Gender Differences in Clinical Outcomes After Left Ventricular Assist Device (LVAD) Implantation – The Role of Psychosocial Risk Factors

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Abstract

Left ventricular assist devices (LVADs) have become a valuable treatment for patients with advanced heart failure. Women appear to be disadvantaged in the usage of LVADs and concerning clinical outcomes such as death and adverse events after LVAD implant. Contrary to typical clinical characteristics (e.g., disease severity), device-related factors such as the intended device strategy, bridge to a heart transplantation or destination therapy, are often not considered in research on gender differences. In addition, the relevance of pre-implant psychosocial risk factors, such as substance abuse and limited social support, for LVAD outcomes is currently unclear. Thus, the aim of this dissertation is to explore the role of pre-implant psychosocial risk factors for gender differences in clinical outcomes, accounting for clinical and device-related risk factors.

In the first article, gender differences in pre-implant characteristics of patients registered in The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) were investigated. It was found that women and men differed in multiple pre-implant characteristics depending on device strategy. In the second article, gender differences in major clinical outcomes (i.e., death, heart transplant, device explant due to cardiac recovery, device replacement due to complications) were evaluated for patients in the device strategy destination therapy in the Interagency Registry for Mechanically Assisted Circulation (INTERMACS). Additionally, the association of gender and psychosocial risk factors with the major outcomes were analyzed. Women had similar probabilities to die on LVAD support, and even higher probabilities to experience explant of the device due to cardiac recovery compared with men in the destination therapy subgroup. Pre-implant psychosocial risk factors were not associated with major outcomes. The third article focused on gender differences in 10 adverse events (e.g., device malfunction, bleeding) after LVAD implant in INTERMACS. The association of a psychosocial risk indicator with gender and adverse events after LVAD

implantation was evaluated. Women were less likely to have psychosocial risk pre-implant but more likely to experience seven out of 10 adverse events compared with men. Pre-implant psychosocial risk was associated with adverse events, even suggesting a dose response-relationship. These associations appeared to be more pronounced in women.

In conclusion, women appear to have similar survival to men when accounting for device strategy. They have higher probabilities of recovery, but higher probabilities of device replacement and adverse events compared with men. Regarding these adverse events, women may be more susceptible to psychosocial risk factors than men. The results of this dissertation illustrate the importance of gender-sensitive research and suggest considering device strategy when studying gender differences in LVAD recipients. Further research is warranted to elucidate the role of specific psychosocial risk factors that lead to higher probabilities of adverse events, to intervene early and improve patient care in both, women and men.

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List of Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin-converting-enzyme inhibitor
AHA	American Heart Association
ARB	Angiotensin II receptor blocker
BDI-II	Beck Depression Inventory II
BMI	Body Mass Index
BP	Blood pressure
BTT	Bridge to transplant
BSA	Body surface area
BUN	Blood urea nitrogen
CF	Continuous flow
DT	Destination therapy
EUROMACS	The European Registry for Patients with Mechanical Circulatory Support
EQ-5D	European Quality of Life 5 Dimensions Questionnaire
HFmrEF	Heart Failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HADS-D	Hospital Anxiety and Depression Scale
HLA	Human leukocyte antigens
ICD	Implantable cardioverter-defibrillator
IMACS	The International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support
INTERMACS	The Interagency Registry for Mechanically Assisted Circulation
ISHLT	The International Society for Heart and Lung Transplantation
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVAD	Left ventricular assist device
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
MCS	Mechanical circulatory support
MCSRN	The Mechanical Circulatory Support Research Network
NYHA	New York Heart Association
PACT	The Psychosocial Assessment of Candidates for Transplantation
TERS	The Transplant Evaluation Rating Scale
SIPAT	The Stanford Integrated Psychosocial Assessment for Transplantation
VAD	Ventricular assist device

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1 Introduction

Cardiovascular diseases are the leading cause of death globally (World Health Organization, 2021). They often result in heart failure, a multi-faceted syndrome with a 5-year mortality between 50 and 75% (Savarese et al., 2023). In the western countries heart failure accounts for one of the highest amounts of health care costs, especially due to hospital readmissions, and the costs continue to rise (Tsao et al., 2023). About 50% of heart failure patients develop a dysfunction of the left ventricle resulting in a reduced ejection fraction of blood into the aorta, causing significant physical and psychological burden (Savarese et al., 2023). In patients with an advanced stage of heart failure, the final therapy option is heart transplant. Due to an increasing donor organ shortage, left ventricular assist devices (LVADs) were developed. Today, the survival rates of > 80% after 1 year are similar to those of heart transplant recipients (Kirklin et al., 2012; Shah et al., 2022). Despite the fact that women account for 40% of the patients with heart failure and reduced ejection fraction (HFrEF), only 20% of the LVAD population is female (Desai et al., 2021; Khazanie, 2019). Women were known to have worse survival compared with men and to have higher rates of adverse events such as strokes and bleedings after implant (Hsich, Naftel, et al., 2012; Kirklin et al., 2008) but there is increasing evidence that women's disadvantages were related to older generations of devices being too large for the female body (Dual et al., 2022; Joshi et al., 2019). However, a worse outcome after LVAD implant in women is still reported in the recent generation of devices (Gruen et al., 2020). In this context, the role of the intended device strategy at implant, that could either be a bridge to transplantation or a final therapy, destination therapy, is currently unclear. In addition, there is still little focus on psychosocial risk factors for outcomes after LVAD implant, even though the biopsychosocial model applies especially in the field of heart diseases (Engel, 1977; Suls & Martin, 2011). First single-center studies suggest that anxiety, depression, and drug abuse are associated with increased rates of

readmission (Lundgren, Lowes, et al., 2017; Snipelisky et al., 2015) and overall high psychosocial risk profiles are associated with adverse events such as device malfunctions and infections (DeFilippis, Breathett, et al., 2020; Dew et al., 2021). It is already known that female LVAD recipients are more likely to have psychiatric diagnoses and are less likely to abuse substances (i.e., alcohol, illicit drugs) compared with their male counterparts.

The aim of this dissertation is to evaluate the association of gender differences in pre-implant psychosocial risk factors with gender differences in outcomes after LVAD implant, which has not been investigated before. Potential confounding effects of clinical (e.g., disease severity) and device-related (e.g., device strategy) risk factors will be considered. Finding a link between high psychosocial risk and poor prognosis in women could yield important knowledge for clinical practice. It may help to close the gender gap in the usage of LVAD therapy, by facilitating the development of gender-specific prevention and intervention strategies for psychosocial risk factors.

2 Background

The first part of this chapter (2.1) provides a short overview of the syndrome heart failure, including epidemiology, etiology, pathophysiology, and heart transplant as the gold standard therapy for end-stage heart failure. The second part of this chapter (2.2) describes LVAD therapy, including LVAD registries, clinical outcomes, and associated risk factors.

Afterwards, gender differences (2.3), the role of psychosocial risk factors (2.4), and the association of gender and psychosocial risk factors (2.5) will be described. In each of these chapters, evidence for the cardiovascular diseases/heart failure population will be reported, followed by results for the heart transplant population, and finally for the LVAD population. This concludes in the derivation of the research objectives of this dissertation (3).

2.1 Heart Failure

Heart failure is an impairment of the ventricular filling (diastolic heart failure) or/and an impairment of the contraction of the heart muscle (systolic heart failure) leading to an undersupply of the body with oxygenated blood (Heidenreich et al., 2022; Metra & Teerlink, 2017). This impairment leads to the typical heart failure symptoms: dyspnea, fluid retention, and fatigue that could occur during exercise or at rest (McDonagh et al., 2021). In about 50% of the heart failure cases, there is a significant reduction of the left ventricular systolic function. This phenotype is defined as heart failure with reduced ejection fraction (HFrEF, ≤ 40%) and characterized by an increased risk of cardiovascular death (Savarese et al., 2023). The ejection fraction may also be mildly reduced (HFmrEF, 41-49%) or preserved (HFpEF, ≥ 50%) (McDonagh et al., 2021; Metra & Teerlink, 2017; Savarese et al., 2023). Despite this phenotype classification of heart failure, three other classification systems are commonly used. The New York Heart Association (NYHA) defines functional NYHA classes (I to IV) based on symptoms severity and physical activity. The classes range from *no limitation of*

physical activity (Class I) to *severe symptoms at rest and with any physical activity* (Class IV) (McDonagh et al., 2021). The disease progression focused stages described by the American College of Cardiology (ACC) and the American Heart Association (AHA) include patients that are at risk of developing heart failure (stage A) to patients with advanced heart failure (stage D). Stage D patients experience severe symptoms that interfere with daily life and recurrent rehospitalizations despite maximal medical therapy (Heidenreich et al., 2022). The Interagency Registry for Mechanically Assisted Circulation (INTERMACS) classification system was developed to stratify patients with advanced heart failure (i.e., stage D) in seven profiles that indicate urgency for an intervention. The INTERMACS profiles range from 1 (critical cardiogenic shock) to 7 (advanced NYHA class III) (Stevenson et al., 2009; Truby & Rogers, 2020; Table 1).

Table 1
Heart failure stages by ACC/AHA, NYHA functional classes, and INTERMACS profile

ACC/AHA Stage A		
ACC/AHA Stage B	NYHA Class I	
ACC/AHA Stage C	NYHA Class II-III	
ACC/AHA Stage D	NYHA Class III-IV	INTERMACS profile 1-7

Epidemiology

The prevalence of heart failure increases with age: ranging from around 1% for those aged < 55 years to > 10% of those older than 70 years in Europe and the United States (McDonagh et al., 2021; Mentzer & Hsich, 2019; Metra et al., 2007; Virani et al., 2021). Due to major improvements in diagnostics and treatments of advanced heart failure that prolong life expectancy after diagnosis, in the western countries, the prevalence is expected to increase whereas the incidence with 2-3 per 1000 persons/year is expected to remain stable (Savarese et al., 2023). 50% of people diagnosed with heart failure die within 5 years (McSweeney et

al., 2012). Especially patients progressing to the state of advanced heart failure (ca. 11.5%) have poor prognosis with a 1 year-mortality ranging from 25-75% (McDonagh et al., 2021; Subramaniam et al., 2022). Typical clinical risk factors for the incidence of heart failure are increased age, hypercholesterolemia, diabetes, obesity, a familial history of heart failure, genetic factors, and exposure to cardiotoxic agents (e.g., alcohol, cancer treatments) (Heidenreich et al., 2022).

In addition to the physical burden, heart failure leads to significant limitation in the quality of life, such as performing work-related tasks, or engaging in recreational activities (Freedland et al., 2021). Also, psychological diseases such as depression and anxiety disorders are more frequent in the heart failure population compared with healthy populations (Rutledge et al., 2006).

Etiology and Pathophysiology

As heart failure is a complex and multifactorial syndrome, there are multiple potential underlying etiologies. The coronary artery disease, or ischemic heart disease, caused by a blockage of the oxygen-rich coronary arteries of the heart, is the most common cause of heart failure in the western countries (Jackson & Gardner, 2022; Savarese et al., 2023). Non-ischemic causes of heart failure are hypertension, cardiomyopathies, congenital heart disease, valvular heart diseases, and arrhythmias (Metra & Teerlink, 2017; Savarese et al., 2023).

The pathophysiology of heart failure mostly results by a complex response to cardiac injuries. On the hemodynamic level, an increase in preload and myocardial hypertrophy is provoked to maintain the cardiac output (McDonagh & Dargie, 2022). The renin-angiotensin-aldosterone system and the sympathetic nervous system are activated to further stimulate contractility. In addition, inflammatory cytokine levels are increased which can be caused by infectious events or oxidative stress (Miliopoulos et al., 2022). These mechanisms are initially adaptive and improve the cardiac performance but chronically contribute to the progression of the

syndrome due to adverse changes in size, shape, and function of the left ventricle (McDonagh & Dargie, 2022).

Therapies for Advanced Heart Failure

When entering stage D of HFrEF, an aggressive use of medications (e.g., renin-angiotensin antagonists, beta-blockers, aldosterone antagonists, angiotensin receptor-neprilysin inhibitors) is indicated. According to underlying diagnoses, cardiac resynchronization or specific mechanical repairs at the heart may be applicable (Truby & Rogers, 2020). If patients still experience ventricular dysfunction and limiting symptoms, advanced heart failure therapies should be considered, which would include vasoactive medication (e.g., inotropes) and short-term devices.

The gold standard of long-term management of advanced heart failure is the heart transplantation. In 1976, the first human heart transplantation was achieved. In the past 50 years, major improvement in the management of heart transplants took place, e.g., in immunosuppression and improved patient selection (Miller et al., 2019). The survival rates today reach > 85% after 1 year and a median survival of 12.2 years (Truby & Rogers, 2020). However, rejection of the transplanted heart remains the most common cause of death. Processes that lead to rejection are primarily directed against human leukocyte antigens (HLA). Besides natural antibodies, main causes of anti-HLA antibody development are pregnancy and blood product transfusion (Mangiola et al., 2017).

In addition, there are several contraindications for heart transplant. Despite typical clinical restrictions (e.g., cerebrovascular diseases, liver dysfunctions) the most outstanding contraindications are life expectancy < 2 years, age > 72 years, and limited social support (Truby & Rogers, 2020), leading to an exclusion of a large proportion of the advanced heart failure patients from this therapy. The increasing prevalence of heart failure and the shortage of donor hearts further limit the potential of heart transplant (Miller et al., 2019).

2.2 LVAD therapy

Addressing the shortage of suitable donors for heart transplantation, mechanical circulatory support (MCS) devices, of which more than 95% are LVADs, were developed (Heidenreich et al., 2022; Kirklin et al., 2012; Molina et al., 2021; Truby & Rogers, 2020). Originally, LVADs were intended to be a bridge to heart transplantation (BTT). In the last decades, they have been increasingly used as a long-term solution, destination therapy (DT), due to the major improvements in technology (Teuteberg et al., 2020). The first pulsatile pumps had several limitations, especially their large size and poor durability (Miller et al., 2019). Today, about 80 % of the devices are continuous-flow (CF-) LVADs (Shah et al., 2022). The second and third generations CF-LVADs are smaller and more durable. CF-LVADs are further differentiated by axial (e.g., Heart Mate II) or centrifugal (e.g., HVAD, Heart Mate III) pump type. The latter devices are smaller and flatter, even more suitable for small body types.

The AHA/ACC guidelines define the indication for LVADs as follows: patients with advanced HFrEF, left ventricular ejection fraction (LVEF) < 25%, with NYHA class IV symptoms despite guideline-directed medical and device therapy and dependence on intravenous inotropes. Contrary to heart transplant, in LVAD therapy, advanced age and a lack of social support are not considered relative contraindications (Miller et al., 2019; Owens & Jessup, 2012). For patients who are initially considered to be heart transplant ineligible because of pulmonary hypertension, obesity, frailty, or other reasons, LVADs can provide time to reverse or modify these conditions (Heidenreich et al., 2022). Thus, pre-implant patients are assigned to an intended device strategy according to their eligibility for heart transplantation. BTT strategy is used in patients already listed for a heart transplantation but who are predicted to have a long waiting time due to body size, ABO blood type, or presence of anti-HLA antibodies (Peura et al., 2012).

Bridge to candidacy or bridge to decision is used to resolve clinical, social or financial barriers or to increase time until final evaluation of a patient to transplantation. Bridge to recovery is rare and only indicated for patients in which a subsequent LVAD explant is planned (e.g., patients with a cardiogenic shock). DT is selected for patients who are ineligible for heart transplant but require life-long support. (Kiamanesh et al., 2020; Peura et al., 2012).

2.2.1 Registries

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), established in 2005, is a North American registry of patients who receive a Food and Drug Administration approved MCS. In June 2023, INTERMACS includes 181 active sites and 40077 patients enrolled (Interagency Registry for Mechanically Assisted Circulatory Support, 2023), the data base is updated annually. Using the same assessment protocols as INTERMACS, the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) started to collect data in Europe in 2011 (de By et al., 2022). Currently, 8322 patients are enrolled in EUROMACS (European Registry for Patients with Mechanical Circulatory Support, 2023). The International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS) is building up as a worldwide registry, including INTERMACS, EUROMACS, UK Registry, and the Japanese Mechanically Assisted Circulatory Support Registry (JMACS) (Kirklin et al., 2018).

The registration procedure in INTERMACS starts with the assessment of multiple clinical (e.g., primary diagnoses, INTERMACS profile, device strategy, hemodynamics laboratory values, medication) and demographic variables (e.g., gender, employment, ethnicity, race, marital status, educational level) before implantation. The checklist *concerns and contraindications for transplant* is also applied. Clinicians are asked to check any condition that is a concern or contraindication for transplant, e.g., pulmonary hypertension (yes vs. no).

This checklist of *concerns and contraindications for transplant* includes the following psychosocial variables: limited cognition/understanding, limited social support, repeated noncompliance, history of illicit drug use, history of alcohol abuse, narcotic dependence, history of smoking, currently smoking, severe depression, and other major psychiatric diagnosis. Patients are asked to fill in quality of life questionnaires, such as the EuroQol (EQ-5D), INTERMACS pre/post-implant Quality of Life, Kansas City Cardiomyopathy Questionnaire (KCCQ) (Interagency Registry for Mechanically Assisted Circulatory Support, 2016).

Patients are under follow up (1 week, 1 month, 3 months, and 1 year post-recovery). Between those time points, all adverse events (e.g., device malfunction, bleeding, infection, neurologic dysfunction, renal dysfunction, and respiratory failure) and rehospitalizations are documented. Patients are under follow-up until one of the major outcomes occurs: death, cardiac recovery to such an extent that the device is explanted, heart transplant, and device exchange due to complications. If patients receive a heart transplant, they are transferred to the according transplant registry. If patients need a subsequent device due to complications, they are reregistered in INTERMACS with the subsequent device.

2.2.2 Clinical Outcomes and Associated Risk Factors

The large registries offer a great insight in risk prediction and outcome evaluation of patients that were implanted with LVADs (Miller et al., 2010). The survival rates for patients with CF-LVAD are comparable today with the survival rates of heart transplant patients, exceeding 82.8% at 1 year, 70% at 2 years, and 48.2% at 5 years after implantation in INTERMACS (Shah et al., 2022; Teuteberg et al., 2020). In EUROMACS, the survival is slightly lower with 73 % at 1 year, 63% at 2 years, (de By et al., 2015) and 45% after 5 years (de By et al., 2022).

Despite the general improvements in survival after LVAD implantation, the occurrence of adverse events after implantation is still high. Major bleeding, infection, and

neurological dysfunctions are the most common adverse events (Molina et al., 2021; Teuteberg et al., 2020). Only 59% of the patients are free from infection and 67% free from bleeding after the first year (Molina et al., 2021). In the current era of devices, patients show a freedom of stroke in 87% after 1 year but the hospital readmission rate remains high with > 70% within 1 year after implant (Molina et al., 2021). The occurrence of adverse events, especially in the first 90 days, is associated with an increased risk of mortality (Kirklin et al., 2017; Molina et al., 2021).

In INTERMAS, at 1-, 3-, and 5-years, 14.3%, 28.3%, and 32.2% patients with LVADs were transplanted (Molina et al., 2021), in EUROMACS it is 7.5%, 20.2%, and 25.3% (de By et al., 2022), respectively. Myocardial recovery remains rare, less than 1% of INTERMACS' (Kormos et al., 2019) and 1.4% of EUROMACS' patients (Antonides et al., 2020) experience a device explant.

LVAD outcomes are associated with several clinical risk factors. An increased severity of heart failure (e.g., INTERMACS profile 1) is linked to increased hazards of early death (Kirklin et al., 2017; Kormos et al., 2019), especially in patients above 65 years of age (Kirklin et al., 2017). Multiple blood parameters, that are indicators of comorbidities are linked to worse LVAD outcome. For example, increased levels of blood urea nitrogen (BUN) and creatinine, indicating renal dysfunction and elevated bilirubin, indicating right heart disfunction, are associated with higher rates of death (Kirklin et al., 2017; Kormos et al., 2019).

Besides clinical risk factors, LVAD therapy comes with specific device-related risk factors. The size of the device must fit the body it gets implanted in. Thus, body surface areas (BSA) < $1.5m^2$ are considered a relative contraindication and risk factor for adverse outcomes (Miller & Rogers, 2018; Owens & Jessup, 2012). Importantly, the newer device generations are smaller and more durable, so that the weight of this risk factor is decreasing (Miller &

Rogers, 2018). Beyond the device type, some authors report that the intended device strategy DT is associated with increased rates of death compared to BTT (Caraffa et al., 2022; Damman et al., 2023; Kirklin et al., 2017; Molina et al., 2021; Teuteberg et al., 2020; Vieira et al., 2020). It was concluded that DT patients are older and have greater comorbidity levels and are therefore more prone to adverse outcomes. However, the association was not reported in the large MOMENTUM 3 trial (Goldstein et al., 2020).

In sum, LVADs are a valuable therapy option for patients in advanced heart failure stage D. The survival rates are comparable with those of heart transplants but adverse events are common. There are several pre-implant clinical (e.g., disease severity, comorbidities) and device-related (e.g., pump type) risk factors for adverse outcomes after LVAD implant. In the following chapter (2.3), gender as a potential risk factor will be evaluated, starting with gender differences in heart failure populations, heart transplant candidates, and concluding with gender differences in LVAD patient characteristics and LVAD outcomes.

2.3 Gender Differences

Women may have a lower prevalence of cardiovascular diseases in general compared with men (Tsao et al., 2023) but importantly, these gender differences depend highly on the specific cardiovascular diagnosis. In heart failure patients, about 50% are female (Eisenberg et al., 2018). The prevalence of heart failure is higher in men than in women in the age groups up to 79 years. Above 80 years, women have a higher prevalence for heart failure than men (11.0 vs. 9.5%) (Tsao et al., 2023). Women and men differ significantly in their typical etiologies of heart failure. Women are less likely to have ischemic heart diseases as primary diagnoses, especially coronary artery disease, but women are more likely to have valvular heart diseases (Hsich et al., 2013; Hsich, Grau-Sepulveda, et al., 2012). Additionally, some heart failure etiologies only occur in women, i.e., postpartum heart failure. Due to these differences in etiologies, women are slightly less likely to develop HFrEF compared with men

(Swaraj et al., 2021). In this HFrEF subgroup, women are older than men when diagnosed (Dewan et al., 2019; Hsich et al., 2013; Hsich, Grau-Sepulveda, et al., 2012), they present with more comorbidities (e.g., hypertension) (Dewan et al., 2019; Hsich et al., 2013; Hsich, Grau-Sepulveda, et al., 2012), and in a more advanced stage of disease. The survival of women appears to be similar to men's (Hsich, Grau-Sepulveda, et al., 2012) or even better (Dewan et al., 2019). However, women report significantly worse quality of life (Dewan et al., 2019).

Despite the fact that 40% of patients with HFrEF are female (Desai et al., 2021), and thus are in need of advanced therapies, these are underused in women. (Cozzi et al., 2022; de By et al., 2022; Hsich, 2019; Khazanie, 2019; Molina et al., 2021).

In the United States, women are less likely to be listed for heart transplant compared with men (24 % vs. 76%) and less likely to receive heart transplant (26% vs. 74%) (Colvin et al., 2023). At time of listing, women are younger than men and are less likely to have an ischemic cardiomyopathy, diabetes mellitus, and hypertension. Women have higher mortality rates while awaiting heart transplantation compared with men, even among patients with similar clinical urgency (Hsich, 2019). Besides blood type, and heart transplant waitlist priority, matching body size between donor and recipient, and human leukocyte antigens are important factors affecting the likelihood to get transplanted (Hsich, 2019). These antibodies occur after blood transfusions or pregnancies; hence women are more likely to be sensitized than men. Matching body size further disadvantages female recipients, as women only compromise about 30% of the donors (Colvin et al., 2023) After transplant, women tend to have better long-term survival than men (Hsich, 2019).

Similarly to the transplant population, only 20% of the LVAD population is female in the United States and in Europe (de By et al., 2022; Molina et al., 2021). At LVAD implant, women are younger (Ahmed et al., 2020; Gruen et al., 2020; Hsich, Naftel, et al., 2012; Joshi

et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021; van Meeteren et al., 2017), less likely to have ischemic diagnoses (Ahmed et al., 2020; Joshi et al., 2019; Magnussen et al., 2018; Nayak, Hu, Ko, Steinberg, et al., 2021; van Meeteren et al., 2017), and less likely to have hypertension (Ahmed et al., 2020; Joshi et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021) compared with their male counterparts. Additionally, women have less evidence of hepatic and renal dysfunction (Gruen et al., 2020; Joshi et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021). However, women are more likely to present in a more severe disease status (INTERMACS profile 1) compared with men (Gruen et al., 2020; Hsich, Naftel, et al., 2012). Often, gender differences in device strategy are not documented (Joshi et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021) but Gruen and colleagues reported than in INTERMACS, women are more likely to receive an LVAD as BTT and less likely as DT compared with men (Gruen et al., 2020).

The evidence regarding gender differences in outcomes after LVAD implant is conflicting. An INTERMACS analysis of CF-LVADs reported women to be of higher risk for mortality (Gruen et al., 2020). In some studies using INTERMACS, EUROMACS, and IMACS data, authors specified that women have a higher probability of *early* mortality (< 3-4 months) (Akin et al., 2020; Kirklin et al., 2017; Kirklin et al., 2018; Nayak, Hu, Ko, Steinberg, et al., 2021) that might balance out over 1-2 years. Some single-center studies did not find gender differences in CF-LVAD recipients (Morris, Cole, et al., 2015; Sherazi et al., 2017; Tsiouris et al., 2014). The results also vary in other studies on gender differences in mortality that do not specify the LVAD type (continuous-flow vs. pulsatile flow). In an EUROMACS analysis, women with LVAD support had a higher risk for death compared with men (Magnussen et al., 2018), whereas an analysis of The Mechanical Circulatory Support Research Network (MCSRN) (van Meeteren et al., 2017), and a retrospective analysis of > 12000 Medicare beneficiaries (Cascino et al., 2022) found no gender differences in mortality. In an analysis of the Nationwide Inpatient Sample between 2004 and 2016, Joshi and colleagues studied gender

differences in outcomes regarding the pulsatile vs. the continuous-flow era (Joshi et al., 2019) and women were of higher risk for death only in the pulsatile era. The former pulsatile devices were large and not suitable for small bodies (i.e., BSA) typical for female candidates. In the newer generation of CF-LVADs, there are no outcome disadvantages in patients withs small BSA (Dual et al., 2022; Molina et al., 2021; Ono et al., 2016; Zafar et al., 2017). However, despite a generally increased utilization of CF-LVADs, the percentage of women receiving LVADs remained similarly low even in the CF era (Joshi et al., 2019).

Regarding adverse events, the evidence appears slightly clearer. Women with CF-LVAD appear to have a higher risk for adverse events, especially neurologic events (Gruen et al., 2020; Morris, Pekarek, et al., 2015; Sherazi et al., 2017). Studies also report women with CF-LVAD to be disadvantaged for rehospitalizations, bleeding, pump thrombosis/or device malfunction. In EUROMACS, with various LVAD types included in the analysis, women had higher risks for bleedings, arrhythmias, and right ventricular failure (Magnussen et al., 2018). No gender differences in adverse events were found in single center studies (e.g., Tsiouris et al., 2014), a complete-case analysis (Ahmed et al., 2020) and an analysis of the MCSRN (van Meeteren et al., 2017), also not specifying for pump type.

Female patients are less likely to receive a heart transplant when bridged to transplant with LVAD support, registered in the United Network for Organ Sharing (DeFilippis, Truby, et al., 2019) and registered in INTERMACS (Gruen et al., 2020). One reason might be that a higher risk of allosensitization (e.g., after pregnancy) in female patients leads to higher waitlist times in women (Bogaev et al., 2011; Wehbe & Anderson, 2019). These gender differences in the likelihood of heart transplantation may interact with gender differences in mortality. It is possible that women have higher rates of death on LVAD support because they are less eligible to be transplanted compared with men (Wehbe & Anderson, 2019).

The outcome recovery is scarce after LVAD therapy. One study of INTERMACS patients described that patients in the intended device strategy bridge to recovery are younger, more likely to be female and to have non-ischemic etiologies (Wever-Pinzon et al., 2016) compared with other device strategies but gender was not significantly associated with recovery as an outcome. A study on myocardial recovery of LVAD patients detected female gender as a predictor for partial recovery, independent of clinical parameters (Topkara et al., 2016). A recent European Postgraduate Course in Heart Failure VAD registry analysis found a trend for women to have higher rates for device explant due to recovery (Radhoe et al., 2023).

In conclusion, women seem to be more likely to experience death after LVAD implantation. Women's disadvantages in outcomes may be partly caused by older generations of devices. Still, women experience higher rates of adverse events, and have lower chances to get transplanted. First hints indicate the female gender may play a role in recovery. The findings on gender differences in outcomes are difficult to interpret, due to differences in the device types that are included in the analyses and different methodological approaches (e.g., handling of missing data, analyses of composite endpoints). The device strategy is mostly not considered, even though there is evidence that it may be related to clinical outcomes. It is still unknown which factors contribute to women's increased probability for death and adverse events. Thus, in the next chapters the role of psychosocial risk factors for outcomes (2.4) and their interaction with gender (2.5) will be evaluated.

2.4 Psychosocial Risk Factors

Psychosocial factors (e.g., stress, addiction, socioeconomic status, mental health) are linked to overall health (Marmot, 2005) and cardiovascular health in particular (Peterson, 2020). A Scientific Statement From the American Heart Association stated that the most important psychosocial factors for cardiovascular health are socioeconomic position (i.e., income, education, occupation), race and ethnicity, social support, culture (including language), access

to clinical care, and residential environments (Havranek et al., 2015). The association of chronic psychosocial stress, including life changes (e.g., job stress, death of loved one), adverse socioeconomic conditions, (e.g., high crime, racial inequalities), and chronic psychiatric conditions (e.g., depression, anxiety) for the increased risk for cardiovascular disease onset and cardiovascular mortality is well documented (Christensen et al., 2011; Dar et al., 2019; Freedland et al., 2016; Osborne et al., 2020; Rutledge et al., 2006; Santosa et al., 2021; Stringhini et al., 2012; Valtorta et al., 2016; Yusuf et al., 2004).

In addition, many studies' results underline the importance of social support for outcomes in heart diseases. For example, loneliness and social isolation (Valtorta et al., 2016) appeared to be associated with increased incidence of coronary artery disease and the absence of a partner was predictive of readmission in heart failure patients (Heidari Gorji et al., 2019; Howie-Esquivel & Spicer, 2012). Social support, by contrast, was associated with self-care, adherence (Gallagher et al., 2011) and reduced mortality in heart failure patients (Kaiser et al., 2020).

The mechanisms of the associations between psychosocial factors and cardiovascular risk are complex, and typical clinical risk factors (e.g., diabetes) interact with psychosocial risk factors dynamically according to the biopsychosocial model (Engel, 1977; Suls & Martin, 2011). From a physiologic perspective, systemic inflammatory, neurohormonal processes, and elevated blood pressure, resulting by psychosocial stress (Suls & Martin, 2011), are clearly related to adverse cardiac outcomes (Osborne et al., 2020; Peterson, 2020). Also, psychosocial stress may trigger other psychosocial risk factors (e.g., substance abuse), unhealthy dietary and a sedentary lifestyle that are in turn associated with immunoinflammation and oxidative stress (O'Neil et al., 2018). In addition, patients with poor psychosocial health may experience increased barriers to the access of clinical care (Havranek et al., 2015; Peterson, 2020).

Thus, according to heart failure guidelines, treatment of comorbidities such as depression and anxiety should be offered for patients and high-risk characteristics such as substance use disorders, limitations in psychosocial support, impaired health literacy, and cognitive impairment should be addressed in transitional care plans (Heidenreich et al., 2022; McDonagh et al., 2021).

Advanced heart failure therapies (i.e., heart transplant and LVAD therapy) require significant engagement from patients and their caregivers at home. Dramatic alterations to daily life and routines are required (e.g., bathing, sleeping, frequent medical appointments, and equipment management) (Abshire et al., 2016). Psychosocial factors can interfere with the understanding of treatment plans and with adherence. The International Society for Heart and Lung Transplantation (ISHLT) in collaboration with other professional societies released a Consensus statement in 2018 (Dew et al., 2018) to help standardize the psychosocial evaluation process and ensure practice consistency across programs. According to this statement, psychosocial factors of particular relevance for health in heart transplant and LVAD patients can be grouped into five distinct domains: cognitive function, adherence, psychopathology, social support, and substance abuse (Bui, Allen, et al., 2019). Based on the recommendations, specific psychosocial evaluation tools such as the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) have been developed. The SIPAT includes readiness level, social support system, psychological stability and psychopathology, lifestyle and effect of substance abuse. The SIPAT score is associated with post-transplant morbidity but not with mortality after heart transplant (Maldonado et al., 2015; Vandenbogaart et al., 2017). Similarly, other tools, e.g., the Transplant Evaluation Rating Scale (TERS) and the Psychosocial Assessment of Candidates for Transplantation (PACT) fail to consistently predict major outcomes in transplant patients (Bui, Allen, et al., 2019). Nevertheless, there is valid evidence regarding the association of independently assessed psychosocial risk factors with outcomes in heart transplant patients. Non-adherence (Dobbels

et al., 2009) and former alcohol and drug abuse (Owen et al., 2006) seem to be associated with survival after heart transplant. There is strong evidence that depression, assessed with validated scales (e.g., Hospital Anxiety and Depression Scale - HADS-D, Zerssen depression scale) or psychiatric interviews, is associated with death while on the waitlist for heart transplant (Gali et al., 2021; Spaderna et al., 2010; Spaderna et al., 2017) and death after transplant (Havik et al., 2007; Owen et al., 2006; Zipfel et al., 2002). A partnership seems to be a protective factor for post-transplant outcomes (Dobbels et al., 2009; Tam et al., 2011). In the Waiting for a New Heart study, the combination of depressive symptoms and isolation was associated with worse outcomes on waitlist (Spaderna et al., 2010) and after transplant (Spaderna et al., 2017). Contrary, patients that were non-depressed and socially integrated did not require mechanical circulatory support as a bridge to transplant (Spaderna et al., 2012).

For the LVAD population, there is no validated tool for the assessment of psychosocial risk. Often, tools developed for transplant patients (i.e., SIPAT, TERS, or PACT) are applied. Similarly, to the heart transplant population, none of the tools predicted death in LVAD populations (Cagliostro et al., 2019; Halkar et al., 2018; Olt et al., 2023; Sperry et al., 2019). However, the number of days after discharge were significantly shorter in the TERS high-risk group compared to the low risk group (Yost et al., 2016) and patients with low-risk mPACT (revision of the PACT for LVAD patients) scores had decreased 30-day readmission rates compared to high-risk scores (26% vs. 67%) after device implantation (Maltby et al., 2014). Cagliostro and colleagues reported that a high-risk SIPAT score was predictive for unplanned health care use (e.g., urgent visits) (Cagliostro et al., 2019). Sperry and colleagues (Sperry et al., 2019) found an association of high-risk SIPAT score with cumulative adverse cardiac events. Importantly, all studies are small single-center studies (n = 50-263 patients), thus they may be underpowered to detect effects for seldom events such as death.

Other authors, assessing single psychosocial risk factors, found that anxiety and depression (Kaiser, 2019; Lundgren, Lowes, et al., 2017; Snipelisky et al., 2015) and drug abuse (Lundgren, Lowes, et al., 2017; Snipelisky et al., 2015) were associated with higher rates of readmission after LVAD implant. Only active smoking (Lundgren, Lowes, et al., 2017) and active substance abuse (Cogswell et al., 2014) at time of implant was associated with mortality after LVAD implant. There is also evidence that an understanding and present caregiver, as documented by a social worker, significantly decreases the risk for death after implant (Bruce et al., 2017).

A single-center study (n = 241) systematically recorded psychosocial data of all five domains according to the Consensus statement. In the study, social workers or psychologists rated psychosocial risk as low, moderate or high. Greater psychosocial risk, particularly mental health problem severity, non-adherence, and substance use, were related to higher rates of adverse events such as post-implant pump exchange, cardiac arrythmias, and device malfunctions (Dew et al., 2021). In a first large INTERMACS analysis DeFilippis and colleagues (2020) computed an overall psychosocial risk factor (including limited social support, history of alcohol abuse, history of illicit drug use, limited cognitive understanding, repeated noncompliance, severe depression, and other major psychiatric illness) as a binary variable (psychosocial risk present vs. not present). Psychosocial risk was associated with increased hazards for adverse events such as device-related infection, gastrointestinal bleeding, pump thrombosis, and readmission (DeFilippis, Breathett, et al., 2020). Both studies did not report a link between psychosocial risk and death (DeFilippis, Breathett, et al., 2020; Dew et al., 2021).

To summarize chapter 2.4, the evidence regarding psychosocial characteristics and their impact on clinical outcomes in LVAD is still scarce and mostly based on single-center studies. Nonetheless, several risk factors (especially mental illness and substance abuse)

appear to be associated with adverse events and readmission; a link to mortality is seldomly reported. The association of gender and psychosocial risk factors will be evaluated in the following chapter.

2.5 Gender and Psychosocial Risk Factors

Gender, contrary to biological sex, is a social determinant of cardiovascular risk, as women experience specific psychosocial stress factors such as domestic violence and discrimination more often than men (Albus et al., 2019; Medina-Inojosa et al., 2019; O'Neil et al., 2018). In addition, women fulfill traditional roles in society. For example, almost two-thirds of caregivers in the United States are women (O'Neil et al., 2018) and caregiving is associated with increased stress levels (Lyons et al., 2015). Also, depression is twice as common among women compared with men, and depression is a predictor for both incidence and recurrence of cardiovascular diseases among women (Chrysohoou et al., 2003; Low et al., 2011; O'Neil et al., 2018). Regarding substance abuse, in the general and the cardiac population, men are known to have higher consumption of alcohol and illicit drugs compared with women (Cesaroni et al., 2021; Faris et al., 2003). Whereas some studies report similar risks for incidence and mortality of heart failure associated with substance abuse in both genders (Chrysohoou et al., 2003; Sillars et al., 2020), many studies found pronounced associations for women (Anand et al., 2008; Cesaroni et al., 2021; Faris et al., 2003).

Investigating the association of a psychosocial stress index (including depression, locus of control, global stress, financial stress, and life events) with the incidence of myocardial infarction at the population level, the authors of the INTERHEART study reported no gender differences (Anand et al., 2008; Rosengren et al., 2004). Similarly, in a large population-based cohort study, men with high stress (work/home stress, major life events, and financial stress) had a higher risk of cardiovascular diseases, coronary heart disease, and stroke compared with men with no stress. These associations were only significant in women for coronary heart

disease (Santosa et al., 2021). However, it may be helpful to differentiate between different types of stress. In female patients with cardiac diseases, who were married/living with a male partner (n = 187), marital stress was associated with a 2.9 increased risk of recurrent events (e.g., death and infarction), whereas work stress did not predict cardiac events (Orth-Gomer, 2000). A similar trend was found in the INTERHEART study (Rosengren et al., 2004). In addition, it appears that marriage is a protective factor only in men (Havranek et al., 2015; Stringhini et al., 2012; Wang et al., 2020), whereas in women the association depends on the quality of marriage (Havranek et al., 2015; Liu & Waite, 2014).

As described in chapter 2.4, advanced heart failure therapies afford demanding adaption processes of patients and caregivers, and the Consensus statement (Dew et al., 2018) defined psychosocial domains specifically relevant for heart transplant and LVAD patients. If women and men differ in these psychosocial risk factors, it is likely that these differences impact gender differences in outcomes. Unfortunately, there is only little evidence about the interplay of gender and psychosocial risk factors for outcomes in heart transplant and LVAD patients. Additionally, the few studies often are underpowered to analyze these research questions, due to the small amount of women in heart transplant and LVAD populations (Hsich, 2019). For example, The Waiting for a New Heart Study evaluated the role of pre-implant psychosocial risk and outcomes on the waitlist for heart transplant, also considering gender differences. Pre-implant women were less likely to be in the high psychosocial risk group (HADS-D and social isolation indicated by low network size) compared with men (Spaderna et al., 2010; Spaderna et al., 2012), but the difference was not statistically significant. Men were significantly more likely to report low emotional support (Weidner et al., 2011). Due to small female sample size, the role of emotional support was emphasized for mortality and removal from the waiting list because of deteriorated health status only in men (Weidner et al., 2011).

For patients receiving LVADs, there is even less evidence. In EUROMACS, there is currently no publication describing gender differences in psychosocial variables. Some authors reported

gender differences in demographic and psychosocial variables in the US LVAD populations. For example, women are less likely to be White (Ahmed et al., 2020; Gruen et al., 2020; Hsich, Naftel, et al., 2012; Joshi et al., 2019), and more likely to be single/divorced or widowed (Hsich, Naftel, et al., 2012; Nayak, Hu, Ko, Steinberg, et al., 2021) compared with men. Women are less likely to be working for an income (Nayak, Hu, Ko, Steinberg, et al., 2021), have more often major depressions or other psychiatric disorders (Joshi et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021) but are less likely to have a history of substance abuse (Ahmed et al., 2020; Hsich, Naftel, et al., 2012; Joshi et al., 2019). In DeFilippis and colleagues' analysis of INTERMACS data, men had more often psychosocial risk (especially due to substance abuse). However, the authors did not further evaluate gender in their outcome analysis (DeFilippis, Breathett, et al., 2020).

To summarize, women in general appear to be more exposed to psychosocial stress factors such as depression and traumatic experiences and are more often involved in caregiving roles. Besides the fact that women are less likely to consume substances compared with men, the association with cardiovascular risk may be increased in women. In addition, particularly depression and poor quality of marriage may be associated with onset of cardiovascular diseases and mortality in women. However, men's cardiovascular risk may be related to being without any partnership. Little is known about the association of gender and psychosocial risk factors in the heart transplant and LVAD populations. Women with LVADs differ from men regarding psychosocial risk factors. Currently, no work has been published assessing the association of these gender differences in psychosocial risk factors pre-implant with gender differences in outcomes after LVAD implant.

3 Research Objectives of the Dissertation

The following synopsis can be drawn from the state of the art summarized in the previous chapters.

Female and male LVAD recipients differ in clinical outcomes. Women seem to be more likely to die and to experience adverse events (Gruen et al., 2020; Kirklin et al., 2017; Magnussen et al., 2018) but the reports are inconsistent. Women and men with LVAD differ in clinical pre-implant characteristics. For example, women are less likely to have ischemic cardiac diagnoses, but they present at a more advanced stage of diseases, and there are gender differences in comorbidities. Hence, diseases severity (e.g., INTERMACS profile), time since diagnosis, primary cardiac diagnosis, blood parameters indicating comorbidities (e.g., bilirubin, creatinine, albumin), and medications should be considered when analyzing gender differences in clinical outcomes. Device-related factors also play a major role for gender differences in LVAD outcomes. The newer generations of devices are more suitable for the female body, leading to less complications. Analyses should therefore focus on the newest generation of devices CF-LVAD and neglect pulsatile devices (Joshi et al., 2019). In general, the role of device strategy for outcomes seems to be unclear. Importantly, women are less likely to receive a transplant, and therefore may be more likely to die on waitlist (Wehbe & Anderson, 2019). This indicates that the intended device strategy should be considered when investigating gender differences in mortality after LVAD implant and a DT specific analyses of gender differences in clinical outcomes has not been conducted before (DeFilippis, Farr, et al., 2019; Wehbe & Anderson, 2019).

It is hypothesized that 1) women's increased risk for mortality is related to the device strategy BTT, and therefore there will be no gender differences in mortality in a DT subgroup.

There is fist evidence that psychosocial risk factors such as substance abuse and low mental health are linked to outcomes after LVAD implant (DeFilippis, Breathett, et al., 2020; Dew et

al., 2021; Lundgren, Lowes, et al., 2017), and women and men differ in these risk factors (DeFilippis, Breathett, et al., 2020; Joshi et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021). However, there is currently no study evaluating the association of gender and psychosocial risk factors for gender differences in outcomes after LVAD implant. To address this major gap in research, following considerations derive from related research areas of cardiovascular diseases and heart transplant candidates. Despite women being more likely to be single/widowed and divorced (Hsich, Naftel, et al., 2012; Nayak, Hu, Ko, Steinberg, et al., 2021), social isolation appears to affect especially men's cardiovascular risk and men report lower rates of emotional support waiting for a heart transplant (Wang et al., 2020; Weidner et al., 2011). Thus, limited social support may be associated with worse clinical outcome after LVAD implant particularly in men. Men are also more likely to abuse substances (Hsich, Naftel, et al., 2012; Joshi et al., 2019), but the association with adverse cardiovascular outcome might be more pronounced in women (Cesaroni et al., 2021; Faris et al., 2003). Generally, women suffer more often from psychiatric diseases such as depression and anxiety (Joshi et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021) that are independently related to worse cardiac outcome (Medina-Inojosa et al., 2019; O'Neil et al., 2018). Additionally, women's pronounced role as a caregiver may increase women's vulnerability when exposed to life changing requirements of LVAD therapy (Abshire et al., 2016; O'Neil et al., 2018).

This leads to the hypotheses that 2) pre-implant psychosocial risk is related to worse clinical outcome in LVAD patients (i.e., death and adverse events) and that 3) women are disadvantaged in most psychosocial risk factors pre-implant and those disadvantages are related to the reported worse clinical outcome (i.e., death and adverse events) in women after LVAD implant.

These three hypotheses were tested within the following three articles.

In the first article, EUROMACS data are analyzed to explore gender differences in pre-implant clinical and psychosocial characteristics depending on device strategy.

The second article addresses gender differences in major clinical outcomes in INTERMACS including death, heart transplant, device explant due to recovery, and device replacement due to complications. Importantly, this analysis focuses on the subgroup DT. Additionally, the association of gender with demographic and psychosocial variables and the major outcomes are evaluated.

The third article focuses on gender differences in 10 adverse events (e.g., device malfunction, bleeding) after LVAD implant in INTERMACS. Ten separate competing risk analyses for each adverse event and accounting for the competing events death, transplant and recovery are modeled. Using a binary psychosocial risk indicator (psychosocial risk vs. no psychosocial risk) and an additive psychosocial risk indicator (0, 1, ≥ 2 risk factors), the association of psychosocial risk with gender and adverse events after LVAD implantation is evaluated.

4 Original Articles

Chapter 4 includes the original articles of this dissertation. The first two articles (chapter 4.1, 4.2) have been published. The third article (4.3) is under third revision in *The Journal of Heart and Lung Transplantation.* The articles appear in chronological order.

4.1 Gender Differences in Psychosocial and Clinical Characteristics in the European Registry for Patients with Mechanical Circulatory Support

Article 1 was published in the *Heart & Lung*: Löchel, S., **Maukel, L.-M**., Weidner, G., de By, T. M. M. H., & Spaderna, H. (2021). Gender differences in psychosocial and clinical characteristics in the European Registry for Patients with Mechanical Circulatory Support. *Heart & Lung, 50*(6), 845-852. https://doi.org/10.1016/j.hrtlng.2021.06.007

Abstract

Background: Not much is known about psychosocial characteristics of men and women receiving continuous flow left ventricular assist devices (CF-LVAD). *Objective:* To investigate gender differences in clinical and psychosocial (demographic, behavioral, psychological) characteristics in CF-LVAD recipients. *Methods*: We analyzed European Registry for Patients with Mechanical Circulatory Support (EUROMACS) data (n = 2395, 16.8% women; 2011 to 2017) and compared pre-implant characteristics in men and women intended for bridge to transplant (BTT) or destination therapy (DT). *Results:* Women were underrepresented [DT (n = 61): 13.4%; BTT (n = 341): 17.6%]. They were more likely to be divorced/separated, widowed, in unstable clinical condition, and non-working (DT only), but less likely to be smokers, to have ischemic cardiomyopathy or diabetes, and younger (BTT only) than men. Missing data were abundant, especially those that reflect psychological characteristics (> 87%). *Conclusion:* Gender differences were noted, some specific to device strategy. Improved collection of psychosocial characteristics is warranted to elucidate their relationship to future prognosis.

Keywords: behavior, continuous flow left ventricular assist device, device strategy, gender, psychosocial characteristics

Introduction

Mechanical circulatory support (MCS) devices are well-established treatments for advanced heart failure in Europe and in the United States (de By et al., 2018; Teuteberg et al., 2020). The representation of women among MCS recipients is low on both continents, with < 25% in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) (Teuteberg et al., 2020) and < 20% in the European pendant European Registry for Patients with Mechanical Circulatory Support (EUROMACS) (de By et al., 2018). In the United States, despite an increase in MCS implantations in general, the proportion of women receiving MCS has slightly dropped from 25.8% in 2004 to 21.9% in 2016 for the total MCS population (Joshi et al., 2019) and remained at approximately 20% between 2008 and 2017 for recipients of the more recent continuous flow left ventricular assist devices (CF-LVADs) (Kormos et al., 2019). These proportions of women are surprising, considering that women represent approximately 30% of patients with reduced ejection fraction (Joshi et al., 2019; Stolfo et al., 2019). However, reasons for the underrepresentation of women are not fully understood (Hsich, 2019; Joshi et al., 2019). A higher risk for worse clinical outcomes after MCS implantation in women compared to men might contribute to this disparity. There is some indication that women have a higher risk for adverse events after device implantation when compared to men (Blumer et al., 2018; Hsich, 2019), particularly regarding neurologic events (Hsich, Naftel, et al., 2012). Reports on survival differences in women and men, however, are conflicting, some indicating similar survival for women and men (Birks et al., 2015; Blumer et al., 2018; Hsich, 2019; Hsich, Naftel, et al., 2012; Kormos et al., 2019), others reduced survival for women (DeFilippis, Truby, et al., 2019; Joshi et al., 2019; Magnussen et al., 2018).

To gain a better understanding of gender differences in clinical outcomes after MCS implantation, a systematic examination of male and female populations before receiving MCS is warranted. Lately, there has been a debate whether device strategies at time of implant,

such as bridge to transplant (BTT) and destination therapy (DT), also need to be taken into account when evaluating associations between patient characteristics and clinical outcomes (DeFilippis, Truby, et al., 2019; Goldstein et al., 2020; Wehbe & Anderson, 2019). To answer this question, it is worthwhile to compare pre-implant patient characteristics of men and women intended for different device strategies to determine whether they constitute different populations.

There is already some knowledge regarding pre-implant gender differences in clinical characteristics both from the United States and from Europe: In the United States, women receiving MCS have different diagnoses than men. They are less likely to have ischemic cardiomyopathy and associated diagnoses including diabetes, hypertension or dyslipidemia (Joshi et al., 2019), but they are more likely to have dilated or restricted cardiomyopathy (Birks et al., 2015), and comorbidities such as thyroid disorder and rheumatoid arthritis (Joshi et al., 2019). One European study so far examined gender differences in pre-implant characteristics in 966 (151 female) patients who received MCS in EUROMACS prior to 2014, combining different types of MCS devices and strategies (Magnussen et al., 2018). Compared to men, women were also less likely to have ischemic heart failure, but were more likely to be in an unstable clinical condition at time of implant (Magnussen et al., 2018).

Even less is known regarding gender differences in pre-implant psychosocial characteristics, which can be conceptualized according to a recent Consensus document (Dew et al., 2018). It recommends to assess four domains of psychosocial characteristics in adult candidates for cardiothoracic transplant and long-term MCS: (A) risk factors for poor outcomes after implantation, including (1) treatment adherence and health behaviors, (2) mental health history, and (3) substance use history; (B) factors related to patients' knowledge and understanding; (C) factors specific to patients' personal, social, and environmental resources, which include amongst others social history characteristics such as marital status, education,

employment experience; and (D), specifically for patients considered for MCS, knowledge about and capacity for device operation (Dew et al., 2018).

A few studies have started to examine gender differences in some of the attributes from the above domains. Joshi and colleagues using the United States Nationwide Inpatient Sample database report higher pre-implant rates of obesity and depression, but lower rates of alcohol abuse in women compared to men. Women were also younger, less likely to be White, and to have a lower household income (Joshi et al., 2019).

INTERMACS data also indicate that women are less likely to have a history of alcohol abuse than men and are less often married (Birks et al., 2015), but the latter study combined all device strategies (BTT, DT, and others) and included pulsatile devices. Single center studies examining psychosocial characteristics often enroll too few women to incorporate gender differences (e.g., Snipelisky et al., 2015; Sperry et al., 2019). Our knowledge about psychosocial gender differences in the EUROMACS is even more limited. It appears that women are less likely to be smoking compared to men (Magnussen et al., 2018), but this also combined different types of MCS devices and strategies.

Psychosocial characteristics such as depression and substance abuse have been associated with higher readmission risk (Bruce et al., 2014; DeFilippis, Breathett, et al., 2020) and with the occurrence of adverse events (Bruce et al., 2014; DeFilippis, Breathett, et al., 2020; Dew et al., 2021; Sperry et al., 2019) after LVAD implantation. Also, depression and social isolation pre-transplant were independently associated with clinical outcomes in patients with similarly severe heart failure (Spaderna et al., 2012; Spaderna et al., 2017). Thus, the distribution of these characteristics in both men and women before implantation of a CF-LVAD as BTT or DT needs to be examined more closely.

The present study has two aims: First, to determine the proportion of women and men registered in each of EUROMACS' device strategies to receive a CF-LVAD; second, to systematically compare clinical and psychosocial characteristics of women and men intended

for the most common device strategies (BTT, DT) in an updated and larger data set compared to previous work on clinical characteristics described above (Magnussen et al., 2018). Of relevance to the present investigation are the psychosocial factors subsumed in the above mentioned categories (A) and (C): specifically demographic (marital status, education, employment), behavioral (licit and illicit tobacco, alcohol and drug use) and psychological (current mood) characteristics and quality of life. To account for device strategy, we will evaluate the interaction of gender and device strategy and their main effects.

Materials and Methods

Participants

The purpose of the present retrospective study is to analyze EUROMACS registry data from 1 January 2011 to 31 December 2017, which was contributed by participating study sites from 18 countries (de By et al., 2018). EUROMACS, analogous to the INTERMACS, collects clinical data on long-term MCS from participating hospitals. Eligibility criteria and the methods of selection of participants and data collection have been reported previously (de By et al., 2018). There were 2653 adult patients (aged 18 and < 80 years), who consented to have their de-identified data entered into the EUROMACS database and who received a primary CF-LVAD in one of the device strategies BTT, DT, bridge to recovery, or rescue therapy. Cross-sectional analyses to compare pre-implant psychosocial characteristics were based on data of 2395 patients who were intended for the main device strategies BTT (n = 1939) or DT (n = 456). Patients who received a right ventricular and biventricular devices, total artificial hearts, and pulsatile devices were excluded. Institutional review board approval from Trier University (66/2018) was obtained before conducting the analyses.

Variables and Measures

The following patient characteristics at time of implant were considered to serve as proxy variables for psychosocial characteristics from the demographic, behavioral, and psychological domain. Demographic characteristics included marital status, educational attainment, working for an income, and reasons for not working. To facilitate international comparisons, educational attainment was recoded to yield similar categories across continents as up to primary (1+2), secondary (3), post-secondary (4) and tertiary (5+6) (UNESCO Institute for Statistics, 2012). Behavioral characteristics included history of smoking, alcohol abuse and drug abuse. Based on Forest et al., who reported that obese and morbidly obese patients are at risk for adverse events, BMI was categorized as underweight (≤ 18.5), non-obese (> 18.5 to < 30), obese (≥ 30 to < 40) and morbidly obese (≥ 40) (Forest et al., 2018). Psychological characteristics included the anxiety/depression item of the EQ-5D (EuroQoL Research Foundation, 2018) as an indicator of mood. In addition, pre-implant health-related quality of life was included using the EQ-5D summary index and self-rated health (Visual Analog Scale) 5D (EuroQoL Research Foundation, 2018), and the dimensions pain/discomfort, mobility, self-care ("washing and dressing myself"), and usual activities. These characteristics were collected by staff members of the collaborating hospitals.

Patients' ethnic origin was excluded from analyses as this information is not collected in every European country. Age and body surface area were analyzed as continuous variables. Clinical variables encompassed primary diagnosis, time since first diagnosis, left ventricular ejection fraction (LVEF), diabetes, and INTERMACS profile, indicating disease severity. Due to low frequencies, INTERMACS profiles 5 to 7 were collapsed, yielding five categories ranging from most severe to least severe: 1 (critical cardiogenic shock), 2 (progressive decline), 3 (stable, but inotrope dependent), 4 (resting symptoms); 5-7 (Shah et al., 2018). Primary diagnosis was categorized into ischemic, idiopathic, and other. The proportions of missing data of the aforementioned characteristics were documented.

Statistical Analyses

All analyses were conducted with R version 3.4.4 (R Development Core Team, 2018). The proportions of women and men intended for each device strategy were compared using chi square tests. Pre-implant characteristics as well as their proportion of missing values were described as absolute and relative frequencies or means and standard deviation, as appropriate. Missing values were left as observed. Amounts of missing data ranged from 3% in clinical characteristics (INTERMACS profile) to > 28% in psychosocial characteristics with largest amounts among psychological variables (EQ-5D > 87%), preventing the application of multiple imputation techniques. Thus, the latter variables are described and examined for exploratory purposes only. Variables were analyzed by gender and by device strategy (BTT vs. DT), and their interactions were also evaluated. For continuous variables 2-factorial analyses of variance (ANOVAs) with the factors gender (male, female) x intended device strategy (BTT, DT) were used. The Tukey post-hoc test was applied for significant interaction terms. For categorical variables, multinomial logistic regression analyses were performed to test for frequency differences in gender, device strategy and their interaction in pre-implant characteristics. If a significant interaction emerged, separate chi-square tests or Fisher's exact tests were performed as appropriate to further explore gender differences separately for BTT- and DT-recipients. A value of $p < .05$ was considered statistically significant. For chi-square tests, Cramer's V was used as effect size with values from 0 to 1. A value of 1 indicates the strongest association of two variables. The McFadden index was used as effect size for multinomial logistic regression interaction effects. Values range from 0 to 1, with a value of 1 indicating the strongest association of two variables.

Results

In the entire sample women represented 16.9% of implanted patients (2129 men and 434 women), when considering all possible device strategies adopted between 2011 and 2017 with

CF-LVADs in EUROMACS (Table 2). Considering each device strategy separately, women were less likely than men to receive a CF-LVAD as DT ($\chi^2(1) = 4.68$, $p = .030$, Cramer's $V = .044$), whereas the somewhat higher proportion of women in BTT did not differ significantly from that of men (Table 2). The remaining strategies comprised only 6.5% of all patients and are not considered further. Thus, the data set for comparing clinical and psychosocial patient characteristics in women and men consisted of 2395 patients registered to receive a CF-LVAD as BTT or DT, including 402 women (16.8%) and 1993 men (83.2%), with 15.2% of the women and 19.8% of the men intended for DT ($p = .036$, Cramer's $V = .044$). Clinical characteristics of men and women in BTT and DT are shown in Table 3.

Pre-implant demographic, behavioral, and psychological characteristics of men and women are presented in Table 4. In order to investigate whether gender differences in pre-implant characteristics occurred depending on device strategy, variable distributions were tested for interaction effects of gender x device strategy.

There was a significant interaction of gender and device strategy for age (F (1, 2391) = 3.88, $p = 0.049$). Women were significantly younger than men in BTT ($M = 49.4$, $SD = 12.7$ vs. $M = 51.6$, $SD = 11.4$, Tukey $q = 2.17$, 95% CI [0.49 - 3.85], $p = 0.005$), but of similar ages in DT ($M = 65.7$, $SD = 5.8$ vs. $M = 64.7$, $SD = 7.5$, Tukey $q = 1.07$, 95% CI [4.95 - 2.81], $p = 0.894$; Figure 1). Both women and men in DT were on average more than a decade older than patients in BTT.

A history of alcohol abuse was least common among women in BTT (0.8%) compared to 12% to 14% in the other three groups (χ^2 (1) = 6.23, $p < .013$, McFadden index = .03). Women in DT were the least likely to be working for an income (4.8%) compared to men in DT (18.3%) and patients in BTT (26% and 28.6%; χ^2 (1) = 4.37, $p < .036$, McFadden index = .02). For all other variables no interaction effects were observed (p-values between .074 for BMI groups and .946 for primary diagnosis).

In addition to these interactions, gender main effects on pre-implant clinical and psychosocial characteristics were observed. Independent of device strategy, women were less likely to be diagnosed with ischemic cardiomyopathy, had a higher LVEF, and were less often diagnosed with diabetes than men (Table 3). However, women were more likely to be in an unstable clinical condition (INTERMACS profiles 1 and 2) and to have a shorter time since first cardiac diagnosis than men. Importantly, missing values in clinical characteristics ranged from 2.9% (INTERMACS profile) to 22.4% for LVEF (Table 5).

Psychosocial characteristics are presented in Table 4. Many data were missing in psychosocial variables, ranging from 27.8% in marital status up to 65% in educational attainment (Table 5). The psychological domain was the most affected with EQ-5D variables having > 87% and the VAS score > 90% of missing data.

Similar proportions of women and men were obese or morbidly obese. The genders also did not differ significantly in anxiety/depression, but fewer women (16%) reported ”no problems“ than men (26.9%). However, statistical comparisons of EQ-5D variables were clearly limited by missing data. Regarding substance abuse, women were less likely than men to be smoking. Compared to men, women were more likely to be divorced/separated or widowed, to have a lower educational attainment, and were more often homemaker as a reason for not working. Women also tended to report more often than men to have self-care problems (p = .051). Compared to BTT-recipients, DT-recipients were more likely to be male, to be diagnosed with ischemic cardiomyopathy or diabetes, and less likely to be in an unstable clinical condition (INTERMACS profile 1 and 2).

Post-hoc Analyses of Gender Differences in Missing Data

The high amounts of missing data we observed were surprising. In light of the finding that women were underrepresented, particularly in DT, we run post-hoc analyses to compare the proportions of missing data for each variable between men and women, also considering the

factor device strategy as before. Proportions of missing data per variable and group are presented in Table 5. Due to missing values in > 87% of cases, the EQ-5D scores are not included here. Of note, in women the amount of missing EQ-5D data was even higher than among men (all *p*-values < .01). Significant interaction effects for history of smoking, drug, and alcohol abuse revealed that gender made a difference in BTT only. Women intended for BTT were more likely to have incomplete data than men, thereby leaving men in BTT as the group with the fewest amount of missing values (Table 5). Independent of device strategy, primary diagnosis and time since first diagnosis were more likely to be incomplete in women than in men (Table 5).

Severe disease such as being in cardiogenic shock might prevent data collection. Because women were more likely to be INTERMACS profiles 1 and 2 than men, these analyses were rerun excluding patients with INTERMACS profiles 1 and 2. Women still had significantly more missing data than men in primary diagnosis (21% vs. 8%, $p < .001$), time since first diagnosis (22% vs. 12%, $p < .001$), LVEF (26% vs. 19%, $p = .039$), marital status (29% vs. 21%, $p = .033$), and EQ-5D variables (88-97% vs. 80-93%, *p*-values between .031-.057).

Table 2
Device strategy of women and men receiving a CF-LVAD at time of registering with EUROMACS

Device Strategy	Men (*n* = 2129 / 83.1%)	Women (*n* = 434 / 16.9%)	Total (*N* = 2563)	*p*-value	Cramer's *V*
Bridge to recovery	30 (1.4)	6 (1.4)	36 (1.4)	1.000	.001
BTT	1598 (75.1)	341 (78.6)	1939 (75.7)	.136	.031
DT	395 (18.6)	61 (14.1)	456 (17.8)	**.030**	.044
Rescue therapy	106 (5.0)	26 (6.0)	132 (5.2)	.453	.017

Note. Presented are numbers (%). BTT: bridge to transplant; DT: destination therapy. *p*-value derived from Chi-square test.

Table 3
Demographic and clinical characteristics of women and men before CF-LVAD implantation

Variable	Men (n = 1993 / 83.1%)	Women (n = 402 / 16.8%)	Total (N = 2395)	p-value
Age in years, mean (SD)*	54.2 (12)	51.9 (13.2)	53.8 (12.2)	< .001
Body surface area, mean (SD)	2.3 (2.7)	1.8 (1.2)	2.2 (2.6)	.002
Primary diagnosis, *n* (%)				< .001
Idiopathic	473 (26.9)	104 (32.7)	577 (27.8)	
Ischemic	941 (53.5)	101 (31.8)	1042 (50.1)	
Other	346 (19.7)	113 (35.5)	459 (22.1)	
Time since first diagnosis, *n* (%)				.039
< 1 month	144 (8.6)	41 (13.6)	185 (9.3)	
1 month – 1 year	242 (14.4)	48 (15.9)	290 (14.6)	
1-2 years	136 (8.1)	26 (8.6)	162 (8.2)	
2 years	1159 (68.9)	187 (61.9)	1346 (67.9)	
LVEF, mean (SD)	18.4 (7.4)	19.6 (7.7)	18.6 (7.4)	.012
INTERMACS profiles, *n* (%)				.002
1	200 (10.3)	50 (13.0)	250 (10.8)	
2	594 (30.7)	151 (39.1)	745 (32.1)	
3	593 (30.6)	106 (27.5)	699 (30.1)	
4	404 (20.9)	61 (15.8)	465 (20.0)	
5-7	145 (7.5)	18 (4.7)	163 (7.0)	
Diabetes, *n* (%)	548 (28.9)	86 (23.0)	634 (28.0)	.028

Note. INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVEF: left ventricular ejection fraction. p-value for gender main effect derived from ANOVA or multinomial regression.*This effect was modified by device strategy (interaction gender × device strategy, $p < .05$). In BTT women were younger than men, but in DT there was no statistical difference between women and men.

Discussion

First of all it should be noted that in EUROMACS women remain underrepresented. They constituted only 16.7% of all CF-LVAD recipients, an even lower level than the percentage in INTERMACS (21% female) (Teuteberg et al., 2020). Of note, women were especially underrepresented in the device strategy DT. Here they represented only 14% of the patients compared to 17.8% among all CF-LVAD patients registered in EUROMACS.

Disadvantages for women compared to men were also observed with regard to pre-implant psychosocial characteristics. Women were more likely to be divorced/separated or widowed, tended to have a lower educational attainment, and to be more often home-maker than men, while being less likely to be not working because of disability. There were also gender differences in age, but this depended on the device strategy. Among patients in BTT, women were younger than men. Women and men in DT did not differ in age. This group of women who are single, not well educated, and unemployed, and also younger when intended for BTT, might constitute a particular risk group for adverse events, impaired survival, and a poor quality of life. Future studies need to examine this in more detail and account for social support, both quantitative and qualitative. Both types of support appear to be differentially associated with outcomes after MCS implantation (Dew et al., 2019). This might provide important information for clinical psychosocial interventions. In addition, socioeconomic status and ethnicity are factors that contribute to health inequity in women with cardiovascular diseases (Vogel et al., 2021). They clearly deserve more attention in EUROMACS.

Of note, in this European cohort patients in DT in general were on average 10 years older than patients bridged for heart transplantation. Reasons why women are less likely to receive CF-LVADs in Europe than men, particularly older women for DT, are currently unclear. Considering that women who develop heart failure are at an advanced age (Magnussen et al., 2019), MCS as a treatment option for this particular patient group also deserves further attention.

Independent of device strategy, women were less likely than men to have ischemic cardiomyopathy and diabetes (Magnussen et al., 2018; van Meeteren et al., 2017). However, women had a shorter time since first diagnosis and were more likely than men to be in clinical unstable conditions, which has been reported before for a smaller EUROMACS cohort (Magnussen et al., 2018). The finding that patients in BTT were more likely to be in unstable clinical condition than patients in DT and the fact that patients in BTT were younger, suggests that CF-LVADs as BTT are particularly considered for younger women, whose hearts fail due to more acute causes. Taken together these findings indicate that women in BTT and DT present different populations. This emphasizes the relevance to look at patients intended for BTT and DT separately.

There were gender differences in substance abuse. Generally, women were less likely to smoke cigarettes than men. This is in line with data from heart transplant candidates (Weidner et al., 2011). Only women intended for BTT were less likely than men to have a history of alcohol abuse, whereas according to US data that combined all devices and strategies women are generally less likely than men to have a history of alcohol abuse (Blumer et al., 2018; Joshi et al., 2019). Whether women's lower substance abuse and smoking are associated with improved clinical outcomes needs to be further determined (Imamura et al., 2020).

Current EUROMACS data do not allow to draw strong conclusions regarding other types of health behaviors such as physical activity or diet, except that women and men did not differ in BMI, which is largely influenced by these health behaviors. Future studies need to incorporate adequate assessments of health behavior such as time spent in physical activity, diet, and medication adherence. These health behaviors appear to be relevant for clinical outcomes in advanced heart failure (Spaderna et al., 2014; Spaderna et al., 2013) and are part of the recommended evaluation (Dew et al., 2018). These data together with socioeconomic status and ethnicity would help to investigate whether the observed gender differences in demographic characteristics translate to an unhealthy lifestyle.

Although a smaller proportion of women than men reported ”no problems” regarding self-care, pain/discomfort, mobility, and anxiety/depression, the difference was not statistically significant. A small single-center study reported a higher proportion of women among LVAD candidates with elevated depression/anxiety at time of implant (Lundgren, Poon, et al., 2017). A more complete assessment of health-related quality of life data in EUROMACS is needed to clarify gender differences in these characteristics.

In this registry data we encountered a huge amount of missing data. This was even more pronounced among women, especially for those intended for BTT. Independent of gender, the high rate of missing data in psychosocial patient characteristics and quality of life, although part of the data assessment protocol, is disconcerting.

Table 4
Psychosocial characteristics of women and men before CF-LVAD implantation

Variable	Men (n = 1993 / 83.1%)	Women (n = 402 / 16.8%)	Total (N = 2395)	p-value
Demographic / Social history				
Marital status, *n* (%)				< .001
Single	264 (18.1)	51 (19.2)	315 (18.2)	
Married	1077 (73.7)	179 (67.3)	1256 (72.7)	
Divorced/Separated	106 (7.3)	24 (9.0)	130 (7.5)	
Widowed	15 (1.0)	12 (4.5)	27 (1.6)	
Educational attainment, *n* (%)				.016
Up to primary	85 (12.0)	24 (19.5)	109 (13.1)	
Secondary	331 (46.7)	65 (52.8)	396 (47.6)	
Post-secondary	122 (17.2)	14 (11.4)	136 (16.3)	
Tertiary	171 (24.1)	20 (16.3)	191 (23.0)	
Working for an income, *n* (%)*	305 (26.3)	46 (21.8)	351 (25.6)	.136
Reasons for not working, *n* (%)				< .001
Demands of treatment	76 (9.3)	7 (4.6)	83 (8.5)	
Disability	301 (36.8)	40 (26.1)	341 (35.1)	

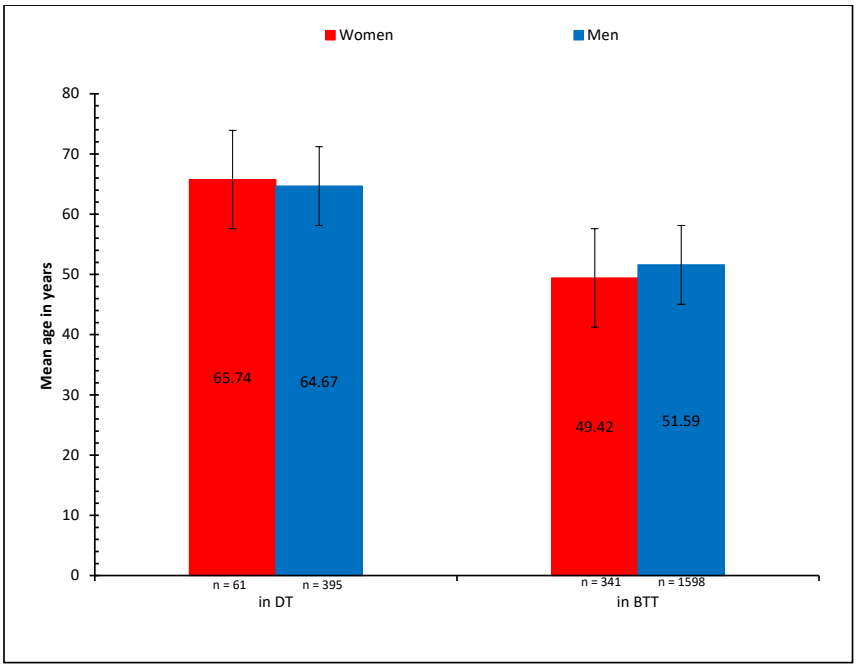
Variable	Men (n = 1993 / 83.1%)	Women (n = 402 / 16.8%)	Total (N = 2395)	p-value
Inability to find work	11 (1.3)	3 (2.0)	14 (1.4)	
Patient in hospital	13 (1.6)	4 (2.6)	17 (1.8)	
Homemaker	1 (0.1)	21 (13.7)	22 (2.3)	
Retired	386 (47.2)	71 (46.4)	457 (47.1)	
Student full/part time	14 (1.7)	4 (2.6)	18 (1.9)	
Other	16 (2.0)	3 (2.0)	19 (2.0)	
Behavioral				
History of smoking, *n* (%)				< .001
Currently	179 (15.1)	20 (10.6)	199 (14.5)	
Within the past 3 months	94 (7.9)	10 (5.3)	104 (7.6)	
More than 3 months ago	578 (48.7)	55 (29.1)	633 (46.0)	
Never	335 (28.2)	104 (55.0)	439 (31.9)	
History of alcohol abuse, *n* (%) *	125 (12.7)	4 (2.6)	129 (11.3)	< .001
History of drug abuse, *n* (%)				.729
Currently	17 (1.7)	2 (1.2)	19 (1.7)	
Within the past 3 months	7 (0.7)	1 (0.6)	8 (0.7)	
More than 3 month ago	14 (1.4)	1 (0.6)	15 (1.3)	
Never	937 (96.1)	163 (97.6)	1100 (96.3)	
BMI categories, *n* (%)				.075
Underweight	47 (2.4)	20 (5.1)	67 (2.9)	
Non-obese	1508 (78.3)	301 (76.6)	1809 (78.0)	
Obese	349 (18.1)	69 (17.6)	418 (1.0)	
Morbidly obese	21 (1.1)	3 (0.8)	24 (18.0)	
Psychological[1)]				
Anxiety/depression, *n* (%)				.330
Extreme problems	47 (19.7)	4 (16.0)	51 (19.4)	
Some problems	127 (53.4)	17 (68.0)	144 (54.8)	
No problems	64 (26.9)	4 (16.0)	68 (25.9)	
EQ-5D summary index, mean (SD)	0.3 (0.4)	0.4 (0.3)	0.3 (0.4)	.910
EQ visual analog scale, mean (SD)	49.3 (21.0)	43.0 (24.4)	49.0 (21.1)	.517
Mobility, *n* (%)				.308

Variable	Men (n = 1993 / 83.1%)	Women (n = 402 / 16.8%)	Total (N = 2395)	p-value
Extreme problems	36 (13.7)	4 (14.8)	40 (13.8)	
Some problems	179 (68.3)	21 (77.8)	200 (69.2)	
No problems	47 (17.9)	2 (7.4)	49 (17.0)	
Self-care, n (%)				.051
Extreme problems	27 (10.4)	2 (7.7)	29 (10.2)	
Some problems	165 (63.7)	22 (84.6)	187 (65.6)	
No problems	67 (25.9)	2 (7.7)	69 (24.2)	
Usual Activities, n (%)				.644
Extreme problems	76 (32.2)	8 (32.0)	84 (32.2)	
Some problems	139 (58.9)	16 (64.0)	155 (59.4)	
No problems	21 (8.9)	1 (4.0)	22 (8.4)	
Pain/discomfort, n (%)				.098
Extreme problems	34 (14.4)	2 (8.0)	36 (13.8)	
Some problems	165 (69.9)	22 (88.0)	187 (71.6)	
No problems	37 (15.7)	1 (4.0)	38 (14.6)	

Note. BMI: body mass index. p-value for gender main effect derived from ANOVA or multinomial regression.*These effects interacted with device strategy ($p < .05$). Only in BTT women were less likely to have a history of alcohol abuse than men. Only in DT women were less likely to be working for an income than men. [1)] Just shown for illustrative purposes. This should not be interpreted because of > 90% missing data.

Figure 1

Mean age with standard error of women and men at time of CF-LVAD implant by device strategy



Note. DT = destination therapy, BTT = bridge to transplant

Table 5
Number and percentage of missing data by gender and device strategy

Variable	BTT		DT		*p*-values		
	Men (*n* = 1598	Women (*n* = 341	Men (*n* = 395)	Women (*n* = 61)	Interaction	Gender	Device strategy
Age (years)	0 (0)	0 (0)	0 (0)	0 (0)	-	-	-
BSA	217 (13.6)	84 (24.6)	7 (1.8)	0 (0)	.050	< .001	< .001
Primary diagnosis	227 (14.2)	82 (24.0)	6 (1.5)	2 (3.3)	.870	< .001	< .001
Time since first diagnosis	267 (16.7)	92 (27.0)	45 (11.4)	8 (13.1)	.285	< .001	< .001
LVEF	406 (25.4)	107 (31.4)	55 (13.9)	7 (11.5)	.229	.030	< .001
INTERMACS profiles	55 (3.4)	16 (4.7)	2 (0.5)	0 (0)	.383	.302	< .001
Diabetes	89 (5.6)	27 (7.9)	10 (2.5)	1 (1.6)	.404	.131	.003
Marital status	456 (28.5)	127 (37.2)	75 (19.0)	9 (14.8)	.069	.004	< .001
Educational attainment	1000 (62.6)	237 (69.5)	284 (71.9)	42 (68.9)	.167	.064	.002
Working for an income	696 (43.6)	172 (50.4)	138 (34.9)	19 (31.1)	.154	.041	< .001
Reasons for not working	980 (61.3)	226 (66.3)	195 (49.4)	23 (37.7)	.024	.291	< .001
BMI categories	54 (3.4)	8 (2.3)	14 (3.5)	1 (1.6)	.697	.289	1.000
History of smoking	605 (37.9)	185 (54.3)	202 (51.1)	28 (45.9)	.004	< .001	.639
History of alcohol abuse	754 (47.2)	209 (61.3)	256 (64.8)	37 (60.7)	.002	< .001	.176
History of drug abuse	756 (47.3)	199 (58.4)	262 (66.3)	36 (59.0)	.015	.008	.245

Note. EQ-5D variables are not shown because > 90% were missing. BTT: bridge to transplant; DT: destination therapy; BMI: body mass index; BSA: body surface area; LVEF: left ventricular ejection fraction.

However, this does not appear to be unique to this registry. INTERMACS investigators have started to document reasons for missing data, indicating that about a quarter of pre-implant quality of life data was missing because patients were too sick to respond (Grady et al., 2017). Interestingly, in the present study a more severe clinical condition among women did not account for their higher amount of missing data in marital status, health-related quality of life, diagnosis, time since diagnosis, and LVEF in EUROMACS. This, together with the observation of fewer missing data in substance abuse variables among men intended for BTT, might indicate some bias in data collection procedures favoring younger men. Clearly, the multitude of reasons that appear to contribute to the problem of missing psychosocial patient characteristics in EUROMACS deserves further attention. Of note, Europe (and thus EUROMACS) is also culturally and linguistically more heterogenous than the United States (and thus INTERMACS). This might further complicate assessments, particularly of psychosocial characteristics, even when instruments such as the EQ-5D exist in various languages. This highlights the need to consistently adopt a useful conceptualization of these characteristics, to use validated instruments, and to implement assessment procedures (Bruce et al., 2014; Dew et al., 2018). The 2018 international Consensus document (Dew et al., 2018) provides not only such a conceptualization of evaluation content, but also recommendations for processes and procedures related to psychosocial evaluations that can guide the development of local standardized procedures (Dew et al., 2018). Considering the clinical importance of psychosocial patient characteristics as summarized by the Consensus document and corroborated recently by retrospective studies reporting associations of high psychosocial risk with adverse events after device implant (DeFilippis, Breathett, et al., 2020; Dew et al., 2021) our understanding of their contribution to outcomes could be greatly enhanced by also (a) following the EUROMACS protocol as to avoid large amounts of missing data, but also by (b) expanding assessments to include standardized valid measures of psychosocial patient characteristics (Bruce et al., 2014; Bui, Allen, et al., 2019; Dew et al., 2018).

Limitations

This study should be interpreted in context of the following limitations. This analysis was conducted retrospectively using registry data from multiple sites across different countries. Thus, completeness of collected data was limited by the available registry data. Missing data in psychological characteristics and quality of life was immense. Thus, we cannot draw any conclusions regarding these characteristics. Demographic and behavioral characteristics were less affected by incomplete data, but efforts to improve psychosocial data completeness are still warranted. This would support the aim of EUROMACS to enable scientific research to improve CF-LVAD treatment (de By et al., 2018). In addition, women comprised only 16.8% of the participants. Therefore, the interaction effects need to be interpreted with caution. The findings need to be re-examined in future research with a higher proportion of women. However, EUROMACS enrollment of women through 31 December 2019 was still only 18.5% (personal communication, Theo de By, 20.03.2020), indicating that there might be a structural imbalance in Europe regarding referral of women for advanced heart failure interventions (Regitz-Zagrosek et al., 2016).

Conclusion

Female and male CF-LVAD patients differ in pre-implant demographic, clinical, and psychosocial characteristics. These differences further depend on device strategy. Our results highlight the necessity (1) to differentiate not only by gender, but also between CF-LVAD patients registered for DT or BTT; and (2) to pay greater attention to psychosocial characteristics both in terms of minimizing the missing data problem as well as considering adoption of validated standardized assessments of these factors to improve clinical outcomes for all patients.

Author Contribution Statement

HS and GW devised the project and encouraged SL to investigate the role of gender in EUROMACS as part of her Master's Thesis. SL analyzed the data under supervision of HS, GW, and LM. SL drafted the manuscript with input from all authors. LM revised the figure and provided additional analyses. HS, GW, TMMHB, and LM participated in revising the manuscript.

Meeting Presentation

Parts of this manuscript have been presented (1) 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 Behavioral Factors", October 10-12, 2019, Trier, Germany, and (2) at the Annual Meeting and Scientific Sessions of the International Society of Heart and Lung Transplantation 2020, J Heart Lung Transpl. 2020;39:S334.

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Conflict of Interest Statement

There is no conflict of interest.

Acknowledgement

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

Article 2 was published in the *Journal of the American Heart Association*: **Maukel, L.-M.,** Weidner, G., Beyersmann, J., & Spaderna, H. (2022). Sex differences in recovery and device replacement after left ventricular assist device as destination therapy. *Journal of the American Heart Association*, *11*(5), e023294. https://doi.org/10.1161/JAHA.121.023294

The Journal replaced the term *gender* with *sex*. As the selected term in this dissertation is *gender*, the following article is adapted accordingly.

Abstract

Background: The relevance of gender and pre-implant factors for clinical outcomes among patients with left ventricular assist devices intended for destination therapy is unclear.

Methods and results: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data (2006-2017) from 6771 men and 1690 women with left ventricular assist devices as destination therapy were analyzed to evaluate the contribution of pre-implant 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 gender 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 non-ischemic 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% vs. 1.6%, $p <$ .001) and device replacement (12.1% vs. 10%, $p = .019$) than men but not for death and transplant ($p > .12$). The gender differences remained after controlling for covariates (HR_{adj} recovery 1.85, 95% CI [1.30–2.70], $p < .001$; HR_{adj} device replacement 1.22, 95% CI [1.04–1.33], $p = .015$). Female-specific diagnoses (e.g., 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 gender differences in outcomes.

Keywords: gender differences, INTERMACS, left ventricular assist device, outcomes

Clinical Perspective

What is new?

- Among patients receiving a continuous-flow LVAD as long-term support, women were more likely than men to experience device explant due to cardiac recovery, especially women presenting with non-ischemic 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 (e.g., diagnoses, INTERMACS profile, pump type)
- Clinically-judged psychosocial patient characteristics did not contribute to gender differences in clinical outcomes

What are the clinical implications?

- In the modern CF-LVAD 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

Introduction

Continuous-flow left ventricular assist device (CF-LVAD) use has become standard therapy for patients with end-stage heart failure. Originally intended as bridge to transplant therapy (BTT), today most of all CF-LVADs are implanted as destination therapy (DT) (Teuteberg et al., 2020). 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.

Gender differences in clinical outcomes of DT patients have been examined previously, but are difficult to interpret, because many studies do not differentiate between device types (LVAD, bi-VAD, total artificial heart, pulsatile vs. continuous) and device strategies. For example, a higher risk of death after LVAD implantation in women compared to men has been reported in four studies using Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) (Gruen et al., 2020; Kirklin et al., 2017), International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (IMACS) (Nayak, Hu, Ko, Mehta, et al., 2021), and The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) data (Magnussen et al., 2018), whereas others could not confirm any gender differences in mortality (Ahmed et al., 2020; Hsich, Naftel, et al., 2012). All these studies combined devices and/or strategies. Considering device improvements over time, Joshi et al. (2019) found that only women in the pulsatile-flow era but not in the continuous-flow era have an increased risk of mortality (Joshi et al., 2019). DeFilippis and colleagues (DeFilippis, Truby, et al., 2019) 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 gender 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 (DeFilippis, Farr, et al., 2019; Wehbe & Anderson, 2019)

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 gender is involved in these outcomes comes from a recent study on myocardial recovery of LVAD patients in general, which detected female gender as a predictor for partial recovery, independent of clinical parameters (Topkara et al., 2016). Other studies could not find independent gender effects regarding recovery (Wever-Pinzon et al., 2016) and evidence that women with LVADs suffer more complications is also mostly based on research neglecting device strategies (Acharya et al., 2017; Hsich, Naftel, et al., 2012).

Gender differences in pre-implant clinical characteristics have been investigated previously (Hsich, Naftel, et al., 2012; Magnussen et al., 2018; Nayak, Hu, Ko, Steinberg, et al., 2021). Therefore, focusing on demographic and psychosocial characteristics (e.g., working for income, marital status, alcohol abuse) might help to further understand gender differences in outcomes. Findings from single-center studies suggest that high psychosocial risk (e.g., substance abuse, depression) is associated with increased rates of complications (Lundgren, Lowes, et al., 2017; Snipelisky et al., 2015) and mortality (Akhter et al., 2013). In one study using INTERMACS data patients with at least one psychosocial risk factor (e.g., substance abuse) were at increased hazards for infection, bleeding, pump thrombosis, and readmission compared to patients without any psychosocial risk (DeFilippis, Breathett, et al., 2020). 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 heart failure, depression and social isolation, standardly assessed, were associated with lower rates of delisting due to clinical improvement, and also with an increased requirement of LVAD implantation while on the

heart transplant waiting list, and decreased survival after heart transplant (Spaderna et al., 2012; Spaderna et al., 2017). Taken together, these studies indicate that psychosocial risk factors contribute to clinical outcomes. However, data on potential gender differences in these characteristics and their associations with clinical outcomes including recovery among male and female LVAD recipients are still lacking.

Thus, the aims of this study are to (1) present gender differences in pre-implant clinical, demographic, and psychosocial characteristics in patients with primary CF-LVADs as DT, (2) to examine gender 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 gender differences in pre-implant characteristics can explain gender difference 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 Kirklin et al., 2017 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 LVAD, right ventricular assist device, biventricular assist device or total artificial hearts were excluded. Data from 8471 patients (20% women), registered between 6/2006 to 12/2017, with primary CF-LVAD in the device strategy DT were analyzed.

Pre-implant Variables

Clinical variables are shown in Table 6. Demographics and psychosocial variables also included behavioral factors (BMI as a proxy of healthy lifestyle, smoking status, history of alcohol and substance abuse; Table 6). 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% (Grady et al., 2017).

Clinical Outcomes

Death, heart transplantation, device explant due to heart recovery, and device replacement due to complications (i.e., device malfunction, device thrombosis, and infection) were considered as competing outcomes. Time until the first occurrence of one 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 (van Buuren & Groothuis-Oudshoorn, 2011; Zahn et al., 2010). 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 (R Development Core Team, 2018; van Buuren & Groothuis-Oudshoorn, 2011). 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.

Pre-implant variables were evaluated as independent variables. Continuous variables were described as mean and *SD*s, and categorical variables were summarized as percentages. Gender differences in pre-implant 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 out- comes, 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 one 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 (Aalen & Johansen, 1978) and compared using Gray's method (Gray, 1988). Univariable event-specific Cox regression was used to investigate the impact of gender and pre-implant characteristics on event-specific hazards (Beyersmann et al., 2012).

In a first multivariable model, additional to gender, all clinical variables significantly associated with at least one of the outcomes were entered stepwise to evaluate whether the effects of gender were accounted for by disease severity or other clinical parameters. For the second multivariable model, additional to gender 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 gender differences in outcomes, independent of clinical parameters

Additionally, potential moderating effects of gender on the association between demographic and psychosocial characteristics with outcomes were examined by adding the interaction of

gender 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 (Schoenfeld, 1980). Significance level was set at $p < .05$. Analyses were performed using R, version 3.5.0, including the packages *cpmrsk* and *survival* (R Development Core Team, 2018).

Table 6

Pre-implant 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* (%)				.763
< 20 %	4260 (67.8)	1080 (67.9)	5346 (67.8)	
20-29 %	1753 (27.9)	436 (27.4)	2192 (27.8)	
> 30 %	272 (4.3)	75 (4.7)	348 (4.4)	
LVEDD	6.82 (1.08)	6.47 (1.06)	6.75 (1.08)	< .001
LVAD axial, *n* (%)	6536 (96.5)	1594 (94.3)	8136 (96.0)	< .001
INTERMACS profiles, *n* (%)				.405
1	960 (14.2)	246 (14.6)	1207 (14.3)	
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* (%)				< .001
Ischemic	3905 (58.2)	593 (35.3)	4503 (53.6)	
Idiopathic	1743 (26.0)	570 (33.9)	2317 (27.6)	
Other	1064 (15.9)	518 (30.8)	1583 (18.8)	
Time since diagnosis, *n* (%)				< .001

Variables†	Men (*n* = 6771)	Women (*n* = 1690)	Total (*N* = 8471)	*p*-value
< 1 month	256 (3.9)	67 (4.1)	323 (4.0)	
1 month – 1 year	565 (8.7)	197 (12.1)	762 (9.4)	
1-2 years	373 (5.7)	160 (9.8)	533 (6.5)	
> 2 years	5312 (81.6)	1202 (73.9)	6523 (80.1)	
Current ICD, *n* (%)	5553 (82.6)	1295 (77.2)	6856 (81.5)	< .001
Severe diabetes, *n* (%)	645 (11.8)	177 (12.7)	822 (12.0)	.380
Allosensitization, *n* (%)	16 (0.3)	39 (2.8)	56 (0.8)	< .001
Diastolic BP	64.84 (11.51)	64.13 (11.74)	64.69 (11.56)	.028
Systolic BP	106.47 (16.32)	107.30 (17.55)	106.63 (16.57)	.083
Mean arterial pressure	78.74 (11.14)	78.52 (11.58)	78.69 (11.22)	.496
Heart rate	86.17 (16.56)	90.81 (17.25)	87.10 (16.79)	< .001
Pulmonary systolic artery pressure	50.48 (14.81)	48.82 (14.59)	50.15 (14.78)	< .001
Preoperative blood values				
Albumin g/dl	3.36 (0.63)	3.32 (0.65)	3.35 (0.64)	.029
Bilirubin total mg/dl	1.39 (1.87)	1.14 (1.58)	1.34 (1.82)	< .001
BUN mg/dl	31.59 (18.67)	28.02 (18.31)	30.87 (18.65)	< .001
Creatinine mg/dl	1.48 (0.67)	1.28 (0.66)	1.44 (0.67)	< .001
Hemoglobin g/dl	11.30 (2.14)	10.62 (1.78)	11.16 (2.09)	< .001
Platelets x1000/µl	188.69 (76.10)	204.86 (84.17)	191.90 (78.01)	< .001
Potassium mmol/l	4.08 (0.48)	4.04 (0.48)	4.07 (0.48)	.002

Variables†	Men (*n* = 6771)	Women (*n* = 1690)	Total (*N* = 8471)	*p*-value
Sodium mmol/l	135.12 (4.67)	135.70 (4.61)	135.24 (4.67)	< .001
Medication *n* (%)				
Beta blocker	5230 (79.7)	1260 (77.3)	6497 (79.2)	.036
ACE	2891 (46.2)	735 (47.0)	3630 (46.3)	.558
ARB	1064 (17.5)	356 (23.1)	1420 (18.6)	< .001
Aldosterone	3369 (52.8)	949 (59.6)	4324 (54.2)	< .001
Demographic and psychosocial characteristics				
Age in years	62.22 (12.30)	58.51 (13.01)	61.48 (12.53)	< .001
Educat. attainment, *n* (%)				.133
Up to primary	210 (4.3)	46 (3.7)	256 (4.2)	
Secondary	2323 (47.2)	615 (49.4)	2940 (47.7)	
Post-secondary	1252 (25.4)	330 (26.5)	1582 (25.7)	
Tertiary	1136 (23.1)	253 (20.3)	1389 (22.5)	
Marital status, *n* (%)				< .001
Single	976 (14.6)	353 (21.4)	1329 (16.0)	
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)	< .001

Variables†	Men (*n* = 6771)	Women (*n* = 1690)	Total (*N* = 8471)	*p*-value
Working for income, *n* (%)	823 (13.2)	164 (10.5)	987 (12.7)	.005
BMI, *n* (%)				< .001
Underweight	199 (3.0)	79 (4.7)	278 (3.3)	
Non-obese	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* (%)				< .001
Currently	343 (6.3)	100 (7.2)	443 (6.5)	
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)	< .001
History drug abuse, *n* (%)	444 (8.1)	86 (6.2)	530 (7.7)	.017
Limited social support, *n* (%)	341 (6.3)	99 (7.1)	440 (6.4)	.264
Severe depression, *n* (%)	137 (2.5)	59 (4.2)	196 (2.9)	< .001

Note. 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).

Results

Gender Differences Pre-implant

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 6). 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 6).

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. Gender-specific cumulative incidence functions are shown in Figure 2 and 3. The probabilities for mortality and transplant did not differ significantly be- tween women and men (mortality: $p = .124$, transplant: $p = .403$). 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 ($p < .001$). 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 ($p = .019$), 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. Gender differences in reasons for device

replacement (i.e., device malfunction, device thrombosis, and infection) were not significant in a chi-square test.

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

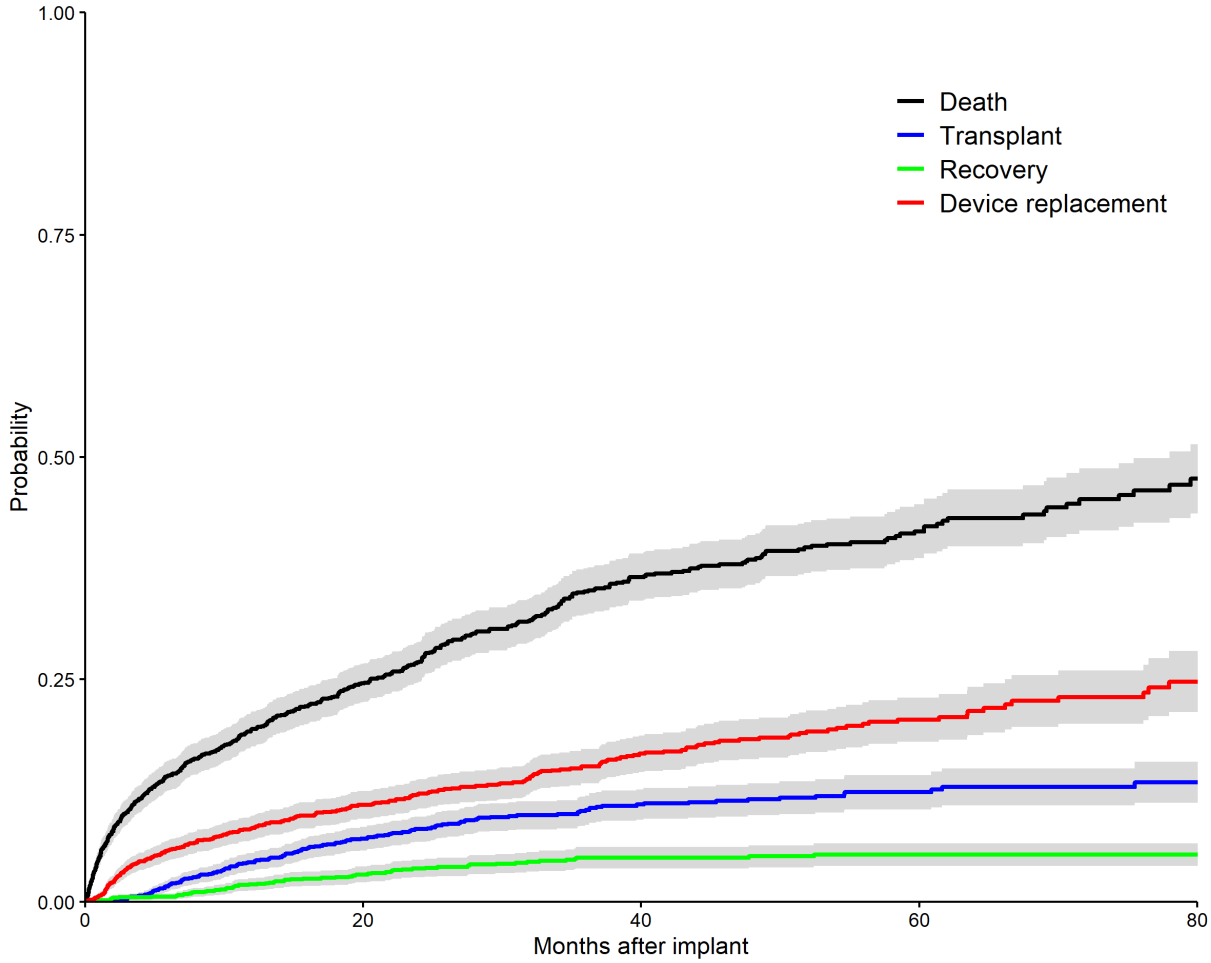
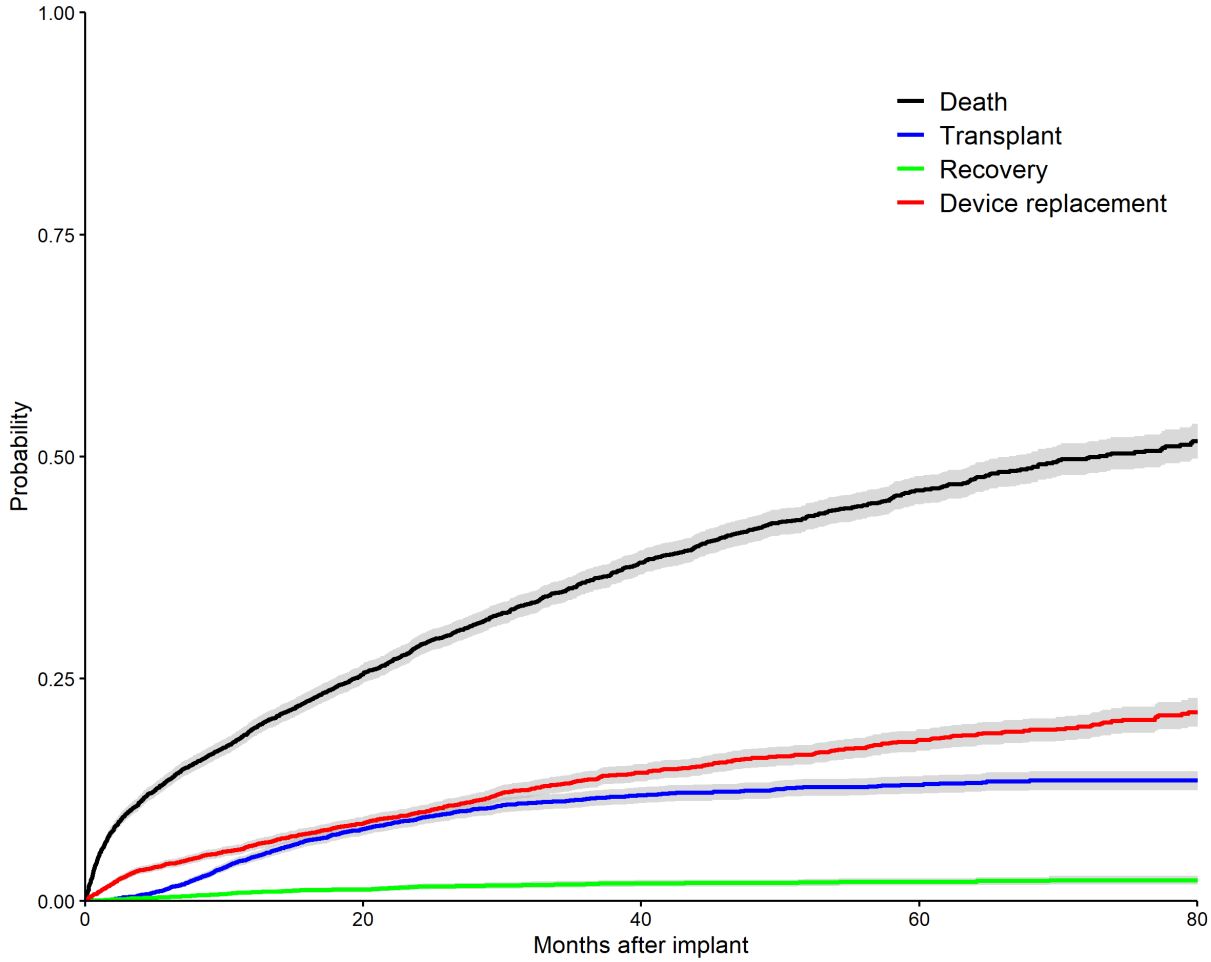


Figure 3

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



Associations of Gender and Pre-implant Characteristics with Clinical Outcomes

Results from regression analyses confirmed the described effects: Female gender was associated with an increased rate for explant due to recovery (HR 2.50, 95% CI [1.82–3.33]. $p < .001$) and device replacement (HR 1.20, 95% CI [1.04–1.37], $p = .011$; Table 7). Univariable event-specific proportional hazards for clinical, demographic, and psychosocial characteristics and the four 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 gender on recovery remained significant, but decreased to 1.82, 95% CI [1.30–2.56], $p < .001$; Table 7). 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 heart failure and heart failure due to adriamycin medication (breast cancer). The HR for female gender and device replacement remained similar to the univariable analysis (HR 1.22, 95% CI [1.04–1.41], $p = .012$), indicating an independent gender 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 gender on the outcome recovery changed marginally to 1.85 (95% CI [1.30–2.70], $p < .001$) and to 1.22 (95% CI [1.04–1.33], $p = .015$) for device replacement (Table 7). Thus, there were no additional effects of demographic and psychosocial characteristics that accounted for the associations of gender with each of these outcomes.

The analyses of the second multivariable model (Table 7 and Table S3) also revealed that independent of gender, several demographic and psychosocial characteristics were associated with at least one of the four 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 in- creased rates of explants due to recovery, independent of gender 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 gender moderated the associations of demographic and psychosocial variables with the outcomes explant due to recovery and device replacement yielded only one

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.

Table 7

Event-Specific Hazard Models for Gender 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 gender				
Female gender	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 gender controlling for all clinical variables †				
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]*
Multivariable model 2: HR for female gender controlling for additional demographic and psychosocial characteristics †				
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]*
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]
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]***

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	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]

Note. 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. ***$p < .001$ **$p < .01$ *$p < .05$

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 four outcomes, thereby avoiding overestimation of outcome probabilities (Beyersmann et al., 2012) and contributing to a more detailed clinical outcome picture. For example, the finding that gender was associated with one favorable outcome (i.e., recovery) as well as one unfavorable outcome (i.e., 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 both genders, we avoided a BTT-specific selection bias (DeFilippis, Farr, et al., 2019; Wehbe & Anderson, 2019). 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 (DeFilippis, Truby, et al., 2019; Gruen et al., 2020; Kirklin et al., 2017; Nayak, Hu, Ko, Mehta, et al., 2021). However, women intended for BTT are generally more clinically disadvantaged (more severely ill, less ideal transplant candidates) when receiving a device than men (Blumer et al., 2018; Hsich, 2019). 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 (Wehbe & Anderson, 2019). Focusing our analyses on DT patients helps to disentangle gender differences in death rates from this selection bias that may be responsible for the higher death rates observed in women intended for BTT (DeFilippis, Truby, et al., 2019; Wehbe & Anderson, 2019). 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 gender-related differences in clinical outcomes, especially as more and more patients receive LVADs as long-term support today (Teuteberg et al., 2020).

Of the four 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 non-ischemic diagnoses, compared with a non-bridge to recovery group (Wever-Pinzon et al., 2016). Furthermore, female gender was found to be a predictor for partial recovery, as indicated by substantial improvement of left ventricular function on CF-LVAD support, but without subsequent device explantation in a general LVAD cohort where all device strategies were combined (Topkara et al., 2016).

The increased rate for explant due to recovery in women compared with men was reduced after controlling for clinical variables. Specifically, gender 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 gender-specific diagnoses: Adriamycin-induced heart failure represented 10.4% (and postpartum heart failure 7.5%) of all diagnoses in women who experienced recovery compared with 4.7% (and 3.6%) in those who died. Heart failure induced by adriamycin, medication often used for breast cancer, or heart failure induced by pregnancy may be more easily reversed if detected early (Cardinale et al., 2020; Topkara et al., 2016), 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 gender 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 gender difference need to be further examined. Keeping in mind that women with heart failure 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 (Vogel et al., 2021).

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 (e.g., specific pump types for women) were not associated with this outcome. Device replacement (e.g., due to device malfunction, pump thrombosis, infection) can be seen as a proxy for complications and adverse events (Forest et al., 2018; Moazami et al., 2013). Therefore, our findings observed in women in DT are in line with prior studies in the general LVAD population (Acharya et al., 2017; Gruen et al., 2020; Hsich, Naftel, et al., 2012), emphasizing women's generally increased risk for complications after device implantation independent of competing outcomes.

It is noteworthy that gender differences in demographic and psychosocial variables (e.g., unmarried, depressed) did not contribute to women's adverse events. It is conceivable that other factors (e.g., device acceptance, mood, coping), not included in INTERMACS, could have influenced the occurrence of adverse events (Modica et al., 2019; Tosto et al., 2019). In line with this reasoning is the observation from a previous INTERMACS report indicating that women report more problems in quality of life dimensions (i.e., usual activities, pain/discomfort, and anxiety/depression) than men before and at 3 and 6 months after LVAD implant (Grady et al., 2016). 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 gender-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 gender differences in adverse events may become less likely in the future (Joshi et al., 2019; Zafar et al., 2017).

The increasing number of studies that report women to be disadvantaged regarding adverse events after LVAD implant (Acharya et al., 2017; Gruen et al., 2020; Hsich, Naftel, et al., 2012) 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 (Cook et al., 2015; Vogel et al., 2021). More research regarding health status and psychosocial factors affecting women's and men's decisions to accept or decline LVAD therapy (Bruce et al., 2015) might further elucidate gender differences in outcomes.

At the time point of a long-term LVAD implant, disease severity (e.g., left ventricular ejection fraction, INTERMACS profile) appeared to be comparable between women and men. Apparently, the focus should shift to gender and gender differences in patient care after implant. Traditionally, women provide support to chronically ill male spouses (Cook et al., 2015). 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 heart failure and rather choose parents and adult children (Steinberg et al., 2022). The impact of traditional gender roles and the perceived social support on outcomes after LVAD implant needs to be further investigated.

Independent of gender, 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 (Forest et al., 2018). These findings highlight the need to clarify who might benefit from early weight reduction programs (e.g., nutritional counseling, regular exercise) in this patient population.

Gender differences in pre-implant 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 gender, the variables of limited social support, substance abuse (drug and alcohol), and severe depression were not associated with any of the four outcomes. This is unexpected considering that the 2018 International Society for Heart and Lung Transplantation Consensus recommendations (Dew et al., 2018) 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 (Dew et al., 2021). 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%) (Grady et al., 2017). 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 gender in the expected direction and possessing high face validity, did not contribute to gender differences in outcomes. The ways to capture these psychosocial aspects are not standardized in INTERMACS and, as a result, vary among participating sites (Clancy et al., 2019; Gupta et al., 2016) reducing their usefulness for empirical analyses.

Conclusion

Of the four 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 gender-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 gender differences in patients with LVAD.

Article Information

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Disclosures

None.

SUPPLEMENTAL MATERIAL

Gender differences in recovery and device replacement after left ventricular assist device implantation as destination therapy

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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]
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]*

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]
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]
> 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]***
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]

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]
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]
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]

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]
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]***
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]**

Note. 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. ***$p < .001$, **$p < .01$, *$p < .05$

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				
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]

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]
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				
< 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]
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]

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]
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]***

Note. 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. ***$p <$ .001, **$p <$ .01, *$p <$ .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]
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]

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]
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]
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]
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	0.96 [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]*

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]
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]
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]
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]

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]
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]

Note. 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. ***$p < .001$, **$p < .01$, *$p < .05$

4.3 Adverse Events After Left Ventricular Assist Device Implantation Linked to Psychosocial Risk in Women and Men

Article 3 is under third revision in *The Journal of Heart and Lung Transplantation*.

Maukel, L.-M., Weidner, G., Beyersmann, J., & Spaderna, H. (submitted). Adverse Events After Left Ventricular Assist Device Implantation Linked to Psychosocial Risk in Women and Men.

As the selected term in this dissertation is *gender*, the following article is adapted accordingly.

Abstract

Background: Reasons for women's increased probability to experience adverse events after left ventricular assist device (LVAD) implantation compared with men's remain uncertain. We explored the role of psychosocial risk in the experience of adverse events in women and men. *Methods:* INTERMACS patients receiving a primary CF-LVAD between 7/2006 and 12/2017, median follow-up 13.6 months, were included (n = 20123, 21.3% women). Time-to-event was calculated with cumulative incidence functions for 10 types of adverse events separately (e.g., infection, device malfunction), each time accounting for the competing outcomes death, heart transplant and device explant due to recovery. Event-specific Cox proportional hazard models were run with a binary psychosocial risk variable (including: substance abuse, psychiatric diagnoses, limited social support, limited cognition, repeated noncompliance), controlled for covariates. *Results:* Psychosocial risk was more prevalent in men than in women (21.4% vs. 17.5%, $p < .001$). Seven out of 10 adverse events were more likely in women than in men (e.g., infection 44.5% vs. 39.2%, $p < .001$). The association of psychosocial risk with each adverse event was either stronger in women than in men (e.g., device malfunction HR_{adj} 1.29, 95% CI [1.06-1.56] vs. HR_{adj} 1.10, 95% CI [0.97-1.25]; rehospitalization HR_{adj} 1.15, 95% CI [1.02-1.29] vs. HR_{adj} 1.03, 95% CI [0.97-1.10]) or similar between genders. *Conclusions:* Independent of clinical parameters, the presence of psychosocial risk is associated with increases in AEs. This suggests that early modification of psychosocial risk factors may have the potential to lower the risk for adverse events in this patient population.

Introduction

Continuous-flow left ventricular assist device (CF-LVAD) use has become standard therapy for patients with heart failure and reduced ejection fraction (HFrEF). Although about 40% of the HFrEF population is female (Desai et al., 2021), women only represent about 20% of patients receiving LVAD therapy (Khazanie, 2019). Recent studies imply that women's survival has improved over the years in the continuous-flow era, as new generation devices are more suitable for the female body (Joshi et al., 2019; Teuteberg et al., 2020). However, women still appear to be more likely to experience complications after LVAD implant compared with men. We previously reported that women on long-term support have higher probabilities to be explanted due to complications compared with men (Maukel et al., 2022). Women are also more likely to experience neurological events (Acharya et al., 2017; Gruen et al., 2020; Hsich, Naftel, et al., 2012; Morris, Pekarek, et al., 2015; Sherazi et al., 2017), bleeding (Gruen et al., 2020; Magnussen et al., 2018), rehospitalization, pump thrombosis and/or device malfunction (Gruen et al., 2020). However, a complete-case-analysis of 3511 inpatients (Ahmed et al., 2020) and an analysis of the Mechanical Circulatory Support Research Network (n = 734) (van Meeteren et al., 2017) did not detect gender difference in the occurrence of adverse events. Importantly, none of the above studies applied a competing risks analysis for each adverse event separately, also including the competing outcomes death, transplant, or recovery. Different probabilities of women and men to experience transplant and recovery (Gruen et al., 2020; Maukel et al., 2022) might impact the probabilities to experience adverse events on LVAD support. Thus, this methodological approach has been recommended for time-to-event analyses of adverse events (Stegherr et al., 2021).

Device-related (e.g., axial vs. centrifugal flow) and clinical risk factors (e.g., primary diagnosis, differences in medication management) for gender differences in adverse events have been evaluated before (Acharya et al., 2017; Gruen et al., 2020; Hsich, 2019), but those factors contributed only minimally to gender differences in adverse events. In the field of

heart failure, especially heart transplantation, it is well documented that psychosocial risk factors contribute to clinical outcomes (Grady et al., 1999; Spaderna et al., 2017). Similar investigations in LVAD populations are scarce. The 2018 ISHLT Consensus recommendations (Dew et al., 2018) for long-term LVAD support emphasize the role of psychosocial aspects for outcomes and recommend to standardize the process of psychosocial evaluation. Only a small single-center study recorded psychosocial data systematically (Dew et al., 2018). In this study, social workers or psychologists rated psychosocial risk and the adverse events were analyzed using a competing risks approach. An increase in psychosocial risk, particularly mental health problem severity, non-adherence, and substance use, was related to higher rates of adverse events (Dew et al., 2021). Gender was unrelated to adverse events, but the number of women in the sample of 241 was only 45.

Large data bases, such as the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), may be more suitable to study gender differences. Unfortunately, standardized and validated tools for psychosocial evaluation are not included in the assessment protocol in INTERMACS (Clancy et al., 2019). DeFilippis and colleagues circumvented this problem by computing a variable psychosocial risk (yes vs. no) based on INTERMACS' *concerns and contraindications for transplant,* which are coded as *applicable* or *not applicable* (DeFilippis, Breathett, et al., 2020). Using this variable, psychosocial risk was associated with increased hazards for adverse events such as device-related infection, gastrointestinal bleeding, pump thrombosis, and readmission. These results emphasize the role of psychosocial factors for clinical outcomes after LVAD implant. In this study, men were more likely than women to have one or more psychosocial risk factors, but gender was only included as a covariate and not further evaluated (DeFilippis, Breathett, et al., 2020).

The present study is based on INTERMACS data and aims to 1) evaluate gender differences in pre-implant psychosocial risk; 2) examine gender differences in 10 adverse events, using separate competing risks analyses; 3) explore the association of psychosocial risk with

adverse events, controlling for clinical, demographic, and behavioral characteristics in women and men.

Materials and Methods

Study Population

INTERMACS is a North-American prospective registry of patients with advanced heart failure receiving durable mechanical circulatory support. Clinical, demographic, behavioral, and psychosocial patient characteristics are recorded before implantation and patients are under follow-up regarding adverse events until death, heart transplantation or recovery (Kirklin et al., 2017). Analyses were based on de-identified data of adult patients (age > 18 years at implant). Informed consent had been obtained before implantation by the participating centers. Patients who received pulsatile-flow LVAD, right ventricular assist device, biventricular assist device, or total artificial hearts were excluded. Data from 20,123 patients (21.3 % women), registered between 7/2006 to 12/2017, with primary CF-LVAD were analyzed. Data were obtained through the Biological Specimen and Data Repository Information Coordinating Center (BioLINCC). This study was approved by the Trier University Institutional Review Board (number 66/2018).

Pre-implant Characteristics

Besides common clinical variables (DeFilippis, Breathett, et al., 2020; Gruen et al., 2020), the following demographic and behavioral variables were considered: age, race, working for income, marital status, education, BMI, and smoking status (Table 8).

The psychosocial variables of INTERMACS' *concerns and contraindications for transplant* were limited social support, limited cognition/understanding, alcohol abuse, drug abuse, severe depression, other major psychiatric diagnosis, and repeated noncompliance. Based on the approach by DeFilippis and colleagues a binary variable was coded as psychosocial risk (1

= present) if at least one of the above conditions was applicable (Table 9)(DeFilippis, Breathett, et al., 2020).

Outcome Measurements

The adverse events cardiac arrhythmia, bleeding, infection, device malfunction and/or pump thrombosis, neurological dysfunction, psychiatric episode, rehospitalization, renal dysfunction, respiratory failure and right heart failure were analyzed. To reduce bias, the following clinical outcomes were considered as competing events: death, heart transplantation, and device explant due to recovery.

Statistical Analysis

For each psychosocial variable of INTERMACS' *concerns and contraindications for transplant* 26.5% of the data were missing (26.6% in men and 26.3% in women, Table S4). The semiparametric multiple imputation procedure of van Buuren and Oudshoorn, recommended if missing data < 30%, was applied (van Buuren & Groothuis-Oudshoorn, 2011) to handle missing values in all covariates, including the psychosocial variables derived from the *concerns and contraindications* (see supplement). Continuous variables were described as means and standard deviations and categorical variables were described as frequencies and percentages. Gender differences in pre-implant characteristics were examined using *t* tests for continuous and chi-square tests for categorical variables.

Each adverse event was analyzed in a competing risks approach with the competing outcomes, death, heart transplant, and device explant due to recovery (Stegherr et al., 2021). Time to first event was calculated as the time from CF-LVAD implantation until one 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 (Aalen & Johansen, 1978) and compared between genders using Gray's method (Gray, 1988).

For each adverse event, the event-specific hazards for the adverse event, death, heart transplant and recovery were calculated. We report HR with their respective 95% CI. Each multivariable model included the following variables: gender, psychosocial risk (yes vs. no), interaction between gender and psychosocial risk, age, race, working for income, marital status, education, BMI, and smoking status. The clinical covariates were device strategy, primary diagnosis, time since diagnosis, left ventricular end-diastolic diameter (LVEDD), INTERMACS profile, pump type (axial vs. centrifugal), implantable cardioverter-defibrillator (ICD), pulmonary hypertension, albumin, bilirubin, creatinine, BUN, platelet count and medications. To illustrate potential interactions between gender and psychosocial risk, we rerun the analyses for the female and male subgroup separately. Here we focused on those adverse events with significant gender differences. The proportional hazards assumption was checked by the global goodness-of-fit test proposed by Schoenfeld (Schoenfeld, 1980). Significance level was set at $p < .05$. Analyses were performed using R, version 4.0.3, including the packages, *mice, cpmrsk* and *survival* (R Development Core Team, 2018).

Results

Gender Differences Pre-implant

Of 20123 patients receiving a primary CF-LVAD, 4282 (21.3%) were female. Women were less likely to have an axial device type and a current ICD than men. Women were more likely to be in INTERMACS profile 1, but less likely to have an ischemic primary diagnosis. Women also had a shorter time since first cardiac diagnosis. Accordingly, women were significantly younger than men and less likely to be implanted in the device strategy destination therapy. Women were less likely to have a smoking history, but more likely to be non-White, unmarried, not working for an income, and in the BMI extremes than men (Table 8).

Table 8
Pre-implant clinical, demographic, and behavioral characteristics for women and men with CF-LVAD

	Women (n = 4282) 21.3%	Men (n = 15817) 78.7%	Total (n = 20123)	p-value
Clinical variables				
Device Strategy, *n* (%)				.001
Destination therapy	1730 (40.4)	6875 (43.5)	8615 (42.8)	
Bridge to transplant	2515 (58.8)	8840 (55.9)	11369 (56.5)	
Bridge to recovery	23 (0.5)	55 (0.3)	78 (0.4)	
Rescue therapy	12 (0.3)	39 (0.2)	51 (0.3)	
Ejection fraction grade, *n* (%)				.640
< 20 %	2765 (69.7)	10186 (70.2)	12969 (70.1)	
20-29 %	1007 (25.4)	3662 (25.2)	4674 (25.3)	
> 30 %	194 (4.9)	661 (4.6)	856 (4.6)	
LVEDD	6.51 (1.08)	6.90 (1.12)	6.82 (1.12)	< .001
LVAD axial, *n* (%)	3245 (75.8)	12704 (80.3)	15961 (79.3)	< .001
INTERMACS profiles, *n* (%)				.005
1	723 (16.9)	2454 (15.6)	3182 (15.9)	
2	1541 (36.1)	5683 (36.1)	7230 (36.1)	
3	1391 (32.6)	5011 (31.8)	6413 (32.0)	
4	487 (11.4)	2031 (12.9)	2518 (12.6)	

	Women (*n* = 4282) 21.3%	Men (*n* = 15817) 78.7%	Total (*n* = 20123)	*p*-value
5-7	127 (3.0)	575 (3.6)	703 (3.5)	
Primary diagnosis, *n* (%)				< .001
Ischemic	1236 (29.1)	7911 (50.4)	9160 (45.8)	
Idiopathic	1504 (35.4)	4841 (30.8)	6355 (31.8)	
Other	1512 (35.6)	2952 (18.8)	4465 (22.3)	
Time since diagnosis, *n* (%)				< .001
<1 month	269 (6.5)	778 (5.1)	1049 (5.4)	
1 month – 1 year	530 (12.8)	1559 (10.2)	2089 (10.8)	
1-2 years	379 (9.2)	985 (6.5)	1365 (7.0)	
>2 years	2947 (71.4)	11921 (78.2)	14886 (76.8)	
Current ICD, *n* (%)	3248 (76.4)	12717 (80.9)	15982 (79.9)	< .001
Severe diabetes, *n* (%)	314 (9.9)	1130 (9.7)	1445 (9.8)	.742
Diastolic BP	64.01 (11.83)	65.13 (11.40)	64.89 (11.50)	< .001
Systolic BP	105.05 (16.90)	104.94 (15.89)	104.96 (16.11)	.702
Mean arterial pressure	77.71 (11.50)	78.42 (11.04)	78.27 (11.14)	< .001
Heart rate	92.42 (17.97)	87.90 (17.32)	88.87 (17.56)	< .001
Pulmonary systolic artery pressure	48.10 (14.43)	50.49 (14.86)	49.99 (14.80)	< .001
Pulmonary Hypertension, *n* (%)	655 (20.7)	2616 (22.5)	3275 (22.1)	.035
Preoperative blood values				

	Women (n = 4282) 21.3%	Men (n = 15817) 78.7%	Total (n = 20123)	p-value
Albumin g/dl	3.38 (0.66)	3.4 (0.65)	3.4 (0.65)	.071
Bilirubin total mg/dl	1.21 (1.61)	1.42 (1.82)	1.38 (1.79)	< .001
BUN mg/dl	26.07 (16.86)	30.14 (18.27)	29.27 (18.05)	< .001
Creatinine mg/dl	1.22 (0.65)	1.45 (0.71)	1.40 (0.70)	< .001
Hemoglobin g/dl	10.64 (1.84)	11.4 (2.17)	11.24 (2.13)	< .001
Platelets x1000/µl	209.32 (87.46)	193.68 (79.19)	197.0 (81.25)	< .001
Potassium mmol/l	4.05 (0.49)	4.08 (0.48)	4.07 (0.49)	< .001
Sodium mmol/l	135.44 (4.65)	134.88 (4.82)	134.99 (4.79)	< .001
Medication *n* (%)				
Beta blocker	3140 (75.8)	11989 (78.5)	15141 (77.9)	< .001
ACE	1911 (48.0)	7317 (49.9)	9233 (49.4)	.034
ARB	817 (20.9)	2555 (18.0)	3372(18.6)	< .001
Aldosterone	2457 (60.6)	8307 (55.9)	10775 (56.9)	< .001
Demographic and behavioral characteristics				
Age in years	54.08 (13.44)	57.55 (12.69)	56.81 (12.93)	< .001
Educat. attainment, *n* (%)				.222
Up to primary	112 (3.5)	434 (3.7)	546 (3.7)	
Secondary	1464(45.5)	5284 (45.2)	6750 (45.2)	
Post secondary	901 (28.0)	3111 (26.6)	4013 (26.9)	

	Women (n = 4282) 21.3%	Men (n = 15817) 78.7%	Total (n = 20123)	p-value
Tertiary	743 (23.1)	2868 (24.5)	3611 (24.2)	
Marital status, n (%)				< .001
Single	999 (23.9)	2778 (17.9)	3777 (19.1)	
Married/Domestic partners	2189 (52.4)	10704 (68.8)	12896 (65.3)	
Divorced	686 (16.4)	1713 (11.0)	2399 (12.2)	
Widowed	305 (7.3)	366 (2.4)	671 (3.4)	
Race White, n (%)	2430 (56.7)	11042 (69.8)	13474 (67.0)	< .001
Working for income, n (%)	563 (14.5)	2717 (18.9)	3280 (18.0)	< .001
BMI, n (%)				< .001
Underweight	208 (4.9)	489 (3.1)	697 (3.5)	
Non-obese	2375 (55.9)	9524 (60.7)	11909 (59.7)	
Obese	1336 (31.4)	4932 (31.4)	6280 (31.4)	
Morbidly obese	332 (7.8)	752 (4.8)	1086 (5.4)	
Smoking history, n (%)				< .001
Currently	162 (5.1)	611 (5.3)	773 (5.2)	
Past	648 (20.5)	3287 (28.3)	3939 (26.6)	
Never	2347 (74.3)	7715 (66.4)	10082 (68.1)	

Note. Original unimputed data, unless otherwise indicated, data are presented as mean (standard deviation). LVEDD, left ventricular end-diastolic diameter; ICD, implantable cardioverter-defibrillator; BP, blood pressure; BUN, blood urea nitrogen; ACE, Angiotensin-converting-enzyme inhibitor; ARB, Angiotensin II receptor blocker; BMI, body mass index.

Table 9
Pre-implant psychosocial risk factors in women and men

	Women (n = 4282)	Men (n = 15817)	p-value
a) Psychosocial risk factors by gender			
History alcohol abuse	101 (3.2)	1070 (9.2)	< .001
History drug abuse	165 (5.2)	957 (8.2)	< .001
Severe depression	136 (4.3)	265 (2.3)	< .001
Other major psych. diagnosis	80 (2.5)	189 (1.6)	< .001
Limited social support	167 (5.3)	562 (4.8)	.322
Limited cognition/understanding	61 (1.9)	217 (1.9)	.873
Repeated noncompliance	104 (3.3)	392 (3.4)	.866
b) Number of psychosocial risk factors by gender			< .001
1 psychosocial risk factor	370 (11.7)	1644 (14.2)	
2 psychosocial risk factors	129 (4.1)	609 (5.2)	
3 psychosocial risk factors	38 (1.2)	174 (1.5)	
4 psychosocial risk factors	14 (0.4)	49 (0.4)	
5 psychosocial risk factors	2 (0.1)	12 (0.1)	
6 psychosocial risk factors	1 (0.0)	2 (0.0.)	
Psychosocial risk (any vs. none)	**554 (17.5)**	**2490 (21.4)**	**< .001**

Note. Data are presented as n (%). Type (a) and number (b) of psychosocial risk factors pre-implant in women and men. *Psychosocial risk* was computed as binary (any vs. none) if at least one psychosocial risk factor was applicable.

Regarding psychosocial risk (Table 9), women were less likely to have a history of alcohol and illicit substance abuse than men, but women were more likely to have severe depression and other major psychiatric diagnoses. There were no gender differences in limited social support, limited cognition/understanding, and repeated noncompliance. In total, men were more likely to have psychosocial risk than women (21.4% vs. 17.5%).

Gender Differences in Adverse Events

Table 10 presents the event counts of the 10 adverse events competing with death, transplant, and recovery, which were observed during a median follow-up of 13.6 months (range = 0 - 113.4 months).

Cumulative incidence functions for the adverse events stratified by genders are shown in Figure 4. After 1 year, women were more likely than men to experience rehospitalization (72.1% vs. 68.9 %, $p = .002$), infection (44.5% vs. 39.2%, $p < .001$), neurological dysfunction (19.8% vs. 16.1%, $p < .001$), bleeding (38.3% vs. 36.0%, $p = .004$), respiratory failure (18.6% vs. 16.3%, $p = .027$), device malfunction and/or pump thrombosis (17.0% vs. 15.4%, $p < .001$), and a psychiatric episode (8.2% vs. 6.4%, $p < .001$). In contrast, women were less likely to experience cardiac arrhythmia (22.6% vs. 25.8%, $p < .001$) and renal dysfunction (10.2% vs. 11.0%, $p = .049$) than men. There were no gender differences for the probability of right heart failure (8.7% vs. 8.8%, $p = .933$). We reran the analyses with axial devices only to evaluate whether pump selection played a role in our findings; the results remained the same. Controlled for clinical, demographic, behavioral covariates, and psychosocial risk, female gender was still significantly associated with a higher rate of bleeding (HR_{adj} 1.21, 95% CI [1.14-1.29], $p < .001$), infection (HR_{adj} 1.19, 95% CI [1.12-1.26], $p < .001$), device malfunction an/or pump thrombosis (HR_{adj} 1.10, 95% CI [1.01-1.19], $p = .021$), neurological dysfunction (HR_{adj} 1.21, 95% CI [1.11-1.33], $p < .001$), psychiatric episode (HR_{adj} 1.24, 95% CI [1.06-1.45], $p = .007$), rehospitalization (HR_{adj} 1.08, 95% CI [1.03-1.14], $p < .001$), and

respiratory failure (HR_{adj} 1.14, 95% CI [1.03-1.25], p = .008), compared with male gender (Table 11). Male gender was no longer associated with higher rates of cardiac arrhythmia and renal dysfunction after controlling for covariates.

Association of Psychosocial Risk with Adverse Events in Women and Men

Independent of gender and other covariates, psychosocial risk was associated with infection (HR_{adj} 1.11, 95% CI [1.02-1.22], p = .027) and psychiatric episode [HR_{adj} 1.58, 95% CI [1.11-2.23], p = .017]. In the multivariable analyses, the interaction term gender and psychosocial risk was significant only for rehospitalization (HR_{adj} 1.15, 95% CI [1.02-1.30)], p = .020) and trends were observed for device malfunction/pump thrombosis (HR_{adj} 1.16, 95% CI [0.97-1.38], p = .0996), neurological dysfunction (HR_{adj} 1.21, 95% CI [0.97-1.50], p = .097), and respiratory failure (HR_{adj} 1.23, 95% CI [0.98-1.54], p = .071; Table 11).

In further exploratory analyses stratified by gender, in women psychosocial risk was significantly associated with increased rates of device malfunction/pump thrombosis (HR_{adj} 1.29, 95% CI [1.06-1.56], p = .012), psychiatric episode (HR_{adj} 1.68, 95% CI [1.06-2.67], p = .037) and rehospitalization (HR_{adj} 1.15, 95% CI [1.02-1.29], p = .024). In men, psychosocial risk was significantly associated with infection (HR_{adj} 1.13, 95% CI [1.03-1.23], p = .016) and psychiatric episode (HR_{adj} 1.55, 95% CI [1.09-2.21], p = .024; Figure 5).

Post-hoc Analyses

Previous analyses used psychosocial risk (based on several indicators) as a dichotomous variable (yes vs. no). In our post-hoc analyses, we also considered psychosocial risk as an additive variable in the male and female samples. Women were less likely than men to have 1, 2 or 3 psychosocial risk factors pre-implant (p < .001, Table 9). Due to the low frequencies in higher numbers of psychosocial risk factors, we used an ordinal factor (0, 1, ≥2 psychosocial risk factors; Figure 6) for the following outcome analyses (DeFilippis, Breathett, et al., 2020). The hazard ratios increased with increasing number of risk factors for infection, malfunction/

pump thrombosis, psychiatric episode, and rehospitalization. The hazard ratios were higher in women than in men (Table 12).

To further explore the association of gender and psychosocial risk with adverse events, we rerun the analyses for each adverse event with all individual factors used to indicate psychosocial risk: limited social support, limited cognition/understanding, alcohol abuse, drug abuse, severe depression, other major psychiatric diagnosis, and repeated noncompliance. Each of the single psychosocial risk factors was significantly associated with higher rates of at least one of the adverse events but no gender specific pattern emerged. E.g., severe depression was associated with increased rates of infection in men, but not in women; and a history of alcohol abuse was associated with neurological dysfunction in women, but not in men (Table S5).

Focusing on behavioral factors and controlling for gender, a history of smoking was associated with higher rates of arrhythmia (HR_{adj} 1.21, 95% CI [1.14-1.30], $p < .001$), bleeding (HR_{adj} 1.10, 95% CI [1.04-1.17], $p = .001$), infection (HR_{adj} 1.10, 95% CI [1.04-1.16], $p < .001$), device malfunction/pump thrombosis (HR_{adj} 1.14, 95% CI [1.06-1.24], $p < .001$), psychiatric episode (HR_{adj} 1.25, 95% CI [1.05-1.50], $p = .016$), rehospitalization (HR_{adj} 1.10, 95% CI [1.06-1.15], $p < .001$), and respiratory failure (HR_{adj} 1.22, 95% CI [1.11-1.33], $p < .001$). Morbidly obese BMI was associated with higher rates of arrhythmia (HR_{adj} 1.16, 95% CI [1.03-1.30], $p = .016$), infection (HR_{adj} 1.18, 95% CI [1.08-1.30], $p < .001$), device malfunction/pump thrombosis (HR_{adj} 1.14, 95% CI [1.02-1.28], $p = .021$), renal dysfunction (HR_{adj} 1.53, 95% CI [1.30-1.79], $p < .001$), and respiratory failure (HR_{adj} 1.46, 95% CI [1.27-1.67], $p < .001$; Table 11).

Finally, in a post-hoc competing risks analyses, psychosocial risk was not associated with the rates for death, controlling for the competing outcomes transplant, device explant due to recovery, and device replacement due to complications, in either gender.

Table 10
Event count of adverse events in women and men

	Women	Men	Total
Cardiac arrhythmia	1100	4608	5711
Bleeding	1861	6484	8355
Infection	2184	7398	9589
Device malfunction and/or pump thrombosis	1205	4004	5214
Neurological dysfunction	1091	3396	4495
Psychiatric episode	380	1164	1544
Rehospitalization	3326	12122	15467
Renal dysfunction	529	2144	2674
Respiratory failure	869	2980	3851
Right heart failure	395	1471	1866

Note. Each event was competing with death, transplant, and recovery as first event.

Table 11
Event-specific hazard models for the adverse events

	Adjusted Cox regression	
Adverse event	HR [95% CI]	*p*-value
Arrhythmia		
Female gender	0.93 [0.85-1.02]	.129
Psychosocial risk	1.05 [0.93-1.17]	.443
Gender*Psychosocial risk	1.06 [0.82-1.37]	.654
Age in years	1.01 [1.00-1.01]	< .001
Marital status		
Married/domestic partners	[REF]	
Widowed	0.85 [0.72-0.99]	.042
Working for income	1.08 [1.01-1.16]	.033
BMI		
Non-obese	[REF]	
Obese	1.12 [1.06-1.19]	< .001
Morbidly obese	1.16 [1.03-1.30]	.016
Smoking history		
Never	[REF]	
Past	1.21 [1.14-1.30]	< .001
Bleeding		
Female gender	1.21 [1.14-1.29]	< .001
Psychosocial risk	1.02 [0.92-1.13]	.744
Gender*Psychosocial risk	1.07 [0.91-1.25]	.413
Age in years	1.02 [1.02-1.02]	< .001
Race white	0.85 [0.81-0.89]	< .001

	Adjusted Cox regression	
Adverse event	HR [95% CI]	*p*-value
Smoking history		
Never	[REF]	
Past	1.10 [1.04-1.17]	.001
Infection		
Female gender	1.19 [1.12-1.26]	< .001
Psychosocial risk	1.11 [1.02-1.22]	.027
Gender*Psychosocial risk	1.03 [0.90-1.19]	.652
BMI		
Non-obese	[REF]	
Obese	1.10 [1.05-1.15]	< .001
Morbidly obese	1.18 [1.08-1.30]	< .001
Smoking history		
Never	[REF]	
Past	1.10 [1.04-1.16]	< .001
Malfunction/ pump thrombosis		
Female gender	1.10 [1.01-1.19]	.021
Psychosocial risk	1.10 [0.97-1.26]	.137
Gender*Psychosocial risk	1.16 [0.97-1.38]	.0996
Age in years	0.99 [0.99-0.99]	< .001
Marital status		
Married/domestic partners	[REF]	
Divorced/separated	1.10 [1.01-1.19]	.037
Race white	1.18 [1.11-1.26]	< .001
BMI		

	Adjusted Cox regression	
Adverse event	HR [95% CI]	*p*-value
Non-obese	[REF]	
Obese	1.12 [1.06-1.19]	< .001
Morbidly obese	1.14 [1.02-1.28]	.021
Smoking history		
Never	[REF]	
Past	1.14 [1.06-1.24]	< .001
Currently	1.25 [1.09-1.44]	.002
Neurological dysfunction		
Female gender	1.21 [1.11-1.33]	< .001
Psychosocial risk	1.07 [0.86-1.34]	.526
Gender*Psychosocial risk	1.21 [0.97-1.50]	.097
Age in years	1.01 [1.00-1.01]	.002
Psychiatric episode		
Female gender	1.24 [1.06-1.45]	.007
Psychosocial risk	1.58 [1.11-2.23]	.017
Gender*Psychosocial risk	1.00 [0.73-1.38]	.976
Smoking history		
Never	[REF]	
Past	1.25 [1.05-1.50]	.016
Rehospitalization		
Female gender	1.08 [1.03-1.14]	< .001
Psychosocial risk	1.02 [0.69-1.08]	.478
Gender*Psychosocial risk	1.15 [1.02-1.30]	.020
Race white	1.07 [1.04-1.11]	< .001

	Adjusted Cox regression	
Adverse event	HR [95% CI]	*p*-value
Smoking history		
Never	[REF]	
Past	1.10 [1.06-1.15]	< .001
Currently	1.11 [1.02-1.21]	.017
Renal dysfunction		
Female gender	0.97 [0.86-1.10]	.663
Psychosocial risk	1.00 [0.71-1.41]	.998
Gender*Psychosocial risk	1.12 [0.80-1.56]	.515
Race white	0.85 [0.78- 0.93]	< .001
BMI		
Non-obese	[REF]	
Obese	1.34 [1.23-1.45]	< .001
Morbidly obese	1.53 [1.30-1.79]	< .001
Respiratory failure		
Female gender	1.14 [1.03-1.25]	.008
Psychosocial risk	0.92 [0.77-1.11]	.398
Gender*Psychosocial risk	1.23 [0.98-1.54]	.071
Age in years	1.01 [1.01-1.01]	< .001
Race white	0.90 [0.84-0.97]	.005
BMI		
Non-obese	[REF]	
Obese	1.21 [1.13-1.30]	< .001
Morbidly obese	1.46 [1.27-1.67]	< .001
Smoking history		

	Adjusted Cox regression	
Adverse event	HR [95% CI]	*p*-value
Never	[REF]	
Past	1.22 [1.11-1.33]	< .001
Right HF		
Female gender	1.11 [0.93-1.33]	.242
Psychosocial risk	9.95 [0.49-1.85]	.892
Gender*Psychosocial risk	0.77 [0.45-1.32]	.341
Race white	0.90 [0.81-0.99]	.038
BMI		
Non-obese	[REF]	
Underweight	0.73 [0.53-0.99]	.044

Note. all models are adjusted for: device strategy, primary diagnosis, time since diagnosis, LVEDD, INTERMACS profile, pump type (axial vs. centrifugal), ICD, pulmonary hypertension, albumin, bilirubin, creatinine, BUN, platelet count and medication (beta blocker, ACE, ARB, Aldosterone). Demographic, behavioral, and psychosocial variables: gender, psychosocial risk, gender*psychosocial risk, age, marital status, educational attainment, race, working for income, BMI, smoking history. Gender was coded 0 = male, 1 = female. Psychosocial risk was coded 0 = not present, 1 = present. Exact *p*-values are presented only for gender, psychosocial risk, and the interaction terms; remaining variables are shown only if $p < .05$. Clinical covariates are not depicted.

Table 12
The additive impact of psychosocial risk factors on adverse events in women and men

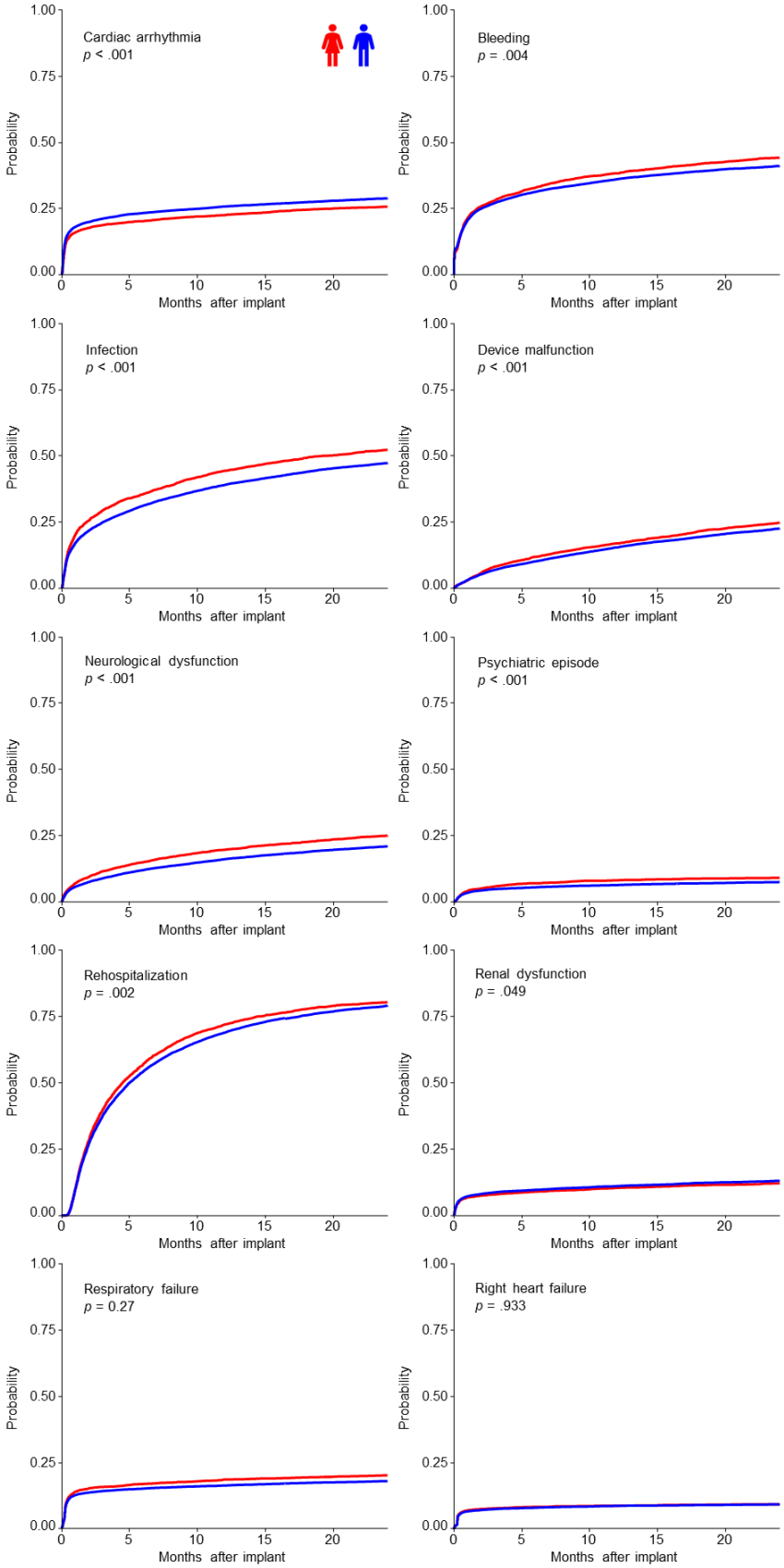
	Adjusted Cox regression in female subgroup		Adjusted Cox regression in male subgroup	
Adverse event	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Bleeding				
0 Psychosocial risk factor	[REF]		[REF]	
1 Psychosocial risk factor	1.07 [0.91-1.26]	.410	1.04 [0.96-1.14]	.340
≥ 2 Psychosocial risk factors	1.06 [0.84-1.33]	.652	1.06 [0.93-1.20]	.401
Infection				
0 Psychosocial risk factor	[REF]		[REF]	
1 Psychosocial risk factor	1.08 [0.92-1.26]	.342	1.11 [1.03-1.19]	.004
≥ 2 Psychosocial risk factors	1.29 [1.05-1.59]	.014	1.24 [1.12-1.38]	< .001
Malfunction/ pump thrombosis				
0 Psychosocial risk factor	[REF]		[REF]	
1 Psychosocial risk factor	1.24 [1.02-1.50]	.033	1.07 [0.97-1.18]	.152
≥ 2 Psychosocial risk factors	1.60 [1.24-2.07]	< .001	1.31 [1.14-1.49]	< .001
Neurological dysfunction				
0 Psychosocial risk factor	[REF]		[REF]	
1 Psychosocial risk factor	1.35 [1.09-1.66]	.006	1.06 [0.95-1.19]	.307
≥ 2 Psychosocial risk factors	1.27 [0.94-1.71]	.119	1.17 [1.00-1.37]	.056
Psychiatric episode				
0 Psychosocial risk factor	[REF]		[REF]	
1 Psychosocial risk factor	1.55 [1.09-2.19]	.015	1.44 [1.18-1.74]	< .001
≥ 2 Psychosocial risk factors	2.32 [1.54-3.51]	< .001	2.06 [1.58-2.70]	< .001
Rehospitalization				
0 Psychosocial risk factor	[REF]		[REF]	

	Adjusted Cox regression in female subgroup		Adjusted Cox regression in male subgroup	
Adverse event	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
1 Psychosocial risk factor	1.13 [1.00-1.28]	.051	1.04 [0.98-1.10]	.235
≥ 2 Psychosocial risk factors	1.19 [1.01-1.41]	.041	1.06 [0.97-1.15]	.184
Respiratory failure				
0 Psychosocial risk factor	[REF]		[REF]	
1 Psychosocial risk factor	1.11 [0.88-1.41]	.381	0.95 [0.83-1.09]	.497
≥ 2 Psychosocial risk factors	1.30 [0.94-1.78]	.112	1.11 [0.93-1.31]	.253

Note. all models are adjusted for: device strategy, primary diagnosis, time since diagnosis, LVEDD, INTERMACS profile, pump type (axial vs. centrifugal), ICD, pulmonary hypertension, albumin, bilirubin, creatinine, BUN, platelet count, medication (beta blocker, ACE, ARB, Aldosterone), age, marital status, educational attainment, race, working for income, BMI, and smoking history.

Figure 4

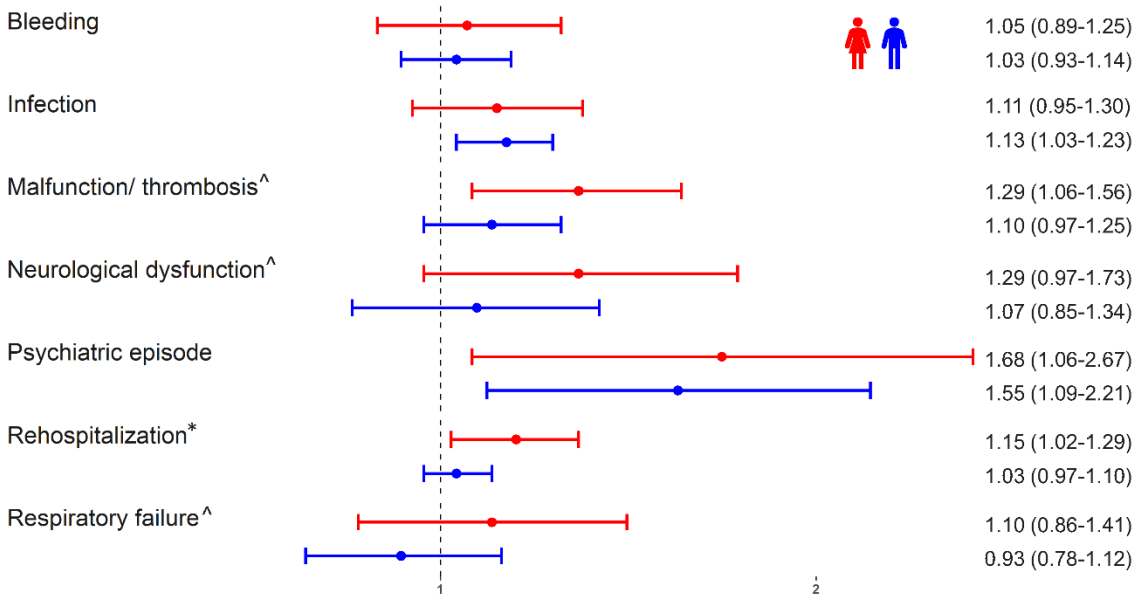
Cumulative incidence functions for the adverse events stratified by gender.



Note. Functions of the competing events death, transplant, and recovery are not depicted for reasons of readability.

Figure 5

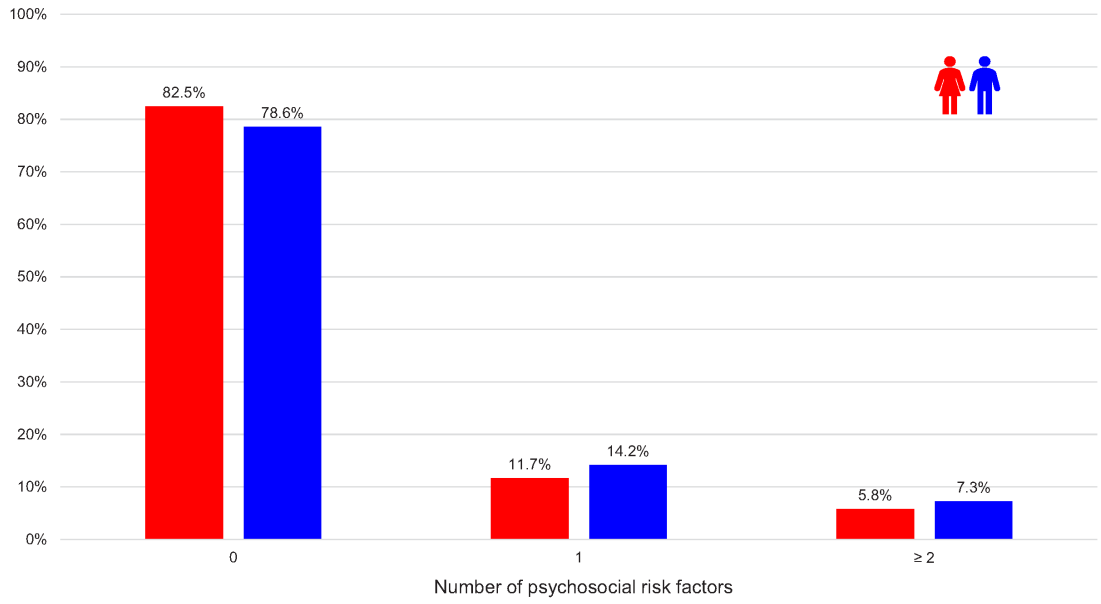
Adjusted HR with 95% CI for the variable psychosocial risk (yes vs. no) and each adverse event in the female and male subgroup.



Note. ^$p < .1$; *$p < .05$. Each HR is adjusted for device strategy, primary diagnosis, time since diagnosis, LVEDD, INTERMACS profile, pump type (axial vs. centrifugal), ICD, pulmonary hypertension, albumin, bilirubin, creatinine, BUN, platelet count and medication (beta blocker, ACE, ARB, Aldosterone), age, marital status, educational attainment, race, working for income, BMI, and smoking history.

Figure 6

Number of psychosocial risk factors pre-implant in women and men



Note. $p < .001$

Discussion

Women with CF-LVAD were more likely than men to experience seven out of the10 adverse events investigated. After 1 year, differences in women's and men's probability for adverse events were most apparent for infection (44.4% in women vs. 39.2% in men, $p < .001$), neurological dysfunction (19.8% vs. 16.1%, $p < .001$), and rehospitalization (72.1% vs. 68.9%, $p = .002$). The results strengthen most former reports on gender differences in adverse events (Acharya et al., 2017; Gruen et al., 2020; Hsich, Naftel, et al., 2012; Magnussen et al., 2018; McIlvennan et al., 2017; Morris, Pekarek, et al., 2015; Sherazi et al., 2017). Importantly, our results are based on data of more than 20000 patients, allowing for statistical control of a multitude of confounding factors. We analyzed adverse events in separate competing risks analyses, thereby avoiding biases and overestimation of outcome probabilities (Beyersmann et al., 2012; Stegherr et al., 2021). Considering that adverse events often lead to higher probabilities of device replacements in women (Maukel et al., 2022), and also increase the risk of mortality (Molina et al., 2021), our results highlight the need to reduce the probability for adverse events post-implant, especially in women.

Pre-implant, women were less likely than men to have any psychosocial risk (17.5% vs. 21.4%) and less likely to have more than two psychosocial risk factors (6% vs. 7%). Interestingly, in women, the presence of psychosocial risk was associated with increased rehospitalizations by 15% vs. 3% in men ($p = .020$). Thus, *if* psychosocial risk is present, women appear to be at higher risk than men to experience rehospitalization. If psychosocial risk also affects women more strongly with regard to other adverse events is less clear. The rates for device malfunction/pump thrombosis, neurological dysfunction, and respiratory failure were also increased in women compared with men, and the association of psychosocial risk with device malfunction/pump thrombosis was significant only in women (Figure 5). However, these potential gender differences did not reach the conventional level of statistical significance. This might be due to smaller effective sample sizes for these adverse events

compared with rehospitalization (Table 10). Interestingly, analyses using psychosocial risk as an additive variable revealed the same pattern of results, suggesting a certain degree of robustness of the findings (Table 12). For example, the rates for device malfunction/pump thrombosis were increased by 24% in women vs. 7% in men with one psychosocial risk factor, and 60% in women vs. 31% in men with two or more psychosocial risk factors.

From a physiological perspective, it has been suggested that women show higher inflammatory reactivity to stress than men, which has been linked to an increased risk of adverse events in a population of cardiovascular patients (Sullivan et al., 2020). Further examination of potential physiological pathways linking psychosocial risk to increased adverse event risk is warranted, particularly in patients receiving LVADs.

From a clinical perspective, increased susceptibility to psychosocial risk raises the issue of adequate patient care and interventions. What kind of support is offered for patients with psychosocial problems if detected pre-implant? Are there differences in women's and men's professional care or is it the caregivers at home that could make the difference? For example, whereas men report their spouse as primary caregiver, women rather list their parents or adult children (Steinberg et al., 2022). There is some indication clinicians perceive male caregivers as inadequate (Breathett et al., 2020). This implies that traditional family roles might still be relevant in the predominantly elderly group of heart failure patients. The impact of gender roles and perceived social support on outcomes after LVAD would clearly benefit from further research.

In both women and men, there was no association of psychosocial risk with death, which is in line with previous study results (DeFilippis, Breathett, et al., 2020; Maukel et al., 2022). Our analysis was a competing risks analysis (i.e., time-to-first-event and type-of-first-event) and as the occurrence of adverse events is clearly related to mortality (Molina et al., 2021), one could argue that psychosocial risk affects death via previous adverse events.

Independent of gender, behavioral risk factors such as smoking history and obesity were associated with multiple adverse events. The negative effects of those risk factors are not surprising and well-studied (Forest et al., 2018; Khan et al., 2020; Youmans et al., 2021). Interestingly, in our analysis, the association of smoking with an adverse event was most pronounced for psychiatric episodes, an adverse event that received little attention in former studies. One reason might be that there are few psychiatric events after LVAD implant. This also applies to this sample, where psychiatric episodes had the smallest event-count of all adverse events investigated (n = 1544, Table 10). However, it might be possible that psychiatric complications are more likely to be overlooked by professionals in the field of cardiology. Our results emphasize to broaden the clinical view on multiple complications after LVAD implant. Consequently, risk reduction programs to reduce body weight and achieve smoking cessation should routinely be more offered, especially considering that these risk factors can be rather easily modified.

Limitations

Recently, a centrifugal device, which was the preferred choice for women, was taken off market due to an increased risk of mortality and neurological adverse events (Salerno et al., 2022). To evaluate whether pump selection could have influenced our findings, we reran the analyses with axial devices only. This did not change the results. Consequently, women's increased probabilities for adverse events cannot be attributed to current pump selection. The single psychosocial variables in INTERMACS' *concerns and contraindications for transplant* are based on unstandardized clinical judgements of unknown construct validity. In the future, an integration of validated psychometric tools or a standardized interview in the protocol of large registries would be helpful (Bui, Braun, et al., 2019; Dew et al., 2021) to more adequately evaluate the role of psychosocial risk and gender differences in LVAD outcomes (Miller et al., 2010). Nevertheless, INTERMACS' variables of *concerns and contraindications for transplant* include the five major psychosocial domains: social support,

cognition, substance use, psychopathology, and noncompliance (Bui, Allen, et al., 2019; DeFilippis, Breathett, et al., 2020; Dew et al., 2018), making it feasible to evaluate overall and additive psychosocial risk. This yielded rather robust associations across multiple adverse events and even suggested a dose-response relationship in some adverse events.

It should be noted that only one of the psychosocial risk by gender interaction terms reached the conventional level of statistical significance ($p < .05$). However, considering the smaller effective female sample size, the marginally significant interactions ($p < .1$) and observed hazard ratios indicating associations with psychosocial risk in women, particularly HR 1.29 [1.06-1.56] for device malfunction/pump thrombosis, are noteworthy. Nevertheless, we cannot be certain that the increased hazard ratios in women reflect real gender differences and the interplay of female gender and psychosocial risk factors for clinical outcomes clearly deserves further investigation.

Conclusion

Psychosocial risk pre-implant is related to increased rates of adverse events. There is some indication that for some adverse events this association may be stronger in women than in men. In the future, gender sensitive research is clearly warranted. Employing a more rigorous assessment of psychosocial risk using psychometric tools may help to detect specific psychosocial risk factors that lead to higher probabilities of adverse events in both genders, to intervene early, and reduce the risk of adverse events in this patient population.

Financial Conflict of Interest Statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Author Contributions

HS and GW were responsible for conception and design of the study. LM, HS, and GW were responsible for analyses, interpretation, and drafting the manuscript. JB was responsible for overseeing the methodological approach and contributed to analyses and writing of the paper.

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SUPPLEMENTAL MATERIAL

Adverse events after left ventricular assist device implantation linked to psychosocial risk in women and men

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Detailed description of the multiple imputation procedure

According to the missing at random (MAR) assumption the 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* 3.13.0 for R 4.0.3 We set the number of imputations to $m = 20$. Each of the 20 imputed data sets was then analyzed and the results were pooled using Rubin's rule. The following imputation techniques were used: numeric variables = bayesian linear regression, factors with 2 levels = logistic regression, factors with > 2 levels = multinomial logit model, ordered factors with > 2 levels = ordered logit model. To screen for plausibility of the multiple imputation the following diagnostic were applied: Diagnostics on distributional discrepancy (between observed and imputed data) were screened graphically using kernel density plots. Additionally, summary statistics of original and imputed data were compared. The application of a Kolmogorow-Smirnow-Test to compare distributions was not considered due to the large sample size, that would lead to statistically but not clinically significant results. Finally, complete-case sensitivity analyses for univariable event-specific Cox regression were run, showing no larger discrepancies between imputed and pooled analyses.

Table S4
Missing values in psychosocial variables of concerns and contraindications for transplant by gender

	Women (*n* = 4282) 21.3%	Men (*n* = 15817) 78.7%	Total
History alcohol abuse	26.3%	26.6%	26.5%
History drug abuse	26.3%	26.6%	26.5%
Severe depression	26.3%	26.6%	26.5%
Other major psych. diagnosis	26.3%	26.6%	26.5%
Limited social support	26.3%	26.6%	26.5%
Limited cognition/understanding	26.3%	26.6%	26.5%
Repeated noncompliance	26.3%	26.6%	26.5%
Psychosocial risk	26.3%	26.6%	26.5%

Table S5
Event-specific hazard models for the single psychosocial risk factors on adverse events in women and men

	Adjusted Cox regression in **female** subgroup		Adjusted Cox regression in **male** subgroup	
Adverse event	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Bleeding				
History alcohol abuse	0.99 [0.72-1.37]	.970	1.09 [0.98-1.21]	.106
History drug abuse	0.93 [0.70-1.22]	.594	0.89 [0.78-1.01]	.074
Severe depression	1.03 [0.79-1.35]	.805	1.07 [0.88-1.30]	.478
Other major psych. diagnosis	1.13 [0.80-1.58]	.499	0.89 [0.70-1.13]	.345
Limited social support	0.92 [0.71-1.19]	.505	1.00 [0.87-1.15]	.984
Limited cognition/understanding	1.47 [1.05-2.06]	.028	0.99 [0.81-1.22]	.940
Repeated noncompliance	1.10 [0.81-1.50]	.528	1.31 [1.11-1.54]	.002
Infection				
History alcohol abuse	1.15 [0.87-1.51]	.332	1.01 [0.92-1.12]	.824
History drug abuse	0.93 [0.74-1.16]	.501	1.06 [0.96-1.18]	.246
Severe depression	1.18 [0.94-1.46]	.148	1.35 [1.17-1.57]	< .001
Other major psych. diagnosis	1.23 [0.93-1.62]	.143	1.30 [1.09-1.56]	.004
Limited social support	1.06 [0.85-1.32]	.604	1.11 [0.99-1.24]	.088
Limited cognition/understanding	1.15 [0.84-1.59]	.383	1.10 [0.90-1.34]	.349
Repeated noncompliance	1.07 [0.80-1.42]	.645	1.08 [0.93-1.24]	.324
Malfunction/ pump thrombosis				
History alcohol abuse	1.06 [0.74-1.52]	.744	0.94 [0.83-1.07]	.346
History drug abuse	1.09 [0.81-1.48]	.557	1.28 [1.12-1.45]	< .001
Severe depression	1.40 [1.07-1.83]	.016	1.26 [1.01-1.58]	.043
Other major psych. diagnosis	1.42 [1.01-1.99]	.042	1.29 [1.00-1.65]	.050
Limited social support	1.13 [0.85-1.51]	.413	1.13 [0.96-1.32]	.149

	Adjusted Cox regression in **female** subgroup		Adjusted Cox regression in **male** subgroup	
Adverse event	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Limited cognition/understanding	1.14 [0.72-1.82]	.572	0.93 [0.72-1.21]	.599
Repeated noncompliance	1.27 [0.91-1.77]	.159	1.10 [0.91-1.33]	.332
Neurological dysfunction				
History alcohol abuse	1.55 [1.07-2.24]	.023	1.05 [0.91-1.21]	.523
History drug abuse	0.87 [0.62-1.23]	.444	1.01 [0.86-1.19]	.886
Severe depression	0.95 [0.67-1.35]	.772	1.08 [0.83-1.40]	.563
Other major psych. diagnosis	1.48 [0.98-2.25]	.066	1.38 [1.06-1.80]	.018
Limited social support	1.26 [0.91-1.75]	.164	0.99 [0.82-1.21]	.957
Limited cognition/understanding	0.98 [0.58-1.65]	.941	1.04 [0.80-1.34]	.783
Repeated noncompliance	1.26 [0.88-1.81]	.212	1.23 [1.01-1.50]	.043
Psychiatric episode				
History alcohol abuse	1.13 [0.60-2.16]	.703	1.23 [0.97-1.58]	.095
History drug abuse	0.74 [0.39-1.42]	.372	0.91 [0.69-1.19]	.484
Severe depression	1.54 [0.88-2.69]	.137	2.29 [1.69-3.11]	< .001
Other major psych. diagnosis	1.99 [1.10-3.62]	.026	2.09 [1.43-3.07]	< .001
Limited social support	1.52 [0.95-2.44]	.083	1.72 [1.33-2.21]	< .001
Limited cognition/understanding	1.75 [0.89-3.44]	.110	1.21 [0.81-1.80]	.353
Repeated noncompliance	1.55 [0.92-2.63]	.104	1.29 [0.93-1.79]	.134
Rehospitalization				
History alcohol abuse	1.21 [0.96-1.53]	.104	1.03 [0.95-1.12]	.427
History drug abuse	0.95 [0.80-1.14]	.597	1.00 [0.93-1.08]	.998
Severe depression	1.04 [0.86-1.25]	.717	1.10 [0.96-1.26]	.180
Other major psych. diagnosis	1.48 [1.16-1.89]	.002	1.15 [0.99-1.35]	.073
Limited social support	1.09 [0.91-1.30]	.345	1.02 [0.92-1.12]	.732

	Adjusted Cox regression in **female** subgroup		Adjusted Cox regression in **male** subgroup	
Adverse event	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Limited cognition/understanding	0.99 [0.74-1.32]	.927	0.98 [0.84-1.15]	.839
Repeated noncompliance	1.07 [0.85-1.34]	.562	1.00 [0.89-1.13]	.980
Respiratory failure				
History alcohol abuse	1.01 [0.65-1.56]	.978	0.90 [0.76-1.07]	.220
History drug abuse	0.89 [0.59-1.34]	.587	1.06 [0.89-1.27]	.496
Severe depression	1.03 [0.72-1.47]	.859	1.19 [0.88-1.60]	.254
Other major psych. diagnosis	0.98 [0.59-1.63]	.935	0.99 [0.69-1.43]	.968
Limited social support	1.25 [0.90-1.73]	.178	1.10 [0.90-1.34]	.357
Limited cognition/understanding	1.58 [1.03-2.43]	.039	1.02 [0.73-1.42]	.907
Repeated noncompliance	1.10 [0.73-1.67]	.644	1.12 [0.89-1.41]	.348

Note. all models are adjusted for: device strategy, primary diagnosis, time since diagnosis, LVEDD, INTERMACS profile, pump type (axial vs. centrifugal), ICD, pulmonary hypertension, albumin, bilirubin, creatinine, BUN, platelet count, medication (beta blocker, ACE, ARB, Aldosterone), age, marital status, educational attainment, race, working for income, BMI, and smoking history. Only single psychosocial risk factors of *concerns and contraindication for transplant* are depicted.

5 General Discussion

The results of each artcile have been discussed in each manuscript. Therefore, the following discussion aims to disseminate the results of all three articles and to discuss the relevance of the present dissertation for the research field. The chapter concludes with clinical implications, limitations, and an outlook on future research.

5.1 Summary of the Results

The specific aim of the present dissertation was to explore the association of gender and pre-implant psychosocial risk factors with clinical outcomes after LVAD implant.

Article 1 investigated gender differences in clinical, demographic, and psychosocial characteristics in CF-LVAD recipients in EUROMACS considering the role of pre-implant device strategy. Female LVAD recipients were underrepresented (16.7%; in DT 13.4%; in BTT 17.6%). Independent of device strategy, women were less likely to be diagnosed with ischemic cardiomyopathy, and less likely to be smokers. However, women were more likely to be in an unstable clinical condition (INTERMACS profiles 1 and 2), to be divorced/separated/widowed, and to have a lower education than men. Only in DT, women were more likely to be non-working. Only in BTT, women were younger than men and a history of alcohol abuse was least common among women in BTT. It was concluded that specifically younger women, with unstable condition, possibly due to a more acute cardiac cause, get implanted in device strategy BTT.

In **article 2**, using INTERMACS data, gender differences in pre-implant characteristics, gender differences in the four outcomes death, transplant, device replacement due to complications, device explant due to recovery, and the association of pre-implant characteristics and gender with outcomes in CF-LVAD recipients in the device strategy DT were investigated. Women were younger, more likely to have non-ischemic diagnoses, and

reported less substance abuse, but were more likely to be unmarried, not working for an income, overweight, and depressed than men. Female and male patients did not differ in the clinical outcomes death nor transplant. However, women were significantly more likely than men to experience device explant due to cardiac recovery which was associated with female-specific diagnoses, such as postpartum heart failure. Women were also more likely to experience device replacement. Unexpectedly, demographics and psychosocial risk factors were unrelated to women's increased event rates for the major outcomes.

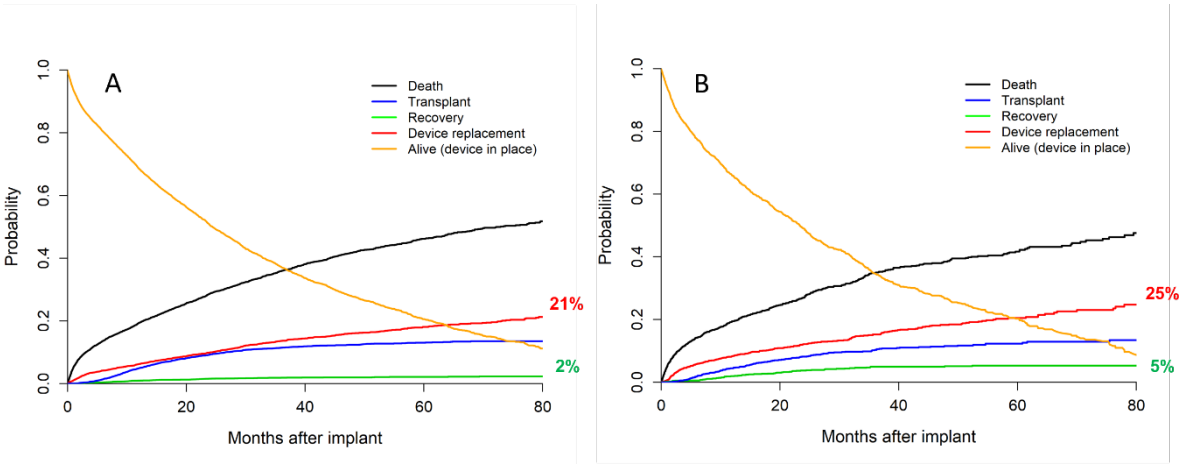
Article 3 focused on gender differences in 10 adverse events (e.g., infection, neurological dysfunction). In these analyses, device strategy was included as a covariate. The association of a binary and an additive psychosocial risk factor with adverse events in women and men was investigated. Psychosocial risk was more prevalent in men than in women (21.4% vs. 17.5%). Women had higher probabilities to experience seven out of 10 adverse events and the association of psychosocial risk with each adverse event appeared to be either stronger in women than in men or similar between genders. This was the case both, for any psychosocial risk and for additive psychosocial risk.

In sum, women and men with CF-LVADs differed in pre-implant psychosocial risk factors and clinical characteristics. These differences depended on the intended device strategy pre-implant. There were no gender differences in survival after LVAD, when the device strategy BTT, possibly biased due to lower transplant rates in women, was excluded. Women had higher probabilities for recovery, primarily due to favorable diagnoses, such as postpartum heart failure. However, women had higher probabilities to experience device explant due to complications. More specifically, women had higher probabilities to experience seven out of 10 adverse events compared with men. Psychosocial risk factors were not associated with major outcomes but with adverse events, even suggesting a dose response-relationship. These associations appeared to be more pronounced in women.

5.2 The Role of Device Strategy

The first article of this dissertation evaluated gender differences in pre-implant patient characteristics with regard to device strategy. This EUROMACS analysis showed that women were underrepresented in DT (in DT 13.4%; in BTT 17.6%) and gender differences in psychosocial characteristics were related to device strategies, e.g., women were significantly younger than men in BTT but of similar age in DT, and a history of alcohol abuse was most uncommon in women in BTT. An analogical analysis was run with INTERMACS data (Maukel et al., 2020), resulting in similar associations of gender, psychosocial variables, and device strategy. Additionally, in the INTERMACS analysis, the role of gender and device strategy for major outcomes (i.e., death, heart transplant, device replacement due to complications, and device explant due to recovery) was evaluated (Figure 7).

Figure 7
Cumulative incidence functions for DT by men (A) and women (B) and BTT by men (C) and women (D)



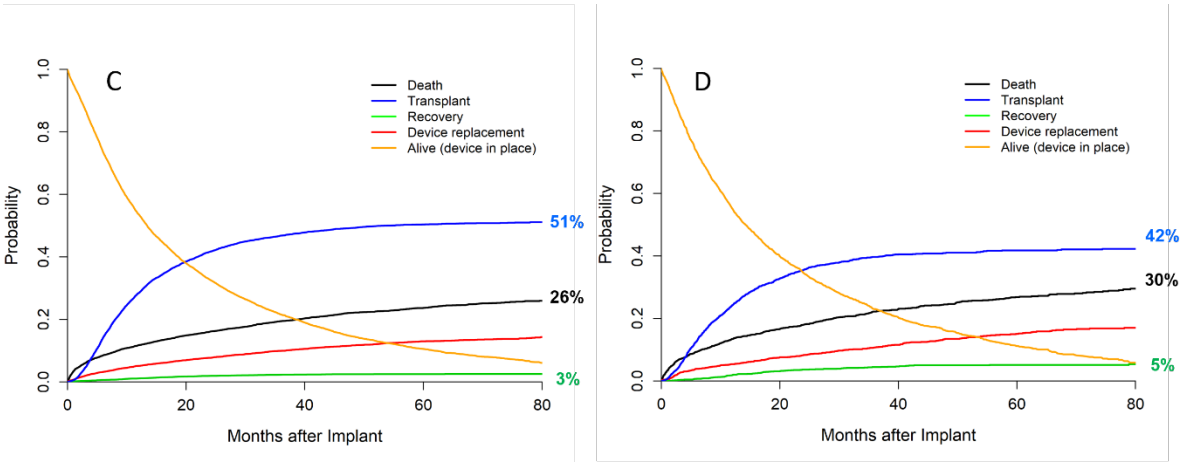


Figure 7 shows that only women in DT had significantly higher probabilities for device replacement due to complications and device explant due to recovery (article 2). Only in BTT, women had significantly lower probabilities for heart transplant and higher probabilities for death. These results may reflect the selection bias that women are less eligible for transplant and therefore more likely to die while waiting (Wehbe & Anderson, 2019). As article 3 focused on adverse events, all CF-LVADs in INTERMACS were included, controlling for the device strategy as a covariate in the multiple models. This was appropriate because the device strategy is not directly associated with an outcome of interest, and the assumption was checked for by running the analyses of article 3 on both device strategy subgroups, leading to similar results.

The role of device strategy is highly debated (Caraffa et al., 2022; Goldstein et al., 2020; Teuteberg et al., 2020). Goldstein and colleagues showed in the MOMENTUM 3 trial that pre-implant strategies were not related to outcomes and suggested to neglect the decision on strategy completely (Goldstein et al., 2020) but the authors did not evaluate the role of device strategy for gender differences. Some authors argue that the intended device strategy often changes over time because many contraindications for transplant are reversible or otherwise occur for the first time while waiting for a transplant (Peura et al., 2012; Teuteberg et al., 2013), reducing the informative value of the intended device strategy pre-implant. Accordingly, Teuteberg and colleagues (2013) showed that after 2 years 43.5% patients were

no longer suitable for transplant. However, once determined to be in DT, less than 5% shift to BTT (Teuteberg et al., 2013), indicating that a DT decision is rather final. Also, advanced age, as one of the main contraindications for heart transplant, is not reversible, making it unlikely for older patients to change in device strategy. Interestingly, compared to a DT group, BTT patients reported significantly higher overall health related quality of life pre-implant and at 2 years after implant using the KCCQ-12 and EQ-5D-3L questionnaires (White-Williams et al., 2020). Apparently, not being suitable for heart transplant and experiencing an assignment to DT, may impact the patients' and caregiver's perception of burden. It is plausible that this increased burden is caused by the finality of the status DT (Streur et al., 2020). These results indicate that device strategy may play a minor role for clinicians but could have greater impact on patients' experiences.

Furthermore, the role of device strategy differs between the United States (INTERMACS) and Europe (EUROMACS) as there are differences in the allocation systems of donor hearts. Up to 2018, in the United States, about 60% of donor hearts were assigned to patients with an LVAD as BTT. In Germany, there is no prioritization of LVAD supported patients, so that 82% of donor hearts fall into the high urgency category (Reineke & Mohacsi, 2017). Naturally, this is reflected in the clinician's decision on device strategies in LVAD candidates. In the United States, about 43% of LVAD patients received the device as DT (article 3). Contrary to the United States, the device strategy BTT was more common in Europe (75.7%, article 1). In the United States, the device strategy may play a minor role in the future era of device implants due to a policy change in the allocation of organs 2018. Whereas the former allocation system qualified LVAD patients for the highest listing status, in the current system, fewer LVAD patients are prioritized and listed for transplant and the majority of LVAD patients are now implanted in DT, although patient characteristics did not change (Mullan et al., 2021). The analyses of this dissertation covered the years from 2006-2017 in INTERMACS, thus the results are not affected by the changes in the allocation system.

Nevertheless, in future analyses, it would be interesting to elucidate the shift from BTT vs. DT to temporary vs. long-term device decisions. This term shift may also have an impact on the patient's perspective.

In sum, the current dissertation shed more light on the role of device strategy in LVAD patients. Article 1, 2, and the published abstract strongly support the first hypothesis, that device strategy BTT is associated with higher probabilities of death in female LVAD patients, helping to disentangle the conflicting results on gender differences in mortality. Nevertheless, the role of device strategy may decline in the future era of devices.

5.3 Psychosocial Risk Factors and LVAD Outcomes

In article 2, there was no association of psychosocial risk factors with the major outcomes death, heart transplant, recovery, and device replacement. Using the same variables to analyze their association with adverse events (article 3), resulted in multiple significant associations, and an overall psychosocial risk indicator even suggested a dose-response relationship.

Similar to article 2, most of the single-center studies and the large INTERMACS analysis did not find psychosocial risk factors to be associated with death after LVAD (DeFilippis, Breathett, et al., 2020; Dew et al., 2021; Lundgren, Lowes, et al., 2017; Snipelisky et al., 2015). However, the studies reported, similar to article 3, that psychosocial risk factors were associated with adverse events (Bui, Braun, et al., 2019; DeFilippis, Breathett, et al., 2020; Dew et al., 2021) and readmission (Cagliostro et al., 2019; DeFilippis, Breathett, et al., 2020; Kaiser, 2019; Lundgren, Lowes, et al., 2017; Maltby et al., 2014; Snipelisky et al., 2015; Yost et al., 2016). The assumption that psychosocial risk is in fact only related to adverse events and not related to survival in LVAD patients is barely plausible as there is strong evidence for the association of psychosocial risk with onset of and mortality after cardiovascular diseases (Dar et al., 2019; Freedland et al., 2016; Santosa et al., 2021; Suls & Martin, 2011). Contrary

to studies in the cardiovascular disease populations, in LVAD studies, only patients that already qualified for the advanced therapy i.e., by having an acceptable psychosocial risk profile, are included. This may lead to ceiling effects and to study designs that are underpowered to detect effects in the high-risk profile patients. On the contrary, heart transplant candidates undergo a psychosocial evaluation at least as thoroughly as LVAD patients (Owens & Jessup, 2012), and it is well documented that psychosocial risk factors pre-transplant are associated with death while waiting and after transplant (Havik et al., 2007; Owen et al., 2006; Spaderna et al., 2010; Spaderna et al., 2017; Zipfel et al., 2002). Importantly, all of these heart transplant studies used psychological scales or psychiatric diagnostic to assess the psychosocial variables, especially depression (e.g., HADS-D, BDI, ZD). Almost all studies in the field of LVAD research are based on unstandardized checklist (i.e., articles 2; 3; DeFilippis, Breathett, et al., 2020) or an evaluation by social workers (Bruce et al., 2017; Dew et al., 2021; Kaiser, 2019; Snipelisky et al., 2015). Only Lundgren and colleagues assessed depression via a psychologist on DSM criteria and additionally used the Beck Depression Inventory II (BDI-II), not finding an association of depression with mortality either. However, the authors did not apply a time-to-event approach and only evaluated the alive status up to 1 year after implant (Lundgren, Lowes, et al., 2017). Studies on the association of an overall psychosocial risk factor using specific tools (e.g., SIPAT) fail to detect associations of psychosocial risk with mortality in both, heart transplant (Vandenbogaart et al., 2017) and LVAD patients (Cagliostro et al., 2019; Halkar et al., 2018; Olt et al., 2023; Sperry et al., 2019). Apparently, the assessment tools differ widely in their prognostic value, and an overall risk indicator may not be appropriate for assessing these complex psychosocial constructs. In addition, many of the assessment tools for psychosocial risk used in LVAD patients derive from heart transplant patients and are based on clinical experience rather than profound evidence (Dew et al., 2018). Developing psychosocial assessment tools for the LVAD population may be necessary, as the populations differ in their

psychosocial risk factors for adverse events. Whereas transplant patients must adhere to a complex medical therapy, LVAD patients have to maintain sterility, as well as prevent and recognize technical complications in the LVAD machinery (Olt et al., 2023). Additionally, using psychometric and validated tools, especially for psychiatric diagnoses (e.g., HADS, BDI-II) but also for social support (e.g., Perceived Support Scale) might be promising. There are still conflicting results on the impact of social support on outcomes in the heart failure populations, even leading to clinicians questioning the role of social support in principle (Bui, Allen, et al., 2019). It is conceivable that the mixed results are caused by the failure of assessing the multiple dimensions of social support (e.g., received vs. perceived; emotional vs. practical) (Gottlieb & Bergen, 2010). Whereas there is no doubt that a better operationalization of psychosocial risk factors is necessary, a poor quality of tools does not explain that psychosocial risk appears to be associated with adverse events but not with major outcomes.

It is important to consider that major events such as death occur more rarely compared to adverse events, such as infections. Small event counts, leading to small effective sample sizes, directly impact the probability to detect effects. In all single center studies, this may be a major methodological issue (e.g., Dew et al., 2021). The large registry analyses, however, (articles 2; 3; DeFilippis, Breathett, et al., 2020) are sufficiently powered to detect these effects. Another explanation for not finding associations of psychosocial risk with survival may be the data structure in time-to-event analyses. The competing risk designs (i.e., time-to-first-event and type-of-first-event) does not account for additive effects of multiple adverse events that occur more than once. Knowing that the occurrence of adverse events is clearly related to mortality (Molina et al., 2021), one could argue that psychosocial risk affects death via previous adverse events, in an indirect way.

Thus, the results of this dissertation only partly support hypothesis 2. Psychosocial risk (as single factors, and as an overall risk indicator) is clearly related to the occurrence of multiple adverse events but not to mortality. It should be noted that only patients that already qualified for LVAD therapy with acceptable risk profiles were included in the samples of this dissertation. It is probable that there is at least an indirect effect of psychosocial risk on mortality via adverse events. Psychometric and LVAD specific evaluation tools of psychosocial risk may help to shed more light on the role of psychosocial risk factors for clinical outcomes and adverse events after LVAD implant.

5.4 Gender and Psychosocial Risk Factors in LVAD Recipients

The major aim of the present dissertation was to evaluate the association of gender differences in pre-implant psychosocial risk factors and their role for gender differences in LVAD outcomes. Women significantly differed from men regarding many psychosocial risk factors, which was in line with former reports. Whereas men were more likely to have a history of alcohol and substance abuse (articles 2; 3; Ahmed et al., 2020; Hsich, Naftel, et al., 2012; Joshi et al., 2019), women were more likely to have severe depression and other psychiatric diagnoses (articles 2; 3; Joshi et al., 2019; Nayak, Hu, Ko, Steinberg, et al., 2021). There were no gender differences in limited social support (articles 2 and 3), limited cognition/understanding, and repeated noncompliance (article 3). In total, men were more likely to have any psychosocial risk than women (21.4% vs. 17.5%, article 3, Figure 6) according to the five domains stated by the Consensus statement (Dew et al., 2018). Thus, in contrast to hypothesis 3, women were not disadvantaged regarding overall psychosocial risk pre-implant. Interestingly, even though men were more likely to have psychosocial risk pre-implant, the association with adverse events seemed to be more pronounced in women. Article 3 delivered the very first evidence that female gender combined with psychosocial risk may lead to worse outcomes after LVAD implant.

The mechanisms of this interaction may be dynamic and could be interpreted in terms of the biopsychosocial model (Engel, 1977; Suls & Martin, 2011). Women's pronounced association of overall psychosocial risk with adverse events after LVAD implant could indicate that psychosocial stress in general leads to a more adverse physiological reactions such as increased inflammatory reactivity in women than in men (Sullivan et al., 2020). This is also supported by the evidence that women have an increased risk of heart failure related to alcohol consumption compared with men, despite women being less likely to consume alcohol (Cesaroni et al., 2021). It is also conceivable that additional factors, which are especially prevalent in women but not assessed in the registries, such as caregiving roles (O'Neil et al., 2018), influence women's susceptibility for psychosocial risk.

Surprisingly, almost no gender-specific associations of single psychosocial risk factors with an adverse event were revealed in this INTERMACS analysis. For example, as in the cardiac population the association of depression with heart failure risk appears to be stronger in women (Chrysohoou et al., 2003; Low et al., 2011), it was expected that depression was a specific risk factor for female LVAD recipients. Solely for social support, there may be a gender-specific association. In the heart failure populations, being without a partner was more strongly associated with cardiovascular risks in men than in women (Havranek et al., 2015; Liu & Waite, 2014; Wang et al., 2020). In INTERMACS, marital status was not associated with male's increased risk for adverse events but the single psychosocial risk factor *limited social support* was associated with only one adverse event (i.e., psychiatric episodes) and only in men (Table S3). Similarly, in the Waiting for a New Heart Study, there was first evidence that male candidates were more burdened by social isolation (Spaderna et al., 2010; Spaderna et al., 2012; Weidner et al., 2011). These results must be interpreted with caution, as in both studies the effective sample sizes were quite small. Unfortunately, INTERMACS offers no opportunity to evaluate quality of relationships and different dimensions of social support. In transplant patients, women rather perceive emotional support whereas male recipients

perceive practical social support (Abshire Saylor et al., 2022), indicating gender differences in the social support dimensions. Importantly, the perceived support may as well mismatch the desired support (Linden & Vodermaier, 2012), further underlining the complexity of the construct. Using a tool such as the Perceived Support Scale (Krause & Markides, 1990), which measures perceived social support of caregivers with the dimensions: tangible support (e.g., help with transportation), emotional support, informational support, satisfaction with support, and negative social interaction (Gottlieb & Bergen, 2010; Krause & Markides, 1990), may shed more light on potential gender differences in perceived and desired aspects of social support in LVAD recipients.

Thus, hypothesis 3 is only partly supported by the results of this dissertation Women were not generally disadvantaged in psychosocial risk factors compared with men. At least in the variables assessed in INTERMACS and EUROMACS, women were even more likely than men to have none of the psychosocial risk factor suggested by the Consensus statement (Dew et al., 2018). *If* women had psychosocial risk, the association with adverse events may be more pronounced in women. Gender differences in the type of psychosocial risk (e.g., substance abuse vs. psychiatric diseases) were mostly not associated with genders-specific risk in outcomes. In future research a *gender-, and risk-factor specific approach,* using validated assessment tools would be promising.

5.5 Gender Gap in Treatment of Advanced Heart Failure

The following chapter integrates the results of this dissertation in the current research topic on the gender gap in treatment of advanced heart failure.

Only 20% of patients that receive an LVAD are women (de By et al., 2022; Khazanie, 2019; Molina et al., 2021), despite the fact that 40% of patients with HFrEF are female (Desai et al., 2021). In Europe and the United States, the amount of women with LVADs did not change in

the eras from 2010 until today (de By et al., 2022; Molina et al., 2021), which is surprising considering the major achievements in LVAD therapy. Smaller devices are available, matching to smaller bodies (Dual et al., 2022). Higher probabilities of death in women compared with men appear to be related to former pulsatile devices (Joshi et al., 2019) and BTT device strategy (article 2; DeFilippis, Truby, et al., 2019). There is even evidence that women with gender-specific diagnoses have great chances for cardiac recovery (article 2; Radhoe et al., 2023). Still, women appear to be more burdened by adverse events than men (articles 2; 3; Gruen et al., 2020). The survival benefits, however, clearly outweigh the risks of adverse events (Hsich, 2019). The reasons for the underusage of LVADs in women remain unknown. Other therapies of advanced heart failure, such as diuretics, anticoagulants, ICD, and heart transplants are also underutilized in women (Chin et al., 2016; Dewan et al., 2019; Hsich, 2019). Hence, after HFrEF diagnoses, women are less likely than men to receive optimal treatment as recommended by guidelines (Chin et al., 2016). Comparing the gender distributions in the HFrEF population (i.e., before selection process of advanced therapies) with gender distributions in LVAD patients shows many similarities. For example, in both populations, women have similar cardiac etiologies, similar psychosocial profiles, and good survival (articles 1; 2; 3; Dewan et al., 2019; Gruen et al., 2020; Hsich, Grau-Sepulveda, et al., 2012; Joshi et al., 2019; Mentzer & Hsich, 2019). However, women in the HFrEF population are more likely to have hypertension and have lower rates of readmission compared with men (Dewan et al., 2019; Swaraj et al., 2021), whereas these associations are reversed in the LVAD population (article 3; Gruen et al., 2020; Joshi et al., 2019). Most strikingly, women are older than men at presentation and when diagnosed with heart failure (Dewan et al., 2019; Swaraj et al., 2021) but younger than men at LVAD implant (articles 1; 2; 3; Gruen et al., 2020; Joshi et al., 2019).

This may indicate that LVAD usage in women is especially applied for specific indications such as postpartum heart failure. Postpartum heart failure is associated with younger age

compared to typical heart failure patients and better chances for recovery (Djordjevic et al., 2021). Also, hypertension is less likely than in other cardiac diagnoses (Table 13).

Table 13
Distribution of hypertension and age in women with all diagnoses and in women with postpartum heart failure in INTERMACS

	Women with all diagnoses (n = 4282)	Women with postpartum heart failure (n = 316)
Hypertension, n (%)	655 (20.7)	25 (10.9)
Age, mean (SD)	54.08 (13.44)	35.09 (9.89)

Is it conceivable that especially elderly female HFrEF patients with a typical age-associated reduction of the heart function do not receive LVADs? Little is known about gender specific barriers after HFrEF diagnosis to advanced therapies such as LVAD implant. In general, barriers to appropriate care can emerge at the provider (e.g., knowledge, communication, personal factors), the individual (e.g., knowledge, adherence, psychosocial factors) or systemic level (e.g., communication, lack of resources) (McEntee et al., 2009).

On the provider level, it is important to consider a potential physician's bias in the referral to advanced heart failure therapies. A study showed that 73.4% of patients referred to nine advanced heart failure centers in the United States were male (Herr et al., 2021). In The REVIVAL study, in female and male HFrEF patients that were clinically comparable (e.g., age, LVEF, INTERMACS profile) and similarly willing to consider MCS, women reported a significant higher burden in quality of life and there was a trend for delayed MCS implantation in women (Stewart et al., 2019). Daugherty and colleagues showed that cardiologists attributed being strong and taking risks more often to male patients (Daugherty et al., 2017). Women may appear more fragile, so clinicians hesitate to recommend advance heart failure therapies. This could lead to a disadvantage in referral especially for elderly women. In addition, social determinants (e.g., low income, under-insurance) are more

common in women, potentially contributing to physicians' implicit bias whether to refer to advanced therapies (Breathett et al., 2020; Morris et al., 2021). Interestingly, the underusage of evidence-based drug therapy in women with heart failure was found more likely if the physician was male (Baumhäkel et al., 2009), further indicating that gender-specific-stereotypes may play a role on the provider level.

Besides, there may also be gender-specific barriers on the individual level. In heart transplant candidates, women were more likely to refuse heart transplant compared with men (Aaronson et al., 1995). In the LVAD population, there is only one small qualitative study suggesting a similar pattern in LVAD patients (Bruce et al., 2015), and there is first evidence that women with LVADs are more likely to regret their decision compared with men (Stahl et al., 2019). It is possible that those regrets are caused by higher rates of adverse events after implant compared with men but interestingly, not only female patients but also female caregivers had higher regrets than their male counterparts (Stahl et al., 2019). The authors assumed that higher rates of anxiety and depression in women (Dewan et al., 2019; Freedland et al., 2016; O'Neil et al., 2018) may impact thoughts of regret regardless of patient or caregiver role (Stahl et al., 2019). Another important effect on the individual level may be the perceived social support and gender-specific family roles. Cardiologists reported that male patients at a heart transplant center were usually accompanied by their wives but female patients rarely by their husbands (Regitz-Zagrosek et al., 2010). Importantly, women are more likely to be the caregiving person in traditional families, and therefore may experience conflicting responsibilities concerning their own care (e.g., time consuming medical consultation, transport)(Mwansa et al., 2021).

In summary, this research stresses that gender-specific stereotypes and traditional gender roles may play a role in underestimating women's resilience leading to less referral in women. On the other hand, women's increased psychosocial burden, e.g., having more regrets, anxiety and depression, potentially decreases their acceptance of aggressive therapies.

On the systemic level, gender differences in education and health literacy which in turn are associated with access to health care should be considered (Diederichs, 2018). Interestingly, women and men did not differ in education in INTERMACS (Table 8), but in EUROMACS (Table 4). This might reflect that the United States already achieved a gender parity in higher education in 1980, which was the case much later for many European countries, e.g., UK in 1996 and Switzerland in 2010 (De Hauw et al., 2017). Also, Europe is culturally more heterogenous. A recent analysis revealed that female LVAD recipients compared with male counterparts are even more underrepresented in Southeast Europe (e.g., Croatia, Lithuania) than in Northwest Europe (e.g., Netherlands, Germany) (Radhoe et al., 2023). Thus, the access to care for women may differ more dramatically for the European women than for the American women. Finally, women's poor representation in clinical trials in Europe and the United States should be considered as another barrier on the systemic level (Ebong et al., 2022), resulting in less gender-specific knowledge of optimal heart failure care.

5.6 Clinical Implications

The results of the present dissertation lead to important clinical implications. First and foremost, clinicians should consider women more often for advanced heart failure therapies. In this context, physicians may reflect on their own implicit biases. Thereby it is important to remember that women compared with men have similar probabilities for survival after LVAD implant in the modern era of device and that women with specific diagnoses have good chances for cardiac recovery. However, clinicians need to closely monitor adverse events and complications in women. It would be promising to check for psychosocial risk factors early and rigorously. Standardized psychometric questionnaires might be useful to circumvent own biases and to detect essential psychosocial risk factors. Importantly, the psychosocial evaluation should not lead to an exclusion of high-risk patients. Canada and the European Union recently removed social support considerations from the list of transplant eligibility

criteria as it may disproportionately impact vulnerable populations (Ladin et al., 2019). These developments support the idea that rather than excluding patients, clinicians may lay a greater focus on interventions and improving communication between disciplines. Especially for psychological comorbidities, such as anxiety and depression, it would be important to detect symptoms early and to refer patients to psychologists (Heidenreich et al., 2022; McDonagh et al., 2021). Psychosocial interventions (i.e., psychoeducative education, psychological support or psychotherapeutic care) and psychotherapy (e.g., cognitive behavioral therapy) improve quality of life (Nahlén Bose, 2023; Samartzis et al., 2013) and decrease symptoms of depression and anxiety (Chernoff et al., 2022; Nahlén Bose, 2023) in patients with heart failure. Besides reduction of psychological symptoms, an important goal of psychotherapy is to reduce individual barriers to lifestyle changes and help to increase confidence and self-efficacy, which may be a specific indication for women considering advanced heart failure therapies (Aggarwal et al., 2018; Albus et al., 2019; Thomas & Clark, 2011).

5.7 Limitations and Outlook

In addition to the limitations presented in each of the articles in chapter 4, the present dissertation contains further limitations, which will be discussed in the following, along with suggestions for further research.

First, the analyses of this dissertation are based on clinical registries. Clearly, the design of the registries is not optimal to assess the role of psychosocial variables as the assessment of these variables is not standardized and varies between participating centers (Clancy et al., 2019). In future research, the application of validated tools and psychometric questionnaires would be helpful to confirm the evidence reported in this dissertation and to elucidate the role of specific psychosocial risk factors. Especially the role of social support should be addressed using a psychometric tool (e.g., The Perceived Support Scale; Krause & Markides, 1990). Concerning psychiatric diagnoses, validated questionnaires and psychiatric

interviews would offer a more profound clinical picture. However, well-designed studies using multiple psychosocial or psychological assessment tools often come with other shortages, such as small effective sample sizes limiting the power of time-to-event analyses (e.g., Dew et al., 2021; Lundgren, Lowes, et al., 2017). Thus, studying the association of gender and psychosocial risk factors in LVAD recipients is particularly challenging, considering the facts that 1) women are less likely to receive LVADs, 2) women are underrepresented in clinical trials and 3) advanced analyses of time-to-event data require a great number of subjects. Considering the amount of patients enrolled and data collected, the large registries such as INTERMACS are the most valuable data source to address these research questions, at least for now (Miller et al., 2019). Consequently, in this research area it may be more feasible to develop an LVAD specific tool for psychosocial evaluation that accounts for population specific differences of LVAD and transplant patients (Olt et al., 2023) and could be integrated in the assessment protocols of the large registries.

Secondly, in this dissertation, outcome analyses were only conducted with INTERMACS data. There is only one study analyzing gender differences in LVAD outcomes in EUROMACS (Magnussen et al., 2018), in which psychosocial variables are not considered. Unfortunately, such an analysis would not be feasible to date, due to the high amount of missing data in EUROMACS' psychosocial variables, especially in female LVAD recipients (article 1). This highlights even more the need for appropriate and standardized psychosocial assessment of LVAD patients and to improve data completeness in both registries. In would be interesting to compare gender differences in outcomes depending on psychosocial risk factors between Europe and the United States, or even globally using the IMACS registry (Kirklin et al., 2018).

Lastly, the INTERMACS and EUROMACS data sets are limited to 2017. Promising new centrifugal devices such as the HeartMate 3 that were approved in the last 5 years are not

included in the analyses. Gender differences in adverse events would be interesting to investigate within the latest generation of devices (Vieira et al., 2020). First single-center studies suggest that there are no significant differences in early mortality between women and men with HeartMate 3 (DeFilippis, Haythe, et al., 2020). This is supported by a recent multi-center study of 13 participating centers across Europe. The authors reported no gender differences in mortality in a CF-LVAD populations of which 28% were implanted with the HeartMate3. Still, women were more likely to experience right ventricular failure (Radhoe et al., 2023). The future LVADs may be completely wireless devices (Horie et al., 2023; Wang et al., 2014), further decreasing the risk of infections and device-related adverse events (Shah et al., 2022). Thus, assessing the independent role of psychosocial risk factors may be facilitated. Additionally taking into account that women are more mandatorily included in heart failure trials (Reza et al., 2022), the future may yield a broader gender-specific knowledge about LVAD recipients potentially leading to an increased usage of LVADs in women.

5.8 Conclusion

Knowledge about gender differences in clinical outcomes after LVAD implant and the association with pre-implant psychosocial risk factors is still rare. The present dissertation contributes to filling this research gap by clarifying the role of the device strategy BTT for women's increased probability of mortality. Furthermore, the results show that psychosocial risk pre-implant increases the rates of adverse event and there is first evidence that women may be more susceptible for psychosocial risk factors.

One conclusion resulting from all three articles of the present dissertation is the importance of considering clinical, device-related, and psychosocial risk factors, when evaluating gender differences in LVAD outcomes. Women present in a more severe stage of disease, experience worse outcomes with older devices and in the device strategy BTT, and may be more

seriously affected by psychosocial risk factors. Importantly, these factors may interact dynamically. Generally, the results of this dissertation promote a gender-sensitive research approach and stress the importance to include more women in clinical heart failure trials to expand gender-specific knowledge in this patient population.

According to the results of this dissertation, clinicians may consider women more often for LVAD therapy. Employing a more rigorous assessment of psychosocial risk factors using psychometric tools may help to detect specific psychosocial risk factors early. The aim should be to improve interprofessional care and communication to inform gender-sensitive interventions of psychosocial risk factors.

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Declaration Regarding the Dissertation

I, Lisa-Marie Maukel, declare that that the submitted thesis with the title “Gender Differences in Clinical Outcomes After Left Ventricular Assist Device (LVAD) Implantation – The Role of Psychosocial Risk Factors” is my own work.

I have only used the sources indicated and have not made unauthorized use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

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