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# N-terminal pro-B-type natriuretic peptide in chronic heart failure: The impact of sex across the ejection fraction spectrum

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ABSTRACT

*Objective:* The aim was to assess sex-specific differences in N-terminal B-type natriuretic peptide (NT-proBNP) regarding concentrations, predictors of high concentrations, and prognostic role, in a large and unselected population with chronic heart failure (HF) with preserved (HFpEF), mid-range (HFmrEF), and reduced ejection fraction (HFrEF).

*Methods and results:* In 9847 outpatients with HFpEF, HFmrEF, and HFrEF (49 vs. 35 vs. 25% females, respectively) from the Swedish HF Registry, median NT-proBNP concentrations were 1598 ng/L in females vs. 1310 ng/L in males in HFpEF, 1764 vs. 1464 ng/L in HFmrEF, and 2543 vs. 2226 ng/L in HFrEF ($p < 0.05$ for all). The differences persisted after multiple adjustment. The largest sex-difference in NT-proBNP levels was observed in HFpEF with sinus rhythm, where median concentrations were 1.4 folds higher in females (923 vs. 647 ng/L). Independent predictors of NT-proBNP levels (defined as above the different medians according to sex and HF phenotype) were overall consistent across sexes and EF. NT-proBNP levels were similarly associated with risk of all-cause death/HF hospitalization in both sexes regardless of EF.

*Conclusion:* Concentrations of NT-proBNP were higher in females across the EF spectrum, with larger relative differences in HFpEF with sinus rhythm. However, similar predictors of high levels were observed in both sexes. There were no sex-differences in the prognostic role of NT-proBNP. These findings support the use of NT-proBNP for prognostic purposes in chronic HF, regardless of sex.



## 1. Introduction

The use of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) is well established for diagnostic, prognostic, and trial selection purposes in heart failure (HF) [1]. Concentrations of natriuretic peptides (NPs) are higher in HF with reduced (HFrEF) compared with preserved (HFpEF) and mid-range ejection fraction (HFmrEF), in both stable and decompensated states [2–4], and higher in HF with atrial fibrillation (AF) vs. sinus rhythm [4].

Regarding NP concentrations, apart from HF phenotype, rhythm, and HF severity, they are also affected by age, comorbidities, and sex [4–6]. Compared with males, both healthy females and those suffering from acute HF have higher concentrations of NPs [3,7,8], although data is not consistent [9–11]. The enrolment of patients with different ejection fraction (EF) phenotypes might at least in part explain previous conflicting results, given the major effect of EF on NP concentrations [9,10]. In chronic HF, comprehensive population-based studies on sex-differences in NT-proBNP across the EF spectrum are lacking, but higher [6], similar [12], or lower [13] concentrations in females vs. males have been described in trial settings.

Regarding the association between NPs and outcomes, BNP is associated with short-term prognosis regardless of sex in patients hospitalized for acute HF [14]. In contrast, for longer-term outcome, there are conflicting data on the prognostic role of NPs in females vs. males [10,15,16], and the simultaneous enrolment of patients with different EF limits their interpretation. In chronic HF, data on sex differences are limited, but evidence from trials in HFpEF/HFmrEF supports similar prognostic power of NT-proBNP across sexes [13].

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In healthy subjects, certain comorbidities affect NP concentrations differently in females vs. males [17]. Considering that NP concentrations are lower with higher EF, sex might have a different impact on NP levels according to the specific HF phenotype [2–4]. Additionally, males and females with HF show different comorbidity profiles, such as different prevalence of AF, kidney and ischemic heart disease, which may differently affect both prognosis and NP concentrations, and hence confound the prognostic role of NPs [18].

Currently, NPs are used for diagnostic and prognostic purposes in HF patients regardless of sex. Our hypothesis is that sex may play a minor role on NT-proBNP concentrations and prognostic role in patients with HF vs. healthy subjects, given the higher concentrations of NPs in the first vs. the latter.

Hence, the aim of the present study was to compare females vs. males with chronic HFpEF, HFmrEF, and HFrEF regarding (1) concentrations of NT-proBNP, (2) independent predictors of NT-proBNP levels, and (3) prognostic role of NT-proBNP, in a large and unselected contemporary cohort of HF patients.

## 2. Methods

### 2.1. Study population

The Swedish Heart Failure Registry (SwedeHF, www.swedehf.se) covers 75% of the hospitals and about 10% of primary care centers in Sweden. The only inclusion criterion is "Clinician–judged HF". About 80 variables are recorded in a web-based case report form. At the registration, EF from the most recent echo is reported if assessed within a reasonable time frame and categorized as <30, 30–39, 40–49, and ≥50% [19]. In the present study, HFpEF was defined as EF ≥50%, HFmrEF as EF 40–49%, and HFrEF as EF <40%, according to the current European Society of Cardiology guidelines on HF [1]. Similarly, at the registration the most recent NT-proBNP measurement is registered if collected within a reasonable time frame. The specific NT-proBNP assay used for each measurement is not available, but the majority of all the centers enrolling patients in SwedeHF use the assay from Roche, Bromma, Sweden (www.equalis.se).

SwedeHF was linked with The Population Registry and the Patient Registry, administered by The Swedish Board of Health and Welfare (www.socialstyrelsen.se), through the Swedish personal identification number. From the Population Registry we obtained the date of death, whereas additional baseline comorbidities and the outcome HF hospitalization, defined according to International Classification of Disease, 10th Edition (ICD-10) codes in the first position, were obtained from The Patient Registry. ICD-10 coding in Sweden has been validated, with an 85–95% positive predictive value for most diagnoses and an HF diagnosis verified in 86–91% of cases [20]. The establishment of the HF registry and the present study conformed to the Declaration of Helsinki and have ethics approval by ethical committee in Sweden [21]. Informed consent is not required to be registered in SwedeHF but patients are allowed to opt out.

Inclusion criteria for our analysis were: registration as outpatient, NT-proBNP measured, no missing data for EF and follow-up ≥1 day. If the same patient reported multiple registrations, the first as outpatient including a NT-proBNP measurement was selected. Between May 11th 2000 and December 31st 2012, there were 80,772 registrations from 51,060 unique patients in SwedeHF. Of these 24,975 were outpatients and 9847 fulfilled all the inclusion criteria (Appendix Fig. 1). Outcomes were the time to all-cause death or HF hospitalization (composite outcome) and time to all-cause death. The index date was defined as the outpatient clinic visit for HF at which NT-proBNP levels were available. End of follow-up was December 31st, 2012.

### 2.2. Statistics

#### 2.2.1. Baseline characteristics and NT-proBNP concentrations

Baseline characteristics were compared in females vs. males for each HF type. Continuous variables are presented as median [interquartile range (IQR)] whereas categorical variables as frequencies (percentages). Statistical significance testing was performed through Mann- Whitney test for continuous variables and Pearson $Chi^2$-test for categorical data.

Median NT-proBNP concentrations were compared in females vs. males according to the EF phenotype. Additional analyses were performed stratifying by presence of AF, obesity, New York Heart Association (NYHA) class, anemia, and kidney function (Table 2, Appendix Fig. 2). Variables were defined/categorized as in Fig. 1A–C.

Multivariable linear regression analysis was used to compare logarithmically transformed NT-proBNP concentrations in females vs. males for each HF phenotype. Covariates in model 1 were age, NYHA class, AF, kidney function, body mass index (BMI), and anemia. In model 2 ischemic heart disease (IHD), diabetes, heart rate, and planned follow-up speciality were added since they differed between sexes. Variables were defined/categorized as in Fig. 1A–C.

In all the multivariable models performed in our analyses, the presence of missing data for covariates was addressed through multiple imputation with chained equations (n = 10), which was separately performed in females and males with the different HF phenotypes. The variables included in the multiple imputation models have been reported in Appendix Table 1.

#### 2.2.2. Predictors of NT-proBNP levels in females vs. males

The independent predictors of NT-proBNP levels, categorized as above (high concentrations) vs. at or below the median (low concentrations), were assessed in each HF phenotype through multivariable logistic regressions. An interaction term between each baseline characteristic and sex was included in order to assess potential sex-differences for the associations. Because of the large sample size and the fact that the different predictors of NT-proBNP levels in females vs. males are largely unknown, besides sex, 32 clinically relevant variables, potentially affecting NT-proBNP, were included as covariates in the models 31 in HFpEF and HFmrEF where HF device as primary prevention Implantable Cardioverter Defibrillator and cardiac resynchronization therapy are not recommended. The covariates included in the models are marked with "*" in Appendix Table 1. Multicollinearity was assessed through the variance inflation factor (VIF) analysis. A VIF <5 was considered as tolerable. Odds Ratios and 95% Confidence Intervals (CI) for particularly relevant variables are presented in Fig. 1A–C, whereas all the remaining data are reported in Appendix Table 2.

#### 2.2.3. Prognostic role of NT-ProBNP in females vs. males

The association between NT-proBNP, defined as above vs. at or below the median, and time to outcomes was assessed within each EF group. Unadjusted survivor functions were estimated through the Kaplan-Meier method. The size of the associations between NT-proBNP and outcomes was assessed by Cox proportional hazard models. Both crude and adjusted (i.e. for the same variables as for the logistic regression models) hazard ratios (HR) (95% CI) were calculated. We also modelled NT-proBNP levels as a quantitative predictor of event rates with the use of restricted cubic splines (3 knots at fixed percentile of the distribution) to flexibly model potential nonlinearity [22]. Statistical interactions between high/low or continuous NT-proBNP levels and sex were tested by Wald-type test.

All statistical analyses were performed by Stata 14.1 (StataCorp, College Station, Texas).

## 3. Results

### 3.1. Baseline characteristics and NT-proBNP concentrations

Of 9847 patients, 1811 (18%) had HFpEF, 2122 (22%) HFmrEF, and 5914 (60%) HFrEF. The proportion of females was higher in HFpEF (49%) vs. HFmrEF (35%) vs. HFrEF (25%). Baseline data are shown in Table 1. Regardless of EF, females were older, with higher NYHA class, and had better renal function compared with males. Prevalence of diabetes, IHD, and anemia was lower in females. In HFpEF and HFrEF, AF was less prevalent in females vs. males. Use of therapies was similar in both sexes except for more use of diuretics in females with HFpEF and HFmrEF and more use of statins in males, regardless of EF.

Concentrations of NT-proBNP were higher in females vs. males in all three HF types. In HFpEF median NT-proBNP (IQR) was 1598 (709, 3186) in females vs. 1310 (536, 2771) in males, in HFmrEF 1764 (670, 3640) vs. 1464 (640, 3173), and in HFrEF 2543 (1100, 5520) vs. 2226 (1003, 4650) ng/L, respectively ($p < 0.05$ for all the crude comparisons) (Table 1 and Appendix Fig. 2A).

Sex-differences in NT-proBNP levels were overall consistent when rhythm status was considered (AF vs. non-AF), except for HFmrEF where there was no statistically significant difference in NT-proBNP concentrations across sexes in patients with sinus rhythm (Table 2 and Appendix Fig. 2B–C). In particular, in females vs. males with HFpEF, median concentrations were 1.4-folds higher in sinus rhythm (923 vs.647 ng/L), and 1.2-folds higher (2158 vs. 1805 ng/L) in presence of concomitant AF. In HFrEF, females vs. males had 1.2-folds higher concentrations in sinus rhythm (2320 vs. 1900 ng/L, respectively) vs. 1.05-fold in the presence of AF (2759 vs. 2628 ng/L, respectively). Females vs. males also had consistently higher NT-proBNP concentrations in both HFpEF and HFrEF when the population was stratified according to concomitant obesity, kidney disease, NYHA class and anemia, with the exceptions of HFpEF patients without anemia who did not show sex-differences in NT-proBNP levels. Sex-differences in NT-proBNP concentrations were overall less pronounced in HFmrEF (Table 2).

When comparing NT-proBNP concentrations in females vs. males adjusting for age, BMI, eGFR, presence of AF, NYHA class, and anemia, which are well-known factors influencing NT-proBNP levels, females still reported significantly higher concentrations (p-value <0.001 in HFpEF and HFrEF; $p = 0.006$ in HFmrEF). When adjusting also for

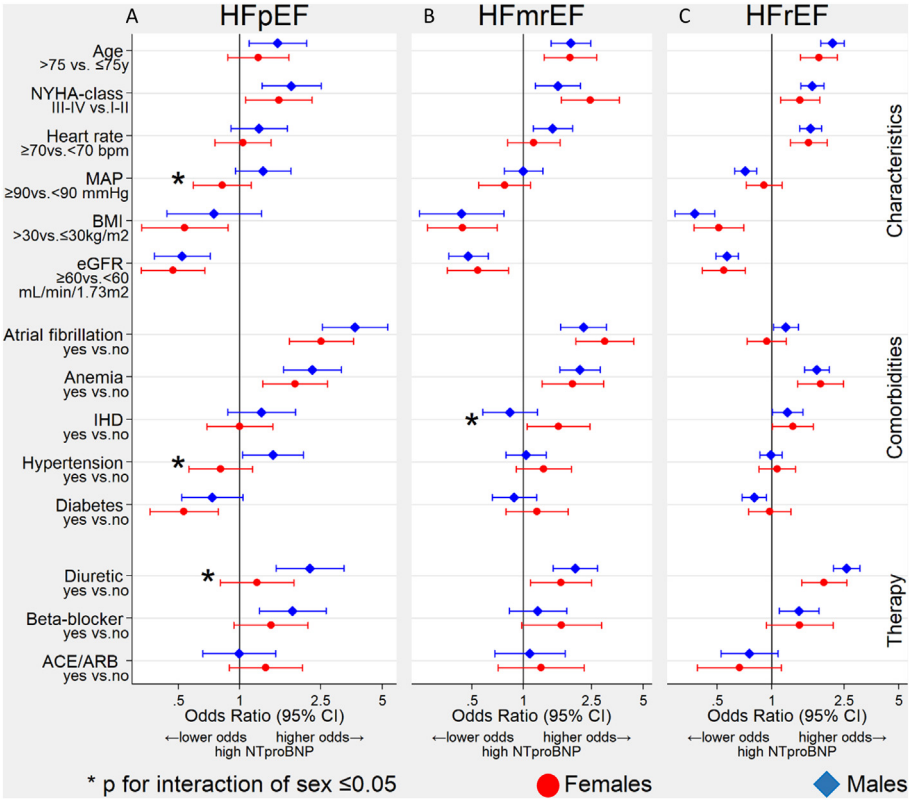


**Fig. 1.** A–C: Independent predictors of high NT-proBNP levels in females (red) and males (blue) with HFpEF (A), HFmrEF (B), and HFrEF (C). High NT-proBNP is defined as above the median in females and males in each heart failure type. "*" denotes p for interaction with sex ≤0.05, i.e. a statistically significant difference in the association between the variable and high NT-proBNP in females vs. males. Abbreviations: HFpEF, heart failure (HF) with preserved ejection fraction (EF); HFmrEF, HF with mid-ranger EF; HFrEF, HF with reduced EF; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; MAP, mean arterial blood pressure, BMI, body mass index; eGFR MDRD, estimated glomerular filtration rate through the Modification of Diet in Renal Disease formula (mL/min/1.73 $m^2$); IHD, ischemic heart disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

IHD, diabetes, heart rate, and follow-up referral speciality, NT-proBNP concentrations were still higher in females, $p < 0.001$ for HFpEF and HFrEF, and $p = 0.002$ for HFmrEF.

### 3.2. Predictors of NT-proBNP levels in females vs. males

Independent associations between relevant demographics/clinical characteristics/therapies and NT-proBNP are shown in Fig. 1A–C and Appendix Table 2. Overall, independent predictors of NT-proBNP concentrations were similar in both sexes regardless of HF phenotype but with some exceptions. In HFpEF, hypertension was associated with high NT-proBNP in males but not in females (p-interaction sex * hypertension = 0.015). A significant association was observed between mean arterial pressure (MAP) and NT-proBNP in males but not in females (p-interaction 0.040). Diuretic use was associated with increased odds of high NT-proBNP in males but not in females (p-interaction = 0.032). In HFmrEF, IHD was associated with high NT-proBNP in females but not in males (p-interaction 0.005). There was no significant interaction between all the variables tested and sex in HFrEF.

Notably, regardless of sex and HF type, anemia, kidney disease, and higher NYHA class (III–IV vs. I–II) were associated with increased odds of high NT-proBNP. In contrast, obesity (BMI ≥30 kg/$m^2$) was associated with reduced odds of high NT-proBNP in HFrEF and HFmrEF only. Finally, AF was associated with higher odds of high NT-proBNP in HFpEF and HFmrEF, but not in HFrEF.

### 3.3. Prognostic role of NT-ProBNP in females vs. males

In HFpEF, over a median (IQR) follow-up of 2.1 (1.0–3.6) years, 100 deaths per 1000 patient-years occurred in females vs. 107 in males. In HFmrEF rates were 89 vs. 100 per 1000 patient-years over 2.0 (1.0–3.6) years, and in HFrEF they were 85 vs. 89 per 1000 patient-years over 2.0 (0.9–3.6) years in females vs. males, respectively.

Rates for the composite endpoint of HF hospitalization or all-cause death were 169 vs. 172 per 1000 person-years in females vs. males in HFpEF, 188 vs. 171 in HFmrEF and 209 vs. 243 in HFrEF.

Fig. 2A and Appendix Fig. 3A show survival free of HF hospitalization and overall survival, respectively, together with crude and adjusted hazard ratios (HRs) for outcomes, for high vs. low NT-proBNP levels in females vs. males with HFpEF, HFmrEF, and HFrEF. NT-proBNP above median was associated with increased unadjusted and adjusted risk of outcomes regardless of sex and EF. No significant interaction between sex and NT-proBNP levels was observed for any HF type. When the association between continuous NT-proBNP levels and outcomes was analysed, a strong positive dose-response association was observed in both females and males in all the HF phenotypes, in absence of any statistical interaction sex * NT-proBNP (Fig. 2B and Appendix Fig. 3B).

## 4. Discussion

In this comprehensive analysis of NT-proBNP in males vs. females with HFpEF, HFmrEF, and HFrEF, we observed higher NT-proBNP concentrations in females. Nevertheless, the prognostic role of NT-proBNP and the predictors of high concentrations were similar in both sexes.

### 4.1. Sex-differences in NT-proBNP concentrations

It has been previously shown that healthy females have higher NPs concentrations than males, which may be partially explained by the effect of sex-hormones [7,17,23,24]. In chronic HF, sex-specific data on

**Table 1**
Baseline characteristics by sex and heart failure phenotype.

| | HFpEF | | | HFmrEF | | | HFrEF | | |
|---|---|---|---|---|---|---|---|---|---|
| | Females n = 882 (49%) | Males n = 929 (51%) | p-Value | Females n = 748 (35%) | Males n = 1374 (65%) | p-Value | Females n = 1484 (25%) | Males n = 4430 (75%) | p-Value |
| *Demographics/clinical variables, median (IQR)* | | | | | | | | | |
| Age (years) | 78 (72, 83) | 75 (67, 81) | <0.001 | 76 (67, 82) | 73 (64, 80) | <0.001 | 73 (64, 80) | 70 (61, 78) | <0.001 |
| NYHA class n (%) I–II | 361 (55) | 480 (63) | 0.002 | 403 (62) | 845 (70) | 0.001 | 743 (54) | 2460 (59) | 0.002 |
| III–IV | 301 (45) | 286 (37) | | 250 (38) | 378 (31) | | 627 (46) | 1704 (41) | |
| HR (beats/min) | 70 (62, 80) | 68 (60, 78) | <0.001 | 70 (61, 80) | 68 (60, 78) | <0.001 | 70 (62, 80) | 70 (60, 80) | 0.011 |
| Systolic blood pressure (mm Hg) | 130 (120, 145) | 130 (120, 140) | 0.034 | 130 (115, 143) | 125 (115, 140) | 0.051 | 120 (110, 140) | 120 (110, 139) | 0.76 |
| Diastolic blood pressure (mm Hg) | 71 (65, 80) | 70 (65, 80) | 0.35 | 70 (65, 80) | 75 (65, 80) | 0.055 | 70 (62, 80) | 70 (65, 80) | <0.001 |
| BMI (kg/m$^2$) | 27 (24, 32) | 28 (25, 31) | 0.42 | 27 (23, 31) | 27 (25, 31) | 0.50 | 26 (22, 30) | 26 (24, 30) | <0.001 |
| *Biochemistry, median (IQR)* | | | | | | | | | |
| NT-proBNP (ng/L) | 1598 (709, 3186) | 1310 (536, 2771) | <0.001 | 1764 (670, 3640) | 1464 (640, 3173) | 0.043 | 2543 (1100, 5520) | 2226 1003, 4650) | <0.001 |
| eGFR MDRD (mL/min/1.73 m$^2$) | 75 (58, 95) | 63 (48, 79) | <0.001 | 79 (61, 100) | 66 (51, 82) | <0.001 | 81 (61, 102) | 67 (52, 82) | <0.001 |
| *Comorbidities, n (%)* | | | | | | | | | |
| Atrial fibrillation | 512 (58) | 593 (64) | 0.012 | 431 (58) | 782 (57) | 0.75 | 613 (41) | 2243 (51) | <0.001 |
| Hypertension | 645 (73) | 654 (70) | 0.20 | 499 (67) | 855 (62) | 0.040 | 840 (57) | 2444 (55) | 0.34 |
| Diabetes | 182 (21) | 254 (27) | <0.001 | 161 (22) | 348 (25) | 0.050 | 339 (23) | 1163 (26) | 0.009 |
| Ischemic heart disease | 323 (37) | 405 (45) | 0.002 | 295 (40) | 765 (57) | <0.001 | 636 (45) | 2284 (54) | <0.001 |
| Previous coronary revascularization | 137 (16) | 248 (27) | <0.001 | 154 (21) | 550 (40) | <0.001 | 325 (22) | 1572 (36) | <0.001 |
| Stroke/TIA | 142 (16) | 144 (16) | 0.73 | 99 (13) | 225 (16) | 0.055 | 167 (11) | 650 (15) | <0.001 |
| Peripheral arterial disease | 63 (7) | 83 (9) | 0.16 | 58 (8) | 145 (11) | 0.036 | 95 (6) | 358 (8) | 0.035 |
| Anemia | 222 (25) | 326 (35) | <0.001 | 173 (23) | 433 (32) | <0.001 | 289 (20) | 1128 (26) | <0.001 |
| History of malignant cancer within 3 years | 114 (13) | 145 (16) | 0.10 | 76 (10) | 199 (15) | 0.005 | 157 (11) | 528 (12) | 0.16 |
| Valve disease | 301 (35) | 271 (30) | 0.025 | 194 (26) | 286 (21) | 0.008 | 304 (21) | 801 (18) | 0.041 |
| Lung disease | 232 (26) | 222 (24) | 0.24 | 200 (27) | 340 (25) | 0.31 | 392 (26) | 967 (22) | <0.001 |
| Never smoker | 426 (61) | 337 (44) | <0.001 | 352 (57) | 478 (41) | <0.001 | 632 (50) | 1419 (36) | <0.001 |
| *Treatments, n (%)* | | | | | | | | | |
| Beta blocker | 717 (82) | 726 (78) | 0.077 | 648 (87) | 1194 (87) | 0.89 | 1361 (92) | 4071 (92) | 0.78 |
| ACEi/ARB | 725 (82) | 770 (83) | 0.74 | 674 (90) | 1265 (92) | 0.11 | 1400 (95) | 4247 (96) | 0.024 |
| Diuretics | 715 (82) | 705 (76) | 0.005 | 544 (73) | 927 (68) | 0.013 | 1152 (78) | 3339 (76) | 0.061 |
| Aldosterone antagonists | 223 (25) | 260 (28) | 0.20 | 213 (28.6) | 335 (24.5) | 0.041 | 545 (36.8) | 1665 (38) | 0.56 |
| Digoxin | 152 (17) | 131 (14) | 0.063 | 129 (17) | 189 (14) | 0.035 | 234 (16) | 681 (15) | 0.71 |
| Statin | 354 (40) | 415 (45) | 0.053 | 311 (42) | 771 (56) | <0.001 | 634 (43) | 2315 (52) | <0.001 |
| Nitrates | 125 (14) | 127 (14) | 0.74 | 87 (12) | 177 (13) | 0.39 | 158 (11) | 467 (11) | 0.94 |
| Oral anticoagulants | 379 (43) | 421 (45) | 0.34 | 314 (42) | 610 (45) | 0.26 | 543 (37) | 2043 (46) | <0.001 |
| Platelet inhibitor | 342 (39) | 376 (41) | 0.47 | 302 (41) | 658 (48) | <0.001 | 674 (45) | 2071 (47) | 0.33 |
| Device therapy (ICD or CRT) | 19 (2) | 13 (2) | 0.35 | 24 (3) | 59 (4) | 0.22 | 88 (6) | 469 (11) | <0.001 |

Abbreviations: HFpEF, heart failure with preserved ejection; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; NYHA, New York Heart Association; HR, heart rate; BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR MDRD, estimated glomerular filtration rate through the Modification of Diet in Renal Disease formula; TIA, transient ischemic attack; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

NPs are limited and contrasting, with higher [6], similar [12], or even lower [13] NT-proBNP concentrations measured in females vs. males. Most of the data available is from randomized clinical trial cohorts, including patients who are younger, with less comorbidities, and better treated than those encountered in daily clinical practice [25]. All these factors may affect NT-proBNP levels, preventing or fostering the observation of potential sex-difference.

SwedeHF, enrolling a large cohort of unselected patients with HFpEF, HFmrEF and HFrEF, represents an extraordinary tool to phenotype HF. Analysing the three different EF groups is also critical for optimizing the design of many nascent HF trials. In our analysis of the SwedeHF population, concentrations of NT-proBNP were higher in females vs. males regardless of EF phenotype, as previously shown for BNP in the acute setting [3]. We also confirmed the results from previous studies showing higher NT-proBNP concentrations in HFrEF compared with HFpEF and HFmrEF [3,4,26]. The observed sex-differences in NT-proBNP levels were almost similar across the EF spectrum. When patients were stratified according to EF and AF status, females had higher NT-proBNP levels regardless of EF and AF status, except for HFmrEF patients with sinus rhythm where concentrations were similar in both sexes. The largest sex-differences in NT-proBNP levels were in patients with HFpEF and sinus rhythm, with females reporting 1.4-folds higher median NT-proBNP concentrations than males. Compared to HFpEF and HFrEF, in HFmrEF sex-differences in NT-proBNP concentrations were less pronounced when patients were stratified according to concomitant AF, NYHA class, obesity, anemia, and kidney disease, possibly reflecting the heterogeneity that characterizes the HFmrEF phenotype.

Importantly, NT-proBNP concentrations were unadjusted and thus the observed sex-related differences might be explained by different demographics, distribution of comorbidities, and use of therapies in females vs. males. Indeed, regardless of HF phenotype, females were older and with higher NYHA class, which could in part explain their higher NT-proBNP concentrations [27,28]. In contrast, females had better renal function, which would instead support lower concentrations in females vs. males [6]. Similarly, in HFpEF and HFrEF, the prevalence of AF was lower in females, which would instead lead to lower NP levels [4,29,30]. Nevertheless, after adjusting for these and other important clinical characteristics known to affect NP levels (age, HF severity, presence of AF, kidney function, BMI, and anemia), NT-proBNP concentrations were still higher in females. These findings are hard to explain by sex-hormones alone. Age-related comorbidities not considered in the current analysis, systemic inflammation, hyperthyroidism and overall a higher prevalence of autoimmune and specific endocrine disorders which are more common in females vs. males may contribute to explain the higher NP concentrations in the first vs. the latter [31].

**Table 2**
Concentrations (median, interquartile range) of NT-proBNP in females vs. males stratified by ejection fraction and heart rhythm, kidney function, obesity, anemia, and heart failure severity.

| | HFpEF | | | HFmrEF | | | HFrEF | | |
|---|---|---|---|---|---|---|---|---|---|
| | Females | Males | p | Females | Males | p | Females | Males | p |
| AF | 2158 (1161,3800) | 1805 (930, 3483) | 0.007 | 2475 (1290,4175) | 1920 (1057, 3804) | 0.006 | 2759 (1494, 5397) | 2628 (1320, 5119) | 0.042 |
| No AF | 923 (413, 2256) | 647 (221, 1560) | <0.001 | 851 (364, 2490) | 928 (344, 2285) | 0.092 | 2320 (873, 5560) | 1900 (789, 4305) | <0.001 |
| eGFR ≥60 mL/1.73 $m^2$ | 1373 (637, 2678) | 995 (306, 1980) | <0.001 | 1352 (540, 3000) | 1065 (434, 2210) | <0.001 | 2180 (956, 4460) | 1724 (782, 3636) | <0.001 |
| eGFR <60 mL/1.73 $m^2$ | 1598 (709, 3186) | 1310 (536, 2771) | <0.001 | 1764 (670, 3640) | 1464 (640, 3173) | 0.043 | 2543 (1100, 5520) | 2226 (1003, 4650) | <0.001 |
| BMI <30 kg/$m^2$ | 1480 (677, 2960) | 1271 (487, 2571) | 0.006 | 1560 (663, 3355) | 1420 (623, 2996) | 0.091 | 2220 (920, 4790) | 1939 (906, 4216) | 0.010 |
| BMI ≥30 kg/$m^2$ | 1634 (711, 3254) | 1346 (546, 2965) | <0.001 | 1876 (694, 3685) | 1550 (681, 3317) | 0.074 | 2640 (1191, 5768) | 2367 (1070, 4901) | 0.003 |
| Anemia | 2250 (1010,4850) | 1961 (881, 4419) | 0.20 | 2657 (1090,5890) | 2440 (1159, 5060) | 0.63 | 4157 (1750, 8485) | 3344 (1679, 6554) | 0.021 |
| No anemia | 1434 (629, 2835) | 1063 (377, 2140) | <0.001 | 1491 (568, 3100) | 1190 (517, 2389) | <0.001 | 2290 (1001, 4760) | 1922 (867, 4041) | <0.001 |
| NYHA I–II | 1440 (623, 2843) | 1110 (406, 2371) | <0.001 | 1410 (552, 3095) | 1350 (605, 2826) | 0.49 | 2160 (960, 4571) | 1900 (866, 3950) | 0.003 |
| NYHA III–IV | 1634 (711, 3254) | 1346 (546, 2965) | <0.001 | 1876 (694, 3685) | 1550 (681, 3317) | 0.74 | 2640 (1191, 5768) | 2367 (1070, 4901) | 0.003 |

Abbreviations: HFpEF, heart failure with preserved ejection; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate through the Modification of Diet in Renal Disease formula; BMI, body mass index; NYHA, New York Heart Association functional class.

### *4.2. Sex-differences in the associations of patient characteristics with high NT-proBNP*

Despite the higher concentrations in females vs. males, independent predictors of high NT-proBNP levels were overall similar across sexes, with only few exceptions. In HFpEF, diuretic use was associated with higher concentrations in males but not in females. As shown in our and previous analyses, females are more likely to receive diuretic therapy compared to other treatments [18]. Perhaps the wider use of diuretics, potentially even in absence of congestion, may confound the association with NT-proBNP concentrations. Another explanation may be that females tend to be undertreated compared to males, and thus they may have been less likely to receive diuretics in presence of increased NT-proBNP levels. In HFpEF, we also observed hypertension and higher blood pressure being associated with higher NT-proBNP in males but not in females. The underlying reason is unclear, but one explanation may be that females with HFpEF display more pronounced left ventricular systolic and diastolic stiffness, leading to less wall tension following increased afterload and thus, less NT-proBNP secretion [12].

In HFmrEF, the only different determinant of NT-proBNP levels across sexes was IHD, which was associated with higher levels in females but not in males. This might reflect residual confounding from unmeasured factors associated with age since IHD occurs later in females than in males and, at the same time, NT-proBNP concentrations increase with aging [27]. Another explanation may be a more severe HF following IHD in females vs. males leading to higher NT-proBNP levels in the first vs. the latter [32]. The reason for this observation in HFmrEF but not in the other phenotypes is unknown and might reflect

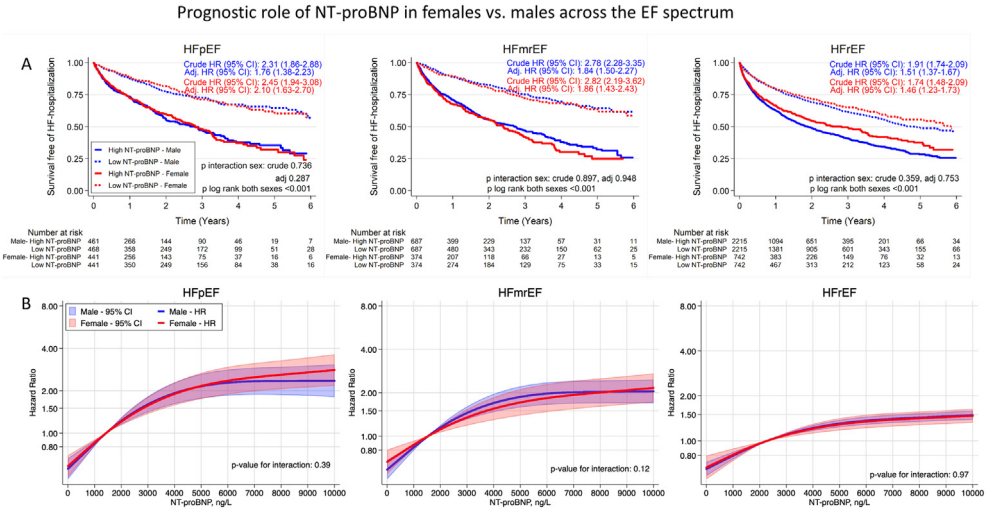


**Fig. 2.** A–B: Prognostic role of NT-proBNP in females vs. males across the EF spectrum. Panel A includes Kaplan Meier curves for survival free of HF hospitalization in females vs. males with NT-proBNP above vs. at or below the median; log rank test for difference high vs. low NT-proBNP in females and males; crude and adjusted hazard ratios and confidence intervals for high vs. low NT-proBNP levels in females and males together with p for the interaction sex * NT-proBNP. Panel B includes splines for survival free of HF hospitalization according to continuous NT-proBNP levels in females vs. males together with p for interaction sex * NT-proBNP. Abbreviations: HFpEF, heart failure (HF) with preserved ejection fraction (EF); HFmrEF, HF with mid-range EF; HFrEF, HF with reduced EF; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HR, hazard ratio; CI, confidence interval.

the heterogeneity that characterizes HFmrEF. Despite higher concentrations in females, there were no significant sex-differences in determinants of high NT-proBNP in HFrEF.

While sex is an important predictor of NP concentrations in healthy subjects [33] and a recent study demonstrated a more relevant role of obesity on NT-proBNP concentrations in females vs. males [17], we could not observe similar evidences in patients with chronic HF. One explanation may be that in HF, given the higher NP concentrations and NP secretion mainly due to increased wall stress, the additive impact of sex on driving NT-proBNP levels is small. However, the large amount of missing data for BMI (around 50%) in the present study requires to be acknowledged and thus, further analyses investigating the effect of BMI on NP concentrations are needed.

Overall, we confirmed kidney function, anemia, and BMI as important predictors of NT-proBNP concentrations in chronic HF [4], and we excluded the presence of any difference in the predictive role of these factors according to sex. Taken together, the higher concentrations of NT-proBNP in females vs. males with chronic HF do not seem to be explained by sex-differences in the predictors of high NT-proBNP explored in the current analysis.

### *4.3. Sex-differences in the prognostic role of high NT-proBNP*

To the best of our knowledge, our analysis focuses, for the first time, on sex-differences in the long-term prognostic role of NT-proBNP in a large and unselected cohort of chronic HFpEF, HFmrEF, and HFrEF patients. A previous study from Get with the Guidelines-HF (GWTG-HF) registry enrolling acute HF patients regardless of EF reported that high BNP was similarly associated with in-hospital mortality in both males and females [3]. Sex-specific data on longer-term outcome in acute HF are scarce, with some evidence from cohorts with mixed EF supporting a better prognostic power of NPs in males vs. females [10,15]. Females with HF have consistently shown better prognosis than males [13,34,35], and one proposed explanation for the observed lower risk of cardiovascular events is the different sex-hormonal profile in females and its link to NPs [36].

We showed in a chronic HF setting that high NT-proBNP levels are associated with increased mortality and morbidity regardless of sex and EF phenotype in chronic HF. The prognostic role of both BNP and NT-proBNP is well known in chronic HFrEF [6,37,38]. Conversely, it has been less investigated in HFpEF [39] and certainly in HFmrEF, that have often been considered together as one category [4,26,40,41]. Sex-specific analyses are even scarcer [13,26]. One previous analysis from the I-PRESERVE trial enrolling HFpEF/HFmrEF patients showed 1-unit log increase in NT-proBNP associated with similar increase in risk of all-cause death in males and females [13]. On the other hand, a subgroup analysis from a SwedeHF study reported slightly higher unadjusted cardiovascular and non-cardiovascular event rates in female in- or outpatients compared with males with the same NT-proBNP concentration [26]. Our adjusted analysis of outpatients with different HF phenotypes is consistent with the previous findings from I-PRESERVE despite the overall higher NT-proBNP concentrations, older age, less obese patients and more prevalent AF in our HFpEF registry cohort vs. I-PRESERVE trial cohort [13]. As compared with our previous SwedeHF analysis, the current findings stress the importance of considering NT-proBNP in the context of all the patients' characteristics for an appropriate prognostic assessment [26].

### *4.4. Limitations*

The retrospective nature of this registry-based study represents a limitation. Furthermore, the only inclusion criterion in SwedeHF is clinician-judged HF and thus we cannot rule out that some patients might not have HF. There were missing data for some variables that were handled by multiple imputation to reduce the bias due to missing data at random and to increase external validity and generalizability. A concern may be the large proportion of patients with missing BMI measurement, given the important association between body fat and NP concentrations. However, baseline characteristics of patients with vs. without BMI assessment available were comparable (Appendix Table 3) and thus, imputing missing data by chained equations multiple imputation may have been effective. Data on the exact timing of echocardiography and NT-proBNP measurement, the exact EF measure/method for assessment, and the specific assay used for NT-proBNP levels evaluation are not reported in the registry. However, NT-proBNP and EF values are recorded as corresponding to a specific SwedeHF registration only whether the time frame between the EF/NT-proBNP assessment and the index date is considered as clinically reasonable. Also other echocardiographic variables, such as cardiac structural and functional parameters (e.g. left ventricular dimensions, left ventricular hypertrophy, estimates of filling pressure and diastolic function, etc.), as well as more information regarding clinical signs of congestion/severity of HF (e.g. oedema, rales, etc.), which may have contributed to explain the different NT-proBNP levels in females vs. males are not collected in SwedeHF.

Further, although we performed extensive adjustments, we cannot rule out potential residual and unmeasured confounding. Indeed, no data on autoimmune and endocrine disorders like hyperthyroidism, which are known to be more prevalent in females and affect NT-proBNP concentrations, were available. Cause-specific hospitalization but not mortality was considered due to the difficulty in assuring cause of death in registries where there is no adjudication of events.

SwedeHF has a relatively low coverage in primary care despite many HF patients are being treated in primary care and, thus, selection bias may represent a limitation. Finally, generalizability of our findings to other countries depends on similarities in population characteristics, health care organization and delivery, and HF management.

## 5. Conclusion

Concentrations of NT-proBNP were higher in females across the EF spectrum, with larger relative differences in HFpEF, but similar predictors of high levels were observed in both sexes. NT-proBNP levels were similarly associated with prognosis in females vs. males. These findings support the use of NT-proBNP for prognostic purposes in chronic HF, regardless of sex.

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## Appendix A. Supplementary data

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