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ARTICLE

Sex-based differences in characteristics, management, and outcomes in heart failure with reduced ejection fraction

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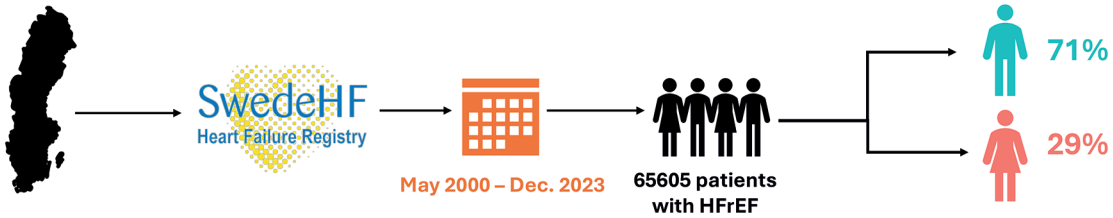
Graphical abstract

Sex-based differences in patients with heart failure and reduced ejection fraction. CI, confidence interval; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ICD, implantable cardioverter defibrillator; SGLT2i, sodium glucose co-transporter type II inhibitor.



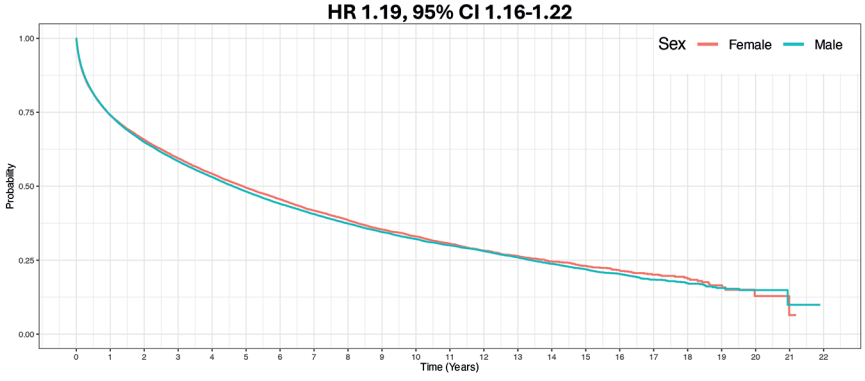
Men vs Women more likely:

- Outpatients
- To have ischemic heart disease
- To have atrial fibrillation
- To have diabetes
- To be a smoker
- Treated with SGLT2i
- To have received ICD/CRT

Women vs Men more likely:

- Older
- To have CKD
- To have hypertension
- To have anemia
- To have higher natriuretic peptides
- Treated with beta-blockers
- Treated with digoxin

Higher risk in men vs women for the primary outcome of time to first cardiovascular mortality or heart failure hospitalization
HR 1.19, 95% CI 1.16-1.22



Key words: heart failure; reduced ejections fraction; sex differences; artificial intelligence; large-language model.

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Abstract

Heart failure with reduced ejection fraction (HFrEF) exhibits significant sex-based differences in clinical presentation, management, and outcomes. This study aimed to evaluate these differences using data from the Swedish Heart Failure Registry (SwedeHF). We analyzed 65,605 patients with HFrEF (EF <40%) from the SwedeHF registry. Baseline characteristics, treatment patterns, and outcomes were compared between females and males. Multivariable logistic regression was used to evaluate predictors of treatment use. Cox proportional hazards models were used to assess the risk of cardiovascular mortality and heart failure (HF) hospitalization, adjusting for demographic and clinical variables. Odds ratios (OR) were reported for treatment use, and hazard ratios (HR) were used for outcome analyses. Females (29.0%) were older than males and had a higher prevalence of hypertension (61.3% *vs* 49.8%) and valvular disease (17.2% *vs* 11.1%), while males had a higher prevalence of ischemic heart disease (70.5% *vs* 40.1%) and diabetes (31.6% *vs* 28.4%). Males were less likely to receive beta-blockers (OR: 0.76, 95% CI 0.71-0.81), and more likely to receive sodium-glucose co-transporter-2 inhibitors (OR: 1.27, 95% CI 1.17-1.38) and implantable cardioverter-defibrillators/cardiac resynchronization therapy (OR: 1.41, 95% CI 1.30-1.52). During a median follow-up of 2.1 years, males had a higher adjusted risk of the composite outcome of cardiovascular death or HF hospitalization (HR: 1.19, 95% CI 1.16-1.22), cardiovascular death (HR: 1.33, 95% CI 1.28-1.37), and HF hospitalization (HR: 1.16, 95% CI 1.12-1.19). In this large cohort of patients with HFrEF, males had worse outcomes across all major cardiovascular endpoints. These findings highlight the need for tailored strategies to address sex-based disparities in HF management and improve outcomes for both sexes.

Introduction

Heart failure (HF) is a complex clinical syndrome associated with high morbidity, mortality, and healthcare utilization worldwide. It is estimated that approximately 64 million individuals are affected globally, making HF a growing public health concern.[1] Despite the availability of guideline-directed medical therapies (GDMT) and device-based interventions, outcomes remain suboptimal, particularly for patients with heart failure with reduced ejection fraction (HFrEF), who have a 5-year mortality rate comparable to many cancers.[2] Emerging evidence has highlighted significant sex-based differences in the clinical presentation, management, and outcomes of HF patients, particularly those with HFrEF.[3-5] However, these disparities are not fully understood, and their implications for optimizing HF management warrant further investigation.

Historically, women have been underrepresented in major HF clinical trials, leading to a predominance of treatment guidelines based on data derived primarily from male patients.[4,6,7] As a result, there is a paucity of sex-specific evidence to guide management in women with HFrEF. Current literature suggests that women with HFrEF are less likely to receive GDMT, including angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (MRAs), and are less frequently referred for device therapies such as implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT).[8,9] This underutilization of therapies in women persists despite their demonstrated benefits across sex groups.[5,10]

Several studies have reported better survival in women compared with men with HFrEF, even though women typically present at a more advanced stage of disease and have a higher prevalence of comorbidities such as hypertension and atrial fibrillation.[10,11] The reasons for this paradoxical survival advantage remain unclear but may involve differences in myocardial remodeling, hormonal influences, and sex-specific pathophysiology.[12] Conversely, men are more likely to have ischemic heart disease as the etiology of HF, which is associated with worse outcomes.[13,14] Understanding these sex-specific differences is critical for the development of tailored treatment strategies that can improve outcomes for both men and women with HF.

The Swedish Heart Failure Registry (SwedeHF) offers a unique opportunity to examine sex-based differences in HF management and outcomes in a real-world population. SwedeHF is one of the largest national HF registries globally, encompassing detailed clinical, demographic, and socioeconomic data from a broad spectrum of healthcare settings. Using this rich dataset, we sought to investigate the baseline characteristics, treatment patterns, and outcomes of male and female patients with HFrEF in Sweden. Specifically, we aimed to identify predictors of sex-based treatment disparities and assess the impact of these disparities on the risk of cardiovascular death and HF hospitalization.

Methods

Study protocol and setting

The study population was selected from the Swedish HF Registry (SwedeHF). SwedeHF has been previously described.[15] Briefly, it is an ongoing voluntary health care quality registry founded in 2000 and implemented on a national basis in 2003. Written consent is not required, but patients are informed of registration and allowed to opt out. A majority of Swedish hospitals (69 out of 76 hospitals) and to a minor extent also primary care centres enroll patients without financial compensation, and collect approximately 80 variables, i.e. data on demographics, comorbidities, clinical parameters, biomarkers, treatments and organizational aspects, from adult inpatient wards and outpatient clinics (www.swedehf.se). The inclusion criterion was

clinician-judged HF until April 2017, and after that a diagnosis of HF according to the following International Statistical Classification of Diseases, 10th revision (ICD-10) codes: I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0 and I13.2. Coverage of SwedeHF in 2022 was 32% of the prevalent HF population in Sweden. Linkage between SwedeHF and Statistics Sweden allowed to consider socioeconomic data, whereas the National Patient Registry provided additional data on comorbidities, the Cause of Death Registry provided the date of death. Linkage between these registries was allowed by the personal identification number, which all residents in Sweden have.

Establishment of the HF registry and this analysis including the linkage across several registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki.

Patients

Patients registered in SwedeHF were considered if outpatients or discharged alive from the hospital (i.e., inpatients) between May 11, 2000, and December 31, 2023, without missing data for EF, an EF<40% and with follow-up ≥1 day. The index date was defined as the date of registration in SwedeHF, i.e. the date of the outpatient visits for outpatients and the date of discharge for inpatients. When a patient reported when a patient reported multiple registrations, the first one was selected. The end of follow-up was December 31, 2023.

Statistical analysis

Baseline characteristics

Baseline characteristics in females were compared with those of males by using Wilcoxon-Mann-Whitney U-tests for continuous variables and chi-square test for categorical variables.

Use of treatments in females vs males

Multivariable logistic regression analyses were performed to calculate the adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for the use of HF treatments in females *versus* those in males.

Prognosis in females vs males

Primary outcome was time to cardiovascular death or HF hospitalization (composite). Secondary outcomes were time to cardiovascular death and time to first HF hospitalization. Univariable and multivariable Cox regression models were fitted to calculate the adjusted proportional hazard ratios (HRs) with 95% CI. Multivariable Cox regression models were used to investigate the independent predictors of the primary outcome occurrence in females *vs* those in males. Because of the large sample size and the fact that the different predictors of prognosis in females *vs* males are unknown, all potential prognostic predictors were tested.

In all multivariable models, missing data in baseline characteristics were handled by chained equation multiple imputation (10 datasets generated). A p-value <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using R.

Results

Baseline characteristics

The final cohort consisted of 65,605 patients with heart failure with reduced ejection fraction, of whom 19,029 (29.0%) were female and 46,576 (71.0%) were male. As shown in Table 1, the median age of the cohort was 73.0 years [IQR: 64.0–81.0], with females being significantly older than males (median 76.0 years [IQR: 67.0–82.0] *vs* 72.0 years [IQR: 63.0–80.0]). Females had a higher prevalence of hypertension (62.0% *vs* 60.0%), valvular heart disease (24.6% *vs* 22.2%), and anemia (26.3% *vs* 31.7%). In contrast, males had a higher prevalence of ischemic heart disease (55.0% *vs* 46.9%) and diabetes (26.7% *vs* 23.5%). Additional differences in comorbidities were observed, with higher rates of atrial fibrillation in males (53.7% *vs* 46.9%) and chronic kidney disease in females (43.6% *vs* 33.5%), whereas males were more frequently smokers (13.6% *vs* 12.5%).

Clinical characteristics also varied between sexes. Females were more likely to have higher systolic blood pressure (median value 123 mmHg vs. 120 mmHg) and higher NT-proBNP levels (median value 2900 pg/L *vs* 2344.50 pg/L). Medication use at baseline indicated that females were more often treated with digoxin (13.5% *vs* 12.1%) and loop diuretics (71.9% *vs* 68.3%), whereas males had higher utilization of renin-angiotensin system inhibitors (RASi) or angiotensin receptor-neprilysin inhibitors (ARNi) (92.3% *vs* 90.4%) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) (63.6% *vs* 58.2%). Moreover, device-based therapies such as cardiac resynchronization therapy or implantable cardioverter-defibrillators were significantly less common in females compared to males (5.4% *vs* 9.7%).

Predictors of treatment use

Table 2 presents the results of the multivariable logistic regression models evaluating sex differences in the use of heart failure therapies after adjusting for baseline characteristics. The findings reveal notable sex disparities in the prescription of several key therapies. Males were significantly more likely to receive SGLT2 inhibitors (adjusted odds ratio [OR]: 1.27, 95% confidence interval [CI]: 1.17-1.38) and device-based therapies such as ICDs or CRT (adjusted OR: 1.41, 95% CI: 1.30-1.52).

Conversely, females were more likely to be prescribed beta-blockers (adjusted OR: 0.76, 95% CI: 0.71-0.81) and digoxin (adjusted OR: 0.74, 95% CI: 0.70-0.79). There was no significant difference between sexes in the use of RASi/ARNi (adjusted OR: 0.99, 95% CI: 0.92-1.06), MRAs (adjusted OR: 0.97, 95% CI: 0.93-1.01), loop diuretics (adjusted OR: 1.05, 95% CI: 0.99-1.11), or nitrates (adjusted OR: 0.94, 95% CI: 0.88-1.01).

Table 1. Baseline characteristics of the enrolled population.

Variable	Overall (n=65605)	Female (n=19029, 29.0%)	Male (n=46576, 71.0%)	*p*-value	Missing %
Demographics/organizational					
Age[*,#] (years), median [IQR]	73.00 [64.00, 81.00]	76.00 [67.00, 82.00]	72.00 [63.00, 80.00]	<0.001	0.0
Location,[*,#] inpatient (%)	36.4	39.5	35.1	<0.001	0.0
Follow-up location,[*,#] speciality (%)	79.2	73.9	81.4	<0.001	3.4
Clinical					
HF duration ≥6 months[*,#] (%)	43.6	40.3	45.0	<0.001	1.9
NYHA class III-IV[*,#] (%)	41.7	45.5	40.3	<0.001	22.9
BMI (kg/m^2), median [IQR]	26.30 [23.40, 29.90]	25.70 [22.30, 29.90]	26.40 [23.70, 29.90]	<0.001	28.6
Obesity[*,#b] (BMI ≥30 kg/m^2) (%)	24.7	24.8	24.6	0.799	28.6
SBP (mmHg), median [IQR]	120.00 [110.00, 138.00]	123.00 [110.00, 140.00]	120.00 [110.00, 136.00]	<0.001	1.9
DBP (mmHg), median [IQR]	72.00 [65.00, 80.00]	70.00 [65.00, 80.00]	73.00 [65.00, 80.00]	<0.001	1.8
MAP[*,#] (mmHg), median [IQR]	90.00 [81.33, 99.00]	90.00 [80.33, 98.67]	90.00 [81.67, 99.00]	0.019	1.8
Heart rate[*,#] (bpm), median [IQR]	72.00 [63.00, 83.00]	74.00 [64.00, 85.00]	72.00 [62.00, 82.00]	<0.001	4.0
Laboratory					
eGFR (mL/min/1.93 m^2), median [IQR]	69.35 [51.33, 87.41]	64.20 [47.15, 82.93]	71.54 [53.46, 88.82]	<0.001	1.5
CKD[*,#] (<60 mL/min/1.93 m^2) (%)	36.4	43.6	33.5	<0.001	1.5
Potassium[*,#] (mEq/L), median [IQR]	4.20 [3.90, 4.50]	4.20 [3.90, 4.50]	4.20 [4.00, 4.50]	<0.001	17.3
NT-proBNP[*,#] (pg/L), median [IQR]	2494.00 [1054.00, 5665.00]	2900.00 [1220.00, 6491.00]	2344.50 [999.00, 5320.00]	<0.001	39.4
Treatments (%)					
RASi/ARNi[*,#]	91.8	90.4	92.3	<0.001	0.9
Beta-blocker[*,#a]	92.0	92.4	91.8	0.009	0.2
MRA[*,#]	43.6	42.2	44.1	<0.001	0.5
SGLT2i[*,#]	62.1	58.2	63.6	<0.001	82.6
Digoxin[*,#]	12.5	13.5	12.1	<0.001	0.3
Loop diuretics[*,#]	69.3	71.9	68.3	<0.001	27.5
Nitrates[*,#]	10.7	11.3	10.4	0.001	0.4
Anticoagulants[*,#]	46.5	41.0	48.7	<0.001	0.3
Antiplatelets[*,#]	41.7	41.1	41.9	0.076	0.4
Statins[*,#]	50.8	43.5	53.8	<0.001	0.3
Devices CRT/ICD[*,#]	8.5	5.4	9.7	<0.001	0.9
Comorbidities (%)					
Current smoker[*,#]	13.3	12.5	13.6	0.001	20.1
Hypertension[*,#]	60.6	62.0	60.0	<0.001	0.0
Diabetes[*,#]	25.8	23.5	26.7	<0.001	0.0
Ischemic heart disease[*,#]	52.6	46.9	55.0	<0.001	0.0
Peripheral artery disease[*,#]	8.5	6.9	9.1	<0.001	0.0
Stroke/TIA[*,#]	14.9	13.7	15.4	<0.001	0.0
Atrial fibrillation[*,#]	51.7	46.9	53.7	<0.001	0.0
Anemia[*,#]	30.1	26.3	31.7	<0.001	5.5
Valvular disease[*,#]	22.9	24.6	22.2	<0.001	0.0
COPD[*,#]	11.2	12.8	10.6	<0.001	0.0
Cancer within the last 3 years[*,#]	11.7	10.0	12.4	<0.001	0.0
Dementia[*,#]	1.3	1.7	1.2	<0.001	0.0
Socioeconomical (%)					
Family type, living alone[*,#]	45.9	56.8	41.4	<0.001	0.2
Education level[*,#]				<0.001	1.8
Compulsory school	39.8	42.6	38.6		
Secondary school	41.7	40.3	42.3		
University	18.5	17.1	19.0		
Income below the median[*,#]	49.9	65.8	43.4	<0.001	0.2
Child[*,#]	82.3	86.4	80.7	<0.001	0.0

*Variables included in the multiple imputation together with the index year and the primary outcome of cardiovascular mortality/hospitalization for heart failure as Nelson-Aelen estimator; #variables included in the logistic regression model and Cox proportional hazard model together with the index year; ARNi, angiotensin-receptor blocker-neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitors; SBP, systolic blood pressure; SGLT2i, inhibitors of the sodium-glucose co-transporter.

Table 2. Likelihood of heart failure treatment use with sex in the logistic regression model.

Treatment	Odds ratio (95% CI) male *vs* female
RASi/ARNi	0.99 (0.92-1.06)
Beta-blocker	0.76 (0.71-0.81)
MRA	0.97 (0.93-1.01)
SGLT2i	1.27 (1.17-1.38)
Loop diuretics	1.05 (0.99-1.11)
Digoxin	0.74 (0.70-0.79)
Nitrates	0.94 (0.88-1.01)
ICD/CRT	1.41 (1.30-1.52)

ARNi, angiotensin-receptor blocker-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitors; SGLT2i, inhibitors of the sodium-glucose co-transporter type II.

Outcome analysis

During a median follow-up of 2.1 years [IQR: 0.6-5.2], a total of 34,042 patients experienced the primary composite outcome of cardiovascular death or HF hospitalization (Table 3). The composite outcome occurred in 51.1% of females (n=9,720) and 52.2% of males (n=24,322). The unadjusted event rate for the composite outcome was similar between the sexes, with 14.48 events per 100 patient-years in females compared with 14.89 events per 100 patient-years in males. After adjustment for baseline characteristics, males had a significantly higher risk for the composite outcome compared with females (adjusted hazard ratio [HR]: 1.19, 95% confidence interval [CI]: 1.16-1.22) (Figure 1).

Table 3. Cox proportional hazard models for the evaluated outcomes

Outcome	Females		Males		HR (95% CI) unadjusted males *vs* females	HR (95% CI) adjusted males *vs* females
	Event rate (n, %)	Event rate (per 100 patient-yrs)	Event rate (n, %)	Event rate (per 100 patient-yrs)		
Cardiovascular mortality/HHF	9720 (51.1)	14.48 (14.19-14.77)	24322 (52.2)	14.89 (14.70-15.08)	1.02 (1.00-1.05)	1.19 (1.16-1.22)
HHF	7170 (37.7)	10.68 (10.43-10.93)	18596 (39.9)	11.39 (11.22-11.55)	1.06 (1.03-1.09)	1.16 (1.12-1.19)
Cardiovascular mortality	6008 (31.6)	6.66 (6.49-6.82)	14788 (31.8)	6.59 (6.48-6.70)	0.99 (0.96-1.02)	1.33 (1.28-1.37)

CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio.

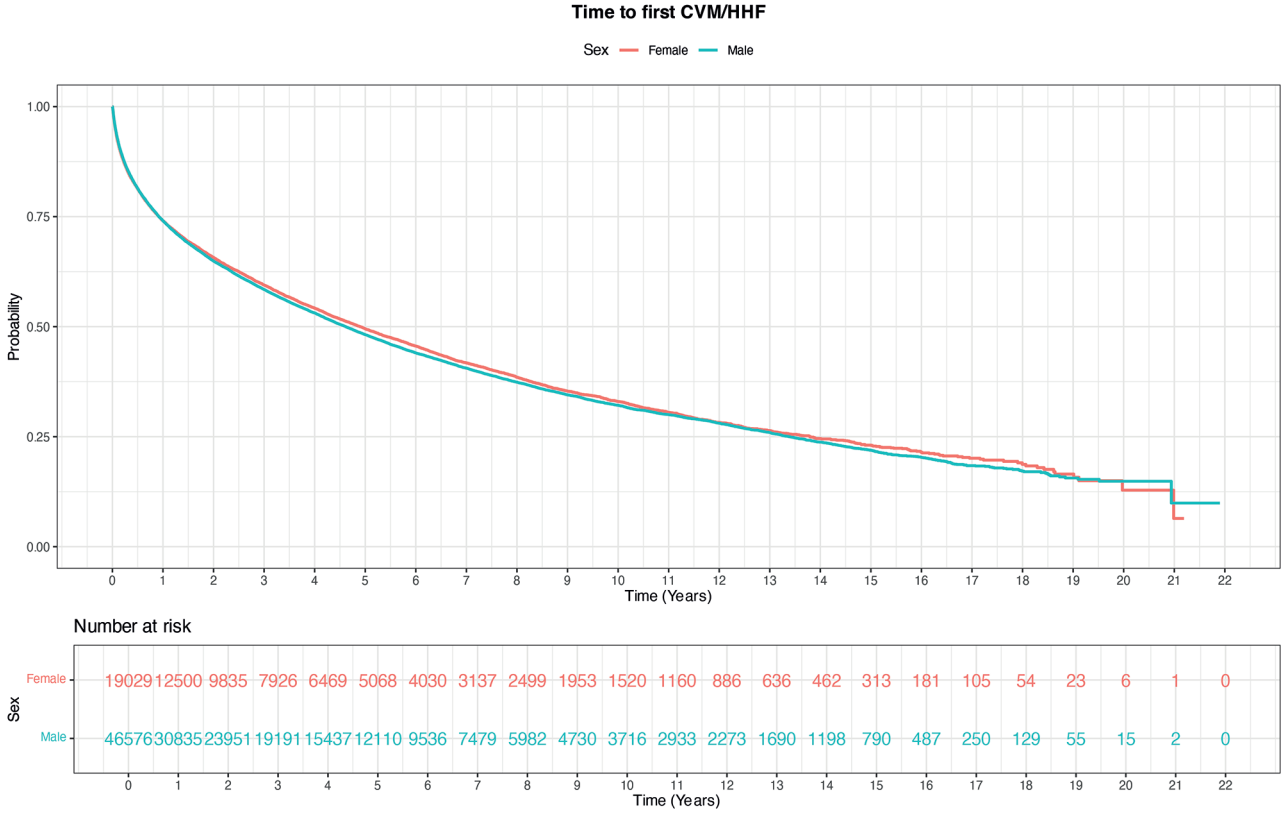

Figure 1. Kaplan Meier plot for the primary outcome of cardiovascular mortality of heart failure hospitalization stratified by sex. CVM, cardiovascular mortality; HHF, hospitalization for heart failure.

For HF hospitalization, 7,170 (37.7%) females and 18,596 (39.9%) males experienced an event. The unadjusted event rate was 10.68 events per 100 patient-years in females and 11.39 events per 100 patient-years in males. After multivariable adjustment, males had a significantly higher risk for HF hospitalization (adjusted HR: 1.16, 95% CI: 1.12-1.19).
Cardiovascular death occurred in 6,008 (31.6%) females and 14,788 (31.8%) males. The unadjusted event rate was 6.66 events per 100 patient-years in females compared with 6.59 events per 100 patient-years in males. However, after adjustment, males had a significantly higher risk of cardiovascular death (adjusted HR: 1.33, 95% CI: 1.28-1.37).

Discussion

Our analysis of 65,605 patients with HFrEF from the SwedeHF registry demonstrates substantial sex-based differences in clinical presentation, treatment patterns, and outcomes (graphical abstract). Females were older, had a higher burden of non-ischemic comorbidities, and presented with more severe symptoms, despite being underrepresented in the use of advanced therapeutic strategies such as implantable cardioverter-defibrillators and cardiac resynchronization therapy. These findings mirror those observed in other large registries and randomized controlled trials, including the CHARM,[14] MERIT-HF,[16] and CIBIS II studies,[17] where females with heart failure consistently show distinct clinical profiles compared with their male counterparts.

Sex differences in patient characteristics

The baseline characteristics of our study population reveal marked sex differences. Females had a higher prevalence of hypertension (62.0% *vs* 60.0%), valvular heart disease (24.6% *vs* 22.2%), and chronic kidney disease (43.6% *vs* 33.5%), whereas males were more likely to have ischemic heart disease (55.0% *vs* 46.9%), diabetes (26.7% *vs* 23.5%), and a history of smoking (13.6% *vs* 12.5%). These patterns are consistent with findings from the Global Congestive Heart Failure registry and the HF-ACTION trial,[3,18] which similarly demonstrated that ischemic heart disease is the dominant etiology in males, while females present more often with hypertension and non-ischemic etiologies.
Additionally, females in our cohort exhibited significantly higher NT-proBNP levels compared with males, indicating a greater degree of hemodynamic stress and elevated ventricular filling pressures (median: 2900 pg/L [IQR: 1220-6491] *vs* 2344.5 pg/L [IQR: 999-5320]). This may reflect sex-specific differences in cardiac adaptation to pressure and volume overload. Previous studies have suggested that females have heightened neurohormonal activation in response to myocardial stress, which could contribute to their more severe symptom burden and higher New York Heart Association (NYHA) class at presentation.[12] The combination of these factors likely contributes to the distinct clinical course observed in females, including a higher prevalence of symptoms such as dyspnea and fatigue, which may be underappreciated in routine clinical care.[6]

Sex differences in HF treatment

Our study adds to the growing body of evidence showing that females with HFrEF are less likely to receive certain guideline-directed medical therapies and device-based interventions compared to males. In our cohort, females were more likely to be prescribed beta-blockers compared to males (adjusted odds ratio: 0.76, 95% confidence interval: 0.71-0.81), while males were more likely to receive SGLT2 inhibitors (adjusted OR: 1.27, 95% CI: 1.17-1.38), even after adjustment for age, comorbidities, and other clinical characteristics. In contrast, there was no significant difference in the use of RASi/ARNi (adjusted OR: 0.99, 95% CI: 0.92-1.06) or MRAs (adjusted OR: 0.97, 95% CI: 0.93-1.01) between males and females. These findings are consistent with previous studies, which have reported that underutilization of certain GDMTs in females may be partly due to concerns about tolerability, higher rates of adverse drug reactions (ADRs), and perceived contraindications.[19]
Moreover, our results show that females were significantly less likely to receive ICDs or CRT compared to males, despite evidence supporting their benefit in both sexes. Specifically, males were 41% more likely to receive an ICD/CRT (adjusted OR: 1.41, 95% CI: 1.30-1.52), a finding that aligns with prior studies, including the FDA meta-analysis of CRT and ICD therapy in women.[9] Possible explanations for this include sex-based differences in arrhythmogenic risk, which might influence clinical decision-making, as well as greater concerns about procedural complications, which have been reported to be higher in females.[8] These disparities in device utilization suggest that even in contemporary practice, females may be under-treated with life-saving device therapies, underscoring the need for increased awareness and adherence to evidence-based guidelines for HF management in women. This is consistent with independent registry data demonstrating that structured HF specialist input, typically a multidisciplinary team of physicians and HF nurses, substantially increases GDMT uptake and translates into ~10% lower in-hospital and long-term mortality, even when healthcare systems are under stress, such as during the COVID-19 pandemic.[20,21]

Sex differences in outcomes

Despite the underuse of GDMT and device therapy, females in our study had a significantly lower risk of cardiovascular mortality compared to males. This paradoxical finding, where females have a worse clinical profile but better survival, has been observed in multiple heart failure studies, including the MAGGIC meta-analysis,[11] the BEST,[4] and CHARM trials.[4] In our cohort, the adjusted hazard ratio (HR) for cardiovascular death was 0.77, and for the composite outcome of cardiovascular death or heart failure hospitalization, the HR was 0.84, indi-

cating a consistent survival advantage in females.

Several potential mechanisms have been proposed to explain this phenomenon. One hypothesis is that females have a distinct myocardial remodeling pattern characterized by less fibrosis and preserved microvascular integrity, leading to a slower progression of heart failure and a lower incidence of sudden cardiac death.[12] Additionally, sex-specific variations in myocardial substrate and neurohormonal activation may result in a more favorable response to heart failure therapies, even when used at lower doses. For example, females may derive a greater benefit from beta-blockers and MRAs due to heightened sympathetic and renin-angiotensin-aldosterone system activity compared to males.[6]

Our findings indicate that males had a significantly higher risk for all outcomes compared to females. The adjusted hazard ratio for the primary composite outcome of cardiovascular death or heart failure hospitalization was 1.19 (95% CI: 1.16-1.22) for males, indicating a higher overall risk. Similarly, the adjusted hazard ratios for cardiovascular death and heart failure hospitalization were 1.33 (95% CI: 1.28-1.37) and 1.16 (95% CI: 1.12-1.19), respectively, reflecting a consistently greater risk in males. These results suggest that males with HFrEF experience a more aggressive disease course and are at a higher risk of adverse cardiovascular events compared to females, despite females presenting with a higher burden of comorbidities and symptom severity at baseline. This pattern is in line with dedicated dilated cardiomyopathy cohorts in which male sex confers higher rates of transplantation, malignant ventricular arrhythmia, and death, whereas females with non-ischemic dilated cardiomyopathy display a sustained survival advantage despite more advanced symptoms at presentation.[22,23]

Study limitations

Several limitations must be acknowledged. First, the observational design of our study precludes establishing causality between sex, treatment differences, and outcomes. Although we employed comprehensive multivariable adjustment and multiple imputation techniques to account for missing data, residual confounding cannot be completely ruled out. Second, the lack of information on patient-reported outcomes, quality of life, and adherence to prescribed therapies limits our ability to assess the impact of these factors on the observed sex differences. Third, device therapy decisions, such as ICD and CRT use, may have been influenced by factors not captured in the registry, such as frailty, patient preferences, and procedural risks. Finally, our analysis focused exclusively on patients with HFrEF (EF <40%) and may not be generalizable to those with heart failure with preserved or midrange ejection fraction, who represent a growing proportion of the heart failure population and may exhibit distinct sex-specific patterns. Finally, the first draft of this manuscript was entirely generated by a large language model (ChatGPT) (*Supplementary Material*). While such tools can efficiently synthesize existing evidence and generate coherent prose when provided with structured results tables, they may also introduce factual inaccuracies, biased phrasing, or erroneous citations; consequently, all AI-generated content was independently verified by the authors to ensure scientific accuracy and integrity, in line with emerging guidance on the responsible use of generative AI in cardiology research.[24]

Conclusions

In this large, national cohort of patients with HFrEF from the SwedeHF registry, we identified substantial sex-based differences in baseline characteristics, treatment utilization, and outcomes. Male patients received more device therapy yet experienced higher risks of cardiovascular death and heart-failure hospitalization; female patients, despite greater comorbidity and less advanced therapy, showed better survival. Future research should focus on elucidating the biological and clinical mechanisms contributing to these differences and on creating targeted strategies to close the sex-based treatment and outcome gaps in heart failure care.

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The first draft of this manuscript was entirely generated by ChatGPT 4o (OpenAI), which was provided with the aggregated results of statistical analyses and selected reference material for the discussion. The final version was reviewed and approved by the authors.

Conflict of interest

See Appendix.

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