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ARTICLE

Sex differences in clinical characteristics and outcomes in heart failure with mildly reduced and preserved ejection fraction

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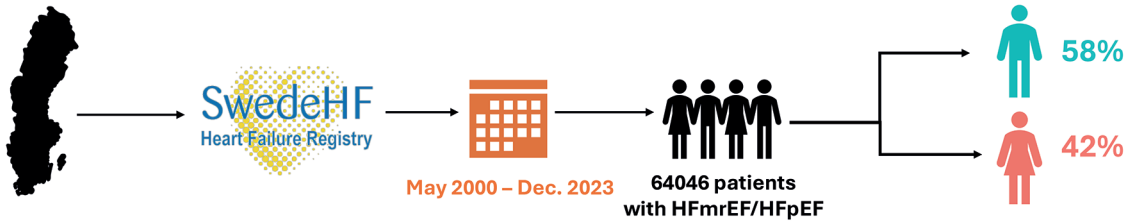
Graphical abstract

Sex-based differences in patients with heart failure and mildly reduced or preserved ejection fraction. CI, confidence interval; CKD, chronic kidney disease; CVM, cardiovascular mortality; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHF, heart failure hospitalization; HR, hazard ratio; SGLT2i, sodium glucose co-transporter type II inhibitor.



Men vs Women more likely:

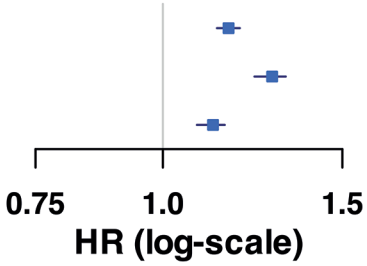
- Outpatients
- To have ischemic heart disease
- To have diabetes
- To be a smoker
- Treated with SGLT2i

Women vs Men more likely:

- Older
- To have CKD
- To have hypertension
- To have valvular heart disease
- To have higher natriuretic peptides
- Treated with beta-blockers
- Treated with digoxin
- Treated with loop diuretics
- Treated with nitrates

Higher adjusted risk in men vs women for all the evaluated outcomes

Outcome	HR (95% CI)
CVM/HHF	1.16 (1.13–1.19)
CVM	1.28 (1.23–1.32)
HHF	1.12 (1.08–1.15)



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

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Abstract

Heart failure with mildly reduced and preserved ejection fraction (HFmrEF and HFpEF) 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 64,046 patients with HFmrEF or HFpEF (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 guideline-directed medical therapy (GDMT) use as odds ratios (OR). Cox proportional hazards models were used to assess the risk of cardiovascular mortality and heart failure (HF) hospitalization as hazard ratios (HR), adjusting for demographic and clinical variables. Females (42.5%) were older than males (median age 79 years *vs* 75 years), had a higher prevalence of hypertension (73.8% *vs* 70.0%), and were more likely to present with severe symptoms (NYHA class III-IV: 36.8% *vs*. 28.8%). Males had a higher prevalence of ischemic heart disease (52.3% *vs* 42.9%) and diabetes (27.4% *vs* 23.8%). Females were significantly less likely to receive SGLT2 inhibitors (OR 1.24, 95% confidence interval [CI] 1.13-1.36), while males were less likely to receive beta-blockers, digoxin, nitrates, and loop diuretics. During a median follow-up of 2.3 years, males had a higher adjusted risk of the composite outcome of cardiovascular mortality or HF hospitalization (HR 1.16, 95% CI 1.13-1.19), as well as higher risks for cardiovascular mortality (HR 1.28, 95% CI 1.23-1.32) and HF hospitalization (HR 1.12, 95% CI 1.08-1.15). Females with HFmrEF and HFpEF in the SwedeHF registry had a distinct clinical profile, were less likely to receive certain GDMTs, yet exhibited a lower risk of cardiovascular mortality compared to males. These findings underscore the importance of targeted strategies to optimize HF care for females.

Introduction

Heart failure (HF) is a complex clinical syndrome associated with high morbidity, mortality, and healthcare costs worldwide. Approximately 64 million individuals are affected globally, making HF a growing public health concern.[1] The spectrum of HF is often divided into three categories based on ejection fraction (EF): heart failure with reduced ejection fraction (HFrEF, EF≤40%), heart failure with preserved ejection fraction (HFpEF, EF≥50), and the intermediate category, heart failure with mildly reduced ejection fraction (HFmrEF, EF 41-49%).[2] Unlike HFrEF, where therapeutic strategies are well established, patients with HFmrEF and HFpEF have been less extensively studied, and there is a lack of robust evidence guiding their treatment.[2]

The prevalence of HFpEF is notably higher in females, and sex-based differences have been reported in disease characteristics, response to treatment, and outcomes among these patients.[3-5] Despite being older and having more comorbidities, females with HFpEF often have a lower risk of cardiovascular mortality but similar or even higher rates of HF hospitalization compared with males.[3] The underlying mechanisms for these differences are not fully understood but may include distinct patterns of cardiac remodeling, inflammation, and diastolic dysfunction, as well as sex-specific variations in myocardial and vascular biology.[6-8]

Sex differences in the management of HFmrEF and HFpEF have also been observed, with females less likely to receive evidence-based therapies such as renin-angiotensin-aldosterone system inhibitors (RASi), beta-blockers, and device therapies compared to males.[9,10] This underutilization of guideline-directed medical therapy (GDMT) may partly explain the poorer prognosis observed in females with HFpEF.[3]

The Swedish Heart Failure Registry (SwedeHF), a nationwide registry, offers a unique opportunity to explore sex-based differences in clinical presentation, treatment patterns, and outcomes in patients with HFmrEF and HFpEF.

The aim of the present study was to investigate sex-based differences in baseline characteristics, treatment utilization, and outcomes in a large cohort of patients with HFmrEF and HFpEF using the SwedeHF registry. Specifically, we sought to determine whether sex disparities exist in the prescription of HF therapies and how these disparities impact the risk of cardiovascular mortality and HF hospitalization. Understanding these differences is crucial for developing tailored therapeutic approaches that optimize care for both sexes.

Methods

Study protocol and setting

The study population was selected from the Swedish Heart Failure Registry (SwedeHF), an ongoing voluntary healthcare quality registry that was founded in 2000 and implemented nationally in 2003. The registry captures data on a broad range of variables, including demographics, comorbidities, clinical parameters, biomarkers, and treatment strategies from inpatient wards and outpatient clinics across Sweden. Written consent is not required for registry participation, but patients are informed about their inclusion and are allowed to opt out. In 2022, SwedeHF captured approximately 32% of the prevalent HF population in Sweden.

Patients

We included all patients registered in SwedeHF between May 11, 2000, and December 31, 2023, who had a docu-

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mented EF of 40% or greater, indicating HFmrEF (40-49%) or HFpEF (≥50%). Patients with missing EF data were excluded, and for those with multiple registrations, only the first encounter was considered. The final study population consisted of patients with a minimum follow-up of one day, with the index date defined as the date of registration in SwedeHF. The end of follow-up was December 31, 2023.

Statistical analysis

Baseline characteristics were summarized using medians and interquartile ranges (IQR) for continuous variables and percentages for categorical variables. Differences between females and males were assessed using the Wilcoxon-Mann-Whitney U-test for continuous variables and the chi-square test for categorical variables.

To evaluate sex differences in the use of HF therapies, multivariable logistic regression models were constructed, adjusting for age, comorbidities, and other clinical characteristics. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs).

For outcomes analysis, the primary endpoint was time to cardiovascular death or HF hospitalization (composite outcome), while secondary endpoints were cardiovascular death and HF hospitalization. Univariable and multivariable Cox proportional hazards models were used to estimate the hazard ratios (HRs) with 95% CIs for each outcome, comparing males and females. A p-value <0.05 was considered statistically significant for all analyses. All statistical analyses were performed using R software.

Results

Baseline characteristics

The study cohort included 64,046 patients with HFmrEF or HFpEF, of whom 27,189 (42.5%) were female and 36,857 (57.5%) were male. The median age of the cohort was 77 years [IQR: 68-83], with females being significantly older than males (79 years [IQR: 72-85] *vs* 75 years [IQR: 66-81]). Females were more likely to be hospitalized at the time of registration (42.7% *vs* 31.0%) and had a higher prevalence of comorbidities such as hypertension (73.8% *vs* 70.0%), valvular heart disease (30.6% *vs* 26.9%), and chronic kidney disease (48.0% *vs* 35.3%). Conversely, males had higher rates of ischemic heart disease (52.3% *vs* 42.9%), diabetes (27.4% *vs* 23.8%), and a history of smoking (9.9% *vs* 8.8%).

Regarding medication use, females were less likely to receive RASi/angiotensin receptor-neprilysin inhibitor (ARNi) (77.0% *vs* 83.5%), SGLT2 inhibitors (40.8% *vs* 48.9%), and anticoagulants (47.4% *vs* 50.9%), but more frequently received digoxin (14.3 *vs* 9.2%) and loop diuretics (71.8% *vs* 62.7%). Baseline differences in comorbidities and treatment utilization between sexes highlight distinct clinical profiles in HFmrEF and HFpEF patients (Table 1).

Predictors of treatment use

Table 2 summarizes the results of the logistic regression models evaluating sex differences in the use of HF therapies. Males were significantly more likely to receive SGLT2 inhibitors (adjusted OR: 1.24, 95% CI: 1.13-1.36) compared with females. In contrast, males were significantly less likely to be prescribed beta-blockers (adjusted OR: 0.73, 95% CI: 0.69-0.77), digoxin (adjusted OR: 0.63, 95% CI: 0.59-0.66), loop diuretics (adjusted OR: 0.92, 95% CI: 0.87-0.97), and nitrates (adjusted OR: 0.90, 95% CI: 0.84-0.95). No significant differences were observed for the use of RASi/ARNi or MRAs between the sexes. These results highlight a distinct pattern of therapeutic use between males and females in this cohort of HFmrEF and HFpEF patients.

Outcome analysis

During a median follow-up of 2.3 years [IQR: 0.8-5.0], a total of 28,401 patients (44.4%) experienced the primary composite outcome of cardiovascular mortality or HF hospitalization. Females had a higher unadjusted event rate for the composite outcome (14.15 per 100 patient-years) compared with males (11.64 per 100 patient-years) (Figure 1). However, after multivariable adjustment, males had a significantly higher risk of the composite outcome (HR: 1.16, 95% CI: 1.13-1.19). Similarly, the adjusted HRs for cardiovascular mortality (HR: 1.28, 95% CI: 1.23-1.32) and HF hospitalization (HR: 1.12, 95% CI: 1.08-1.15) indicated a higher risk in males compared with females (Table 3). These findings suggest that after accounting for a comprehensive set of clinical variables, males have a consistently higher risk of adverse outcomes compared to females in this cohort of HFmrEF and HFpEF patients.

Discussion

The findings from this large, national cohort of HFmrEF and HFpEF patients from the SwedeHF registry demonstrate substantial sex-based differences in clinical presentation, treatment patterns, and outcomes. Despite being older and having a higher burden of comorbidities, females were less likely to receive GDMT and device interventions. Yet, after adjusting for these differences, males had a significantly higher risk of cardiovascular death and HF hospitalization. These results underscore the need for targeted therapeutic strategies that consider sex-specific differences in HFmrEF and HFpEF management.

Our results are consistent with prior studies reporting that males tend to have a worse prognosis in HFpEF despite similar or lower event rates.[4,11] Further research is warranted to elucidate the mechanisms driving these disparities and to optimize care for both sexes.

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Table 1. Baseline characteristics of the enrolled population.

Variable	Overall (n=64046)	Female (n=27189, 42.4%)	Male (n=36857, 57.6%)	*p*-value	Missing %
Demographics/organizational					
Age[*,#] (years), median [IQR]	77.00 [68.00, 83.00]	79.00 [72.00, 85.00]	75.00 [66.00, 81.00]	<0.001	0.0
Location,[*,#] inpatient (%)	36.0	42.7	31.0	<0.001	0.0
Follow-up location,[*,#] speciality (%)	61.2	54.0	66.5	<0.001	4.6
Clinical					
EF category, HFpEF (%)	46.8	55.6	40.2	<0.001	0.0
HF duration ≥6 months[*,#] (%)	54.0	52.4	55.2	<0.001	3.0
NYHA class III-IV[*,#] (%)	32.0	36.8	28.8	<0.001	30.0
BMI (kg/m^2), median [IQR]	27.00 [23.80, 30.90]	26.80 [23.10, 31.20]	27.10 [24.20, 30.70]	<0.001	33.2
Obesity[*,#b] (BMI ≥30 kg/m^2) (%)	30.1	31.0	29.4	<0.001	33.1
S. BP (mmHg), median [IQR]	130.00 [116.00, 142.00]	130.00 [118.00, 145.00]	130.00 [115.00, 140.00]	<0.001	3.4
DBP (mmHg), median [IQR]	73.00 [65.00, 80.00]	72.00 [65.00, 80.00]	75.00 [66.00, 80.00]	<0.001	3.4
MAP[*,#] (mmHg), median [IQR]	92.67 [83.33, 100.00]	92.67 [83.33, 100.33]	92.67 [83.33, 100.00]	0.855	3.4
Heart rate[*,#] (bpm), median [IQR]	70.00 [62.00, 80.00]	72.00 [64.00, 83.00]	70.00 [60.00, 80.00]	<0.001	5.9
Laboratory					
eGFR (mL/min/1.93 m^2), median [IQR]	66.41 [48.82, 85.03]	61.31 [44.98, 79.50]	70.35 [52.36, 87.83]	<0.001	3.0
CKD[*,#] (<60 mL/min/1.93 m^2) (%)	40.7	48.0	35.3	<0.001	3.0
Potassium[*,#] (mEq/L), median [IQR]	4.20 [3.90, 4.50]	4.10 [3.80, 4.40]	4.20 [3.90, 4.50]	<0.001	16.3
NT-proBNP[*,#] (pg/L), median [IQR]	1519.00 [582.00, 3369.00]	1757.50 [699.25, 3802.00]	1370.00 [515.00, 3084.00]	<0.001	37.3
Treatments (%)					
RASi/ARNi[*,#]	80.7	77.0	83.5	<0.001	0.8
Beta-blocker[*,#a]	85.0	85.1	84.9	0.488	0.3
MRA[*,#]	35.2	33.6	36.4	<0.001	0.5
SGLT2i[*,#]	45.8	40.8	48.9	<0.001	79.6
Digoxin[*,#]	11.4	14.3	9.2	<0.001	0.3
Loop diuretics[*,#]	66.5	71.8	62.7	<0.001	22.9
Nitrates[*,#]	11.7	12.8	10.8	<0.001	0.4
Anticoagulants[*,#]	49.4	47.4	50.9	<0.001	0.3
Antiplatelets[*,#]	35.6	33.7	36.9	<0.001	0.4
Statins[*,#]	48.1	40.2	53.9	<0.001	0.3
Devices CRT/ICD[*,#]	4.2	2.6	5.4	<0.001	1.6
Comorbidities (%)					
Current smoker[*,#]	9.5	8.8	9.9	<0.001	27.1
Hypertension[*,#]	71.6	73.8	70.0	<0.001	0.0
Diabetes[*,#]	25.9	23.8	27.4	<0.001	0.0
Ischemic heart disease[*,#]	48.3	42.9	52.3	<0.001	0.0
Peripheral artery disease[*,#]	8.8	7.5	9.8	<0.001	0.0
Stroke/TIA[*,#]	16.0	16.0	15.9	0.780	0.0
Atrial fibrillation[*,#]	59.3	58.7	59.8	0.003	0.0
Anemia[*,#]	35.6	32.0	38.2	<0.001	7.8
Valvular disease[*,#]	28.4	30.6	26.9	<0.001	0.0
COPD[*,#]	13.4	14.6	12.5	<0.001	0.0
Cancer within the last 3 years[*,#]	13.6	11.6	15.0	<0.001	0.0
Dementia[*,#]	1.5	1.8	1.3	<0.001	0.0
Socioeconomical (%)					
Family type, living alone[*,#]	48.8	61.2	39.6	<0.001	0.1
Education level[*,#]				<0.001	1.9
Compulsory school	40.9	44.8	38.0		
Secondary school	39.9	37.4	41.6		
University	19.2	17.8	20.3		
Income below the median[*,#]	50.0	65.8	38.4	<0.001	0.1
Child[*,#]	84.6	86.9	82.9	<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 type II.

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Sex differences in patient characteristics

The observed sex differences in clinical characteristics highlight distinct phenotypes of HFmrEF and HFpEF between females and males. Females were significantly older and had a higher prevalence of non-ischemic comorbidities such as hypertension, chronic kidney disease, and valvular heart disease. In contrast, males presented with a higher prevalence of ischemic heart disease, diabetes, and smoking history. These findings are consistent with previous studies, including the Global Congestive Heart Failure registry and the HF-ACTION trial, which reported similar sex-related disparities in comorbidity profiles.[12,13] Additionally, the higher NT-proBNP levels observed in females suggest greater hemodynamic stress and volume overload compared with males, which may contribute to their increased symptom burden and higher New York Heart Association (NYHA) functional class at presentation.[3]

Sex-based differences in HF pathophysiology may play a role in shaping these phenotypic differences. For example, females are more likely to develop HFpEF due to a combination of fac-

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	1.03 (0.98-1.08)
Beta-blocker	0.73 (0.69-0.77)
MRA	1.02 (0.98-1.06)
SGLT2i	1.24 (1.13-1.36)
Loop diuretics	0.92 (0.87-0.97)
Digoxin	0.63 (0.59-0.66)
Nitrates	0.90 (0.84-0.95)

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.

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	13,065 (48.1)	14.15 (13.91-14.40)	15336 (41.6)	11.64 (11.46-11.83)	0.83 (0.81-0.85)	1.16 (1.13-1.19)
HHF	9085 (33.4)	9.84 (9.64-10.04)	11030 (29.9)	8.37 (8.22-8.53)	0.86 (0.84-0.88)	1.12 (1.08-1.15)
Cardiovascular mortality	8603 (31.6)	7.50 (7.35-7.66)	9512 (25.8)	6.00 (5.88-6.12)	0.80 (0.78-0.82)	1.28 (1.23-1.32)

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

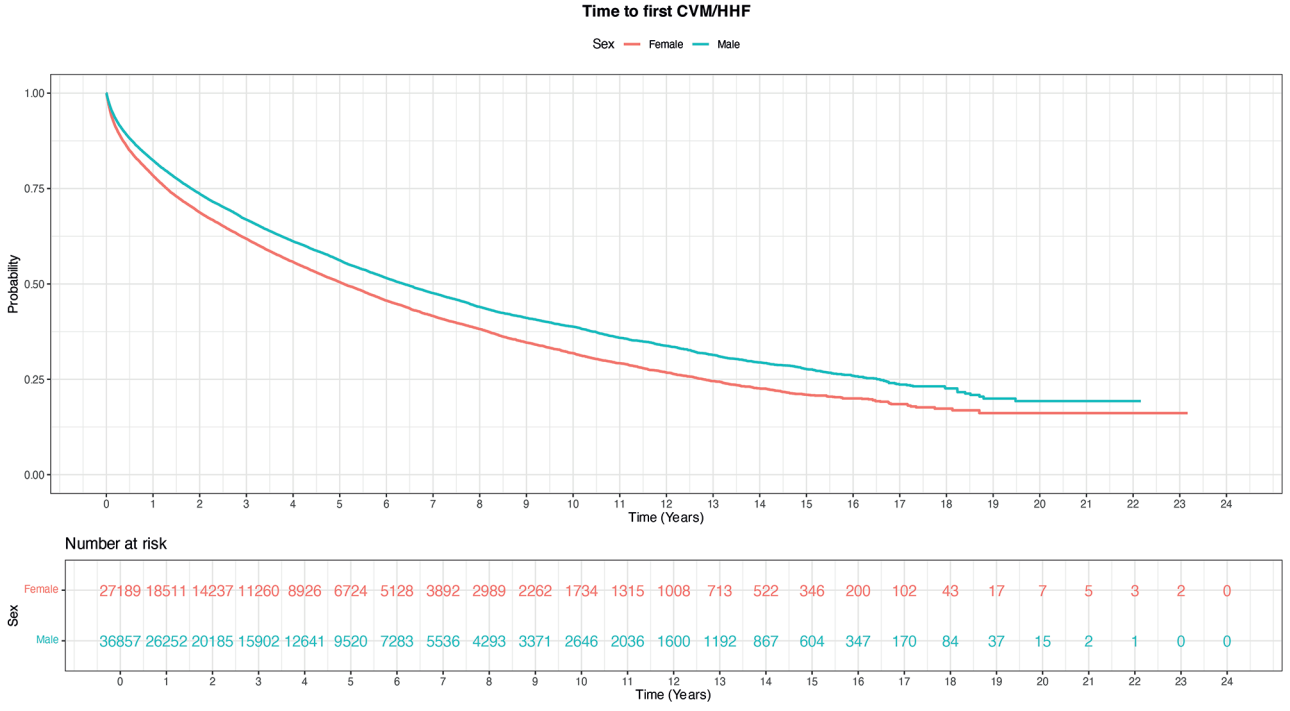

Figure 1. Kaplan Meier plot for the primary outcome of cardiovascular mortality of heart failure hospitalization stratified by sex. CVM, cardiovascular mortality; HHF, hospitalization for heart failure.

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tors such as obesity, diastolic dysfunction, and increased arterial stiffness.[4] The heightened neurohormonal activation and inflammatory state observed in females with HF may also contribute to their distinct clinical profile.[7] These differences underscore the importance of considering sex-specific factors when evaluating and managing patients with HFmrEF and HFpEF.

Sex differences in HF treatment

Our study adds to the growing body of evidence showing that females with HF are less likely to receive guideline-directed medical therapies and device-based interventions compared with males. In our cohort, males were significantly more likely to receive SGLT2 inhibitors (OR: 1.24, 95% CI: 1.13-1.36), while females were more likely to be treated with beta-blockers (OR: 0.73, 95% CI: 0.69-0.77), digoxin (OR: 0.63, 95% CI: 0.59-0.66), nitrates (OR: 0.90, 95% CI: 0.84-0.95), and loop diuretics (OR: 0.92, 95% CI: 0.87-0.97). No significant sex differences were observed in the use of RASi/ARNi or MRAs after adjusting for baseline characteristics. These disparities persist despite adjustment for a comprehensive set of variables, suggesting that factors beyond clinical eligibility may influence treatment decisions. Importantly, contemporary nationwide analyses demonstrate that enrollment in dedicated HF-specialist programs, irrespective of EF, improves the prescription of quadruple GDMT and confers ~10-15% relative reductions in both in-hospital and long-term mortality.[14,15]

The underuse of SGLT2 inhibitors and other evidence-based therapies in females has been attributed to concerns about tolerability, increased risk of adverse drug reactions, and perceived contraindications.[16] Additionally, historical underrepresentation of females in HF trials has resulted in a lack of sex-specific data, which may contribute to a more conservative treatment approach in clinical practice.[8] Moreover, our findings that males were more likely to receive SGLT2 inhibitors suggest that females may be under-treated for HFmrEF and HFpEF, a gap that needs to be addressed to optimize treatment outcomes for both sexes.

Sex differences in outcomes

Consistent with previous studies, males in our cohort had a higher adjusted risk of cardiovascular mortality and HF hospitalization compared with females (HR: 1.28 and HR: 1.12, respectively). This finding is in line with reports from large observational studies and clinical trials, including the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) program and the MAGGIC meta-analysis, which showed that females with HFmrEF and HFpEF generally have a better prognosis than males.[17,18]

Several hypotheses have been proposed to explain the survival advantage in females. One theory is that females have a distinct myocardial remodeling pattern characterized by less fibrosis and preserved microvascular integrity, leading to slower HF progression and a lower incidence of adverse outcomes.[6] Additionally, sex-specific variations in myocardial substrate and neurohormonal activation may result in a more favorable response to HF 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 with males.[16]

The higher risk of HF hospitalization observed in males may be driven by more severe left ventricular dysfunction and greater comorbidity burden, particularly ischemic heart disease and diabetes, which are known to worsen HF outcomes.[19,20] In contrast, females tend to present with HFpEF, a phenotype characterized by preserved systolic function but increased diastolic dysfunction and ventricular stiffness. This distinction may partly explain why females have a lower risk of cardiovascular death but similar or even higher rates of HF hospitalization compared with males.

Study limitations

This study has several limitations inherent to its observational design. Although we adjusted for a broad range of clinical and demographic variables, residual confounding cannot be completely excluded. The lack of randomization limits our ability to establish causality between sex, treatment differences, and outcomes. Additionally, information on patient-reported outcomes, quality of life, and adherence to prescribed therapies was not available in the SwedeHF registry, which may have influenced the observed associations.

Furthermore, the current analysis is focused on patients with HFmrEF and HFpEF, and the findings may not be generalizable to those with HFrEF. Differences in pathophysiology, treatment response, and outcomes between HF subtypes warrant further investigation. Finally, the first draft of this manuscript was entirely generated by a large language model (ChatGPT) (*Supplementary Material*). Such tools can expedite evidence synthesis when supplied with structured results tables; however, they may introduce factual inaccuracies or biased language. Therefore, all AI-assisted text was independently verified, in line with emerging guidance on the responsible use of generative AI in cardiology research.[21]

Future research should aim to identify the specific biological, clinical, and healthcare system factors that contribute to sex-based disparities in HF management and outcomes.

Conclusions

In this large, national cohort of patients with HFmrEF and HFpEF from the SwedeHF registry, we identified significant sex-based differences in baseline characteristics, treatment utilization, and outcomes. Female patients, despite greater age, comorbidity, and lower use of SGLT2 inhibitors, had lower adjusted risks of cardiovascular death and HF hospitalization than males, who were less frequently treated with beta-blockers and loop diuretics**.** Further research is warranted to better understand the biological, clinical, and healthcare system fac-

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tors contributing to these observed differences and to develop targeted interventions to reduce sex-based disparities in HF care and outcomes.

Acknowledgments

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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Online supplementary material:
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