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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Differences in medical treatment and clinical characteristics between men and women with heart failure – a single-centre multivariable analysis

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Abstract

Purpose The aims of this study were to examine sex differences in a heart failure population with regards to treatment and patient characteristics and to investigate the impact of sex on achieved doses of heart failure medications.

Methods and results A total of 1924 patients with heart failure in a regional hospital were analysed, 622 patients had ejection fraction ≤ 40% of which 30% were women. In patients with reduced ejection fraction, women were older (79 ± 11 vs. 74 ± 12 years, $P < 0.001$), had lower body weight (70 ± 17 vs. 86 ± 18 kg, $P < 0.001$), lower estimated glomerular filtration rate (eGFR) (49 ± 24 vs. 71 ± 30 ml/min, $P < 0.001$) and received lower doses of heart failure medications than men. Multivariable linear regression on patients with reduced ejection fraction showed that sex was not associated with achieved dose of any heart failure medication. For angiotensin-converting enzyme inhibitors and angiotensin receptor blockers associated factors were eGFR, systolic blood pressure, age, ejection fraction, and heart rate. For beta-blockers associated factors were body weight, atrial fibrillation and age. For mineralocorticoid receptor antagonists associated factors were eGFR, serum potassium, age, systolic blood pressure, ejection fraction and heart rate.

Conclusion Women with heart failure and reduced ejection fraction were prescribed lower doses of heart failure medications, were older, had worse renal function, and lower body weight than men. Sex was not independently associated with achieved doses of heart failure medications, instead age, renal function and body weight explained the differences in treatment.

Keywords Heart failure · HFrEF · Target dose · Sex differences

Introduction

In heart failure (HF) with reduced ejection fraction (HFrEF) guidelines recommend uptitration of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), as well as beta-blockers and mineralocorticoid receptor antagonists (MRA) to specified target doses [1, 2]. Target doses are based on landmark trials in which the representation of women has been between 20 and 25% [3–11]. There is a large discrepancy in the proportion of women represented in randomized landmark studies compared to real-world HF populations. The proportion of women in real-world populations with HF is between 47–53% and 36–42% for HFrEF [12–16] and in surveys or registries with a more selected patient population the proportion of women with HF is 28% [17] and for HFrEF between 21 and 23% [17, 18]. This discrepancy is a contributing factor to the present knowledge gap of how to treat women with HF. The knowledge gap was recently highlighted in two studies where the proportion of women enrolled in HF trials from 2001 to 2016 were investigated [19, 20]. These studies confirmed that HFrEF trials included only 24% women.

Studies have also shown that women are prescribed standard HF therapies to lesser extent and in lower doses compared to men [15, 21–23], and the reasons for this are still unknown. Previous studies were conducted in a wide range of settings, in different countries. Study design varies from

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large prospective multicentre surveys to observational single-centre studies, based on registries or clinical data, both on reduced and preserved HF. The majority of the studies were performed about two decades ago, but they all show that women receive less evidence-based treatment than men. However, these studies do not include a multivariable analysis that includes biological differences between men and women with HF. The aims of this study were to examine sex differences in a HF population with regards to treatment and patient characteristics, as well as to investigate if sex is an independent predictor for achieved doses of ACE-I/ARB, beta-blockers and MRA.

Methods

Study population and data collection

All patients alive at March 2016 living within the catchment area of Umeå University Hospital, Sweden with a HF diagnosis and at least one visit to the cardiology or internal medicine department between January 2010 and March 2016 were included. The HF diagnosis was derived from medical records as primary or secondary diagnosis according to the *International Classification of Diseases, 10th revision* codes I50.X, I42.X, I11.0. All diagnoses had been signed or countersigned by a specialist in cardiology or internal medicine. For the diagnosis of HFrEF, the patients also needed to have an ejection fraction of ≤ 40%. The diagnosis of HF with preserved or mid-range ejection fraction was not validated by any other means. Only patients with HFrEF were included in the multivariable analysis.

Data collection were performed between 1 June 2015 and 31 March 2016 from the medical records according to a standardized form consisting of clinical characteristics, laboratory data, medications, electrocardiography and echocardiography parameters. The latest available data were used in the analyses. We used the Cockcroft-Gault formula to calculate estimated glomerular filtration rate (eGFR).

Setting

Umeå University Hospital is serving approximately 150,000 residents with a mixed rural and urban population in Northern Sweden. The hospital represents the only cardiology clinic in the region. According to local guidelines, all patients with suspected heart failure should be referred to the cardiology clinic for diagnosis and uptitration of heart failure medications. The hospital uses an electronically medical records system (NCS Cross) from which patients with heart failure have been identified and data manually collected. This study complied with the Declaration of Helsinki and has received ethical approval by the Regional Ethical Review Board in Umeå, Sweden.

Statistical analysis

Patient characteristics were analysed with t-, chi-square, and Mann Whitney U test as appropriate. Continuous variables were reported as mean and standard deviation, or, as median and interquartile range if non-normally distributed. Categorical variables were reported as numbers and percentages.

To determine factors predicting the percentage of achieved target dose of ACE-I/ARB, beta-blocker and MRA in the HFrEF population (ejection fraction ≤40%), we used a manual stepwise backward multivariable linear regression model. Percentage of achieved target doses was calculated as the latest prescribed dose divided by the target dose of the individual substance, according to European Society of Cardiology guidelines [1], for each patient separately as a continuous variable. Target doses are defined in Appendix. The selected target doses were in strict accordance to the guidelines and did not consider individual decisions for lower target doses due to kidney function, body weight or other reasons.

The linear regression models were constructed with initial bivariate analyses of the most relevant patient characteristics: age, sex, body weight, eGFR, systolic blood pressure, heart rate, ejection fraction, N-terminal pro–B-type natriuretic peptide (NTproBNP), serum potassium, atrial fibrillation, coronary artery disease, diabetes and hypertension. Variables were reviewed to explore distribution, outliers and dependency. Distribution and outliers were reviewed with histograms for each variable and with histograms and Normal P-P plots of the residuals for each analysis. To review dependence, we used Pearson's correlation between dependent and independent variables one by one. We also applied Pearson's correlation analysis with eGFR, body weight, age and creatinine. Furthermore, as part of the linear regression analysis, we assessed multicollinearity with tolerance and Variance Inflation Factor (VIF). If dependency was apparent, one of the variables was selected and the others omitted (e.g. body weight and height versus body mass index). Five percent of eGFR values were outliers (> 130 ml/min) due to extreme body weight or muscle mass. We consequently truncated all eGFR values over 130 ml/min to this maximum limit to reduce the statistical impact of those values in the multivariable analyses. Variables with a significance level less than 0.25 in the bivariate analyses were included in the multivariable linear regression models, where manual stepwise backward analysis was performed to determine the final prediction models. Interaction terms for sex*age, sex*body weight and sex*eGFR were also included in the multivariable analyses. Sex was kept in the backward analysis, even if nonsignificant, since it was central to our aims. P values less than 0.05 were

considered statistically significant in the final models. IBM SPSS Statistics, Version 25.0 (Armonk, NY: IBM Corp.) was used for all analyses.

Results

In total, the HF population of Umeå University Hospital consisted of 1924 patients (43% women). Of these, 622 patients (30% women) had an ejection fraction of ≤ 40%. A total of 29 patients with HFrEF had received their diagnosis within 3 months of data collection and possibly did not have ample time for complete uptitration. Seven of these had received maximum target dose ACE-I/ARB, and nine had received maximum target dose beta blockers. Patient characteristics of the two populations are shown in Table 1. Women were significantly older, had lower body weight, lower eGFR, higher systolic blood pressure, less coronary artery disease, lower doses of HF medications and less devices than men in both the HFrEF and total HF population. Women in the total HF population also had significantly higher heart rate and ejection fraction compared to men, which was not shown among patients with HFrEF.

In the HFrEF population, ACE-I/ARB and beta-blockers were prescribed to approximately 90% and MRA to 47% of patients. Men were prescribed significantly higher doses of ACE-I/ARB and MRA compared to women, while no differences in beta-blocker dose were shown (Fig. 1A). Patients were prescribed target doses of ACE-I/ARB, beta-blockers and MRA in full extent in 37%, 29% and 4%, respectively (Fig. 1B). The proportion of patients achieving different dosing levels of ACE-I/ARB, beta-blockers and MRA are presented in Fig. 2.

The linear regression models for ACE-I/ARB, beta-blockers and MRA in patients with HFrEF are shown in Table 2. Sex was not an independent predictor for achieved proportion of target dose ACE-I/ARB, beta-blockers or MRA. Systolic blood pressure ($p = 0.012$) and eGFR ($p < 0.001$) were independently associated with higher proportion of target dose ACE-I/ARB, while age ($p < 0.001$), ejection fraction ($p = 0.028$) and heart rate ($p = 0.006$) were negatively associated. For beta-blockers, body weight ($p = 0.002$) and atrial fibrillation ($p = 0.018$) were independently associated with higher proportion of target dose, while age ($p < 0.001$) was negatively associated. Heart rate was not associated with achieved beta-blocker dose. For MRA, eGFR ($p < 0.001$) and serum potassium level ($p = 0.001$) were independently associated with higher proportion of target dose, while age ($p = 0.012$), systolic blood pressure ($p = 0.038$), ejection fraction ($p = 0.001$) and heart rate ($p = 0.001$) were negatively associated. None of the interaction terms were significant in the multivariable analyses and were omitted from the final models.

Discussion

Women with HF were older, had lower body weight and worse renal function than men. Women were also less likely to present with HFrEF and women with HFrEF received ACE-I/ARB and MRA to a lesser extent and in lower doses compared to men. Sex did not predict achieved dose for ACE-I/ARB, beta-blockers or MRA in patients with HFrEF. Factors associated with achieved doses were age, renal function and body weight.

Age was a significant associated factor for achieved doses of all three groups of HF medications in HFrEF. This is expected since older patients often are frailer and with more comorbidities, which reduces the tolerance of HF medications. Also, the increased percentage body fat in elderly patients can reduce the tolerance of HF drugs [24, 25].

Body weight was associated with achieved target dose for beta-blockers, but not for ACE-I/ARB or MRA in HFrEF. This may be explained as a probable dependency matter as body weight is a factor in the Cockcroft-Gault formula which was used to estimate GFR. Renal function was in turn a predictor for achieved doses of ACE-I/ARB and MRA. Since beta-blockers are, in general, not as dependent on renal function for excretion as ACE-I/ARB and MRA, body weight is probably a more important factor for tolerance of beta-blocker dose.

Systolic blood pressure, heart rate and ejection fraction were associated factors for both ACE-I/ARB and MRA but not for beta-blockers in HFrEF. Why heart rate did not predict achieved beta-blocker dose may be because heart rate was based on the latest available measurement; hence after uptitration and since the heart rate is often the limiting factor in the uptitration, patients with both high and low doses of beta blockade may end up with similar heart rate.

Previous studies support that MRAs are often underused in clinical practice [18, 26–28], especially in patients with moderately impaired renal function [26, 28]. Guidelines are unclear about how to best manage patients who do not tolerate evidence-based target doses of ACE-I/ARB and beta-blockers but who are still symptomatic and have reduced ejection fraction. Should an MRA be added at the expense of lower doses of ACE-I/ARB and beta-blockers? This is also important with novel HF medications such as sacubitril-valsartan where the old and frail would not receive treatment if adherence to the PARADIGM-HF trial [11] (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure) inclusion criteria is strict [23, 29, 30].

There are some established sex differences associated with HF which our study also confirm; women are older and are less likely to develop HFrEF than men [15, 22, 31, 32]. In HF aetiology, women more often have a history of hypertension, while ischemic heart disease is less

Table 1 Patient characteristics by sex

Characteristics	Total HF population			HFrEF (EF ≤ 40%) population		
	Women (*n* = 830)	Men (*n* = 1094)	*p* value	Women (*n* = 188)	Men (*n* = 434)	*p* value
Age – years	79.0 ± 12.1	74.0 ± 12.4	<0.001	79.1 ± 11.1	74.3 ± 11.7	<0.001
Body weight – kg	71.7 ± 17.8	86.7 ± 18.0	<0.001	69.6 ± 16.5	85.5 ± 17.6	<0.001
Height – cm	160.8 ± 6.8	175.9 ± 7.1	<0.001	161.0 ± 6.5	175.4 ± 7.4	<0.001
Body mass index - kg/m^2	27.7 ± 6.3	28.0 ± 5.3	0.33	26.8 ± 5.8	27.7 ± 5.1	0.047
Serum creatinine - μmol/L*	97.1 ± 57.7	113.6 ± 77.3	<0.001	104.1 ± 50.5	111.9 ± 68.1	0.16
eGFR - ml/min	54.3 ± 26.3	71.9 ± 30.4	<0.001	49.2 ± 24.4	70.8 ± 30.4	<0.001
Systolic blood pressure – mmHg	132 ± 21	127 ± 19	<0.001	129 ± 20	124 ± 18	0.001
Diastolic blood pressure – mmHg	73 ± 12	75 ± 11	0.03	73 ± 11	74 ± 11	0.28
Heart rate – beats/min	76 ± 17	73 ± 16	<0.001	77 ± 15	75 ± 16	0.12
Ejection fraction – %	50.1 ± 10.7	44.8 ± 11.5	<0.001	34.4 ± 5.9	33.3 ± 6.3	0.04
NTproBNP, median (IQR) – pg/ml	1084 (392-25-10)	927 (331-21-77)	0.01	1884 (578-40-80)	1401 (579-31-19)	0.10
Serum potassium – mmol/L	4.22 ± 0.4	4.30 ± 0.4	<0.001	4.26 ± 0.4	4.35 ± 0.4	0.02
Hemoglobin – g/L	127.5 ± 14.0	136.8 ± 17.3	<0.001	126.7 ± 13.1	137.0 ± 16.8	<0.001
Medical history, n (%)						
Atrial fibrillation	422 (51)	563 (52)	0.79	88 (47)	213 (49)	0.60
Coronary artery disease	294 (35)	525 (48)	<0.001	72 (38)	243 (56)	<0.001
Diabetes	174 (21)	251 (23)	0.30	43 (23)	107 (25)	0.63
Hypertension	619 (75)	793 (73)	0.30	126 (67)	297 (68)	0.73
Previous HF hospitalization	328 (40)	407 (37)	0.30	96 (51)	215 (50)	0.73
Medications and devices, n (%)						
ACE-I or ARB	692 (83)	965 (88)	0.002	164 (87)	403 (93)	0.02
Beta-blocker	686 (83)	943 (86)	0.03	169 (90)	395 (91)	0.66
Mineralocorticoid receptor antagonist	254 (31)	392 (36)	0.02	76 (40)	219 (51)	0.02
Loop diuretics	541 (65)	621 (57)	<0.001	138 (73)	259 (60)	0.001
Digitalis	109 (13)	119 (11)	0.13	27 (14)	50 (12)	0.32
Implantable cardioverter--defibrillator†	28 (3)	108 (10)	<0.001	14 (7)	78 (18)	0.001
Cardiac resynchronization therapy†	30 (4)	102 (9)	<0.001	19 (10)	71 (16)	0.04

ACE-I, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *EF*, ejection fraction; *eGFR*, estimated glomerular filtration rate; *HF*, heart failure; *HFrEF*, heart failure with reduced ejection fraction; *IQR*, interquartile range; *NTproBNP*, N-terminal pro–B-type natriuretic peptide

* To convert the values for creatinine to mg/dl, divide by 88.4

† Including patients with cardiac resynchronization therapy defibrillator (CRT-D)

common than in men. Women also have a different body fat composition compared to men, which together with other biological aspects, such as longer gut transit time, higher CYP3A4 enzyme activity, lower renal blood flow, GFR and body weight, can affect both the pharmacodynamics and pharmacokinetics of HF drugs [24, 25]. Compared to previous studies on sex differences in HF treatment [15, 21, 22], this study includes a multivariable analysis to investigate possible other reasons than gender bias to explain treatment differences and offers updated knowledge of treatment differences. We hope this study can contribute to increased attention of a lower tolerance

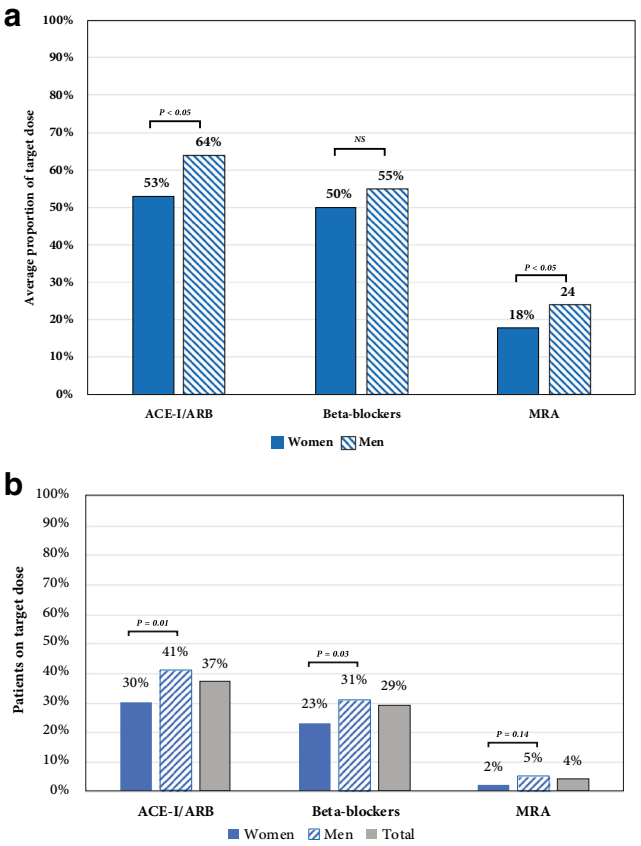

Fig. 1 Patients with heart failure and ejection fraction ≤ 40% with **a**) Average proportion of target dose of ACE inhibitors (ACE-I) or angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor antagonists (MRA), and **b**) Total proportion of patients on target dose of ACE-I/ARB, beta-blockers and MRA, according to sex. *p* values refer to differences between men and women. NS; Not significant

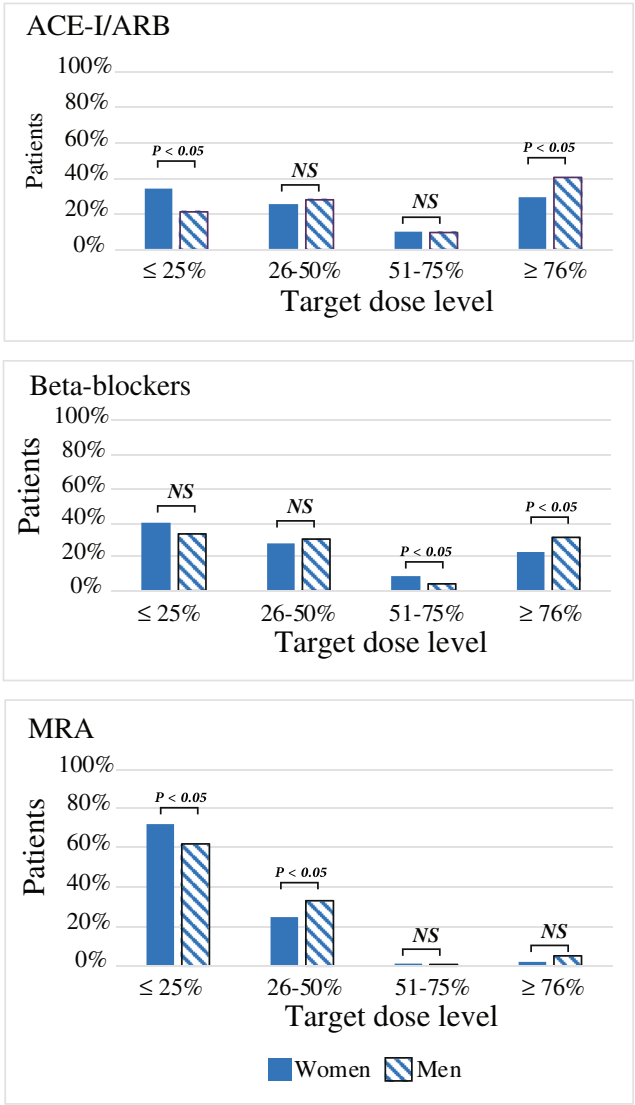

Fig. 2 Proportion of patients with heart failure and ejection fraction ≤ 40% according to target dose level of ACE inhibitors (ACE-I) or angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor blockers (MRA). NS; Not significant

of HF medications among female and frail patients and better guidance for clinicians. We did not find a significant association between sex and achieved doses in the HFrEF population which indicates that there is not a clear gender bias in HF treatment. However, the biological differences between men and women may explain differences in pharmacological tolerance and highlights the need for clinical trials that include patients with characteristics that better resemble the real-world HF population.

Most HF trials have aimed for the highest tolerable dose of HF medications, but some newer trials, such as the PARADIGM-HF study [11], only included patients who tolerated a fixed target dose during a run-in phase before randomization. When strict target doses are used as inclusion criteria, together with the shown differences between male and female patients in tolerance of HF medications, it is pharmacologically reasonable that elderly, frail and female patients are underrepresented in clinical trials. Previous studies have shown that approximately 50–75% of patients tolerate target doses of HF medications in clinical trials [3, 4, 8, 10, 11], compared with 7–50% of HFrEF patients in clinical practice [18, 29, 33, 34]. To gain more knowledge of how to offer the most appropriate HF treatment to the elderly and women, we need to increase the representation of these patients in clinical trials [35].

Limitations

The study only included a single-centre cohort, which limits the external validity of the results. On the other hand, it is based on a HF population without exclusion of old, frail patients with dementia or other comorbidities, which is especially important when analysing sex differences. The data collection period was relatively long (June 2015 to March 2016), as

Table 2 Bivariate and final regression models of percentage of achieved target doses of ACE-I/ARB, Beta-blockers and MRA in patients with heart failure and ejection fraction ≤40%

Bivariate models*

	ACE-I/ARB			Beta-blockers			MRA		
Variables	B	95% CI	*p* value	B	95% CI	*p* value	B	95% CI	*p* value
Sex†	0.107	0.043 to 0.170	0.001	0.053	−0.008 to 0.113	0.089	0.059	0.013 to 0.106	0.013
Age	−0.011	−0.014 to −0.009	<0.001	−0.008	−0.01 to −0.005	< 0.001	−0.008	−0.009 to −0.006	< 0.001
Body weight	0.005	0.003 to 0.007	<0.001	0.004	0.003 to 0.006	< 0.001	0.003	0.002 to 0.005	< 0.001
eGFR	0.005	0.004 to 0.006	<0.001	0.002	0.001 to 0.003	< 0.001	0.003	0.002 to 0.004	< 0.001
Systolic blood pressure	0.001	0.000 to 0.003	0.170	0.000	−0.002 to 0.001	0.736	−0.002	−0.003 to 0.000	0.006
Heart rate	−0.003	−0.005 to −0.001	0.001	0.000	−0.002 to 0.001	0.723	−0.002	−0.003 to −0.001	0.005
Ejection fraction	−0.003	−0.008 to 0.002	0.208	−0.001	−0.006 to 0.003	0.548	−0.005	−0.009 to −0.002	0.002
NTproBNP	−0.000	0.000 to 0.000	<0.001	−0.000	0.000 to 0.000	0.106	−0.000	0.000 to 0.000	0.003
Serum potassium	0.066	−0.004 to 0.135	0.064	0.031	−0.035 to 0.097	0.359	0.073	0.022 to 0.124	0.005
Atrial fibrillation	−0.079	−0.137 to -0.021	0.008	0.035	−0.021 to 0.090	0.222	−0.031	−0.074 to 0.012	0.158
Coronary artery disease	−0.017	−0.076 to 0.042	0.575	−0.015	−0.071 to 0.041	0.592	0.005	−0.038 to 0.048	0.820
Diabetes	−0.024	−0.092 to 0.045	0.499	0.06	−0.005 to 0.125	0.073	−0.009	−0.059 to 0.041	0.725
Hypertension	−0.029	−0.092 to 0.034	0.361	0.013	−0.046 to 0.073	0.662	−0.020	−0.066 to 0.027	0.406

Final regression models*,‡

ACE-I/ARB

	B	95% CI	*p* value
Sex†	−0.002	−0.067 to 0.064	0.959
Age	−0.006	−0.009 to −0.003	< 0.001
eGFR	0.003	0.002 to 0.004	< 0.001
Systolic blood pressure	0.002	0.000 to 0.003	0.012
Heart rate	−0.002	−0.004 to −0.001	0.006
Ejection fraction	−0.005	−0.009 to −0.001	0.028
Adjusted R^2 = 0.177			

Beta-blockers

	B	95% CI	*p* value
Sex†	−0.021	−0.085 to 0.043	0.527
Age	−0.007	−0.010 to −0.005	< 0.001
Body weight	0.002	0.001 to 0.004	0.002
Atrial fibrillation	0.067	0.012 to 0.123	0.018
Adjusted R^2 = 0.089			

MRA

	B	95% CI	*p* value
Sex†	−0.040	−0.088 to 0.009	0.108
Age	−0.003	−0.005 to −0.001	0.012
eGFR	0.002	0.001 to 0.003	< 0.001
Systolic blood pressure	−0.001	−0.002 to 0.000	0.038
Heart rate	−0.001	−0.003 to 0.000	0.026
Ejection fraction	−0.005	−0.008 to −0.002	0.001
Serum potassium	0.078	0.030 to 0.125	0.001
Adjusted R^2 = 0.168			

ACE-I, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *B*, unstandardised B-coefficients; *eGFR*, estimated glomerular filtration rate; *NTproBNP*, N-terminal pro-B-type natriuretic peptide; *MRA*, mineralocorticoid receptor blockers

* N = 622, NTproBNP N = 611

† Reference female

‡ Adjusted for body weight, NTproBNP, serum potassium, atrial fibrillation, coronary artery disease, diabetes, hypertension

well as the inclusion time period of patients visiting the hospital (January 2010 to March 2016). This also affects the statistical analyses and the generalisability of the results. Furthermore, the analyses including systolic blood pressure were based on the latest available blood pressure, often measured during ongoing HF treatment, which may have influenced the results. Additionally, the HF diagnoses extracted from the medical records were not all formally validated. It is therefore possible that a minor portion of the included patients with HF and preserved ejection fraction were misdiagnosed. However, the multivariable analysis only included HFrEF patients where the echocardiography showed a reduced ejection fraction. Unfortunately, the data in the medical records did not include enough information to assess the New York Heart Association (NYHA) functional class and is why we omitted this parameter in the statistical analyses.

Conclusions

Women with heart failure and reduced ejection fraction were prescribed lower doses of evidence-based heart failure medications. Women with heart failure were older, had worse renal function and lower body weight than men. Sex was not independently associated with achieved doses of heart failure medications; instead age, renal function and body weight explained the differences in treatment in patients with heart failure and reduced ejection fraction.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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