Title: Sex-related differences in heart failure with preserved ejection fraction.

Authors:

Pooja Dewan MBBS[1]

Rasmus Rørth MD[1,2]

Valeria Raparelli MD PhD[3,4]

Ross T. Campbell MBChB PhD[1]

Li Shen MBChB PhD[1]

Pardeep S Jhund, MBChB PhD[1]

Mark C Petrie, MBChB[1]

Inder S Anand MD DPhil[5]

Peter E Carson MD[6]

Akshay S Desai MD MPH[7]

Christopher B Granger MD[8]

Lars Køber MD DMSc[2]

Michel Komajda MD[9]

Robert S McKelvie MD PhD[10]

Eileen O'Meara MD[11]

Marc A Pfeffer MD PhD[7]

Bertram Pitt MD[12]

Scott D Solomon MD[7]

Karl Swedberg MD PhD[13]

Michael R. Zile MD[14]

John JV McMurray MD[1]

Affiliations: [1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [2]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [3]Center for Outcomes Research and Evaluation, Research Institute, McGill University Health Centre, Montreal, Quebec, Canada; [4]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy; [5]VA Medical Center, University of Minnesota, MN; [6]Georgetown University and Washington DC Veterans Affairs Medical Center, Washington DC; [7]Cardiovascular Medicine, Brigham and Women's Hospital, Boston MA, USA; [8]Duke Clinical Research Institute, Duke University, Durham, North Carolina, USA; [9]Department of Cardiology, Hospital Saint Joseph, France; [10]Western University and St. Joseph's Healthcare Centre, London, Ontario, Canada; [11]Montreal Heart Institute and Université de Montreal, Montreal, Quebec, Canada. [12]Department of Internal Medicine-Cardiology, University of Michigan School of Medicine, Ann Arbor; [13]Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden and National Heart and Lung Institute, Imperial College, London; [14]Medical University of South Carolina and Ralph H. Johnson Veterans Administration Medical Center, Charleston, South Carolina, USA.

Disclosures: No author has any disclosure relevant to the subject of this manuscript.

Address for correspondence:

Professor John J.V. McMurray,

British Heart Foundation Cardiovascular Research Centre,

University of Glasgow,

126 University Place,

Glasgow, G12 8TA,

United Kingdom.

Tel: +44 141 330 3479

Fax: +44 141 330 6955

Email: john.mcmurray@glasgow.ac.uk

Word count - text only: 3326

ABSTRACT

Background: To describe characteristics and outcomes in women and men with heart failure (HF) and preserved ejection fraction (HFpEF).

Methods & Results: Baseline characteristics (including biomarkers and quality-of-life) and outcomes (primary outcome: composite of first HF hospitalization or cardiovascular [CV] death) were compared in 4458 women and 4010 men enrolled in CHARM-Preserved (EF ≥ 45%), I-Preserve and TOPCAT-Americas.

Women were older and more often obese and hypertensive, but less likely to have coronary artery disease and atrial fibrillation. Women had more symptoms and signs of congestion, and worse quality-of-life. Despite this, the risk of the primary outcome was lower in women (HR 0.80; 95% CI 0.73-0.88), as was the risk of CV death (HR 0.70; 95% CI 0.62-0.80) but there was no difference in the rate for first hospitalization for HF (HR 0.92; 95% CI 0.82-1.02). The lower risk of CV death in women, compared with men, was in part explained a by a substantially lower risk of sudden death (HR 0.53, 0.43-0.65; P<0.001). E/A ratio was lower in women (1.1 vs 1.2).

Conclusions: There are significant differences between women and men with HFpEF. Despite worse symptoms, more congestion, and lower quality-of-life, women had similar rates of hospitalization and better survival than men. Their risk of sudden death was half that of men.

Clinical Trial Registration:

URL: https://www.clinicaltrials.gov. ATMOSPHERE: Unique identifier: NCT00853658.

PARADIGM-HF: Unique identifier: NCT01035255

Word count: 213

Non-standard Abbreviations and Acronyms

HFrEF – Heart failure with reduced ejection fraction

HFpEF – Heart failure with preserved ejection fraction.

CHARM – Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity.

LVEF – Left ventricular ejection fraction.

I-Preserve – Irbesartan in heart failure with Preserved ejection fraction.

TOPCAT – Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial.

BioLINCC – Blood Institute, Biologic Specimen and Data Repository Information Coordinating Center.

NYHA – New York heart association.

BNP – Brain natriuretic peptide.

NT-proBNP – N-terminal pro brain natriuretic peptide.

HR – Hazard ratio.

eGFR – estimated glomerular filtration rate.

IRR – Incidence rate ratio.

KCCQ – Kansas city cardiomyopathy questionnaire.

MLWHF – Minnesota living with heart failure.

PARAGON-HF – Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction.

ARNI – Angiotensin receptor neprilysin inhibitor.

ARB – Angiotensin receptor blocker.

INTRODUCTION

Although much has been written about differences in the characteristics of, and outcomes in, men and women with heart failure (HF) with reduced ejection fraction (HFrEF), much less is known about these differences in heart failure with preserved ejection fraction (HFpEF).[1–3] In part, this reflects the few large trials in patients with the latter phenotype. Moreover, the first major report on women with HFpEF was from Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved trial which enrolled patients with a left ventricular ejection fraction (LVEF) >40%.[4] Subsequent large trials have used 45% as the threshold for the identification of HFpEF and, in retrospect, it is clear that many patients in CHARM-Preserved had characteristics more typical of HFrEF than HFpEF.[5] The second of the large HFpEF trials to report, the Irbesartan in heart failure with Preserved ejection fraction trial (I-Preserve), described outcomes in women compared with men, but that analysis was limited by inclusion of only 1637 men.[6] With the availability of a third large trial, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT), and using CHARM data on patients with a LVEF≥45%, it is now possible in an individual patient data meta-analysis, using a common definition of HFpEF, to conduct a more comprehensive analysis of outcomes according to sex (4458 women and 4010 men) in all three trials.[5,7,8] Although there was an echocardiographic sub-study in (I-Preserve), cardiac structure and function were not analyzed by sex.[6] TOPCAT also had an echocardiographic sub-study meaning that, along with I-Preserve, information on cardiac structure and function is available for 774 women and 625 men with HFpEF.[9]

METHODS

The data that support the findings of this study for IPreserve and CHARM-preserved are available from the corresponding author on request. The data for TOPCAT is available upon request from a third party (BioLINCC).

Study population

For the present analyses, we pooled patients enrolled in CHARM-Preserved, I-Preserve and TOPCAT. The designs and results of these trials are published.[5,10,11] Briefly, in CHARM-Preserved 3023 HF patients in New York Heart Association (NYHA) class II to IV with a LVEF >40% were randomized to receive candesartan or placebo. I-Preserve compared irbesartan with placebo in 4128 patients aged ≥60 years in NYHA functional class II to IV, a LVEF ≥45% and echocardiographic, electrocardiographic or radiologic evidence supporting a diagnosis of HF. Patients in NYHA functional class II were required to have had a HF hospitalization within the previous 6 months. TOPCAT compared spironolactone with placebo in 3445 patients who aged ≥50 years in functional class II to IV with a LVEF ≥45%; patients were also required to have been hospitalized within the previous 12 months for HF or to have an elevated natriuretic peptide level within 60 days before randomization (i.e. Brain natriuretic peptide (BNP) ≥100 pg/ml or N-terminal pro Brain natriuretic peptide (NT-proBNP ≥360 pg/ml)).

For this analysis, we excluded 450 patients from CHARM-Preserved who had a LVEF<45% to ensure a consistent lower LVEF threshold across trials. Patients from TOPCAT who were randomized in Russia(N=1066) and Georgia (N=612) were also excluded because of doubts about diagnosis raised by the substantially lower event rates in this region, compared to those in the Americas, as well as doubts about treatment adherence.[12] Accordingly, we have

analyzed 2573 patients enrolled in CHARM-preserved, 4128 patients from I-Preserve and 1767 patients enrolled in TOPCAT-Americas.

Each trial was approved by the ethics committee at participating centers and all patients provided written informed consent.

The median duration of follow up was 41.3 months in the pooled cohort (36.6 months in CHARM-Preserved, 52.9 months in I-Preserve and 41.1 months in TOPCAT).

Outcomes

The primary outcome was a composite of cardiovascular (CV) death or HF hospitalization in CHARM-Preserved, all-cause death or CV hospitalization in I-Preserve, and a composite of CV death, HF hospitalization or aborted cardiac arrest in TOPCAT. In the present study, we used a composite of CV death or HF hospitalization as the primary outcome as this is now the most widely used endpoint in HF trials. We also analyzed each of the components of this composite, the two main modes of CV death (sudden death and death due to worsening HF), non-CV death and all-cause death. In addition, risk of other hospitalizations (CV, non-CV and all-cause) and fatal or non-fatal myocardial infarction and stroke were examined. Lastly, given the high burden of hospitalization in HFpEF, we examined recurrent as well as first admissions (for HF, all CV causes, non-CV causes and any cause).

HF hospitalization and causes/modes of death were adjudicated by a central endpoint committee according to similar pre-specified criteria in each trial (the same committee adjudicated the events in CHARM-Preserved and TOPCAT).

Statistical analyses

Baseline characteristics are presented as means with standard deviations or medians with interquartile ranges for continuous variables and frequencies and percentages for categorical

variables. Baseline characteristics according to sex were compared using Student's t-test or Mann-Whitney U test as appropriate for continuous variables, and chi-square test for categorical variables.

Competing risk regression using the Fine-Grey method was employed to analyze outcomes (to account for the risk of multiple potential competing events). All outcomes are reported as number of events and sub-distribution hazard ratios (HRs) with 95% confidence intervals (CIs). Both the primary outcome and CV death were tested for the competing risk of non-CV death. First hospitalization for HF was tested for competing risk of all-cause death. Sudden death was tested for the competing risk of non-sudden death and death due to worsening HF was tested for death not caused by worsening HF. Non-CV death was tested for competing risk of CV death. Fatal and nonfatal myocardial infarction (MI) and strokes were tested for competing risk of all cause death not due to MI or stroke. HRs adjusted for trial, randomized treatment, region, age, heart rate, systolic blood pressure (SBP), body mass index (BMI), NYHA functional class, LVEF, estimated glomerular filtration rate(eGFR) and NT-proBNP (with missing indicator method used to handle missing eGFR and NT-proBNP values) have been reported (Model 1).[13] We have also reported outcomes adjusted for a second model which includes comorbidities in addition to variables incorporated in model 1.

A sensitivity analysis for unobserved confounding (potentially not otherwise corrected by covariate adjustment) for the main outcomes by propensity score matching to balance available baseline covariates was also carried out. This analysis only included IPreserve and TOPCAT so that eGFR, which was missing in > 50% of patients in CHARM-preserved, could be used as one of the matching covariates. We matched 830 women with 830 men based on the propensity scores so derived.

Recurrent hospitalizations were analyzed using negative binomial regression which is a counting method for the analysis of recurrent events and incidence risk ratios (IRRs) with

95% CIs are reported. IRRs adjusted for the two models as mentioned above are reported. Event rates per 1000 person-years are also reported, calculated by dividing the total number of events in each patient for each type of hospitalization by the total follow-up time for each patient.

All analyses were performed using Stata version 15 (Stata Corp. College Station, Texas, USA). A two-sided p-value <0.05 was considered significant.

Analysis of echocardiography subset

Measures of left ventricular (LV) structure were indexed to body surface area (BSA) and diastolic dysfunction is described as recommended in current guidelines.[14] Baseline characteristics of the patients in the echocardiography subset are reported in the supplementary tables. The outcomes of interest were further adjusted for in the echocardiography subgroup by adding E wave velocity, LV mass index and left atrial (LA) volume index to Model 1.

RESULTS

There were 4010 men and 4558 women in our analysis, accounting for 47.4% and 52.6% of the cohort respectively.

Baseline characteristics

The baseline characteristics in men and women have been shown in Table 1. Women were at an average 2.5 years older than men, had higher SBP, heart rate and BMI. A greater proportion of women than men (48.7% vs. 41.2% men) were obese.[15]

Comorbidities

Apart from hypertension (86.6% women vs. 76.6% men), women were less likely to have a history of major comorbidities such as atrial fibrillation (30.6% vs. 33.9%), and coronary heart disease (49.1% vs. 62.9%). Electrocardiographically documented atrial fibrillation was also less common in women than men (16.9% vs. 20.4%). Among non-CV comorbidities, women had a similar prevalence of diabetes (30.7% vs. 32.0%) but a lower prevalence of chronic obstructive pulmonary disease/ asthma (11.2% vs. 13.8%).

Women were also less likely to be current smokers (6.8% vs. 13.2%) and had lower intake of alcohol than men.

Heart failure characteristics and investigations

As shown in Table 1, women had been hospitalized for HF as often as men within the 6 months before randomization. Women had more symptoms of HF than men, with a higher prevalence of orthopnea (28.9% vs. 21.0%) and paroxysmal nocturnal dyspnea (14.3% vs. 12.0%; only recorded in I-Preserve and TOPCAT-Americas) and more evidence of congestion (peripheral edema and rales). Women were considerably more likely to be in a

worse NYHA functional class (62.8% NYHA class III/IV vs. 51.3% in men) and had poorer health-related quality-of-life (QoL) i.e. lower (worse) median Kansas City Cardiomyopathy Questionnaire (KCCQ) scores (56.3 vs. 64.6 in men) or higher (worse) Minnesota Living with Heart Failure (MLWHF) scores (44.0 vs. 37.0). Each individual KCCQ domain score was also lower in women [Supplementary Figure 1] and each of the MLWHF domains and majority of the scores to questions in the MLWHF questionnaire were higher in women [Supplementary Figures 2 and 3].

Women had a significantly higher LVEF (59.8% vs. 56.3%) than men and a lower median NT-proBNP (women 348pg/ml vs. men 484pg/ml), although the latter difference was confined to patients without atrial fibrillation.

Mean eGFR was lower in women than men and a higher proportion of women had an eGFR <60 ml/min/1.73m^2 (38.9% vs. 32.4% in men). There was no other difference in measures of blood chemistry.

Background treatment

The proportion treated with a diuretic was larger in women than in men (84.7% vs. 78.5%) [Table 1]. Women were less likely to receive digoxin (15.5% vs. 19.1%). Beta-blocker use was also slightly less in women (60.8% vs. 63.0%) whereas use of calcium channel blockers (CCBs) was more frequent (40.1% vs. 34.2%). The differences between men and women in the proportions using statins, aspirin and anticoagulants were larger (all used less commonly in women).

Echocardiographic measurements (I-Preserve and TOPCAT-Americas only)

Women in the echocardiography subset were older, were more obese, and had fewer major comorbidities apart from hypertension similar to what was observed in the main cohort

[Table 2 and Supplementary Table 2]. As shown in Table 2, indexed LV volumes and LV mass were lower in women than in men. Indexed LA volume was increased above normal in both sexes but did not differ between men and women (even though men had greater LV volumes). Stroke volume was low in both sexes. While peak E wave velocity was similar in both sexes, women had a higher peak A wave velocity (83.7cm/s vs. 73.2cm/s). Consequently, E/A ratio was lower in women (1.1 vs. 1.2). Other measures of diastolic function, generally, did not differ notably between men and women.

Outcomes

Women had a significantly lower risk of the primary composite with an HR (model 1) of 0.80 (95% CI 0.73–0.88), as shown in Table 3 & Figures 1 and 2.

Looking at the components of this composite, the risk of first hospitalization for HF did not differ significantly between women and men (HR 0.92; 95% CI 0.82–1.02).

By contrast, the risk of CV death (HR 0.70; 95% CI 0.62-0.80) was lower, as were each of the two major modes of CV death, that is sudden death and death due to worsening HF. The risk of sudden death in women was about half that in men (HR 0.53; 95% CI 0.43-0.65; P<0.001).

The risk of non-CV death was also lower in women and, as a result, so was the risk of all-cause death (HR 0.62; 95% CI 0.52–0.74 and 0.65; 95% CI 0.59–0.72, respectively).

While women were less likely to have a fatal/non-fatal MI than men (HR 0.75; 95% CI 0.61-0.94), the risk of stroke was similar (HR 0.87; 95% CI 0.70-1.07).

The results were not altered in the subset of patients with echocardiographic data or in a sensitivity analysis using propensity score to match men and women [Supplementary Tables 3 and 4 & Supplementary Figure 4].

Recurrent events

During a median follow up of 1255 (1-2278) days, there were a total of 6610 hospitalizations for any cause in women and 6507 hospitalizations for any cause in men [Table 4]. Of these, 1479 (22.4%) were due to HF in women and 1327 (20.4%) were due to HF in men. Among women, 7.4% had more than one hospitalization for HF and the same was true for 7.2% of men [Supplementary Table 1].

The incidence risk ratio (IRR) for recurrent HF hospitalization for women compared with men was 0.87 (95% CI 0.77–1.00). The IRRs for CV hospitalization (0.84; 0.77–0.91), all-cause hospitalization (0.85; 0.79–0.90) and non-CV hospitalizations (0.86; 0.79–0.93) were similar to those for HF hospitalization.

DISCUSSION

Epidemiologic and registry studies show that women are as likely as men to suffer from HFpEF and this is what we also found in our pooled clinical trial cohort.[16,17] Among the 8468 individuals randomized, 4458 (53%) were women. There were notable differences between men and women: in our study women were older than men, more often had a history of hypertension and were more often obese than men (but did not have a greater prevalence of diabetes). Most comorbid conditions were less common in women than in men, with a particularly large difference in prevalence of CAD. These differences are consistent with prior studies.[18,19] More novel were our findings related to the impact of HF on women, compared with men. Women had worse NYHA functional class, worse symptoms and more signs of congestion (and more often received diuretics) than men. These physician reported/recorded indicators of worse heart failure status in women were supported by patient reported outcomes. Specifically, health-related QoL (as measured by KCCQ in TOPCAT-Americas and MLWHF in I-Preserve and CHARM-Preserved) was worse in women than men an all domains of QoL were worse in women compared to men. Interestingly, this worse clinical picture was apparent despite a lower median NT proBNP and higher LVEF (and smaller indexed LV volumes and mass) in women, compared with men. How one interprets this dissociation between symptoms/signs/QoL and physiological measures of cardiac function in women compared with men is uncertain. Is it that women experience worse symptoms of HF for any given level of cardiac dysfunction? Or is it that their symptoms and signs of congestion reflect an inadequate natriuretic peptide response in women? Alternatively, are women relatively undertreated with diuretics? While the proportion of patients treated with a loop diuretic was similar in men and women, more women were treated with a thiazide diuretic. Arguably, diuretics were underutilized in view of the greater congestion in women. Renal function may be relevant here too as it was worse in women.

With respect to outcomes, women were at a lower risk of the primary composite endpoint than men, due to a substantially lower risk of CV death (and not HF hospitalization). This was also true for the two main modes of CV death, non-CV death and, therefore, death overall. However, the most striking difference between women and men was in the risk of sudden death, which occurred almost twice as frequently in men as in women. This may be explained the lower prevalence of CAD in women and because sudden death is linked to CAD.[20] However, this may not be the whole answer as when just individuals with CAD were examined, women still appeared less likely than men to die suddenly.

By contrast, the proportion of patients experiencing one or more hospitalization for HF did not differ between women and men. When HF admissions were examined (using both first and repeat hospitalizations), taking account of the competing risk of death, women still had a similar rate of events to men in the unadjusted analysis.

Overall, therefore, the impact of HFpEF seems to differ in men and women with women having worse symptoms and QoL, similar rates of hospital admission but lower rates of death than men. This raises the possibility that the goals of management of HFpEF in men and women might have a different emphasis, with women needing relatively more attention paid to well-being than men. This difference in impact may also extend to and have implications on pharmacological therapy in HFpEF. An analysis of TOPCAT showed that while there was no sex based difference in the risk of the primary composite outcome according to randomized treatment, women who received spironolactone had a lower risk of all-cause and cardiovascular death while no such benefit was seen in men.[21] Similarly, in the recent Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial, only women receiving sacubitril/valsartan had a statistically significant reduction in risk of the primary outcome while there was no risk reduction observed in men.[22]

Finally, it is also of interest to compare these findings in HFpEF with a recent similar analysis in HFrEF.[23] Both men and women with HFpEF were quite different than people with HFrEF e.g. people with HFpEF were 6 years older on average and had a 12mmHg higher average systolic blood pressure.[23] Obesity was more common in HFpEF than HFrEF and this difference was more marked in women (48.7% in HFpEF vs. 33.4% in HFrEF) than men (41.2% vs. 29.2%, respectively). Women had more symptoms/signs of congestion in both HFpEF and HFrEF. QoL was worse in HFpEF than in HFrEF, overall, but worse in women than men in both HF phenotypes. A notable distinction between HFpEF and HFrEF, with respect to sex differences, was the similar rate of hospital admission in women and men with HFpEF (contrasting with the lower risk in women, compared to men, with HFrEF). The risk of sudden death was less in women with HFrEF than in men with HFrEF, although the between-sex difference was smaller than in HFpEF.[23]

Strengths and limitations

We studied patients enrolled in clinical trials who had to fulfil specific inclusion and exclusion criteria and they may not be representative of HFpEF patients more generally. However, because these patients were enrolled in trials, they were well characterized at baseline and had systematic and complete follow-up, with adjudication of clinical outcomes. Not all data were available in all three trials.

In conclusion, we found significant sex-based differences in patients with HFpEF. Women were older and more likely than men to be hypertensive and obese (but less likely to have CHD). Despite worse symptoms, more evidence of congestion, and lower QoL, women had similar rates of hospitalization to men and a better survival. Their risk of sudden death was half that of men.

What is new

- Women with HFpEF live longer when compared to men with HFpEF but have a poorer quality of life and a greater symptom burden.
- Overall mortality in both genders with HFpEF is lesser than that observed in HFrEF. Fewer men with HFpEF had hospitalizations for heart failure when compared with HFrEF but no such difference was observed in women with HFpEF and HFrEF.

Clinical implications

- While no pharmacological therapy to date has been approved for the treatment of HFpEF patients overall, recent evidence suggests there may be benefit from certain agents in women with this heart failure phenotype.
- The former findings, plus the striking contrasts reported here, between the characteristics and outcomes of women, compared with men with HFpEF, argue for intensified efforts to understand and explain these sex-related differences. We believe this should be a clinical priority given the worse quality of life and symptoms experienced by women with HFpEF and the fact that this is the major type of heart failure afflicting women.

Sources of funding

None

REFERENCES

1. Ghali JK, Krause-Steinrauf HJ, Adams KF, Khan SS, Rosenberg YD, Yancy CW, Young JB, Goldman S, Peberdy MA, Lindenfeld J. Gender Differences in Advanced Heart Failure: Insights from the BEST Study. *J Am Coll Cardiol*. 2003;42:2128–2134.
2. Rathore SS, Wang Y, Krumholz HM. Sex-Based Differences in the Effect of Digoxin for the Treatment of Heart Failure. *N Engl J Med*. 2002;347:1403–1411.
3. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation*. 2001;103:375–380.
4. O'Meara E, Clayton T, McEntegart MB, McMurray JJ V, Piña IL, Granger CB, Östergren J, Michelson EL, Solomon SD, Pocock S, Yusuf S, Swedberg K, Pfeffer MA. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure - Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007;115:3111–3120.
5. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Östergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-preserved trial. *Lancet*. 2003;362:777–781.
6. Lam CSP, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, McKelvie RS, McMurray JJ, Zile MR, Massie BM, Kitzman DW. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Hear Fail*. 2012;5:571–578.
7. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson

S, Donovan M, Iverson E, Staiger C, Ptaszynska A, I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–67.

8. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2014;370:1383–1392.
9. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF, Sopko G, Li G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac structure and function in heart failure with preserved ejection fraction: Baseline findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Hear Fail*. 2014;7:104–115.
10. Carson P, Massie BM, Mckelvie R, Mcmurray J, Komajda M, Zile M, Ptaszynska A, Frangin G. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial: Rationale and design. *J Card Fail*. 2005;11:576–585.
11. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, Clausell N, Diaz R, Fleg JL, Gordeev I, McKinlay S, O'Meara E, Shaburishvili T, Pitt B, Pfeffer MA. Rationale and design of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial: A randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J*. 2011;162:966-972.e10.
12. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau J-LLJ-L, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM,

Pitt B, O'Meara E, Rouleau J-LLJ-L, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.

13. Huberman M, Langholz B. Application of the Missing-Indicator Method in Matched Case-Control Studies with Incomplete Data. *Am J Epidemiol* [Internet]. 1999;150:1340–1345. Available from: https://academic.oup.com/aje/article-lookup/doi/10.1093/oxfordjournals.aje.a009966

14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Hear J – Cardiovasc Imaging*. 2016;17:1321–1360.

15. The World Health Orginisation. WHO | Mean Body Mass Index (BMI). *WHO* [Internet]. 2017 [cited 2019 Sep 28];Available from: https://www.who.int/gho/ncd/risk_factors/bmi_text/en/

16. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Cameron VA, Poppe K, Lund M, Devlin G, Troughton R, Richards AM, Doughty RN. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J*. 2018;39:1770–1780.

17. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based

cohort: 11-year follow-up of PREVEND. *Eur Heart J*. 2013;34:1424–1431.

18. Lloyd-Jones DM, Allen NB, Greenland P, Ayers C, Kuller LH, Eaton CB, Klein L, LaMonte M, Pandey A, Berry JD, Gottdiener JS, Omar W. Sex and Race Differences in Lifetime Risk of Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction. *Circulation*. 2018;137:1814–1823.
19. Gori M, Lam CSP, Gupta DK, Santos ABS, Cheng S, Shah AM, Claggett B, Zile MR, Kraigher-Krainer E, Pieske B, Voors AA, Packer M, Bransford T, Lefkowitz M, McMurray JJ V., Solomon SD. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2014;16:535–542.
20. Yarnoz MJ, Curtis AB. More Reasons Why Men and Women Are Not the Same (Gender Differences in Electrophysiology and Arrhythmias). *Am J Cardiol*. 2008;101:1291–1296.
21. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction: A Secondary Analysis of TOPCAT Trial. *JACC Hear Fail*. 2019;7:228–238.
22. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen H-D, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* [Internet]. 2019;NEJMoa1908655. DOI: 10.1056/NEJMoa1908655
23. Dewan P, Rørth R, Jhund PS, Shen L, Raparelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Køber L, Mogensen UM, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJV. Differential Impact of Heart Failure With

Reduced Ejection Fraction on Men and Women. *J Am Coll Cardiol*. 2019;73:29–40.

TABLE LEGENDS

Table 1: Characteristics of women and men with HFpEF.

Table 2: Echocardiographic parameters in women and men with HFpEF. (I-Preserve and TOPCAT).

Table 3: Clinical outcomes in women and men with HFpEF.

Table 4: Analysis of repeat hospitalizations in women and men with HFpEF (negative binomial model).

FIGURE LEGENDS

Figure 1: Central Figure - Sex based differences in Heart Failure with preserved Ejection Fraction.

Figure 2: Clinical outcomes in women and men with HFpEF: a) Primary composite outcome b) Hospitalization for Heart Failure c) Cardiovascular Death d) All-cause Death e) Sudden Death f) Death due to worsening HF i) Fatal/Non-fatal Myocardial Infarction j) Fatal/Non-fatal Stroke. All figures are cumulative incidence plots except all-cause death (Kaplan-Meier).

Table 1: Patient Characteristics			
	Women 4458 (52.6)	**Men 4010 (47.4)**	**p-value**
Baseline Characteristics			
Age–mean ± SD	71.4 ± 8.7	68.9 ± 9.6	<0.001
Age Groups–no.(%)			<0.001
≤40 years	9 (0.2)	24 (0.6)	
41-55 years	177 (4.0)	312 (7.8)	
56–70 years	1800 (40.4)	1852 (46.2)	
>70 years	2472 (55.5)	1822 (45.4)	
Region-no. (%)			<0.001
North America	1332 (29.9)	1483 (37.0)	
Latin America	679 (15.2)	327 (8.2)	
Western Europe & other	1351 (30.3)	1361 (33.9)	
Central Europe	1019 (23.9)	735 (18.3)	
Asia-Pacific	77 (1.7)	104 (2.6)	
Race–no. (%)			<0.001
White	3925 (88.0)	3671 (91.5)	
Black	327 (7.3)	165 (4.1)	
Asian	48 (1.1)	70 (1.7)	
Other	158 (3.5)	104 (2.6)	
SBP (mmHg)–mean ± SD	136.0 ± 16.4	133.0 ± 17.1	<0.001
DBP (mmHg)–mean ± SD	77.0 ± 10.4	77.0 ± 10.7	0.27
HR (bpm)–mean ± SD	72.0 ± 11.2	70.0 ± 11.6	<0.001
BMI (kg/m^2)–median (Q1, Q3)	29.8 (26.1,34.4)	28.7 (25.9,32.7)	<0.001
Weight Category–no. (%)			<0.001
Underweight	31 (0.7)	18 (0.5)	
Normal	753 (17.0)	687 (17.2)	
Overweight	1493 (33.6)	1643 (41.2)	
Obese	2165 (48.7)	1642 (41.2)	
Comorbidities-no. (%)			
Cardiovascular			
Atrial fibrillation(history)	1362 (30.6)	1359 (33.9)	<0.001
Hypertension	3859 (86.6)	3071 (76.6)	<0.001
Coronary heart disease	2191 (49.1)	2522 (62.9)	<0.001
Myocardial infarction	879 (19.7)	1505 (37.5)	<0.001
Angina	1834 (41.1)	1950 (48.7)	<0.001

PCI or CABG	681 (15.3)	1263 (31.5)	<0.001
Stroke or TIA	393 (8.8)	386 (9.6)	0.20
Other Systems			
Type II Diabetes	1369 (30.7)	1284 (32.0)	0.1887
COPD/Asthma	498 (11.2)	553 (13.8)	0.0003
Peripheral arterial disease*	733 (21.7)	567 (22.5)	0.481
Anemia*	553 (16.4)	628 (24.9)	<0.001
Any alcohol intake*	291 (8.6)	617 (24.5)	<0.001
Current smoker†	134 (6.8)	313 (13.2)	<0.001
Heart Failure Characteristics, Investigations and Treatment			
HF hospitalization within past 6 months–no. (%)	1883 (42.2)	1625 (40.5)	0.11
NYHA III/IV–no. (%)	2801 (62.8)	2059 (51.3)	<0.001
Quality of Life scores			
Minnesota LWHF–median (Q1, Q3)	44.0 (29.0,61.0)	37.0 (22.0,54.0)	<0.001
KCCQ Clinical Summary Score–median (Q1, Q3)	56.3 (39.1,72.9)	64.6 (45.8,82.3)	<0.001
Markers of Congestion–no (%)			
Dyspnea on effort†	1922 (97.7)	2312 (97.5)	0.61
Orthopnea†	565 (28.9)	496 (21.0)	<0.001
PND†	279 (14.3)	282 (12.0)	0.02
Peripheral edema	2371 (53.2)	1920 (47.9)	<0.001
JVD	410 (9.2)	428 (10.7)	0.02
Rales	1033 (23.2)	830 (20.7)	0.008
ECG–no. (%)			
Atrial fibrillation	752 (16.9)	816 (20.4)	<0.001
LVH	1043 (23.5)	760 (19.0)	<0.001
Echocardiography and other Investigations			
LVEF (%)-mean ± SD	59.8 ± 9.0	56.3 ± 8.3	<0.001
CXR demonstrating pleural effusion or pulmonary. Congestion	1057 (23.7)	611 (15.2)	<0.001
NT-proBNP(pg/ml)–median (Q1, Q3) *‡	348 (133, 967)	484 (177, 1159)	<0.001
No Atrial fibrillation on ECG* (1934/2800)	261 (115, 619)	340 (138, 796)	0.001
Atrial fibrillation on ECG* (574/569)	1349 (816, 2155)	1231 (733, 2015)	0.20
Sodium(mmol/L)–mean ± SD	139.8 ± 3.1	139.7 ± 3.0	0.05
Potassium(mmol/L)-mean ± SD	4.36 ± 0.5	4.37 ± 0.46	0.21
eGFR(ml/min/1.73m^2)-mean ± SD§	68.8 ± 23.2	72.4 ± 23.0	<0.001
eGFR <60 ml/min/m^2–no. (%)	1454 (38.9)	972 (32.4)	<0.001

Drugs and Interventions–no. (%)			
Diuretic	3772 (84.7)	3143 (78.5)	<0.001
Loop diuretics	2675 (60.1)	2449 (61.1)	0.32
Thiazide diuretics	1417 (31.8)	942 (23.5)	<0.001
Digoxin	688 (15.5)	764 (19.1)	<0.001
Beta- blocker	2709 (60.8)	2523 (63.0)	0.04
Calcium Channel Blocker	1784 (40.1)	1372 (34.2)	<0.001
Antiarrhythmics	380 (8.5)	382 (9.5)	0.11
Antiplatelets	2482 (55.7)	2577 (64.3)	<0.001
Anticoagulants	977 (21.9)	1078 (26.9)	<0.001
History of atrial fibrillation(n=1362/1359)	819 (60.1)	870 (64.0)	0.04
Statins	1628 (36.6)	1902 (47.5)	<0.001
Pacemaker	319 (7.2)	363 (9.1)	0.001
ICD	29 (0.7)	42 (1.0)	0.045

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body mass index (BMI), inter quartile range (IQR), chronic obstructive pulmonary disease (COPD).
COPD/Asthma in CHARM derived from patients using bronchodilators at baseline.
New York heart association (NYHA), living with heart failure (LWHF), Kansas City cardiomyopathy questionnaire (KCCQ), jugular venous distension (JVD), left ventricular hypertrophy (LVH), left ventricular ejection fraction (LVEF), chest x-ray (CXR), N terminal -pro brain natriuretic peptide (NT-proBNP) – only available in I-Preserve and TOPCAT, estimated glomerular filtration rate (eGFR), angiotensin converting enzyme inhibitor (ACEI), implantable cardioverter defibrillator (ICD).
Outlined box encloses values not available for the complete dataset.
[*] Only I-Preserve and TOPCAT (2522 men, 3373 women).
[†] Only CHARM-preserved and TOPCAT (2373 men, 1967 women).
[‡] Missing – 2057
[§] Missing - 1732

Table 2: Echocardiographic parameters in women and men with HFpEF. (I-Preserve and TOPCAT).			
	Women 774 (55.3)	**Men 625 (44.7)**	**p-value**
Age-years	71.8 ± 8.3	71.2 ± 8.7	0.1673
LV Structure			
End-diastolic diameter(cm)	4.7 ± 0.6	5.0 ± 0.6	<0.001
End-diastolic diameter index(cm/m^2)	2.5 ± 0.4	2.4 ± 0.4	<0.001
End-diastolic volume(ml)	82.3 ± 28.6	110.3 ± 36.1	<0.001
End-diastolic volume index(ml/m^2)	43.6 ± 14.6	52.2 ± 16.8	<0.001
End-systolic diameter(cm)	3.1 ± 0.6	3.5 ± 0.6	<0.001
End-systolic diameter index(cm/m^2)	1.7 ± 0.3	1.7 ± 0.3	0.59
End-systolic volume(ml)	30.6 ± 14.5	44.6 ± 20.0	<0.001
End-systolic volume index(ml/m^2)	16.2 ± 7.7	21.2 ± 9.7	<0.001
Interventricular septum thickness(cm)	1.0 ± 0.2	1.2 ± 0.2	<0.001
LV mass(gm)	191.5 ± 58.7	241.5 ± 65.6	<0.001
LV mass index(gm/m^2)	101.7 ± 29.4	113.7 ± 28.9	<0.001
Relative wall thickness(cm)	0.4 ± 0.1	0.5 ± 0.1	0.02
LV Systolic Properties			
Ejection fraction (%)	61.8 ± 8.5	58.2 ± 7.9	<0.001
Stroke volume(ml)	51.7 ± 18.1	65.6 ± 22.0	<0.001
LV Diastolic properties			
Diastolic dysfunction*-no. (%)			0.65
Grade I	202 (6.1)	152 (24.3)	
Grade II	32 (4.1)	20 (3.2)	
Grade III	62 (8.0)	50 (8.0)	
Undetermined	278 (61.8)	403 (64.5)	
Peak E wave velocity(cm/s)	81.1 ± 28.6	78.8 ± 28.0	0.18
E/E' lateral ratio	11.3 ± 5.6	10.3 ± 5.0	0.01
E/E' septal ratio	14.3 ± 6.6	14.1 ± 6.8	0.75
E/E' average ratio	12.1 ± 5.4	11.6 ± 5.1	0.20
Peak A wave velocity(cm/s)	83.7 ± 26.6	73.2 ± 23.9	<0.001
E/A ratio	1.1 ± 0.7	1.2 ± 0.8	0.005
Lateral early diastolic myocardial velocity(cm/s)	8.6 ± 3.4	9.2 ± 3.5	0.01
Septal early diastolic myocardial velocity(cm/s)	6.8 ± 2.9	6.9 ± 2.7	0.71
Mitral deceleration time(msec)	212.7 ± 73.8	203.9 ± 65.6	0.02
Left atrial volume(ml)	69.0 ± 30.1	77.3 ± 35.6	<0.001
Left atrial volume index(ml/m^2)	37.1 ± 16.8	36.9 ± 17.9	0.85

All values expressed as mean ± standard deviation except where indicated.
***627 missing**

Table 3: Clinical outcomes in men and women with HFpEF

	Women 4458 (52.6)	Men 4010 (47.4)	Adjusted HR (Model 1) p-value	Adjusted HR (Model 2) p-value
	Total patients with events			
Primary composite outcome	1087	1069	0.80 (0.73–0.88) <0.001	0.84 (0.76–0.92) <0.001
Hospitalization				
Heart Failure	787	703	0.92 (0.82–1.02) 0.123	0.95 (0.85–1.06) 0.385
Cardiovascular	1690	1682	0.86 (0.80–0.92) <0.001	0.90 (0.83–0.96) 0.004
Non-cardiovascular	1622	1525	0.90 (0.84–0.97) 0.008	0.92 (0.85–0.99) 0.032
All-cause	2517	2359	0.91 (0.85–0.96) 0.001	0.94 (0.88–1.00) 0.040
Death				
Cardiovascular	533	583	0.70 (0.62–0.80) <0.001	0.72 (0.63–0.82) <0.001
Sudden death	161	243	0.53 (0.43– 0.65) <0.001	0.53 (0.43–0.66) <0.001
Death due to worsening HF	129	139	0.69 (0.54–0.89) 0.005	0.72 (0.55–0.93) 0.012
Non-cardiovascular	261	301	0.62 (0.52–0.74) <0.001	0.63 (0.53–0.75) <0.001
All-cause (HR)	794	884	0.65 (0.59–0.72) <0.001	0.67 (0.60–0.74) <0.001
Others				
Fatal/Non-fatal MI	154	193	0.75 (0.61–0.94) 0.012	0.80 (0.64–1.00) 0.050
Fatal/Non-fatal stroke	193	179	0.87 (0.70–1.07) 0.191	0.88 (0.71–1.09) 0.242

Hazard Ratios are reported with 95% confidence intervals (CI) within ()
All outcomes have been adjusted for trial, randomized treatment and region at baseline.
Adjustment Model 1– age, HR, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP.

Adjustment Model 2– age, HR, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP, H/o atrial fibrillation, H/o coronary heart disease, H/o hypertension, H/o stroke, H/o diabetes
All outcomes were tested for competing risks of all-cause and non-cardiovascular death. Sudden death was tested for competing risk of all non-sudden deaths and death due to worsening HF for all deaths not due to worsening HF. Non-CV death was tested for competing risk of CV death.
Missing indicator method was used to handle missing eGFR and NT-proBNP values were imputed for missing values.

Table 4: Recurrent Admissions in men and women with HFpEF.

	Women 4458 (52.6)	Men 4010 (47.4)	Women 4458 (52.6)	Men 4010 (47.4)	Adjusted IRR (Model 1)	Adjusted IRR (Model 2)
	Total events		Admissions per 100 patient years (95%CI)			
HF hospitalization	1479	1327	9.14 (8.68–9.62)	9.91 (9.39–10.46)	0.87 (0.77–1.00) 0.045	0.87 (0.77–0.99) 0.122
CV hospitalization	3560	3590	22.0 (21.29–22.73)	26.81 (25.95–27.70)	0.84 (0.77–0.91) <0.001	0.87 (0.80–0.94) <0.000
Non-CV hospitalization	3054	2919	18.87 (18.21–19.55)	21.80 (21.02–22.60)	0.86 (0.79–0.93) <0.001	0.88 (0.81–0.95) 0.002
All-cause hospitalization	6610	6507	40.84 (39.87–41.84)	48.59 (47.43–49.79)	0.85 (0.79–0.90) <0.001	0.87 (0.82–0.93) <0.001

IRR denotes incident rate ratios with 95% confidence intervals (CI) within ().
All outcomes adjusted for trial, randomized treatment and region at baseline.
Adjustment Model 1 – age, HR, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP.
Adjustment Model 2– age, HR, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP, H/o atrial fibrillation H/o coronary heart disease, H/o hypertension, H/o stroke, H/o diabetes.
Missing indicator method used to handle missing eGFR and NT-proBNP.

Figure 1: Central Figure

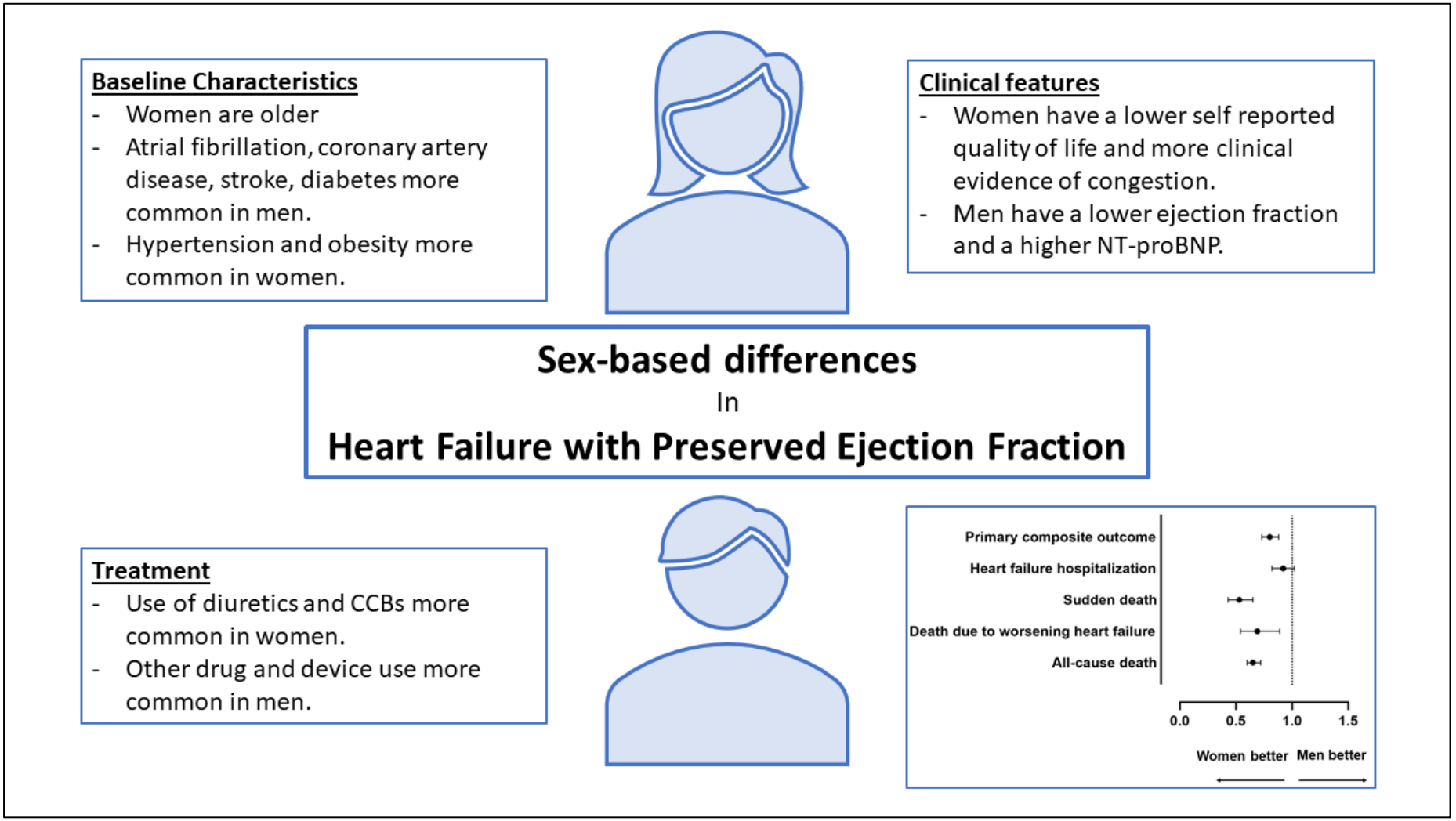
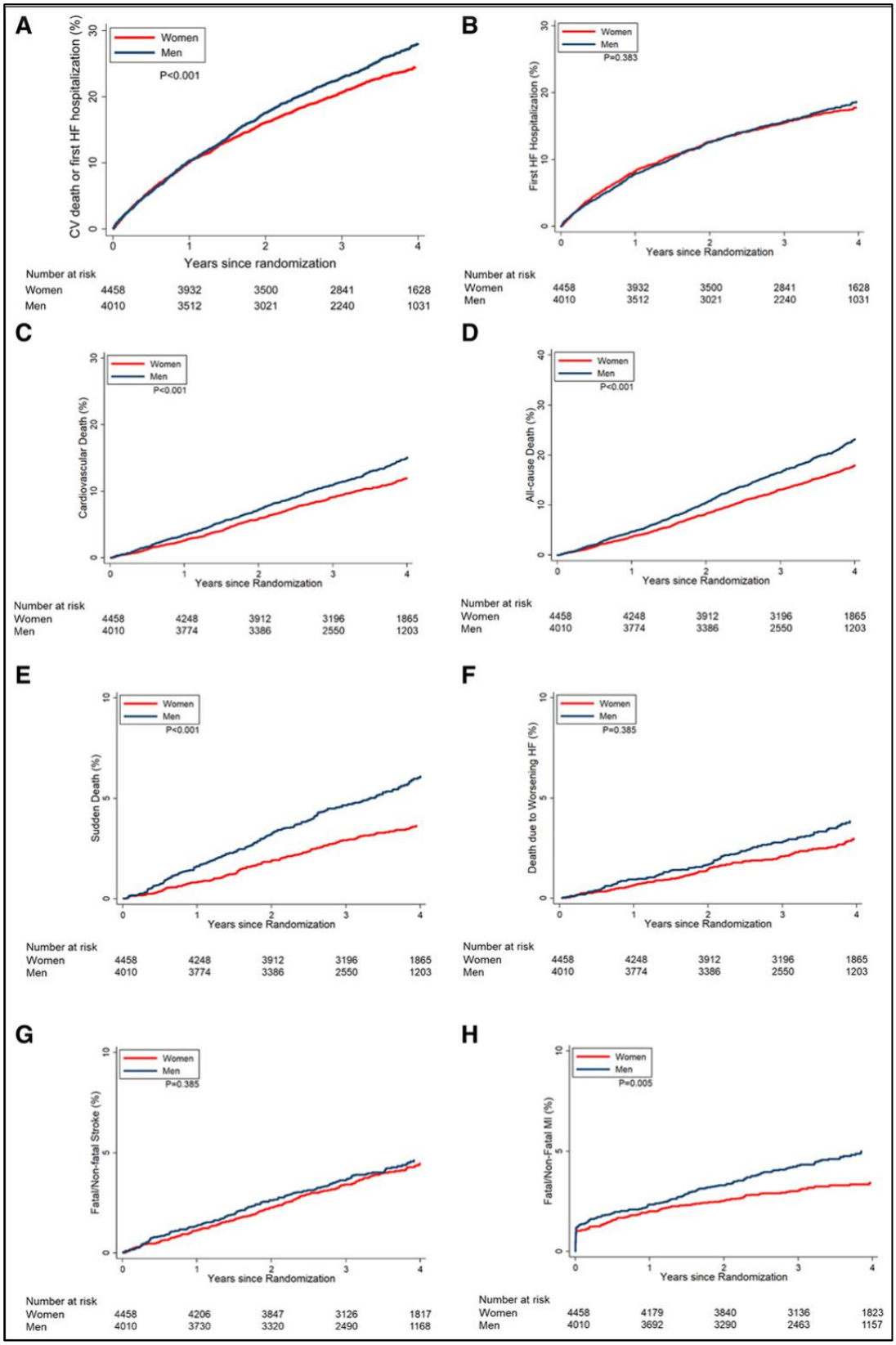


Figure 2: Clinical outcomes: a) Primary composite outcome b) Hospitalization for heart failure c) Cardiovascular death d) All-cause death e) Sudden death f) Death due to worsening HF i) Fatal/non-fatal myocardial infarction j) Fatal/non-fatal stroke. All figures are cumulative incidence plots except all-cause death (Kaplan-Meier).



APPENDIX

TABLE LEGEND

Supplementary Table 1: Number of hospital admissions women and men with heart failure and preserved ejection fraction.

Supplementary Table 2: Characteristics of women and men with heart failure and preserved ejection fraction in the echocardiography sub-study.

Supplementary Table 3: Clinical outcomes in women and men with heart failure and preserved ejection fraction in the echocardiography sub-study.

Supplementary Table 4: Clinical outcomes in women and men with heart failure and preserved ejection fraction before and after matching by propensity score.

FIGURE LEGEND

Supplementary Figure 1: Kansas City Cardiomyopathy Scores. Y axis represents score out of a possible 100 (with lower score representing worse quality of life). Bars show median score for each domain/summary score (except mean for symptom severity).

Supplementary Figure 2: Minnesota Living with Heart Failure Scores. Y axis represents score out of a possible 100 (with higher score representing worse quality of life). Bars show mean score for each domain/summary score (except median for physical dimension).

Supplementary Figure 3: Responses to individual questions in the Minnesota Living with Heart Failure questionnaire. Y axis represents response to questions (0 – 5) and bars show mean response to each question.

Supplementary Figure 4: Standardized differences of covariates between men and women before and after propensity score matching.

Supplementary Table 1: Number of hospital admissions – no. (%)		
	Women 4458 (52.6)	**Men 4010 (47.4)**
Heart failure		
0	3657 (82.0)	3302 (82.3)
1	469 (10.5)	419 (10.5)
≥2	332 (7.4)	289 (7.2)
Cardiovascular		
0	2768 (62.1)	2328 (58.1)
1	863 (19.4)	849 (21.2)
≥2	827 (18.5)	833 (20.7)
Non-cardiovascular		
0	2836 (63.6)	2485 (62.0)
1	909 (20.4)	854 (21.3)
≥2	713 (16.0)	671 (16.7)
All-cause hospitalizations		
0	1941 (43.5)	1651 (41.2)
1	1054 (23.6)	907 (22.6)
≥2	1463 (32.9)	1452 (36.2)

Supplementary Table 2: Patient Characteristics (Echo substudy)			
	Women 774 (55.3)	**Men 625 (44.7)**	**p-value**
Baseline Characteristics			
Age – mean (SD)	71.8 (8.3)	71.2 (8.7)	0.17
Age Groups – no. (%)			0.18
41 – 55 years	22 (2.8)	20 (3.2)	
56 – 70 years	309 (39.9)	278 (44.5)	
>70 years	443 (57.2)	327 (52.3)	
Race – no. (%)			0.03
White	648 (83.7)	554 (88.6)	
Black	93 (12.0)	46 (7.4)	
Asian	2 (0.3)	2 (0.3)	
Other	31 (4.0)	23 (3.7)	
SBP (mmHg) – mean (SD)	133.0 (16.3)	130.6 (15.2)	0.003
DBP (mmHg) – mean (SD)	75.8 (10.4)	74.3 (11.0)	0.01
HR (bpm) – mean (SD)	70.0 (11.0)	68.9 (11.1)	0.07
BMI (kg/m^2) – median (Q1, Q3)	30.9 (26.8, 35.4)	30.4 (26.8, 34.7)	0.31
Weight Category – no. (%)			0.80
Underweight	4 (0.5)	2 (0.3)	
Normal	102 (13.2)	85 (13.6)	
Overweight	241 (21.1)	206 (33.0)	
Obese	422 (54.5)	330 (52.8)	
Comorbidities -no. (%)			
Atrial fibrillation (Hx)	228(29.5)	245(39.3)	0.0001
Hypertension	725(93.7)	553(88.6)	0.0008
Coronary heart disease			
Myocardial infarction	116(15.0)	170(27.2)	<0.001
Angina	238(30.7)	235(37.7)	0.0066
PCI or CABG	115(14.9)	185(29.6)	<0.001
Stroke or TIA	64 (8.3)	66 (10.6)	0.14
Other Systems			
Type II Diabetes	241(31.1)	254(40.7)	0.0002
COPD/Asthma	105(13.6)	123(19.7)	0.0021
Peripheral vascular disease	168 (21.7)	112 (17.9)	0.08
Anemia	151 (19.5)	199 (21.8)	<0.001
Any alcohol intake	81 (10.5)	157 (25.2)	0.0001
Heart Failure Characteristics, Investigations and Treatment			
HF hospitalization within past 6 months –	183 (58.1)	207 (61.2)	

no. (%)			
NYHA 3& 4 – no. (%)	484 (62.5)	333 (53.3)	0.0005
Quality of Life scores			
Minnesota LWHF – median (Q1, Q3)	43.0 (32.0, 57.0)	38.5 (25.0, 53.0)	0.0028
KCCQ (Clinical Summary) score – median (Q1, Q3)	56.0 (38.8, 72.9)	60.4 (40.6, 79.7)	0.009
Peripheral edema	506 (65.4)	409 (65.5)	0.95
JVD	101 (13.4)	103 (16.9)	0.0683
Rales	163 (21.1)	129 (21.0)	0.9747
ECG – no. (%)			
Atrial fibrillation	118 (15.3)	156 (25.0)	<0.001
LVH	167 (21.7)	109 (17.5)	0.052
Other Investigations			
CXR demonstrating pleural effusion or pulmonary. congestion	196 (25.3)	105 (16.8)	<0.001
NT-proBNP (pg/ml) – median (IQR)	335.0 (126, 981)	517 (203, 1166)	0.0040
Sodium (mmol/L) - mean (SD)	140.0 (3.1)	139.4 (2.8)	0.21
Potassium (mmol/L) - mean (SD)	4.3 (0.5)	4.3 (0.4)	0.24
eGFR (ml/min/1.73m^2) - mean (SD)	67.2 (23.7)	69.9 (21.4)	0.03
eGFR <60 ml/min/m^2 – no. (%)	325 (42.7)	222 (36.0)	0.01
Drugs and Interventions – no. (%)			
Diuretic	659 (85.1)	541 (86.6)	0.45
Loop diuretics	466 (60.2)	434 (69.4)	0.0003
Thiazide diuretics	299 (38.6)	178 (28.5)	<0.001
Digitalis	60 (7.8)	70 (11.2)	0.03
Beta- blocker	538 (69.5)	460 (73.6)	0.09
Calcium Channel Blocker	343 (44.3)	240 (38.4)	0.03
Antiarrhythmics	63 (8.1)	47 (7.5)	0.67
Antiplatelets	437 (56.5)	387 (61.9)	0.03
Aspirin	413 (53.4)	373 (59.7)	0.02
Anticoagulants	170 (22.0)	193 (30.9)	0.0002
Statins	332 (42.9)	345 (55.2)	<0.001
Pacemaker	63 (8.1)	70 (11.2)	0.05
ICD	4 (0.5)	10 (1.6)	0.04

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body mass index (BMI), inter quartile range (IQR), history of (Hx), chronic obstructive pulmonary disease (COPD).
New York heart association (NYHA), living with heart failure (LWHF), Kansas City cardiomyopathy questionnaire (KCCQ), jugular venous distension (JVD), left ventricular hypertrophy (LVH), bundle branch block (BBB), left ventricular ejection fraction (LVEF), chest x-ray (CXR), N terminal -pro brain natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR), implantable cardioverter defibrillator (ICD).

Supplementary Table 3: Clinical outcomes in HFpEF (Echo substudy)

	Women 774 (55.3)	Men 625 (44.7)	Adjusted HR (Model 1) p-value	Adjusted HR (Model 2) p-value
	Total patients with events			
Primary composite outcome	167	188	0.65 (0.52 – 0.82) <0.001	0.78 (0.60 – 1.02) 0.067
Heart Failure Hospitalization	131	123	0.83 (0.64 – 1.08) 0.171	1.09 (0.80 – 1.49) 0.586
Cardiovascular Death	63	89	0.51 (0.36 – 0.71) <0.001	0.48 (0.32 – 0.73) <0.001
Sudden Death	17	34	0.34 (0.19 – 0.63) 0.001	0.24 (0.12 – 0.50) <0.001
All-cause Death	109	143	0.52 (0.40 – 0.68) <0.001	0.55 (0.40 – 0.75) <0.001

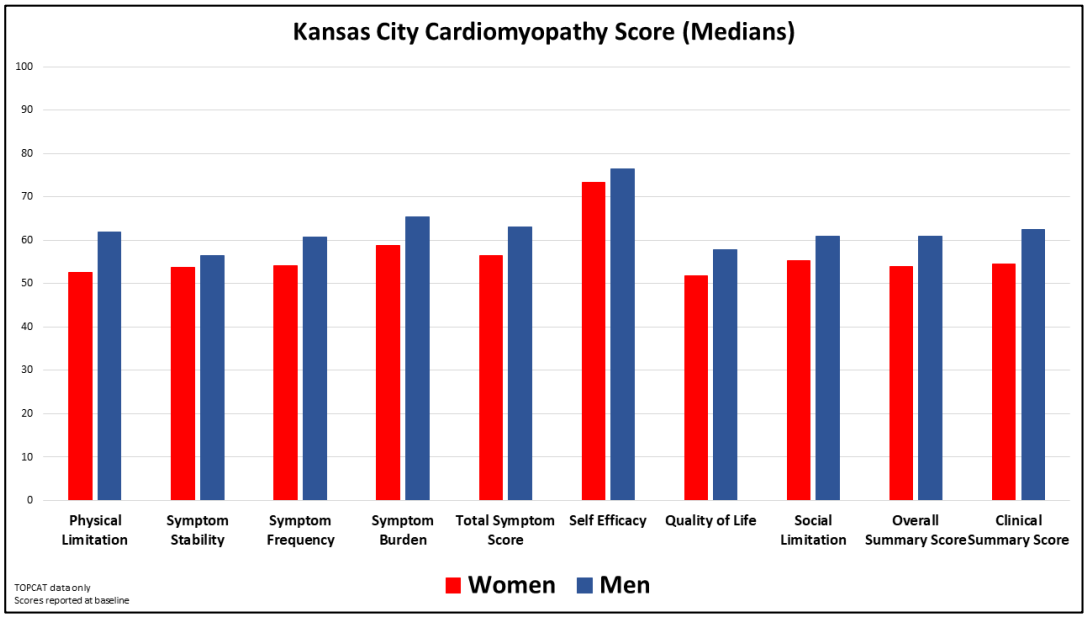
Hazard Ratios are reported with 95 confidence intervals (CI) within ()
All outcomes have been adjusted for trial, randomized treatment and region at baseline.
Adjustment Model 1 – age, HR, SBP, DBP, BMI, NYHA classes 3 & 4, LVEF, eGFR, NT-proBNP.
Adjustment Model 2 – age, HR, SBP, DBP, BMI, NYHA classes 3 & 4, LVEF, eGFR, NT-proBNP, e-wave, left ventricular mass indexed to body surface area (BSA) and left atrial volume indexed to BSA.
All outcomes were tested for competing risks of all-cause and non-cardiovascular death.
Missing indicator method was used to handle missing eGFR and NT-proBNP values

Supplementary Table 4: Clinical outcomes before and after matching by propensity score.

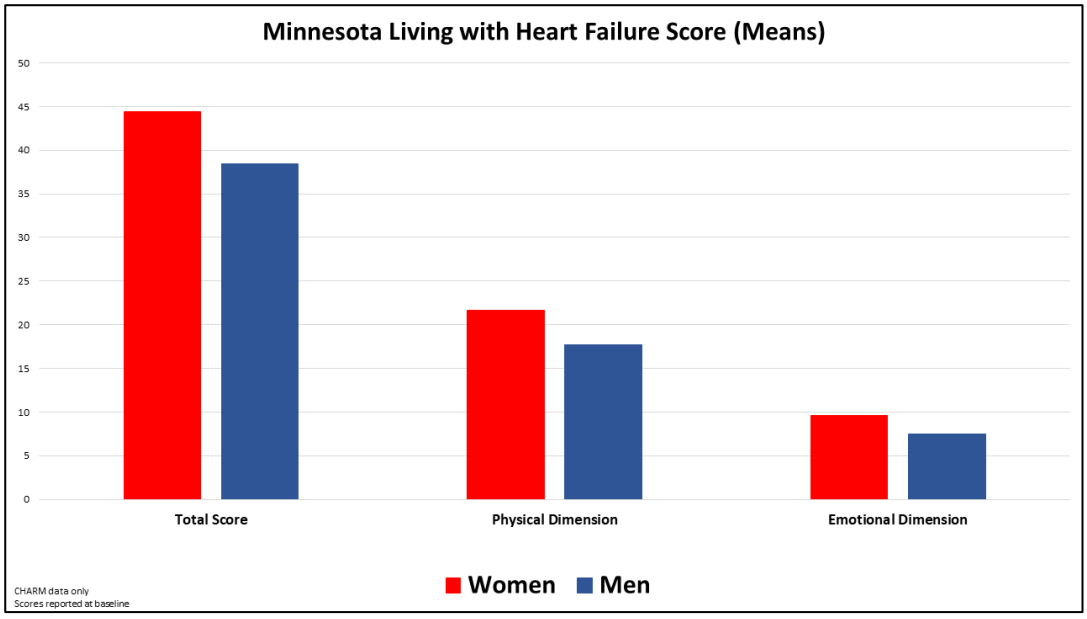
	Before matching			After matching		
	No. of events		Hazard Ratio* (women vs. men)	No. of events		Hazard Ratio (women vs. men)
	Women 3373 (57.2)	Men 2522 (42.8)		Women 830	Men 830	
Primary outcome	824	747	0.84 (0.76 – 0.94) 0.002	210	241	0.83 (0.69 – 0.99) 0.043
HF hospitalization	580	481	0.96 (0.84 – 1.09) 0.505	144	147	0.95 (0.76 – 1.20) 0.693
CV death	415	421	0.71 (0.61 – 0.82) <0.001	106	138	0.72 (0.56 – 0.93) 0.010
All-cause death	615	653	0.66 (0.59 – 0.74) <0.001	150	214	0.65 (0.53 – 0.81) <0.001

Adjusted for trial, region, randomized treatment, age, HR, SBP, DBP, BMI, NYHA classes III/IV, LVEF, eGFR, NT-proBNP, H/o atrial fibrillation, H/o coronary heart disease, , H/o hypertension, H/o stroke, H/o diabetes.
HR with 95% CI and p-value.

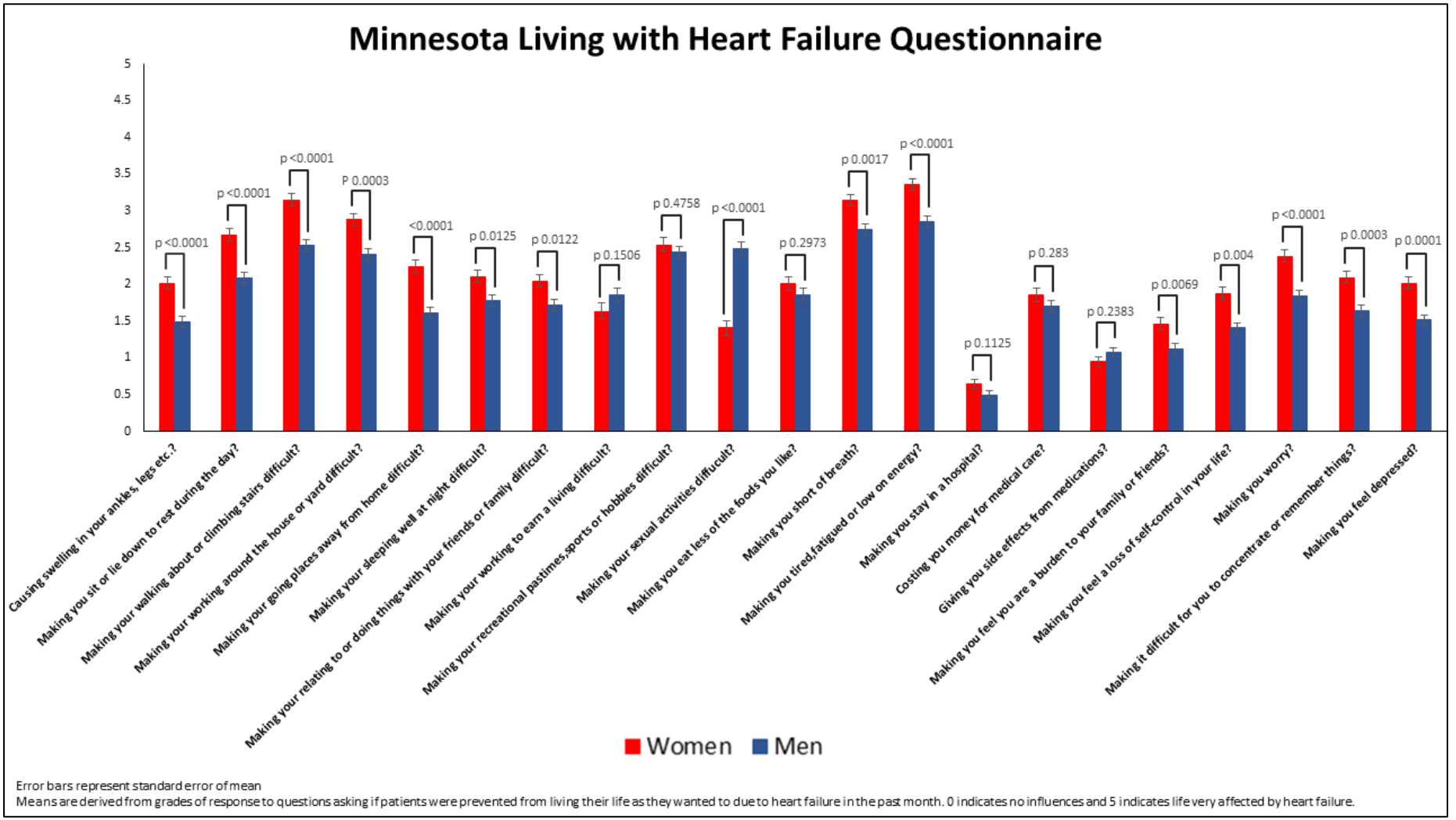
Supplementary Figure 1: Kansas City Cardiomyopathy Scores. Y axis represents score out of a possible 100 (with lower score representing worse quality of life).



Supplementary Figure 2: Minnesota Living with Heart Failure Scores. Y axis represents score out of a possible 100 (with higher score representing worse quality of life).



Supplementary Figure 3: Responses to individual questions in the Minnesota Living with Heart Failure questionnaire. Y axis represents response to questions (0 – 5) and bars show mean response to each question.



Supplementary Figure 4: Standardized differences of covariates between men and women before and after propensity score matching.