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RESEARCH ARTICLE

Sex differences in the prognostic role of achieving target doses of heart failure medications: Data from the Swedish Heart Failure Registry

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Aims Guidelines recommend target doses (TD) of heart failure (HF) with reduced ejection fraction (HFrEF) medications regardless of sex. Differences in pharmacokinetics and pharmacodynamics may explain heterogeneity in treatment response, adverse reactions, and tolerability issues across sexes. The aim of this study was to explore sex-based differences in the association between TD achievement and mortality/morbidity in HFrEF.

Methods and results Patients with HFrEF and HF duration ≥6 months registered in the Swedish HF Registry between May 2000 and December 2020 (follow-up until December 2021) were analysed. Treatments of interest were renin–angiotensin system inhibitors (RASI) or angiotensin receptor–neprilysin inhibitors (ARNI), and beta-blockers. Multivariable Cox regression models were performed to explore the risk of cardiovascular mortality or hospitalization for HF across dose categories in females versus males. A total of 17 912 patients were analysed (median age 77.0 years, interquartile range [IQR] 70.0–83.0), 29% were female. Over a median follow-up of 1.33 years (IQR 0.29–3.22), for RASI/ARNI there was no significant difference in outcome for females achieving 50–99% versus 100% of TD (hazard ratio 0.92, 95% confidence interval 0.83–1.03), whereas males showed a gradual lowering in risk together with the achievement of higher % of TD (p-interaction = 0.030). For beta-blockers the achievement of TD was associated with the lowest risk of outcome regardless of sex.

Conclusions Our findings suggest that females and males might differently benefit from the same dose of RASI/ARNI, and do represent a general call for randomized controlled trials to consider sex-specific up-titration schemes when testing HFrEF treatments in need of up-titration.

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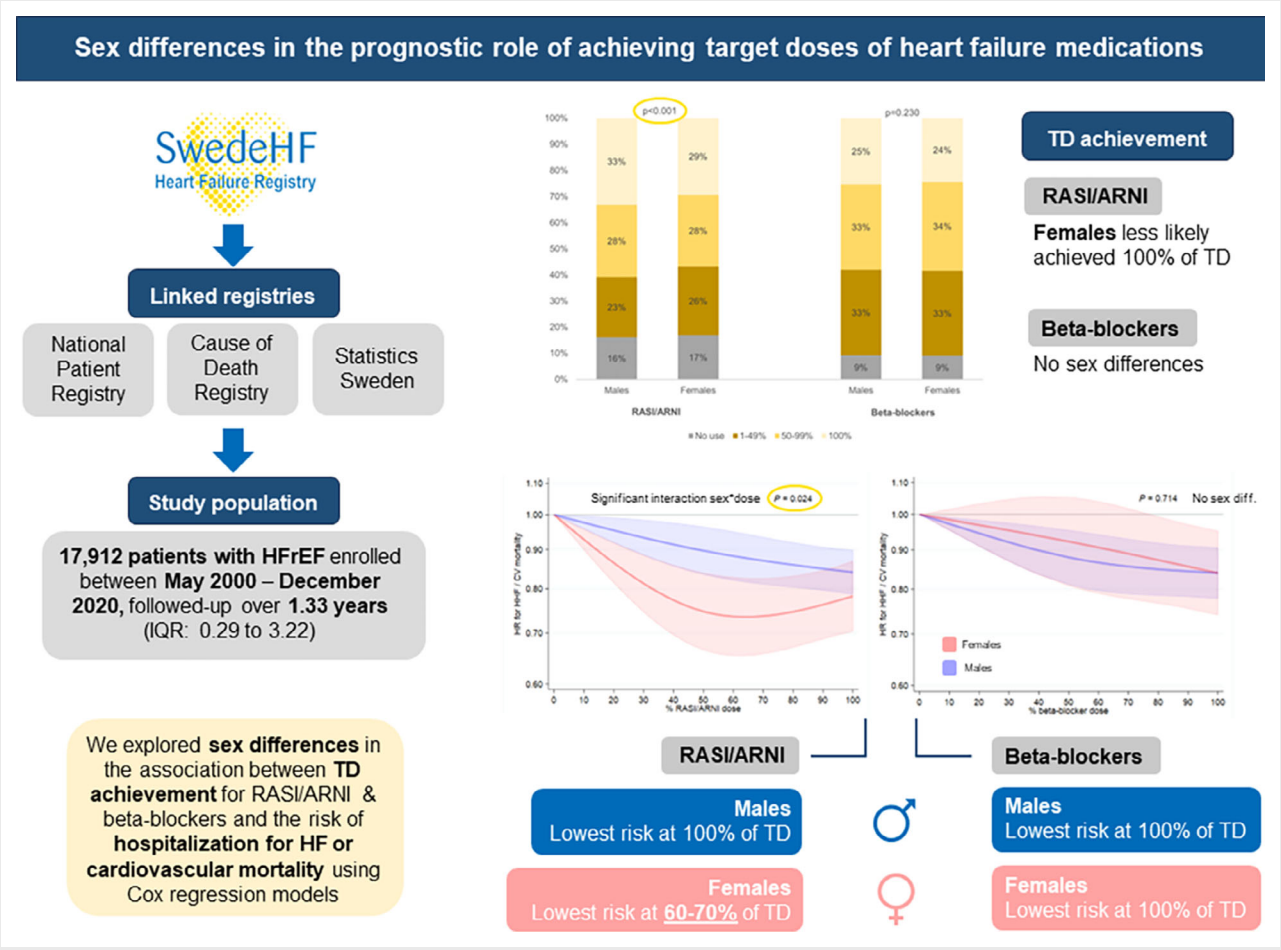
Graphical Abstract



Sex differences in the prognostic role of achieving target doses of heart failure (HF) medications. In females TD of RASI/ARNI was less likely achieved and achieving TD of RASI/ARNI was not associated with lower mortality/morbidity as compared with lower dose, whereas in males increasing doses of RASI/ARNI were associated with lower mortality/morbidity. For beta-blockers there were no differences in doses achieved and higher doses were associated with better outcome regardless of sex. ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; IQR, interquartile range; RASI, renin–angiotensin system inhibitor; TD, target dose.

Keywords Heart failure with reduced ejection fraction • Treatment • Sex • Renin–angiotensin system inhibitors • Beta-blocker • SwedeHF

Introduction

Heart failure (HF) represents a global pandemic due to its high and increasing prevalence. It imposes a heavy burden on patients in terms of mortality/morbidity and quality of life, but also on worldwide healthcare systems in terms of costs and resource utilization.[1–3]

Males and females show significant differences in physiology which can translate into different pharmacokinetics and pharmacodynamics of medications.[4–6] Females more often report adverse reactions, which are more likely occurring at higher doses of medications.[7] However, guideline recommendations for the pharmacological management of HF with reduced ejection fraction (HFrEF) are consistent regardless of sex, as well as the recommended target doses (TD) for drugs requiring up-titration.[8]

The under-representation of females in randomized controlled trials (RCTs) prevents from solid conclusions on sex-based differences in treatment effect. In HFrEF, one post-hoc analysis of

a RCT and one registry-based study suggested females requiring lower doses of renin–angiotensin system inhibitors (RASI) and beta-blockers to achieve the same benefits as males, but these findings are in need of further validation.[9,10]

Therefore, we sought to investigate the use and dose achievement of RASI, angiotensin receptor–neprilysin inhibitors (ARNI) and beta-blockers, and the related associations with mortality/morbidity in females versus males, in a large, contemporary nationwide cohort of patients with HFrEF.

Methods

Study design and data sources

The Swedish HF Registry (SwedeHF, www.swedehf.se) is an ongoing voluntary healthcare quality registry founded in 2000 and implemented on a national basis in 2003.[11] Written consent is not required, but patients are informed of registration into national registries and allowed to opt out. Most Swedish hospitals, and to a minor extent also primary care centres, enrol patients and collect approximately 80 variables, that is, data on demographics, comorbidities, clinical parameters, biomarkers, treatments, and organizational aspects, from adult inpatient wards and outpatient clinics. No financial compensation is expected. The criterion for inclusion in SwedeHF was clinician-judged HF until April 2017, and thereafter a diagnosis of HF according to the following International Classification of Diseases, Tenth 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.

For the current study, data from SwedeHF were linked to the National Patient Registry which provided additional data on comorbidities (online supplementary *Table S1*) and hospitalization for HF (HHF); to the Cause of Death Registry which provided data on date and cause-specific death; and to Statistics Sweden which allowed examining patients' socioeconomic characteristics. Linkage across different registries was performed by the personal identification number, which all the residents in Sweden have. Establishment of the HF registry and the linkage across several registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki.

Patients and treatments

Patients registered in SwedeHF between 11 May 2000 and 31 December 2020 with HFrEF (i.e. ejection fraction <40%), HF duration ≥6 months (to allow for up-titration of guideline-directed medical therapy [GDMT]) and no missing data for use and doses of the treatments of interest were included (online supplementary *Figure S1*). Index date was defined as the date of registration in SwedeHF, that is, the date of the outpatient visit for outpatients and the date of discharge for inpatients. If multiple registrations were available for the same patient, the most recent one was considered as being the most representative of contemporary care. Patients who died during hospitalization were excluded. The end of follow-up was on 31 December 2021.

Data on HF medications and dosage are collected in the SwedeHF at the time of the outpatient visit or hospital discharge. We separately analysed the following treatments: (i) RASI (including angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor-blockers [ARBs]) or ARNI; (ii) beta-blockers. As sensitivity analysis, we analysed RASI and ARNI separately.

Only patients receiving RASI and beta-blockers currently recommended for the treatment of HFrEF were considered as treated.[8] TD were defined according to the 2021 European Society of Cardiology guidelines on HF (online supplementary *Table S2*).[8] Doses were categorized as: 0% of TD (no use), 1–49%, 50–99% and 100% of TD.[10] We excluded patients treated with >100% of TD, as well those receiving a combination of ACEi and/or ARB and/or ARNI. In the analyses focusing on ARNI, we considered only the subpopulation of patients receiving the treatment since a large proportion of non-users might have been registered before this therapy was approved in Sweden.

Outcomes

The primary outcome was a composite of cardiovascular (CV) mortality or HHF (with censoring for non-CV death). The secondary outcomes were all-cause mortality, CV mortality (with censoring for non-CV deaths) and HHF (with censoring for any death). Censoring was performed at 5 years of follow-up or in case of emigration from Sweden.

Statistical analyses

Continuous variables were reported as median and interquartile range (IQR) and compared by Kruskal–Wallis test. Categorical variables were reported as counts and proportions (%) and compared by χ^2 test.

The associations between the achieved percentage of TD and outcomes were investigated by (i) unadjusted survivor functions estimated by using the Kaplan–Meier method; (ii) univariable Cox proportional hazard models; (iii) multivariable Cox proportional hazard models adjusting for all the variables reported in *Table 1*. An interaction term between the achieved percentage of TD and sex was included in the models and tested by a Wald-type test to assess whether the association between percentage of TD achievement and outcomes was consistent in females versus males. Hazard ratios (HRs) with 95% confidence intervals (CI) were provided. The reference category for the dose variable was set at 100% of TD. To assess the association between the achieved percentage of TD expressed as a continuous rather than categorical variable and the primary outcome, we further modelled TDs as restricted cubic splines (with three knots) in the multivariable Cox regression models, using 0% of TD as reference.

Missing data for the variables included in the multivariable models were handled by chained equation multiple imputation, generating 10 imputed datasets (and 10 iterations). We included in the models the achieved percentages of TD for RASI/ARNI and beta-blockers as categorical variables, the patient characteristics (*Table 1*) and the primary outcome.

Statistical analyses were performed by Stata Software version 17.0 (Stata-Corp, LLC, College Station, TX, USA). Statistical significance was set at a p-value <0.05 (two-tailed).

Results

Of 203 428 patients registered in SwedeHF during the study period, a total of 17 912 patients met the inclusion criteria and were included in the study (online supplementary *Figure S1*). Of these patients, 71% were male (median age 77 years, IQR: 69–83) and 29% female (median age 80 years, IQR: 72–85). Median follow-up was 1.33 years (IQR: 0.29–3.22). Patient characteristics are shown in *Table 1*.

Table 1 Patient characteristics in males versus females

	Males ($n = 12\,760$, 71%)	Females ($n = 5152$, 29%)	p-value
Sociodemographic features			
Age[a] (years), median (IQR)	77.0 (69.0–83.0)	80.0 (72.0–85.0)	<0.001
Age class, *n* (%)			<0.001
<75 years	5378 (42.1)	1654 (32.1)	
≥75 years	7382 (57.9)	3498 (67.9)	
Year of registration[a], *n* (%)			<0.001
2000–2005	507 (4.0)	241 (4.7)	
2006–2011	3729 (29.2)	1582 (30.7)	
2012–2017	5108 (40.0)	2094 (40.6)	
2018–2020	3416 (26.8)	1235 (24.0)	
Caregiver at registration[a], *n* (%)			<0.001
Inpatient	4728 (37.1)	2189 (42.5)	
Outpatient	8032 (62.9)	2963 (57.5)	
Location of follow-up[a], *n* (%)			<0.001
Hospital	8387 (68.7)	2809 (57.2)	
Primary care	3417 (28.0)	1904 (38.8)	
Other	412 (3.3)	196 (4.0)	
Follow-up referral to HF clinic[a]	7175 (59.3)	2543 (52.3)	<0.001
Education[a], *n* (%)			<0.001
Compulsory school	5418 (43.2)	2477 (49.5)	
Secondary school	4965 (39.6)	1839 (36.7)	
University	2161 (17.2)	689 (13.8)	
Family situation[a], *n* (%)			<0.001
Cohabitating	7458 (58.5)	1887 (36.6)	
Living alone	5285 (41.5)	3264 (63.4)	
Disposable income[a] (euro), median (IQR)	1601 (1307–2090)	1326 (1086–1603)	<0.001
Children[a], *n* (%)	10 576 (82.9)	4479 (86.9)	<0.001
Clinical features			
NYHA class[a], *n* (%)			0.21
I–II	4369 (44.2)	1648 (43.0)	
III–IV	5524 (55.8)	2186 (57.0)	
Ejection fraction[a], *n* (%)			<0.001
30–39%	6509 (51.0)	3048 (59.2)	
<30%	6251 (49.0)	2104 (40.8)	
Heart rate[a] (bpm), median (IQR)	70.0 (63.0–80.0)	72.0 (64.0–82.0)	<0.001
MAP[a] (mmHg), median (IQR)	86.7 (78.3–95.0)	86.7 (79.3–96.7)	<0.001
BMI (kg/m^2), median (IQR)	25.9 (23.2–29.4)	25.4 (22.0–29.7)	<0.001
Body surface area[a,b] (m^2), median (IQR)	2.0 (1.9–2.1)	1.7 (1.6–1.8)	<0.001
Laboratory			
NT-proBNP[a] (pg/ml), median (IQR)	2980 (1167–7214)	3295 (1317–7995)	<0.001
NT-proBNP ≥ median (3039 pg/ml), *n* (%)			0.007
<median (3039 pg/ml)	3654 (50.8)	1338 (47.8)	
	3534 (49.2)	1459 (52.2)	
eGFR[c] (ml/min/1.73 m^2), median (IQR)	55.8 (40.2–75.7)	50.6 (36.5–68.9)	<0.001
eGFR class[a], *n* (%)			<0.001
≥60 ml/min/1.73 m^2	5461 (43.8)	1802 (35.7)	
30–59 ml/min/1.73 m^2	5597 (44.9)	2484 (49.3)	
<30 ml/min/1.73 m^2	1419 (11.4)	755 (15.0)	
Potassium[a] (mmol/L), median (IQR)	4.3 (4.0–4.6)	4.2 (3.9–4.5)	<0.001
Haemoglobin (g/L), median (IQR)	132 (119–144)	126 (116–137)	<0.001
Comorbidities, *n* (%)			
Anaemia[a,d]	6226 (48.8)	1934 (37.5)	<0.001
Atrial fibrillation[a]	8115 (63.6)	2945 (57.2)	<0.001
Hypertension[a]	8443 (66.2)	3565 (69.2)	<0.001

Table 1 (Continued)

	Males ($n = 12\,760$, 71%)	Females ($n = 5152$, 29%)	p-value
Diabetes[a]	4344 (34.0)	1543 (29.9)	<0.001
COPD[a]	2086 (16.3)	842 (16.3)	0.99
Ischaemic heart disease[a]	8972 (70.3)	3140 (60.9)	<0.001
Peripheral artery disease[a]	1736 (13.6)	493 (9.6)	<0.001
Stroke or TIA[a]	2696 (21.1)	936 (18.2)	<0.001
Kidney disease	3613 (28.3)	1127 (21.9)	<0.001
Liver disease[a]	405 (3.2)	103 (2.0)	<0.001
Major bleeding[a]	2941 (23.0)	1159 (22.5)	0.43
Dementia[a]	286 (2.2)	155 (3.0)	0.003
Depression[a]	466 (3.7)	273 (5.3)	<0.001
Cancer history in the last 3 years[a]	1951 (15.3)	527 (10.2)	<0.001
Musculoskeletal disease in the last 3 years[a]	4177 (32.7)	2056 (39.9)	<0.001
Smoking[a]			<0.001
Current	1088 (10.9)	353 (9.2)	
Former	5149 (51.6)	1347 (35.3)	
Never	3749 (37.5)	2123 (55.5)	
Myocardial infarction[a]	7116 (55.8)	2393 (46.4)	<0.001
Coronary revascularization[a]	9137 (71.6)	3178 (61.7)	<0.001
Valve disease[a]	4011 (31.4)	1833 (35.6)	<0.001
Concomitant treatments, *n* (%)			
MRA[a]	5428 (42.7)	2106 (41.0)	0.047
Diuretic[a]	10 610 (83.4)	4374 (85.2)	0.003
Digoxin[a]	1726 (13.6)	785 (15.3)	0.003
Statin[a]	7123 (55.9)	2201 (42.8)	<0.001
Device[a]	948 (8.6)	222 (4.8)	<0.001
Antiplatelet therapy[a]	5351 (42.1)	2215 (43.1)	0.19
Anticoagulant therapy[a]	6649 (52.2)	2249 (43.8)	<0.001
Nitrates[a]	2130 (16.7)	1010 (19.7)	<0.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF; heart failure; 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; TIA, transient ischaemic attack.

[a]These variables were included in multiple imputation models and used as covariates in multivariable models.

[b]Body surface area was computed with the Du Bois and Du Bois formula.

[c]eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula.

[d]Anaemia was defined as haemoglobin <120 g/L in females and <130 g/L in males.

As compared with males, females were older, more likely registered as inpatients and less likely referred to specialty care and/or HF nurse-led clinics. They were also more likely living alone and had a lower income. No significant differences were observed in New York Heart Association class, although females less likely had EF <30% but had higher N-terminal pro-B-type natriuretic peptide. In terms of comorbidities, females were more likely to have hypertension, chronic kidney disease, dementia and depression, musculoskeletal disease and valve disease, whereas less likely to have anaemia, atrial fibrillation, diabetes, ischaemic heart disease, peripheral artery disease, history of stroke/transient ischaemic attack, liver disease and recent (i.e. last 3 years) history of cancer. Body mass index was lower in females. Regarding treatments other than our exposures, females were less likely treated with mineralocorticoid receptor antagonists, statins and anticoagulants, but more likely with loop diuretics, digoxin and nitrates. HF devices (i.e. implantable cardioverter-defibrillator and/or cardiac resynchronization therapy) were less likely used in females.

Use and doses of renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors and beta-blockers in males versus females

Use of RASI/ARNI (83% in females vs. 84% in males) and beta-blockers (91% in both sexes) was consistent across sexes (*Figure 1*). For RASI/ARNI, females less likely achieved 100% of TD (29% in females vs. 33% in males), consistently received 50–99% of TD (28% in both sexes), and therefore were more likely treated with 1–49% of TD (26% in females vs. 23% in males). For beta-blockers, females as compared with males were as likely to achieve TD (24% in females vs. 25% in males) as well as 50–99% (34% in females vs. 33% in males) and 1–49% of TD (33% in both sexes). The distribution of percentages of TD achievement modelled a continuous variable in males and females is shown in online supplementary *Figure S2*. Of 1400 patients receiving

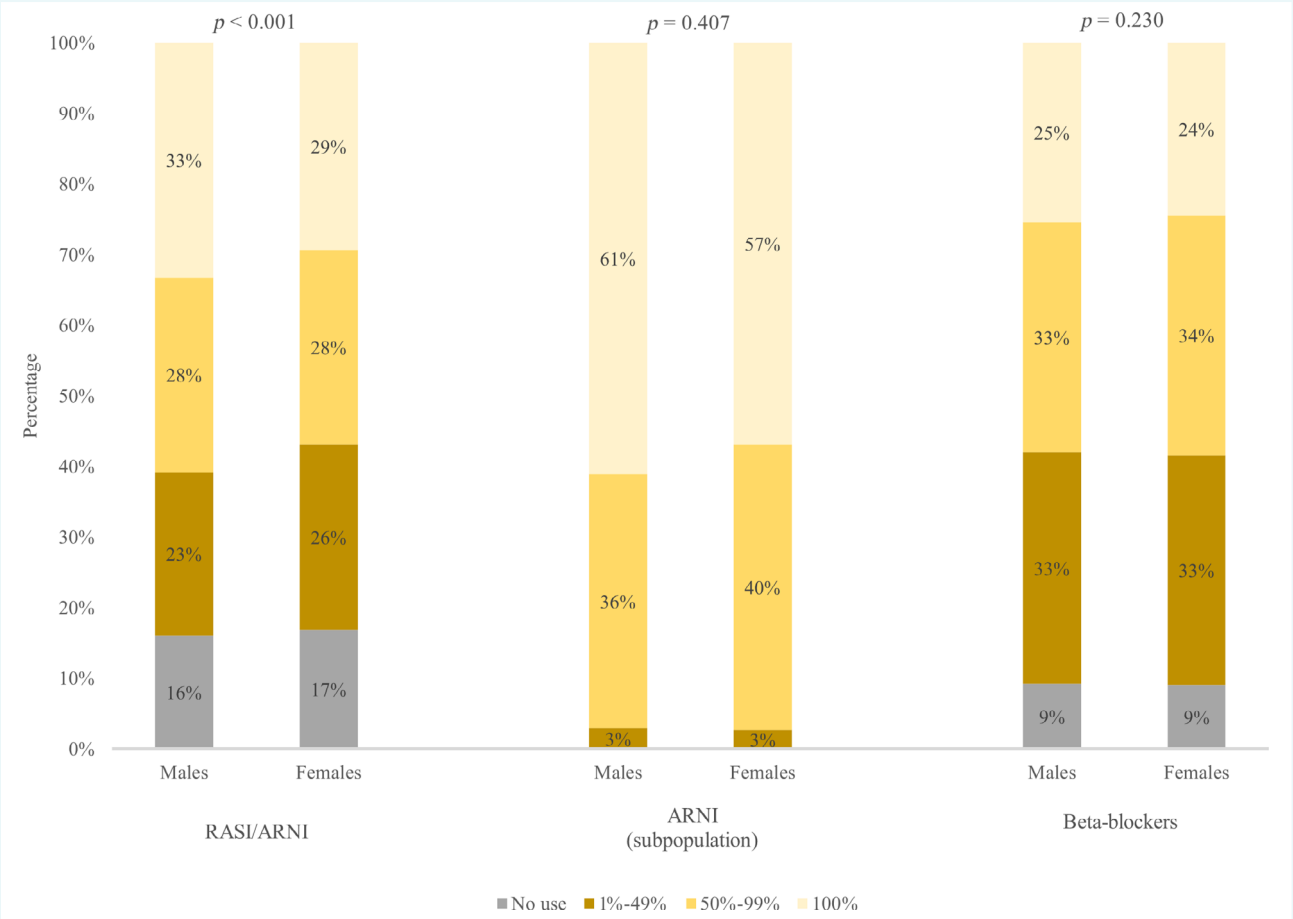


Figure 1 Rates of use and percentage of target dose achievement for renin–angiotensin system inhibitor/angiotensin receptor–neprilysin inhibitor (RASI/ARNI), ARNI, and beta-blocker in males versus females. The analysis on ARNI considers only the subpopulation of users ($n = 1400$).

ARNI (18.7% female), in females versus males, respectively, the use of 100% of TD was 57% versus 61%, the use of 50–99% of TD was 40% versus 36%, and the use of 1–49% of TD was 3% in both sexes.

Online supplementary *Tables S3* and *S4* show patient characteristics according to percentage of TD achievement in males and females.

Outcomes

Renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors

The crude risk of CV mortality/HHF was lower whether a higher percentage of TD was achieved regardless of sex (online supplementary *Figure S3*). After adjustments, in the overall cohort patients achieving 100% or 50–99% of TD reported comparable risk of CV mortality/HHF, whereas risk was significantly higher in patients not receiving the medication or treated with 1–49% of TD (online supplementary *Table S5*). Males achieving 100% of TD showed a significant 7% lower risk of outcome as compared with those achieving 50–99% of TD, whereas in females there was no significant difference in outcome with 50–99% versus 100% of TD (*Figure 2* and online supplementary *Table S6*; *p*-value for interaction = 0.030 for differences across sexes). Consistent results were obtained in the spline analysis which showed a linear decrease in risk with increasing doses for males, and an inverted J-shaped association in females, with the lowest risk observed at 60–70% of TD (*Figure 3*, *p*-value for interaction = 0.024).

For all-cause and CV mortality, in the overall cohort achieving 100% of TD was associated with the lowest adjusted risk (online supplementary *Table S5*, *Figures S4* and *S5*). Although adjusted models showed no significant difference in risk in females achieving 1–49% or 50–99% or 100% of TD (online supplementary *Table S6* and *Figure S6*), the interaction between sex and TD was not significant.

In the overall cohort, as compared with 100% of TD, a higher risk of HHF was observed with non-use or use of 1–49% of TD, but a similar risk with 50–99% of TD (online supplementary *Table S5 and Figure S7*). Results were consistent regardless of sex (*p*-value for interaction non-statistically significant) (online supplementary *Table S6* and *Figure S6*).

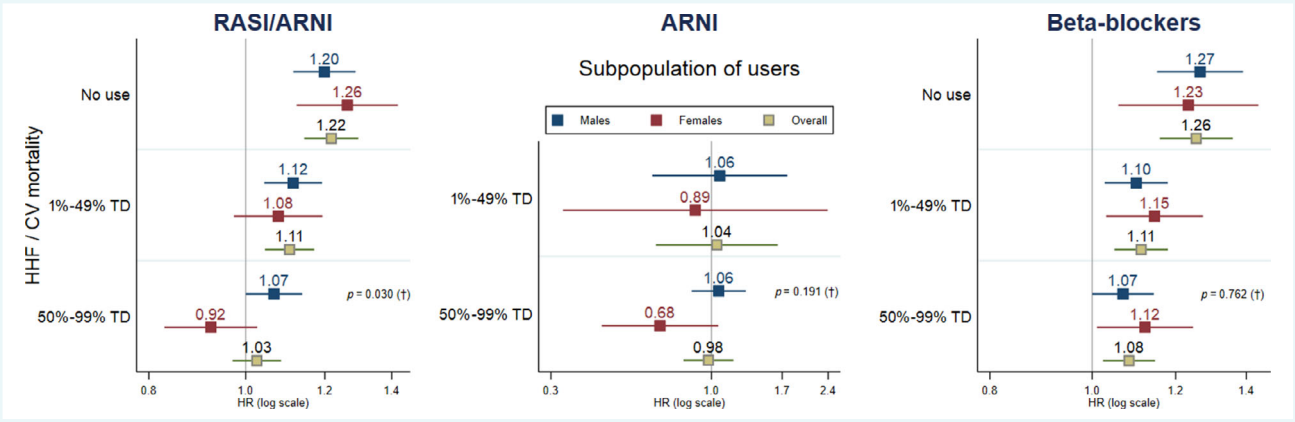


Figure 2 Adjusted hazard ratios (HR) for the primary composite outcome (cardiovascular mortality/hospitalization for heart failure) in the overall population (green) and separately in males (blue) versus females (red) according to the achieved percentage of target dose (TD) category for renin–angiotensin system inhibitor/angiotensin receptor–neprilysin inhibitor (RASI/ARNI), ARNI, and beta-blockers. CV, cardiovascular; HHF, hospitalization for heart failure. 100% of TD used as reference. *P*-values for interactions between sex and target dose class are reported (†). The analysis on ARNI includes only the subpopulation of users.

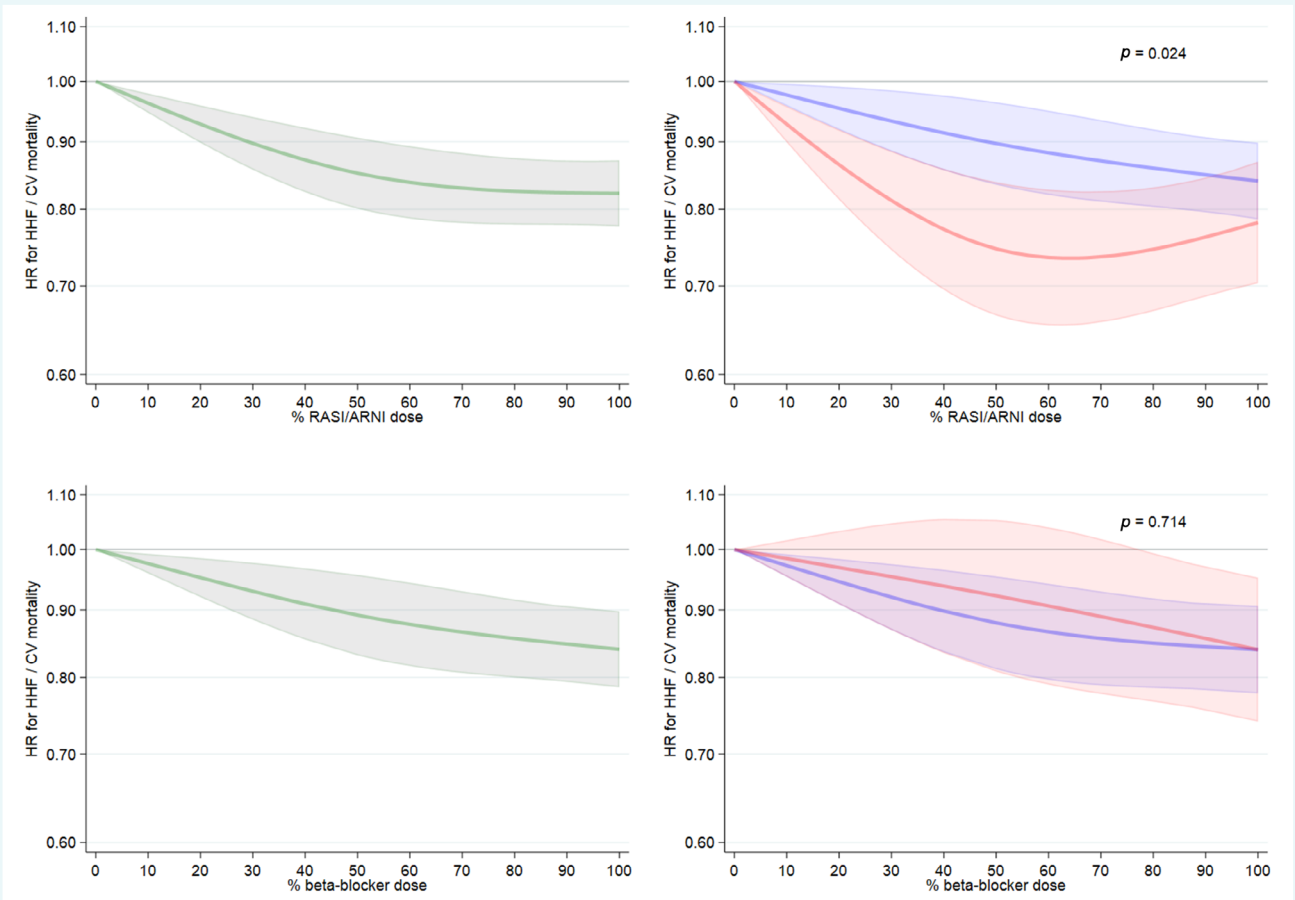


Figure 3 Restricted cubic splines for the association of achieved percentage of target dose of renin–angiotensin system inhibitor/angiotensin receptor–neprilysin inhibitor (RASI/ARNI) (top panels) and beta-blockers (bottom panels) with the risk of the primary outcome (i.e. cardiovascular [CV] mortality/hospitalization for heart failure [HHF]) in the overall population (green line, left panels), and in males (blue line, right panels) and females (red line, right panels) separately. No medication use (0% of target dose) was taken as the reference. *P*-values for interactions between sex and target dose class are reported. HR, hazard ratio.

Sensitivity analysis on renin–angiotensin system inhibitors alone

The results obtained both in the overall population and separately in the two sexes are consistent with those on RASI/ARNI (online supplementary *Figure S8*).

Sensitivity analysis on angiotensin receptor–neprilysin inhibitors alone

In the overall subpopulation of ARNI users, achieving 1–49% or 50–99% of TD was not significantly associated with a higher risk of any outcome as compared with 100% of TD (online supplementary *Table S5*). Consistent results were observed regardless of sex (*Figure 2*, online supplementary *Table S6* and *Figure S6*).

Beta-blockers

The pattern of the crude associations between achieved percentage of TD and risk of CV mortality/HHF was similar in males and females, with a progressive lower risk of outcome together with the achievement of a higher dose (online supplementary *Figure S3*). Consistent results were observed after adjustments (online supplementary *Tables S5* and *S6*; *Figure 2*, *p*-value for interaction non-statistically significant). Spline analyses provided consistent results (*Figure 3*, *p*-value for interaction non-statistically significant).

The adjusted risk of all-cause and CV mortality consistently decreased whether higher percentage of TD was achieved regardless of sex (online supplementary *Table S6* and *Figure S6*, *p*-value for interaction non-statistically significant). Risk of HHF did not significantly differ with 50–99% or 100% of TD regardless of sex (online supplementary *Table S6*, *Figures S6* and *S7*, *p*-value for interaction non-statistically significant).

Discussion

In the current analysis, by exploring the associations between percentage of TD achievement for HFrEF GDMT and mortality/morbidity in females versus males, we found that (i) females less likely achieved TD of RASI/ARNI, whereas there were no differences across sexes for beta-blockers; (ii) in females, achieving TD of RASI/ARNI was not associated with lower mortality/morbidity as compared with lower doses, whereas in males the risk of CV death/HHF progressively decreased together with increasing doses; (iii) higher doses of beta-blockers were associated with better outcome regardless of sex; and (iv) achieving higher % of TD for ARNI was not associated with better outcome regardless of sex (*Graphical Abstract*).

Our findings suggest potentially important clinical implications of sex-related differences for HFrEF pharmacotherapy that are worthy of dedicated investigation, emphasize the role of sex in the process of treatment individualization, and further underline the need of ad-hoc designed RCTs aiming to further explore this important clinical and research question in a setting free of residual confounding.

Sex-based differences in dose optimization

Underuse and underdosing of HFrEF GDMT have been more likely reported in females versus males in some, but not all studies.[10,12–15] In our analysis, we showed that the use of TD for RASI/ARNI was slightly better implemented in males versus females. Indeed, 33% versus 29% of our population received 100% of TD for RASI/ARNI, while the use of 100% of TD for beta-blockers was similar across sexes (25% vs. 24%); among patients receiving ARNI, 61% versus 57% achieved the TD.

Females may be exposed to higher drug plasma concentrations due to physiological, hormonal, and pharmacodynamic/pharmacokinetic differences from males, and among these a smaller volume of distribution and different body composition.[16–20] Consistently, plasma concentration of anti-neurohormonal medications has been found to be >2-fold higher in females versus males.[16]

Therefore, sex could be linked to a different risk of adverse reactions and tolerability issues, which might contribute to explain sex-based differences in the use of HFrEF treatments observed in previous studies.[21] We might speculate that a similar explanation could stand behind the different dose optimization achieved across sexes which has been observed in the current and other studies, and further raises the question of whether TD should be similarly defined in males and females.

Sex-based differences in the association between dose optimization and outcomes

International guidelines recommend same TD for HFrEF pharmacotherapy in males and females. However, females were poorly represented in RCTs, limiting the chance of detecting sex-based differences in the treatment effect and safety profile of HFrEF pharmacotherapy through post-hoc and subgroup analyses. Also, RCTs may not be enough powered to specifically test differences in treatment effects between subgroups.

Despite the above-reported potential reasons supporting the need for defining a different TD for HFrEF medications in females versus males, few studies specifically investigated this topic.[22] In a post-hoc analysis of the prospective observational BIOSTAT-CHF study, females but not males reported the lowest HR for all-cause mortality or HHF with 50% of TD of RASI and beta-blockers, whereas the lowest risk in males was observed in those achieving the TD of these medications.[10] In a recent post-hoc analysis of the dose-comparison HEAAL trial, higher versus lower dose of losartan reduced the risk of all-cause mortality or hospitalization in males but not in females.[9]

Consistent with the results from these studies, we showed that the HR for our primary outcome, that is, CV death or HHF, reached a plateau at 60–70% of TD for RASI/ARNI in females, whereas in males the risk progressively decreased with increasing doses; the inverted J-shaped association between % of TD achievement and risk of outcome observed in females was very similar to what observed in the BIOSTAT-CHF study.[10] Regarding the

secondary outcomes of our study, that is, all-cause and CV mortality and HHF, we observed similar trends, but the lack of a significant interaction precluded any assumption on the potential influence of sex on the prognostic role of up-titrating doses. We cannot exclude that the lower statistical power when outcomes were assessed separately, or, alternatively, residual confounding might have precluded the chance of observing a statistically significant association.

In contrast with previous studies,[9,10,23] we could not identify any sex-based difference for the association between the achieved % of TD and outcomes for beta-blockers. The inverted J-shaped association found in the female subpopulation of the BIOSTAT-CHF study was not observed in our analysis, where we rather observed an association of higher doses with better outcome regardless of sex in the unadjusted analysis which was then confirmed in the adjusted models. This finding seems not to be supported by pharmacokinetic data suggesting higher drug plasma concentrations with the same dose of beta-blocker in females versus males.[24,25] We hypothesize that the higher heart rate in females could lead to the need for a proportionally higher drug concentration to achieve the same target of heart rate reduction as in males, which might translate into clinical benefit. Unlike previous studies[10] we adjusted our models for heart rate, which might further corroborate the validity of our results. The different characteristics between the populations of this and previous studies as well as an the differences in adjustments might further contribute to explain the discrepant results. Our finding contributes to reinforce the compelling hypothesis that attaining a pre-defined target heart rate, rather than striving for a specific TD of beta-blockers, might assume greater significance to get a benefit in terms of outcome, even though this assumption remains extremely controversial.[26,27] In a previous meta-analysis including patients with chronic HF and sinus rhythm, lower heart rate was predictive of better survival regardless of the dose of beta-blocker.[26]

The lack of an association between TD achievement for ARNI and outcome observed in our sensitivity analysis on ARNI users was consistent regardless of sex and might be explained by the lower statistical power due to the reduced sample size and the shorter follow-up. Furthermore, only 3% of ARNI users were on the lower TD range. The results of the PARADIGM-HF trial were influenced by the use of run-in periods, which prevented the possibility of evaluating the efficacy of lower ARNI doses, albeit achieving 100% TD in real life may be difficult.[28] In a recent post-hoc analysis of the PROVE-HF study, the efficacy of ARNI on health status, left ventricular reverse remodelling and cardiac biomarkers was consistent across dose tertiles.[29]

Limitations

The specific reasons for not prescribing or not up-titrating or discontinuing therapies, as for instance adverse effects, are not collected in SwedeHF. Also, we had no information on dose changes during follow-up since this study had a cross-sectional design and longitudinal data were not available. However, our analyses were extensively adjusted for many potential reasons for underuse, underdosing, or low tolerability. The role of residual confounding cannot be ruled out in this as in any observational study, despite the extensive adjustments. Use of treatments was defined at the index date and a later implementation/discontinuation cannot be excluded. We did not investigate mineralocorticoid receptor antagonists since 71% of our study population received 25 mg of spironolactone which limits the power to perform outcome analyses according to doses and sex. Additionally, in clinical practice up-titration of mineralocorticoid receptor antagonist dose is less pursued compared with RASI/ARNI and beta-blockers. We jointly analysed different medications belonging to the same class that may have different pharmacokinetic/pharmacodynamic profile. In addition, generalizability of our results is partially limited by the national setting and by the coverage of SwedeHF. For instance, the different characteristics of our study population compared with that of the BIOSTAT-CHF study may also contribute to explain the difference in the observed results. However, our study included a larger cohort of patients with HFrEF compared with previous studies and allowed to assess a longer follow-up for the outcome analysis.

Conclusions

In a large nationwide registry, doses lower than TD were independently associated with the lowest risk of CV mortality or HHF for RASI/ARNI in females, whereas in males TD seemed to be linked with the maximum benefit; there were no sex-based differences in the association between TD achievement for beta-blockers and lower risk of outcomes. Our findings advocate for the need of considering sex when designing dose–response studies for HFrEF pharmacotherapy requiring dose up-titration, in order to identify potentially different TD in males versus females.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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