02 (0.99-1.05)

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
BUN mg/dl	1.01 (1.00-1.01)***	0.99 (0.99-1.00)*	0.98 (0.97-0.99)**	1.00 (0.99-1.00)*
Creatinine mg/dL	1.07 (1.01-1.13)*	0.83 (0.71-0.98)*	1.32 (1.07-1.62)**	1.09 (0.99-1.21)
Hemoglobin g/dl	0.96 (0.92-1.13)***	1.02 (0.99-1.06)	1.09 (1.00-1.18)*	1.05 (1.02-1.09)**
Platelets x1000/µl	1.00 (1.00-1.00)***	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)**
Beta blocker	1.02 (0.92-1.13)	0.86 (0.72-1.03)	0.79 (0.55-1.13)	1.00 (0.85-1.17)
ACE	0.96 (0.88-1.04)	1.12 (0.96-1.30)	0.88 (0.64-1.23)	0.90 (0.79-1.02)
Aldosterone	0.98 (0.90-1.06)	0.97 (0.83-1.12)	1.05 (0.76-1.46)	1.24 (1.09-1.41)***

Imputed data (*m* = 100). HR, hazard ratio; CI, confidence interval; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; BUN, blood urea nitrogen; ACE, Angiotensin-converting-enzyme inhibitor. Each cell contains the HR adjusted for the other variables in the given hazard model. Because of a suppressor effect of race on age, this variable was not used in the multivariable models. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

Table S3. Multivariable event-specific hazard models for gender, clinical, demographic and psychosocial characteristics for death, transplant, explant due to recovery, and device replacement

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Female gender	1.02 (0.92-1.12)	0.88 (0.72-1.08)	1.85 (1.30-2.70)***	1.22 (1.04-1.33)*
Ejection fraction				
>30	[Ref]	[Ref]	[Ref]	[Ref]
20-29	0.92 (0.77-1.10)	1.01 (0.65-1.56)	1.01 (0.65-1.56)	1.29 (0.91-1.84)
<20	0.86 (0.73-1.02)	1.22 (0.81-1.85)	1.22 (0.81-1.85)	1.18 (0.83-1.67)
LVEDD	0.92 (0.88-0.96)***	1.00 (0.93-1.09)	1.00 (0.93-1.09)	1.07 (1.00-1.14)
LVAD axial	0.76 (0.62-0.95)*	0.70 (0.48-1.01)	1.59 (0.50-5.00)	1.47 (0.90-2.50)
INTERMACS profile				
5-7	[Ref]	[Ref]	[Ref]	[Ref]

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
4	1.05 (0.85-1.29)	0.92 (0.60-1.42)	0.92 (0.60-1.42)	1.04 (0.76-1.43)
3	1.06 (0.87-1.30)	1.06 (0.72-1.57)	1.06 (0.72-1.57)	0.99 (0.73-1.33)
2	1.11 (0.90-1.36)	1.17 (0.79-1.74)	1.17 (0.79-1.74)	0.99 (0.73-1.34)
1	1.29 (1.03-1.62)*	1.41 (0.92-2.15)	1.41 (0.92-2.15)	1.23 (0.87-1.73)
Primary diagnosis				
Ischemic	[Ref]	[Ref]	[Ref]	[Ref]
Idiopathic	0.91 (0.83-1.00)*	1.07 (0.89-1.28)	1.67 (1.10-2.53)*	0.92 (0.79-1.07)
Other	0.98 (0.88-1.10)	1.04 (0.85-1.27)	1.39 (0.89-2.19)	1.01 (0.85-1.20)
Time since first diagnosis				
<1 month	[Ref]	[Ref]	[Ref]	[Ref]

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
1 month – 1 year	1.12 (0.86-1.47)	0.67 (0.46-0.99)*	1.67 (0.91-3.10)	1.00 (0.66-1.51)
1-2 years	1.39 (1.04-1.85)*	1.11 (0.73-1.70)	1.91 (0.92-3.94)	1.02 (0.65-1.61)
>2 years	1.44 (1.12-1.85)**	0.96 (0.67-1.37)	0.75 (0.39-1.44)	1.20 (0.82-1.78)
Current ICD	1.12 (1.00-1.26)	1.16 (0.93-1.43)	0.51 (0.35-0.75)***	1.08 (0.90-1.31)
Mean arterial pressure	1.00 (1.00-1.00)	1.00 (0.99-1.01)	1.01 (0.99-1.02)	1.00 (1.00-1.01)
Heart rate	1.00 (1.00-1.00)	1.00 (1.00-1.01)	1.00 (0.99-1.01)	1.00 (1.00-1.01)
Pul. systolic artery pressure	1.00 (0.99-1.00)*	1.00 (1.00-1.01)	0.99 (0.97-1.00)*	1.00 (0.99-1.00)
Albumin g/dl	0.95 (0.89-1.01)	0.98 (0.87-1.11)	0.81 (0.63-1.03)	0.98 (0.89-1.09)
Bilirubin Total mg/dl	1.02 (1.01-1.04)**	1.00 (0.96-1.04)	0.89 (0.76-1.05)	1.02 (0.99-1.04)
BUN mg/dl	1.01 (1.00-1.01)***	1.00 (0.99-1.00)	0.98 (0.97-1.00)**	1.00 (0.99-1.00)

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Creatinine mg/dL	1.07 (1.01-1,14)*	0.87 (0.74-1.01)	1.3 (1.05-1.61)*	1.07 (0.97-1.19)
Hemoglobin g/dl	0.96 (0.94-0.97)***	1.03 (0.99-1.06)	1.10 (1.01-1.19)*	1.05 (1.02-1.08)**
Platelets x1000/µl	1.00 (1.00-1.00)**	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)*
Beta blocker	1.02 (0.92-1.12)	0.89 (0.75-1.06)	0.84 (0.58-1.21)	0.99 (0.84-1.16)
ACE	0.97 (0.90-1.05)	1.05 (0.90-1.22)	0.80 (0.57-1.12)	0.88 (0.78-1.00)*
Aldosterone	1.00 (0.93-1.09)	0.90 (0.78-1.05)	0.94 (0.67-1.31)	1.18 (1.04-1.34)*
Age in years	1.01 (1.01-1.02)***	0.96 (0.95-0.97)***	0.96 (0.95-0.97)***	0.99 (0.98-0.99)***
Marital status				
Married/domestic partners	[Ref]	[Ref]	[Ref]	[Ref]
Single	1.08 (0.96-1.22)	0.83 (0.68-1.02)	0.83 (0.55-1.26)	0.91 (0.76-1.08)

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Divorced/separated	1.10 (0.98-1.25)	1.18 (0.95-1.45)	1.12 (0.72-1.75)	0.95 (0.79-1.15)
Widowed	1.14 (0.97-1.34)	0.75 (0.48-1.19)	1.25 (0.57-2.78)	0.74 (0.53-1.04)
Working for income	0.88 (0.77-1.00)*	1.79 (1.48-2.16)***	1.41 (0.94-2.12)	0.86 (0.70-1.06)
BMI				
Non obese	[Ref]	[Ref]	[Ref]	[Ref]
Underweight	1.08 (0.87-1.33)	0.79 (0.51-1.23)	0.69 (0.27-1.73)	0.86 (0.58-1.30)
Obese	1.11 (1.01-1.20)*	0.80 (0.68-0.95)**	1.04 (0.74-1.48)	1.26 (1.10-1.44)***
Morbidly obese	1.07 (0.90-1.27)	0.42 (0.30-0.58)***	1.12 (0.65-1.92)	1.38 (1.11-1.71)**
Smoking history				
Never	[Ref]	[Ref]	[Ref]	[Ref]

Variable	Death (*n* = 2878) HR (95% CI)	Transplant (*n* = 818) HR (95% CI)	Recovery (*n* = 178) HR (95% CI)	Device replacement (*n* = 1139) HR (95% CI)
Past	1.07 (0.97-1.18)	0.90 (0.75-1.09)	0.77 (0.50-1.20)	1.10 (0.95-1.28)
Currently	1.22 (1.01-1.47)*	0.76 (0.55-1.05)	1.60 (0.94-2.73)	1.22 (0.94-1.59)
History of alcohol abuse	0.96 (0.79-1.16)	1.19 (0.92-1.55)	1.63 (0.97-2.72)	1.15 (0.90-1.47)
History of drug abuse	0.90 (0.72-1.12)	0.90 (0.68-1.20)	0.88 (0.50-1.55)	1.10 (0.86-1.41)
Limited social support	0.92 (0.75-1.14)	0.99 (0.73-1.35)	1.61 (0.94-2.74)	1.16 (0.90-1.50)
Severe depression	0.82 (0.60-1.13)	0.89 (0.56-1.42)	1.46 (0.68-3.17)	1.36 (0.98-1.88)

Imputed data (*m* = 100). HR, hazard ratio; CI, confidence interval; BMI, body mass index; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; BUN, blood urea nitrogen; ACE, Angiotensin-converting-enzyme inhibitor. Each cell contains the HR adjusted for the other variables in the given hazard model. Because of a suppressor effect of race on age, this variable was not used in the multivariable models. The results for death and transplant should be interpreted as time-averaged hazard ratios, as the proportional hazard assumption was violated for these outcomes in the multiple models. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$