Gender differences in characteristics and outcomes in heart failure patients referred for end-stage treatment

Nina Fluschnik1,2†, Felix Strangl1†, Christoph Kondziella1, Alina Gößling1, Peter Moritz Becher1,2, Benedikt Schrage1,2, Renate B. Schnabel1,2, Julia Bernardyn1, Wiebke Bremer1, Hanno Grahn1, Alexander M. Bernhardt3, Hermann Reichenspurner3, Meike Rybczynski1, Stefan Blankenberg1,2, Paulus Kirchhof1,2, Christina Magnussen1,2† and Dorit Knappe1*†

1Department of Cardiology, University Heart & Vascular Centre Hamburg, Martinistrasse 52, Hamburg, 20246, Germany; 2German Centre for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; and 3Department of Cardiovascular Surgery, University Heart & Vascular Centre Hamburg, Hamburg, Germany

Abstract

Aims Despite signals from clinical trials and mechanistic studies implying different resilience to heart failure (HF) depending on gender, the impact of gender on presentation and outcomes in patients with HF remains unclear. This study assessed the impact of gender on clinical presentation and outcomes in patients with HF referred to a specialised tertiary HF service.

Methods and results Consecutive patients with HF referred to a specialised tertiary HF service offering advanced therapy options including left ventricular assist devices (LVAD) and heart transplantation were prospectively enrolled from August 2015 until March 2018. We assessed clinical characteristics at baseline and performed survival analyses and age-adjusted Cox regression analyses in men vs. women for all-cause death and a combined disease-related endpoint comprising death, heart transplantation, and LVAD implantation. Analyses were performed for the overall study population and for patients with HF with reduced ejection fraction (HFrEF). Of 356 patients included, 283 (79.5%) were male. The median age was 58 years (interquartile range 50–67). Two hundred and fifty-one (74.5%) patients had HFrEF. HF aetiology, ejection fraction, functional status measures, and most of the cardiac and non-cardiac comorbidities did not differ between men and women. In a median follow-up of 3.2 years, 50 patients died (45 men, 5 women), 15 patients underwent LVAD implantation, and 8 patients heart transplantation. While all-cause death was not significantly different between both genders in the overall population [16.9 vs. 6.0%, P = 0.065, hazard ratio (HR) 2.29 (95% confidence interval 0.91–5.78), P = 0.078], in the HFrEF subgroup, a significant difference between men and women was observed [20.7% vs. 3.9%, P = 0.017, HR 3.67 (95% confidence interval 1.13–11.91), P = 0.031]. The combined endpoint was more often reached in men than in women in both the overall population [21.6% vs. 9.0%, P = 0.053, HR 2.51 (1.08–5.82), P = 0.032] and the HFrEF subgroup [27.1% vs. 7.7%, P = 0.015, HR 3.58 (1.29–9.94), P = 0.014].

Conclusions Patients referred to a specialised tertiary HF service showed a similar clinical profile without relevant gender differences. In the mid-term follow-up, more male than female patients died or underwent heart transplantation and LVAD implantation. These findings call for independent validation and for further research into gender-specific drivers of HF progression.

Keywords Heart failure; All-comers cohort; Gender differences

© 2021 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
**Introduction**

Heart failure (HF) is found in approximately 2% of the population in developed parts of the world and affects more than 26 million people worldwide. The prevalence of HF is much higher in older populations, leading to a marked projected increase in HF in the coming decade. While the consequences of myocardial infarction, which affect more men than women, were historically the main cause of HF, other diseases associated with HF such as arterial hypertension or diabetes, which appear to contribute more to HF at an older age, could be more common in women.

Women have consistently been under-represented in recent clinical HF trials, so the effect of evidence-based therapies on outcomes is less clear in women than in men with HF. Sex differences in HF treatment and treatment response have been described. Moreover, it has been shown that women are less likely to receive definite HF therapies such as left ventricular assist device (LVAD) and heart transplantation, but reasons for this under-treatment are still unclear. Therefore, we analysed differences in clinical presentation, comorbidities, medical therapy, and outcomes between men and women with HF referred for further treatment to a specialised HF service.

**Methods**

**Study population**

The study population consisted of a prospectively enrolled cohort of patients with HF referred for further evaluation of HF treatment as LVAD and heart transplantation to our specialist HF service. All patients referred for specialist treatment of either known or recently diagnosed HF from August 2015 until March 2018 were considered eligible to participate. Patients aged <18 years, presenting with acute decompensated HF, on LVAD support and transplant recipients were not included. In patients with recurrent presentations to our outpatient clinic, the first referral was considered for the analyses.

Clinical variables were assessed at baseline and included age, sex, weight, height, body mass index (BMI), systolic and diastolic blood pressure, aetiology of HF, and New York Heart Association (NYHA) class and 6 min walk distance as functional parameters. Cardiac history and non-cardiac comorbidities [viz. arterial hypertension, hypercholesterolaemia, diabetes, chronic obstructive pulmonary disease (COPD), asthma or other lung diseases, chronic renal failure, history of severe hepatic failure, transient ischaemic attack/ ischaemic stroke in history, haemorrhagic stroke, peripheral artery disease, hyperthyroidism, or hypothyroidism] were physician-diagnosed. All patients underwent standardised imaging by echocardiography. Echocardiographic measurements including ejection fraction (EF) with the biplane Simpson’s method and diastolic function (using Doppler patterns of mitral valve inflow and tissue Doppler), current HF medication and device therapy such as pacemaker, implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT), and laboratory values were assessed at baseline as well.

Follow-up was obtained by regular clinical review. Information on outpatient and inpatient visits was captured electronically. All-cause death data were obtained from the death register.

The study was approved by the local ethics committee (PV 6079) and conducted in concordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation or as median (25th percentile, 75th percentile), respectively, and categorical variables as absolute numbers (relative frequencies). For between-group comparisons, the Mann–Whitney test was used for continuous variables and the chi² test for binary variables. The first outcome parameter of the analysis was all-cause death. The second outcome was a composite endpoint of ‘death from any cause, heart transplantation, or LVAD implantation’ during follow-up. Survival curves were produced using the Kaplan–Meier method, and the log-rank test was used to test for survival curve differences. Stratified by gender, we performed age-adjusted Cox regression analyses for all-cause death and the composite endpoint ‘death from any cause, heart transplantation, or LVAD implantation’. Analyses were performed for the overall study population and for the subgroup of patients with HF with reduced ejection fraction (HFrEF). A two-tailed P-value < 0.05 was considered statistically significant. All calculations were performed using R Version 3.5.2.

**Results**

**Clinical characteristics at baseline**

A total of 356 patients were studied, 283 men (79.5%) and 73 women (20.5%). Clinical characteristics, EF, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), HF therapy, comorbidities, and age were not different between men and women (Table 1). In detail, patients referred for advanced HF treatment had a low mean EF (30.0%), median NT-proBNP values of 1194 ng/L in men and
| Clinical variables | All (N = 356) | Men (N = 283) | Women (N = 73) | P-value |
|--------------------|--------------|--------------|---------------|---------|
| **Age (years)**    | 58.0 (50.0, 67.0) | 58.0 (50.0, 67.0) | 57.0 (47.9, 68.0) | 0.86    |
| **Weight (kg)**     | 83.1 (72.9, 98.0) | 87.00 (77.0, 102.8) | 66.0 (58.0, 80.0) | <0.001  |
| **Height (cm)**     | 178.0 (172.0, 183.1) | 180.0 (175.0, 185.0) | 168.0 (163.0, 172.80) | <0.001  |
| **BMI (kg/m²)**     | 26.3 (23.8, 30.3) | 26.8 (24.5, 30.6) | 23.9 (20.8, 28.3) | <0.001  |
| **Systolic blood pressure (mmHg)** | 115 (100.4, 134.0) | 116 (101.2, 135.0) | 111 (95.0, 130.0) | 0.07    |
| **Diastolic blood pressure (mmHg)** | 69 (60.0, 78.0) | 70 (62.0, 78.0) | 61 (57.0, 74.0) | <0.001  |
| **Aetiology of heart failure, n (%)** | | | | |
| Dilated cardiomyopathy | 151 (42.5) | 121 (42.8) | 30 (41.7) | 0.97 |
| Ischaemic cardiomyopathy | 134 (37.8) | 113 (39.9) | 21 (29.2) | 0.12 |
| Ischaemic cardiomyopathy/dilated cardiomyopathy | 1 (0.3) | 0 (0) | 1 (1.4) | 0.46 |
| Hypertrophic cardiomyopathy | 8 (2.3) | 5 (1.8) | 3 (4.2) | 0.44 |
| Valvular cardiomyopathy | 9 (2.5) | 9 (3.2) | 0 (0) | 0.27 |
| Toxic cardiomyopathy | 7 (2.0) | 4 (1.4) | 3 (4.2) | 0.31 |
| Others | 42 (11.8) | 30 (10.6) | 12 (16.7) | 0.22 |
| **Functional parameters, n (%)** | | | | |
| NYHA I | 73 (22.1) | 59 (22.4) | 14 (21.2) | 0.97 |
| NYHA I–II | 7 (2.1) | 6 (2.3) | 1 (1.5) | 1.00 |
| NYHA II | 133 (40.3) | 107 (40.5) | 26 (39.4) | 0.98 |
| NYHA II–III | 25 (7.6) | 21 (8.0) | 4 (6.1) | 0.79 |
| NYHA III | 86 (26.1) | 66 (25.0) | 20 (30.3) | 0.47 |
| NYHA III–IV | 5 (1.5) | 4 (1.5) | 1 (1.5) | 1.00 |
| NYHA IV | 1 (0.3) | 1 (0.4) | 0 (0) | 1.00 |
| **6 min walk distance (m)** | 349.4 ± 144.3 | 360.4 ± 135.8 | 310.9 ± 173.4 | 0.34 |
| **Comorbidities, n (%)** | | | | |
| Arterial hypertension | 175 (50.3) | 146 (52.7) | 29 (40.9) | 0.01 |
| Hypercholesterolaemia | 125 (41.8) | 108 (43.1) | 22 (36.7) | 0.45 |
| Diabetes | 71 (20.3) | 61 (22.0) | 10 (13.9) | 0.17 |
| COPD | 33 (11.0) | 28 (11.6) | 5 (8.5) | 0.65 |
| Asthma bronchiale | 28 (9.3) | 24 (9.9) | 4 (6.8) | 0.36 |
| Chronic renal failure | 124 (41.5) | 102 (42.3) | 22 (37.9) | 0.64 |
| Severe hepatic failure | 13 (4.3) | 11 (4.6) | 2 (3.4) | 0.97 |
| Transient ischaemic attack/ischaemic stroke | 30 (10.0) | 24 (10.0) | 6 (10.0) | 1.00 |
| Haemorrhagic stroke | 2 (0.7) | 1 (0.4) | 1 (1.8) | 0.84 |
| Peripheral arterial disease | 12 (4.0) | 10 (4.1) | 2 (3.3) | 1.00 |
| Hyperthyroidism | 30 (9.3) | 24 (9.3) | 6 (9.0) | 1.00 |
| Hypothyroidism | 48 (15.9) | 37 (15.3) | 11 (18.3) | 0.70 |
| **Cardiac history, n (%)** | | | | |
| Myocardial infarction | 102 (33.8) | 85 (35.1) | 17 (28.3) | 0.40 |
| Cardiogenic shock | 44 (16.4) | 34 (15.8) | 10 (18.5) | 0.78 |
| Left ventricular thrombus | 32 (10.6) | 28 (11.5) | 4 (6.8) | 0.62 |
| Atrial fibrillation | 109 (36.3) | 96 (39.8) | 12 (22.0) | 0.02 |
| Atrial flutter | 21 (7.0) | 20 (8.3) | 1 (1.7) | 0.13 |
| Ventricular tachycardia | 55 (18.7) | 43 (18.2) | 12 (20.7) | 0.81 |
| Ventricular fibrillation | 28 (9.3) | 23 (9.5) | 5 (8.3) | 0.98 |
| **Echocardiography, n (%)** | | | | |
| EF (Simpson) | 30.0 (25.0, 40.0) | 30.0 (25.0, 40.0) | 31.0 (27.0, 30.0) | 0.53 |
| EF < 40% | 251 (74.5) | 195 (73.0) | 56 (80.0) | 0.30 |
| EF 40–49% | 80 (23.7) | 67 (25.1) | 13 (18.6) | 0.33 |
| EF > 50% | 6 (1.8) | 5 (1.9) | 1 (1.4) | 1.00 |
| Diastolic dysfunction: none | 58 (20.6) | 43 (19.4) | 15 (25.4) | 0.40 |
| Diastolic dysfunction I° | 116 (41.3) | 86 (38.7) | 30 (50.9) | 0.13 |
| Diastolic dysfunction II° | 60 (21.4) | 54 (24.3) | 6 (10.2) | 0.03 |
| Diastolic dysfunction: III° | 47 (16.7) | 39 (17.6) | 8 (13.6) | 0.59 |
| E/E' | 11.5 (8.6, 15.7) | 11.4 (8.6, 15.7) | 12.3 (8.2, 15.8) | 1.00 |
| E/A | 1.3 (0.8, 2.1) | 1.4 (0.8, 2.4) | 1.0 (0.7, 1.5) | 0.01 |
| RVP (mmHg) | 29.0 (22.0, 36.0) | 30.0 (21.7, 36.3) | 27.0 (23.0, 36.7) | 0.71 |
| TAPSE (mm) | 18.0 (15.0, 21.0) | 18.0 (14.1, 20.1) | 18.4 (16.0, 22.1) | 0.07 |
| Aortic valve stenosis moderate/severe (%) | 3 (0.8) | 2 (0.7) | 1 (1.4) | 1.00 |
| Aortic valve regurgitation moderate/severe (%) | 9 (2.5) | 9 (3.2) | 0 (0) | 0.26 |
| Mitral valve stenosis moderate/severe (%) | 1 (0.3) | 0 (0) | 1 (1.4) | 0.46 |
| Mitral valve regurgitation moderate/severe (%) | 77 (21.6) | 55 (19.4) | 22 (30.1) | 0.07 |
| Tricuspid valve regurgitation moderate/severe (%) | 54 (15.2) | 41 (14.5) | 13 (17.8) | 0.60 |

(Continues)

ESC Heart Failure 2021; 8: 5031–5039
DOI: 10.1002/ehf2.13567
1254 ng/L in women, and a high proportion of patients receiving device therapy (57.6% men and 50.0% women with ICD; 28.8% men and 19.0% women with CRT) (Tables 1 and 2). In turn, the low symptom status (22.4% of men and 21.2% of women with NYHA class I, 40.5% of men and 39.4% in women with NYHA class II) and high adherence to HF therapy are representative of decent HF management (Table 2).

Outcomes

In 24 patients, outcome information was not retrievable, and 1 patient was excluded due to incomplete data. During a median follow-up of 3.2 years, 50 patients of 332 at risk died (45 men and 5 women, 15.1%, annualized rate ~5%). Fifteen patients underwent LVAD implantation (4.5%) and 6 patients heart transplantation (1.8%), of whom 2 had earlier received
an LVAD (Figure 1 and Supporting Information). The combined outcome of death, heart transplantation, or LVAD implantation was observed in 64 patients (19.3%, annualized rate ~6%).

For the overall cohort, all-cause death was not significantly higher in men than in women (3 year all-cause death 16.9% vs. 6.0%, \( P = 0.065 \)) with an age-adjusted hazard ratio (HR) of 2.29 [95% confidence interval (CI) 0.91–5.78, \( P = 0.078 \)] (Figure 2A). In the HFrEF subgroup, all-cause death was significantly higher in men vs. women [20.7% vs. 3.9%, \( P = 0.017 \), HR 3.67 (95% CI 1.13–11.91), \( P = 0.031 \)] (Figure 2B). The combined endpoint ‘death from any cause, heart transplantation, or LVAD’ at 3 years was more often reached in men than in women in the overall population (21.6% vs. 9.0%, \( P = 0.053 \)) with an age-adjusted hazard ratio of 2.51 (95% CI 1.08–5.82, \( P = 0.032 \)) and the HFrEF subgroup [27.1% vs. 7.7%, \( P = 0.015 \), HR 3.58 (1.29–9.94), \( P = 0.014 \)] (Figure 3A and 3B).

**Discussion**

In this prospective all-comers cohort of patients referred to a specialised tertiary HF outpatient service, we observed differences in referral strategies to the disadvantage of women. Ultimately, at a 3 year follow-up, men had a higher risk of death or need for cardiac replacement therapy than women, despite similar clinical characteristics at baseline.
In our study, ischaemic aetiology of HF was more common in men than in women, which is consistent with prior reports.\textsuperscript{11,12} Men generally tend to have a worse cardiovascular risk profile,\textsuperscript{7,11,13} which could be a simple explanation for differences in outcome. However, there were no major gender differences in risk factor profile, comorbidities, and cardiac history in our study population. Also, functional parameters (NYHA class and 6 min walk distance) and treatment characteristics were comparable in the two groups, as both men and women received guideline-recommended HF medication and device therapy in a similarly high proportion. This reflects the high standard of care offered to patients referred to our tertiary care centre.

Participants in the presented study were predominantly male (~80%). While a more homogeneous gender distribution would be more desirable when investigating gender differences in HF, the reasons for this disproportion are complex and multifactorial. Referral strategies could play a significant role. Women have been reported to be referred to specialized tertiary HF services with a consistently low rate,\textsuperscript{14,15} and thus, similar gender imbalances have been presented in previous registries\textsuperscript{11,16}—in contrast to the distribution of HF in the general population.\textsuperscript{4,17} The fact that women suffering from HF often present at older ages and with higher or preserved EF\textsuperscript{1,7,18} may also contribute to a lower referral rate to specialized HF clinics for end-stage HF treatment. Further aspects such as lower willingness to participate in clinical trials, socio-economic disparities, or psychological issues resulting in underestimation of HF symptoms\textsuperscript{6,19} may have further aggravated the underrepresentation of female patients. Although this gender imbalance might bias the outcomes of our study, this disproportion represents the real-world all-comers cohort of our specialized HF service.

Additionally, the reported reluctance of women to be referred to specialist services is likely to result in ‘sicker’ women accepting referral. Thus, this imbalance could be expected to lead to worse outcomes in women than in men. The fact that we find the opposite strengthens the main findings in our study, despite the acknowledged limitation. In the study, patients were enrolled consecutively, without any stratification, randomization, or prior selection.

Our data from a well-characterized cohort of patients with HF referred to a specialised service demonstrated higher rates of death and cardiac replacement therapy in men than in women, especially in the subgroup of patients with HFrEF. These observations are in line with earlier reports suggesting higher event rates in male HF patients.\textsuperscript{20,21} Despite the relatively young median age in our study population and despite guideline-recommended HF therapy, we observed a considerably high event rate compared with other HF cohorts,\textsuperscript{11,22} illustrating the advanced character of HF among study participants. Our findings documented a gender-specific difference in the risk of death or need for cardiac replacement therapy to the disadvantage of men, as is known from literature.\textsuperscript{20,21,23,24} In contrast to some previous studies, the proportion of patients receiving HF medication and device therapy according to current guidelines was very high. Nevertheless, gender differences in pharmacokinetics and pharmacodynamics leading to a different response to therapy might have contributed to differences in outcome.\textsuperscript{25}
While lifetime risk for HF remains comparable in both genders, there are disparities in the utilization of definite HF therapies, in particular heart transplantation and LVAD. Although the use of mechanical circulatory support increased in recent years in both genders, women appear to receive LVAD therapy less often. Our results confirmed this trend, as in our study, all patients undergoing LVAD implantation during follow-up happened to be male. While published data from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) cohort suggest that women are less likely to be referred for mechanical circulatory support or may present in advanced critical HF states or unstable conditions, possibly too sick to undergo LVAD implantation, the preference for men to receive LVAD therapy will have other reasons in our cohort as men were also more likely to die.

Finally, our study represents the actual clinical situation in a specialised outpatient service (‘real-world’ HF population), rather than a selected collective of patients with ‘real’ advanced HF. Our HF cohort also constitutes a population suitable for advanced HF therapy, thus probably excluding HF ‘beyond repair’.

Limitations

This study has several limitations. While this analysis drew prospective patients from a large tertiary HF centre, resulting in good and homogeneous therapy, the single-centre nature of the data and the small sample size are limitations. We report a heterogeneous gender distribution that reflects an unselected, real-world HF population referred to a highly specialised tertiary outpatient clinic for evaluation of end-stage HF therapies such as LVAD implantation or heart transplantation; however, the gender distribution might have biased the results. Independent validation of our findings might mitigate these limitations.

Conclusions

Patients referred to a specialised tertiary HF service showed a similar clinical profile without relevant gender differences. In the mid-term follow-up, more male than female patients died or underwent heart transplantation and LVAD implantation. These findings call for independent validation and for further research into gender-specific drivers of HF progression.

Conflict of interest

A.M.B. reports personal fees from Abbott, Abiomed, AstraZeneca, BerlinHeart, Medtronic, and Novartis (unrelated to the submitted work).

B.S. received funding from the German Research Foundation and the Else Kroener-Fresenius-Stiftung and speakers fees from AstraZeneca, all outside the submitted work.

C.M. receives funding from the German Center for Cardiovascular Research (DZHK) within the Promotion of Women Scientists’ programme and from the Deutsche Stiftung fuer Herzforschung unrelated to the current work.

C.M. has received speaker fees from Astra Zeneca, Novartis, and Loewenstein medical outside this work.

H.R. has received honoraria from Abiomed and Medtronic (unrelated to the submitted work).

P.K. receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last 3 years (unrelated to the submitted work). P.K. is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2018012783).

P.M.B. received funding from the German Research Foundation outside the submitted work.

R.B.S. has received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme under the grant agreement no. 648131, from the European Union’s Horizon 2020 research and innovation programme under the grant agreement no. 847770 (AFFECT-EU), and from the German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103), German Ministry of Research and Education (BMBF 01ZX1408A), and ERACoSysMed3 (031L0239) (unrelated to the submitted work). RBS conflicts: RBS has received lecture fees and advisory board fees from BMS/Pfizer outside this work.

S.B. has received speakers fee from Medtronic, Pfizer, Roche, Novartis, and SiemensDiagnostics (unrelated to the submitted work).

Funding

The authors did not receive any funding for this study.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Table S1. Baseline characteristics stratified by gender for patients who underwent heart transplantation or LVAD during follow-up.

Table S2. Therapy stratified by gender for patients who underwent heart transplantation or LVAD during follow-up.

Figure S1. Kaplan–Meier curves for ‘freedom from death and heart transplantation’ in HF patients stratified by gender.
Seferovic PM, Tousoulis D, Kavoliuniene A, Frühwald F, Fazlilbegovic E, Temizhan A, Gatzov P, Erglis A, Laroché C, Mebazaa A, Cardiology obotHFaoETSo. European society of cardiology heart failure long-term registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail. 2016; 18: 613–625.

23. O’Meara E, Clayton T, McEntegart MB, McMurray JJ, Pina IL, Granger CB, O’Connor J, Michelson EL, Solomon SD, Pocock S, Yusuf S, Swedberg K, Packer M, Investigators C. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. Circulation. 2007; 115: 3111–3120.

24. Dewan P, Rørth R, Jhund PS, Shen L, Raparelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Køber L, Mogensen UM, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray J. Differential impact of heart failure with reduced ejection fraction on men and women. J Am Coll Cardiol. 2019; 73: 29–40.

25. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009; 48: 143–157.

26. McIlvennan CK, Lindenfeld J, Kao DP. Sex differences and in-hospital outcomes in patients undergoing mechanical circulatory support implantation. J Heart Lung Transplant. 2017; 36: 82–90.

27. Colvin M, Smith JM, Hadley N, Skeans MA, Uccellini K, Goff R, Foutz J, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Heart. Am J Transplant. 2020; 20: 340–426.

28. Magnussen C, Bernardt AM, Ojeda FM, Wagner FM, Gummert J, de By T, Krabatsch T, Mohacsi P, Rybczynski M, Knappe D, Sill B, Deuse T, Blankenberg S, Schnabel RB, Reichenspurner H. Gender differences and outcomes in left ventricular assist device support: the European registry for patients with mechanical circulatory support. J Heart Lung Transplant. 2018; 37: 61–70.