Title: Effects of sacubitril-valsartan, versus valsartan, in women compared to men with heart failure and preserved ejection fraction: Insights from PARAGON-HF.

Running title: Women and men in PARAGON-HF.

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ABSTRACT

Background: Unlike heart failure with reduced ejection fraction, there is no approved treatment for heart failure with preserved ejection fraction (HFpEF), the predominant phenotype in women. Therefore, there is a greater heart failure therapeutic deficit in women, compared with men.

Methods: In a pre-specified subgroup analysis, we examined outcomes according to sex in the PARAGON-HF trial which compared sacubitril-valsartan and valsartan in patients with HFpEF. The primary outcome was a composite of first and recurrent hospitalizations for heart failure and death from cardiovascular causes. We also report secondary efficacy and safety outcomes.

Results: Overall, 2479 women (51.7%) and 2317 men (48.3%) were randomized. Women were older, had more obesity, less coronary disease, and lower estimated glomerular filtration rate and NT-proBNP levels than men. For the primary outcome, the rate ratio for sacubitril-valsartan versus valsartan was 0.73 (95% CI 0.59-0.90) in women and 1.03 (0.84-1.25) in men; P interaction=0.017. The benefit from sacubitril-valsartan was due to reduction in heart failure hospitalization. The improvement in NYHA class and renal function with sacubitril-valsartan was similar in women and men, whereas the improvement in KCCQ-CSS was less in women than in men. The difference in adverse events, between sacubitril-valsartan and valsartan, was similar in women and men.

Conclusion: As compared with valsartan, sacubitril-valsartan seemed to reduce the risk of heart failure hospitalization more in women than in men. While the possible sex-related modification of the effect of treatment has several potential explanations, the present study does not provide a definite mechanistic basis for this finding.

Clinical Trial Registration: PARAGON-HF: ClinicalTrials.gov Identifier NCT01920711

Keywords: Heart failure; preserved ejection fraction; sacubitril-valsartan; women; outcomes

Non-standard Abbreviations and Acronyms: HF – heart failure; EF – ejection fraction; HFrEF – heart failure with reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; eGFR – estimated glomerular filtration rate; KCCQ-CSS – Kansas City Cardiomyopathy Questionnaire clinical summary score; NT-proBNP – N-terminal pro-B-type natriuretic peptide; cGMP – cyclic guanosine monophosphate; PKG – protein kinase G; ACE – angiotensin-converting enzyme; ARBs – angiotensin receptor blockers; MRAs - mineralocorticoid receptor antagonists

CLINICAL PERSPECTIVE

What is new?

- Women represent approximately a quarter of people with HF and reduced EF (HFrEF) and over half of those with HF and preserved EF (HFpEF).
- There are multiple effective drug and device therapies for HFrEF, but none approved for HFpEF; thus, there is a greater heart failure "therapeutic deficit" in women, compared with men.
- In PARAGON-HF, sex and LVEF appeared to modify the effect of sacubitril-valsartan, versus valsartan, on the primary outcome (total heart failure hospitalizations and cardiovascular death), with a more favorable treatment effect in women than in men (rate ratio 0.73 (0.59-0.90) in women, 1.03 (0.84-1.25) in men; P interaction=0.017).

What are the clinical implications?

- While the apparent sex-related modification of the effect of sacubitril-valsartan has several potential explanations, the present study does not provide a definite mechanistic basis for this finding.
- Our findings raise the possibility that the effects of pharmacological treatments for HFpEF may differ between men and women.
- This hypothesis should be investigated further, given the therapeutic deficit in this heart failure phenotype in general and, particularly, in women.

INTRODUCTION

Healthy women, on average, have higher a left ventricular ejection fraction (LVEF) than men and the pattern of left ventricular remodeling seen in response to increased afterload and with aging differs between women and men. [1-6] Among patients with heart failure (HF), women are less likely than men to have a markedly reduced LVEF (i.e. ≤40%).[1-6] While women represent approximately a quarter of people with HF and reduced EF (HFrEF), they account for over half of those with HF and preserved EF (HFpEF). [1-6] Although there are multiple effective drug and device therapies for HFrEF, there are none with regulatory approval for the treatment of HFpEF and guidelines largely focus on management of hypertension and volume overload and treatment of concomitant comorbidities such as atrial fibrillation .[7,8] In addition, the 2017 update of the American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines gave a Class IIb Level B-R recommendation for an aldosterone receptor antagonist in selected patients with HFpEF.[8] For this and other reasons, there is a greater heart failure "therapeutic deficit" in women, compared with men.[1,5,6]

In PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction trial), the effects of sacubitril-valsartan were compared with those of valsartan, and the primary outcome was a composite of heart failure hospitalization (first and repeat) and cardiovascular death.[9-11] Among the 4796 participants analyzed (52% women), there were fewer primary endpoints in the sacubitril-valsartan group, compared with the valsartan group, although the difference was of borderline statistical significance (894 versus 1009 primary events; rate ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P = 0.059). In PARAGON-HF, there were 12 pre-specified subgroup analyses.[11] Of these, only sex and LVEF appeared to modify the effect of sacubitril-valsartan versus valsartan on the primary composite outcome, with a more favorable treatment effect in women than in men. In view of the potential importance of this finding, we defined, in detail,

the differences between women and men in PARAGON-HF and further investigated the interaction between sex and the effect of treatment.

METHODS

The design and primary results of the PARAGON-HF trial are published.[9-11] The Ethics Committee of each of the participating institutions approved the protocol, and all patients gave written, informed consent. Novartis is committed to sharing, with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

Study patients

Eligibility for the study included New York Heart Association (NYHA) class II-IV symptoms, an ejection fraction of 45% or higher at, or within 6 months of, screening, an elevated natriuretic peptide level, evidence of structural heart disease and diuretic therapy. The natriuretic peptide level threshold for inclusion varied according to whether there had been a recent hospitalization for heart failure and the presence of atrial fibrillation or flutter. The main exclusion criteria included any prior echocardiographic measurement of LVEF <40%, recent acute coronary syndrome, cardiac surgery or percutaneous coronary intervention, acute decompensated heart failure at the time of screening, intolerance to either study drug (or similar classes) or a history of angioedema, systolic blood pressure >180 mmHg or <110mmHg, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 and serum potassium >5.2 mmol/l.

Trial procedures

All patients initially received valsartan at half the target dose (single-blind run-in period) and then sacubitril-valsartan at half the target dose (single-blind run-in period). If tolerated,

patients were then randomized to treatment with either sacubitril-valsartan or valsartan in a 1:1 fashion. The target doses were sacubitril-valsartan 97mg/103mg twice daily or 160mg of valsartan twice daily. The 103 mg of valsartan in sacubitril-valsartan is equivalent to 160 mg of the standard valsartan formulation.

Trial outcomes

The primary outcome was a composite of first and recurrent hospitalizations for heart failure and death from cardiovascular causes. Secondary outcomes were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS[12]) from baseline to 8 months (with a score from 0-100 and higher scores corresponding to fewer symptoms and limitations), change in NYHA class from baseline to 8 months, the time to the first occurrence of a decline in renal function (defined as a reduction of 50% of more in estimated glomerular filtration rate, development of end-stage renal disease or death due to renal failure) and time to death from any cause. Safety outcomes included hypotension (defined as a systolic blood pressure <100mmHg), elevation of serum creatinine, elevation of serum potassium, and angioedema

Statistical analysis

The trial was designed to recruit 4600 patients and continue until 1847 primary events occurred. Between 2014 and 2016, 10, 359 patients in 43 countries were screened and a total of 4796 patients were finally included. In the present study, patients were analyzed according to sex (baseline characteristics were compared using t-tests, Wilcoxon rank-sum test, and chi-squared tests where appropriate). The primary composite outcome, its components, change in KCCQ-CSS from baseline to 8 months, change in NYHA class from baseline to 8 months and death from any cause were analyzed, as was safety. An additional expanded primary composite outcome, which included urgent heart failure visits, was also analyzed. For each sex, the effect of sacubitril-valsartan compared with valsartan on the primary composite outcome, its components, and the expanded primary composite outcome

was examined using the semiparametric proportional rates method of Lin et al stratified according to region.[13] The cumulative recurrent events were displayed using Nelson-Aalen cumulative hazard curves and cumulative first events were displayed using Kaplan-Meier curves. The primary composite outcome and its components were also analyzed using Cox regression for time-to-first event, as were the renal composite outcome and death from any cause. Changes from baseline to 8 months in KCCQ-CSS, systolic blood pressure and pulse pressure, and from baseline to 1 year in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and urinary cyclic guanosine monophosphate (cGMP)/creatinine, were analyzed using a repeated measures analysis of covariance model, together with the mixed-effect logistic responder analyses for a 5-point or greater change in KCCQ-CSS. Change from baseline to 8 months in NYHA class was analyzed using a repeated measures proportional cumulative odds model. The interaction between sex and treatment on each outcome was assessed in each respective statistical test and in a logistic regression model for the safety outcomes. Models were adjusted for differences in baseline characteristics between women and men (specifically, age, heart rate, systolic blood pressure, body mass index, smoking status, NT-proBNP (log), eGFR, NYHA class, LVEF, prior HF hospitalization, myocardial infarction, diabetes and atrial fibrillation); analyses were either stratified (prespecified primary and secondary outcomes) or adjusted for geographical region. A fractional polynomial was constructed using left ventricular ejection fraction and entered into the model as an interaction term with treatment. The results of the interaction were displayed graphically using the mfpi command in STATA. The effect of sacubitril-valsartan compared with valsartan was modelled over the spectrum of left ventricular ejection fraction in women and men separately. All analyses were conducted using STATA version 16 (College Station, TX: StataCorp LLC). A P value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Overall, 2479 women (51.7%) and 2317 men (48.3%) were randomized. Women were older than men and had more obesity and a lower median NT-proBNP level and a lower mean eGFR than men (Table 1). The distribution of LVEF in women and men is shown in Supplemental Figure 1. The median LVEF in women was 60% and in men it was 55%. Women had a worse NYHA class distribution, worse KCCQ-CSS (and overall summary score), and more symptoms of heart failure. Women were much less likely than men to be a current or past smoker and had a lower prevalence of coronary heart disease, diabetes and chronic obstructive pulmonary disease. Women were significantly less likely than men to be treated with each of a nitrate, statin, antiplatelet therapy, an anticoagulant and a mineralocorticoid receptor antagonist. Baseline characteristics were balanced between treatment groups, in both women and men (Supplemental Tables 1 and 2).

Clinical outcomes: women versus men (control group)

Comparison of event rates in the control (valsartan) group showed that women and men had similar rates of the composite of heart failure hospitalization or death from cardiovascular causes, whether analyzed as total events, including first and recurrent hospitalizations (Figure 1) or as time-to-first event (Figure S2). When the components of this composite were analyzed individually, women were observed to have higher rates of heart failure hospitalization and lower rates of cardiovascular death (and death from any cause), as compared with men (Table 2, Figure 1 and S2). The proportions of women and men reported to have an improvement in NYHA Class between baseline and 8 months was similar, but the proportion of women describing a clinically important increase in KCCQ-CSS over this period was greater than the corresponding proportion in men (Table 2).

Effect of sacubitril-valsartan: women versus men

The rate ratio for the primary outcome with sacubitril-valsartan, compared to valsartan, in women was 0.73 (95% CI 0.59-0.90) and in men it was 1.03 (0.84-1.25); P interaction=0.017 (Table 2 and Figure 1). Adjustment for the baseline differences between women and men did not change this result (Table 2). An alternative approach to analysis of recurrent events (negative binomial method) gave qualitatively similar findings to the LWYY method (Figure S3). The composite of heart failure hospitalization or cardiovascular death, analyzed as time to first event, gave similar findings to the analysis of total events (Table 2 and Figure S2).

Further examination of the apparent benefit of sacubitril-valsartan over valsartan, in women, showed that the effect was predominantly related to heart failure hospitalization, with no discernible reduction in death from cardiovascular causes (or from any cause) (Table 2, Figures 1 and S2). The magnitude of the effect on first and recurrent hospitalizations for heart failure was substantial, with a 33 (95% CI 15-47)% relative risk reduction in women; P interaction=0.005 for effect in women versus men. Analysis of first hospitalizations for heart failure gave similar findings to total (first and recurrent) admissions (Figure S2).

Examination of the effect of treatment across the range of LVEF studied suggested more benefit from sacubitril-valsartan at a lower LVEF, whether using analysis of total events (Figure 2) or analyzing first events only (Figure S4). These fractional polynomial analyses also suggested that the upper threshold at which benefit diminished was higher in women than in men (Figures 2 and S4).

The proportional improvement in NYHA class with sacubitril-valsartan was similar in women and men, whereas the relative improvement in KCCQ-CSS seemed to be less in women than in men (although in this “responder analysis”, examining patients with a ≥5-point improvement, there was no statistically significant interaction between sex and response to sacubitril-valsartan). When examined as a continuous variable, the sacubitril-

valsartan versus valsartan difference in KCCQ-CSS change was also more favorable in men, compared with women (P interaction=0.038, adjusted P interaction=0.067).

The improvement in renal function with sacubitril-valsartan, compared with valsartan, was similar in women and men (Table 2).

New-onset atrial fibrillation

The risk of new-onset atrial fibrillation was higher in women treated with sacubitril-valsartan, compared with valsartan, whereas the opposite was true for men. Although this resulted in a significant interaction between sex and the effect of treatment, the numbers of events were small.

Other measures: change in NT-proBNP, systolic blood pressure and pulse pressure and urinary cGMP/creatinine

The reductions from baseline to 8 months in systolic blood pressure and pulse pressure, and from baseline to 1 year in NT-proBNP, with sacubitril-valsartan, as compared with valsartan, were similar in men and women (Table 2). The increase from baseline to 1 year in urinary cGMP to creatinine ratio with sacubitril-valsartan treatment was also similar in women and men (Table 2).

Effect of sacubitril-valsartan: Safety in women versus men

Hypotension was more common, and increases in creatinine and potassium less common, with sacubitril-valsartan, as compared with valsartan (Table 3). The difference in these adverse events of interest, between sacubitril-valsartan and valsartan, was similar in women and men. There were too few cases of angioedema for meaningful analysis by sex.

DISCUSSION

Over half the participants in PARAGON-HF were female, representing one of the largest populations of women with HFpEF ever studied. We found that women and men with HFpEF have distinct clinical profiles and that, compared with valsartan, treatment with sacubitril-valsartan led to a greater reduction in heart failure hospitalization in women, than in men. The difference in the clinical profile between men and women with HFpEF is consistent with prior results, particularly in relation to the lower risk of death and greater severity of symptoms in women.[1-6] That we observed a greater treatment effect on heart failure hospitalization in women than men, is more novel, and of some interest, given that HFpEF is the predominant phenotype in women.[1-6] Indeed, the proportion of HFpEF in the population may be even higher than in PARAGON-HF as, in keeping with trials in general, our patients were younger and had less comorbidity than reported in epidemiologic studies.[3,5,6]

The major question arising is whether this subgroup finding was due to the play of chance or represents a real difference between women and men in response to therapy? A framework for interpretation of treatment heterogeneity in subgroups has been provided by several authors.[14-17] Key principles include pre-specification of the subgroup of interest, that the subgroup should be of sufficient size and that a statistical test for interaction is carried out. Each of these conditions was fulfilled in the present study and in a further step, an interaction between sex (along with ejection fraction) and the effect of treatment persisted in a multivariable analysis including all pre-specified subgroups.[11]

Other key considerations are biological plausibility and internal consistency and external validation. In terms of the first of these, there are several reasons why women might have a more favorable response to neprilysin inhibition. The normal LVEF range is higher in women than in men, reflecting sex-related differences in cardiac remodeling in response to

blood pressure, age etc.[3-6,18] Importantly, for a given LVEF, more women than men may have other evidence of contractile dysfunction.[2-6,19,20] If correct, this would mean that more women than men in the present study had mild left ventricular systolic dysfunction. This view is consistent with the apparent benefit of sacubitril-valsartan, a drug clearly effective in patients with left ventricular systolic dysfunction, to a higher LVEF value in women, compared with men, in the fractional polynomial analyses (Figure 2).

Alternatively, age-related arterial stiffening is more pronounced in women than men and has been postulated to be a key pathophysiologic factor in HFpEF.[21] However, the reduction in pulse-pressure (and systolic blood pressure) with sacubitril-valsartan (compared with valsartan) was similar in women and men, pulse-pressure is a relatively crude measure of arterial stiffness.[22]

We confirmed that natriuretic peptide levels are lower in women with HFpEF, than in men, despite more severe symptoms and known higher left ventricular diastolic and systolic stiffness, and filling pressures, in women, compared with men.[2-6, 19] However, women have much more visceral obesity than men with HFpEF (as evidenced by waist circumference in the present study) and obesity is associated with lower natriuretic peptide levels. There are also known sex differences in natriuretic peptide biology, with “cross talk” between these peptides and sex hormones, possibly leading to a decrease in natriuretic peptide levels after the menopause.[5,23-28] This potential relative natriuretic peptide deficiency will lead to reduced cGMP-protein kinase G (PKG) signaling.[24-31] Any reduction in cGMP-PKG signaling due to a relative natriuretic peptide deficiency may be exacerbated in postmenopausal women by of loss of alternative, estrogen-dependent, stimulation of this pathway through endothelial nitric oxide synthase activation and nitric oxide generation.[5, 24-31] Consequently, by augmenting natriuretic peptides, sacubitril-valsartan may be of greater benefit in women, than in men, if women are viewed as having deficient cGMP-PKG signaling. [5, 24-31] Certainly, the increase in

urinary cGMP/creatinine with sacubitril-valsartan, was as large in women as in men. The present trial, however, does not provide direct mechanistic evidence to support this hypothesis.

Neprilysin also degrades other biologically active peptides and it is possible that there could be a sex-related difference in these alternative actions of sacubitril-valsartan. Women may have a greater increase than men in bradykinin production with neprilysin inhibition as they are more likely to develop angioedema than men with both neprilysin and angiotensin-converting enzyme (ACE) inihibition.[32]

A much smaller proportion of women, compared with men, were current or former smokers which may be relevant because in a population study, smoking was the variable most strongly associated with plasma neprilysin level.[33] However, adjustment for smoking status did not change the apparently greater effect of sacubitril-valsartan in women, compared with men.

We also considered whether the precipitants of heart failure hospitalization might differ between women and men, one of which is new-onset atrial fibrillation.[34] Confirmed new-onset atrial fibrillation was relatively infrequent in the trial and the effect of sacubitril-valsartan on this outcome was less favorable in women than men. This means that incident atrial fibrillation cannot account for the sex-related difference in the effect of sacubitril-valsartan on heart failure hospitalization.

Finally, there may have been a larger subgroup of patients not responsive to treatment with sacubitril-valsartan among men, compared with women, in PARAGON-HF e.g. patients with undiagnosed cardiac amyloidosis or genetic hypertrophic cardiomyopathy, although it is uncertain whether these conditions are more prevalent in males than females with HFpEF.[35]

From the point of view of internal consistency, we found that improvements in patient-reported and physician-reported outcomes did not show greater improvements with sacubitril-valsartan in women, compared with men. Indeed, change in KCCQ-CSS showed a more favorable response to sacubitril-valsartan in men, than in women. This may reflect the much worse KCCQ scores at baseline in women (with less possibility of improvement) or may reflect the play of chance. NYHA class improved to a similar extent in women and men. While there is a relatively weak correlation between functional class and health-related quality of life and risk of hospital admission, it is still somewhat surprising that the sex-related responses to sacubitril-valsartan were directionally different for these outcomes. The improvement in renal function with sacubitril-valsartan over valsartan, was similar in women and men. Overall, therefore, sacubitril-valsartan had similar (or greater, in the case of KCCQ-CSS) benefits in men as women, with the exception of reduction in heart failure hospitalization, which was greater in women.

In terms of external validation, sex does seem to modify response to some treatments in patients with heart failure. In HFrEF, women appear to obtain more benefit from cardiac resynchronization therapy but less from digoxin.[36,37] In HFpEF, sex-specific spline analysis examining the effect of spironolactone across the range of LVEF studied in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), showed that women appeared to benefit across the whole LVEF spectrum, whereas in men there was only benefit at a lower ejection fraction.[38] Unpublished data from the CHARM-Preserved (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) trial report the same pattern (Supplemental Figure 5).[39] While these examples support the possibility of sex as a modifier of treatment effect, no such interaction was found for sacubitril-valsartan (compared with enalapril) in patients with HFrEF in PARADIGM-HF, suggesting that any modification of the effect of this treatment by sex is only apparent at higher ejection fractions.[40] However, direct comparison of PARADIGM-HF and PARAGON-

HF is not straightforward as the comparator therapy in the former trial was enalapril and there is less evidence for benefit of ACE inhibitors, compared with angiotensin receptor blockers (ARBs), in women, and the comparator therapy in PARAGON-HF was an ARB.[39,41] The possible discrepancy in sex differences in treatment response by type of HF (HFpEF versus. HFrEF) also seems to be the case for mineralocorticoid receptor antagonists (MRAs) when the findings of TOPCAT (see above) are compared with the HFrEF trials using MRAs and for candesartan (CHARM reduced LVEF trials compared with CHARM-Preserved).[39, 42]

It is also important to note that PARAGON-HF was an active-controlled trial and, therefore, the possible benefit of sacubitril-valsartan over valsartan in women could reflect lower efficacy of valsartan in women (compared with men), though this is not supported by published analyses of trials using ARBs in HFrEF. [39,41]

We also believe that it is unlikely that a greater degree of neprilysin inhibition or angiotensin receptor blockade in women might explain the apparent difference between women and men in response to sacubitril-valsartan.[43] Women did not achieve a higher target dose of sacubitril-valsartan than men and did not have a lower treatment discontinuation-rate. Moreover, the pharmacokinetics of sacubitril-valsartan and its metabolites do not differ in women and in men.[44] As mentioned above, the reduction in blood pressure and NT-proBNP, and rise in urinary cGMP, was similar in women and men. Collectively, this information makes it unlikely that a greater effective dose leading to a greater neprilysin inhibition or angiotensin receptor blockade could account for the difference between women and men with respect to heart failure hospitalization.

As with any study of this type there are some limitations. We do not have information on more sensitive measures of left ventricular systolic function than ejection fraction. We do not

have information on cardiac and other biomarkers, including neprilysin levels or sex hormones, except for NT-proBNP and cGMP.

In summary, as compared with valsartan, sacubitril-valsartan seemed to reduce the risk of heart failure hospitalization more in women than in men. While the possible sex-related modification of the effect of treatment has several potential explanations, the present study does not provide a definite mechanistic basis for this finding.

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Conflict of Interest Disclosures

AMJ reports no conflicts. JJVM reports that his employer, Glasgow University, has been paid by Novartis for serving as an Executive Committee member and co-principal investigator of ATMOSPHERE, PARADIGM-HF and PARAGON-HF trials and Executive/Steering Committee member of the PARADISE-MI and PERSPECTIVE trials (with sacubitril-

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Table 1. Baseline characteristics for women and men in PARAGON-HF.

	Women (n=2479)	**Men (n=2317)**	**P value**
Age – years	73.6±8.0	71.8±8.7	<0.001
Age category			<0.001
50-59	143 (5.8)	232 (10.0)	
60-69	562 (22.7)	676 (29.2)	
70-79	1168 (47.1)	942 (40.7)	
≥80	606 (24.4)	467 (20.2)	
Region			0.003
Asia-Pacific and other	379 (15.3)	383 (16.5)	
Central Europe	885 (35.7)	830 (35.8)	
Latin America	222 (9.0)	148 (6.4)	
North America	264 (10.6)	295 (12.7)	
Western Europe	729 (29.4)	661 (28.5)	
Race			<0.001
Asian	287 (11.6)	320 (13.8)	
Black	61 (2.5)	41 (1.8)	
Other	124 (5.0)	56 (2.4)	
White	2007 (81.0)	1900 (82.0)	
Duration of heart failure			0.41
0-3 months	417 (16.9)	356 (15.4)	
3-6 months	319 (12.9)	267 (11.5)	
6-12 months	309 (12.5)	307 (13.3)	
1-2 years	340 (13.8)	339 (14.7)	
2-5 years	508 (20.6)	485 (21.0)	
>5 years	578 (23.4)	559 (24.2)	
Systolic blood pressure – mmHg	131±16	130±15	0.04
Diastolic blood pressure – mmHg	74±11	74±10	0.99
Pulse pressure – mmHg	57±15	56±14	0.029
Heart rate – beats/min	71±12	70±12	0.047
Left ventricular ejection fraction – %	58.9±7.9	56.0±7.6	<0.001
Body mass index – kg/m^2	30.4±5.2	30.0±4.8	0.001
Body mass index >30 kg/m^2	1272 (51.3)	1082 (46.7)	0.001
Waist circumference – cm	101.8±14.5	107.6±14.7	<0.001
Abnormal*	1953 (82.8)	1339 (61.6)	<0.001
Waist/hip ratio	0.93±0.12	1.00±0.11	<0.001
Estimated GFR – mL/min/1.73m2	60±18	65±20	<0.001
Estimated GFR <60 mL/min/1.73m2	1320 (53.2)	1021 (44.1)	<0.001
N-terminal-pro B-type natriuretic peptide – pg/ml	836 (446-1601)	954 (496-1631)	0.002
In patients with atrial fibrillation†	1712 (1252-2360)	1508 (1124-2210)	<0.001

In patients without atrial fibrillation†	575 (378-1018)	625 (381-1103)	0.022
Urinary cGMP/creatinine	129±70	120±61	0.013
NYHA functional class			<0.001
I	49 (2.0)	88 (3.8)	
II	1865 (75.3)	1841 (79.5)	
III	554 (22.4)	378 (16.3)	
IV	10 (0.4)	9 (0.4)	
KCCQ			
Clinical summary score	70.8 (56.3-83.9)	79.2 (64.6-90.6)	<0.001
Overall summary score	70.8 (55.7-83.6)	77.6 (63.5-88.8)	<0.001
Medical history			
Atrial fibrillation†	725 (29.4)	827 (35.8)	<0.001
Any history of atrial fibrillation	1280 (51.6)	1241 (53.6)	0.18
Angina pectoris	664 (26.8)	724 (31.2)	<0.001
Myocardial infarction	389 (15.7)	694 (30.0)	<0.001
Hypertension	2392 (96.5)	2192 (94.6)	0.002
Diabetes	1001 (40.4)	1061 (45.8)	<0.001
Prior heart failure hospitalization	1113 (44.9)	1193 (51.5)	<0.001
Stroke	256 (10.3)	252 (10.9)	0.53
Chronic obstructive pulmonary disease	286 (11.5)	384 (16.6)	<0.001
Cancer	228 (9.2)	205 (8.9)	0.67
Anemia	366 (14.8)	341 (14.7)	0.96
Renal disease	589 (23.9)	635 (27.5)	0.004
Other vascular disease	266 (10.8)	354 (15.4)	<0.001
Coronary artery bypass grafting	172 (6.9)	398 (17.2)	<0.001
Percutaneous coronary intervention	369 (14.9)	608 (26.2)	<0.001
Smoker (current or former)	546 (22.2)	1308 (56.8)	<0.001
ACE inhibitor intolerance	155 (6.3)	107 (4.6)	0.013
Treatments			
Diuretic	2352 (94.9)	2233 (96.4)	0.011
Mineralocorticoid receptor antagonist	590 (23.8)	649 (28.0)	<0.001
ACE inhibitor or ARB at screening	2145 (86.5)	1994 (86.1)	0.64
Beta-blocker	1985 (80.1)	1836 (79.2)	0.47
Calcium channel blocker	861 (34.7)	779 (33.6)	0.42
Digoxin	248 (10.0)	202 (8.7)	0.13
Nitrate	308 (12.4)	391 (16.9)	<0.001
Statin	1503 (60.6)	1552 (67.0)	<0.001
Antiplatelet	256 (10.3)	379 (16.4)	<0.001
Anticoagulant	762 (30.7)	789 (34.1)	0.014
Signs and symptoms			
Dyspnea on effort	2316 (93.5)	2108 (91.1)	0.002

Paroxysmal nocturnal dyspnea	108 (4.4)	83 (3.6)	0.17
Orthopnea	511 (20.6)	375 (16.2)	<0.001
Edema	930 (37.6)	896 (38.7)	0.41
Rales	163 (6.6)	182 (7.9)	0.086
Third heart sound	57 (2.3)	54 (2.3)	0.94
Jugular venous distension	321 (13.0)	334 (14.6)	0.13
Fatigue	1328 (53.6)	1109 (48.0)	<0.001

* Defined as >88 cm in women and >102 cm in men

† Defined as the presence of atrial fibrillation or atrial flutter on screening ECG

Data are presented as mean ± standard deviation or median (interquartile range) for continuous measures and number (%) for categorical measures

All drugs are at randomization unless otherwise specified

GFR = glomerular filtration rate; cGMP = cyclic guanosine monophosphate; NYHA = New York Heart Association; KCCQ = Kansas City Cardiomyopathy Questionnaire; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker

Table 2. Outcomes for women and men in PARAGON-HF.

	Women (n=2479)			Men (n=2317)			
	All	Sacubitril-valsartan (n=1241)	Valsartan (n=1238)	All	Sacubitril-valsartan (n=1666)	Valsartan (n=1151)	Interaction P value
Primary composite outcome							
Number of events	923	391	532	980	503	477	
Event rate (95% CI)	12.7 (11.9-13.6)	10.8 (9.8-11.9)	14.7 (13.5-16.0)	14.8 (13.9-15.8)	15.1 (13.8-16.5)	14.6 (13.3-16.0)	
Unadjusted rate ratio (95% CI)*		0.73 (0.59-0.90)			1.03 (0.84-1.25)		0.0168*
Adjusted rate ratio (95% CI)†		0.73 (0.60-0.90)			1.02 (0.83-1.24)		0.0225†
Primary composite outcome plus urgent HF visits							
Number of events	964	411	553	1034	523	511	
Event rate (95% CI)	13.3 (12.5-14.2)	11.3 (10.3-12.5)	15.3 (14.1-16.6)	15.7 (14.7-16.6)	15.7 (14.4-17.1)	15.6 (14.3-17.0)	
Unadjusted rate ratio (95% CI)*		0.73 (0.60-0.91)			1.00 (0.82-1.21)		0.0329*
Adjusted rate ratio (95% CI)†		0.74 (0.61-0.91)			0.99 (0.81-1.20)		0.0449†
Total hospitalizations for HF							
Number of events	738	298	440	749	392	357	
Event rate (95% CI)	10.2 (9.5-11.0)	8.2 (7.3-9.2)	12.2 (11.1-13.3)	11.3 (10.6-12.2)	11.8 (10.6-13.0)	10.9 (9.8-12.1)	
Unadjusted rate ratio (95% CI)*		0.67 (0.53-0.85)			1.07 (0.85-1.34)		0.0046*
Adjusted rate ratio (95% CI)†		0.67 (0.54-0.84)			1.06 (0.84-1.34)		0.0048†
CV death							
Number of events	185	93	92	231	111	120	
Event rate (95% CI)	2.6 (2.2-2.9)	2.6 (2.1-3.1)	2.5 (2.1-3.1)	3.5 (3.1-4.0)	3.3 (2.8-4.0)	3.7 (3.1-4.4)	
Unadjusted hazard ratio (95% CI)*		1.02 (0.76-1.36)			0.90 (0.70-1.17)		0.5763*
Adjusted hazard ratio (95% CI)†		1.05 (0.78-1.41)			0.88 (0.67-1.14)		0.3688†

Death from any cause							
Number of events	312	153	159	379	189	190	
Event rate (95% CI)	4.3 (3.9-4.8)	4.2 (3.6-4.9)	4.4 (3.8-5.1)	5.7 (5.2-6.3)	5.7 (4.9-6.5)	5.8 (5.0-6.7)	
Unadjusted hazard ratio (95% CI)*		0.96 (0.77-1.20)			0.97 (0.80-1.19)		0.9040*
Adjusted hazard ratio (95% CI)†		0.99 (0.79-1.24)			0.95 (0.77-1.17)		0.8703†
First hospitalization for HF or CV death							
Number of events	524	239	285	559	287	272	
Event rate (95% CI)	7.9 (7.3-8.6)	7.1 (6.3-8.1)	8.8 (7.8-9.8)	9.3 (8.5-10.1)	9.5 (8.4-10.6)	9.1 (8.0-10.2)	
Unadjusted hazard ratio (95% CI)*		0.81 (0.68-0.96)			1.03 (0.87-1.21)		0.0440*
Adjusted hazard ratio (95% CI)†		0.78 (0.65-0.92)			1.03 (0.87-1.22)		0.0213†
First hospitalization for HF							
Number of events	417	183	234	421	222	199	
Event rate (95% CI)	6.3 (5.7-7.0)	5.5 (4.7-6.3)	7.2 (6.3-8.2)	7.0 (6.3-7.7)	7.3 (6.4-8.4)	6.6 (5.8-7.6)	
Unadjusted hazard ratio (95% CI)*		0.75 (0.62-0.91)			1.08 (0.89-1.31)		0.0070*
Adjusted hazard ratio (95% CI)†		0.72 (0.59-0.87)			1.09 (0.90-1.33)		0.0025†
Change in NYHA from baseline to 8 months							
Improved – no. (%)	344 (14.5)	193 (16.4)	151 (12.7)	292 (13.0)	154 (13.5)	138 (12.4)	
Unchanged – no. (%)	1817 (76.8)	881 (74.9)	936 (78.6)	1742 (77.4)	886 (77.7)	856 (77.1)	
Worsened – no. (%)	206 (8.7)	102 (8.7)	104 (8.7)	217 (9.6)	100 (8.8)	117 (10.5)	
Unadjusted odds ratio (95% CI)*‡		1.43 (1.02-2.03)			1.45 (1.01-2.07)		0.9791*
Adjusted odds ratio (95% CI)†‡		1.45 (1.03-2.06)			1.46 (1.02-2.09)		0.9890†
Change in KCCQ clinical summary score from baseline to 8 months							
Change	-1.3±0.4	-1.6±0.5	-1.0±0.5	-2.9±0.4	-1.5±0.5	-4.3±0.5	

Difference		-0.6 (-2.1 to 0.8)			2.8 (1.3 to 4.3)		0.0013* 0.0032
Increase ≥5 points – no. (%)	761 (33.3)	386 (34.0)	375 (32.7)	640 (29.2)	357 (32.0)	283 (26.3)	
Unadjusted odds ratio (95% CI)*§		1.09 (0.81-1.46)			1.57 (1.14-2.15)		0.1080*
Adjusted odds ratio (95% CI)†§		1.11 (0.83-1.50)			1.55 (1.13-2.13)		0.1602†
Renal composite outcome							
Number of events	48	16	32	49	17	32	
Event rate (95% CI)	0.7 (0.5-0.9)	0.4 (0.3-0.7)	0.9 (0.6-1.3)	0.7 (0.6-1.0)	0.5 (0.3-0.8)	1.0 (0.7-1.4)	
Unadjusted hazard ratio (95% CI)*		0.49 (0.27-0.89)			0.53 (0.29-0.95)		0.8956*
Adjusted hazard ratio (95% CI)†		0.46 (0.25-0.84)			0.47 (0.26-0.86)		0.9714†
New-onset atrial fibrillation							
Number of events	144	84	60	118	53	65	
Event rate (95% CI)	2.1 (1.7-2.4)	2.4 (1.9-3.0)	1.7 (1.3-2.2)	1.8 (1.5-2.2)	1.6 (1.2-2.1)	2.1 (1.6-2.6)	
Unadjusted hazard ratio (95% CI)*		1.41 (1.02-1.97)			0.79 (0.55-1.13)		0.0189*
Adjusted hazard ratio (95% CI)†		1.43 (1.02-1.99)			0.78 (0.54-1.12)		0.0139†
Change in NT-proBNP from baseline to 1 year							
Change – pg/ml	-114±39	-182±55	-45±55	-133±53	-259±73	2±76	
Difference		-137 (-289 to 15)			-261 (-468 to -54)		0.3573* 0.3764†
Change in urinary cGMP/creatinine from baseline to 1 year							
Change	-22.4±2.5	4.7±3.6	-49.9±3.6	-20.5±2.2	5.8±3.0	-48.7±3.2	
Difference		54.6 (44.6 to 64.5)			54.5 (45.8 to 63.1)		0.9935* 0.9087†

Change in systolic blood pressure from baseline to 8 months							
Change – mmHg	1.9±0.3	-0.3±0.5	4.1±0.5	0.8±0.3	-1.4±0.5	3.1±0.5	
Difference		-4.3 (-5.6 to -3.0)			-4.6 (-5.9 to -3.3)		0.8058*
							0.8727†
Change in pulse pressure from baseline to 8 months							
Change – mmHg	1.2±0.3	-0.3±0.4	2.6±0.4	0.6±0.3	-0.9±0.4	2.2±0.4	
Difference		-2.9 (-4.0 to -1.8)			-3.1 (-4.2 to -2.0)		0.8109*
							0.9559†

Event rate is number of events per 100 person-years.

Plus-minus values are means ± standard error.

* Model stratified by or adjusted for region

† Model adjusted for age, heart rate, systolic blood pressure, body mass index, N-terminal pro-B-type natriuretic peptide level (log), estimated glomerular filtration rate, New York Heart Association functional class, left ventricular ejection fraction, prior heart failure hospitalization, myocardial infarction, diabetes, smoking, atrial fibrillation (except for time to new-onset atrial fibrillation) and either stratified by or adjusted for region

Unadjusted models for change in New York Heart Association functional class, Kansas City Cardiomyopathy Questionnaire clinical summary score, N-terminal pro-B-type natriuretic peptide level, urinary cGMP/creatinine, systolic blood pressure and pulse pressure also include the baseline value.

‡ Odds ratio for improvement

§ Odds ratio for increase ≥5 points

Table 3. Tolerability and adverse events in women and men in PARAGON-HF

	Women (n=2479)			**Men (n=2317)**			**Interaction P value**
	All	Sacubitril-valsartan (n=1241)	Valsartan (n=1238)	All	Sacubitril-valsartan (n=1666)	Valsartan (n=1151)	
Hypotension	317 (12.8)	195 (15.7)	122 (9.9)	320 (13.8)	185 (15.9)	135 (11.7)	0.3796* 0.5045†
Elevated serum creatinine							
≥2.0 mg/dl	181 (7.3)	75 (6.0)	106 (8.6)	408 (17.6)	186 (16.0)	222 (19.3)	0.4070* 0.3638†
≥2.5 mg/dl	58 (2.3)	28 (2.3)	30 (2.4)	148 (6.4)	69 (5.9)	79 (6.9)	0.8181* 0.8860†
≥3.0 mg/dl	22 (0.9)	12 (1.0)	10 (0.8)	56 (2.4)	26 (2.2)	30 (2.6)	0.5118* 0.6355†
Elevated serum potassium							
>5.5 mmol/l	330 (13.3)	160 (12.9)	170 (13.7)	347 (15.0)	156 (13.4)	191 (16.6)	0.2515* 0.1085†
>6.0 mmol/l	86 (3.5)	35 (2.8)	51 (4.1)	90 (3.9)	40 (3.4)	50 (4.3)	0.6491* 0.7087†
Angioedema	14 (0.6)	11 (0.9)	3 (0.2)	4 (0.2)	3 (0.3)	1 (0.1)	0.8840* 0.6968†
Liver-related adverse event	143 (5.8)	64 (5.2)	79 (6.4)	186 (8.0)	87 (7.5)	99 (8.6)	0.7200* 0.7360†
Target dose	1368 (82.6)	675 (80.6)	693 (84.5)	1314 (84.5)	665 (83.3)	649 (85.7)	-

Discontinuation for reasons other than death	679 (27.4)	336 (27.1)	343 (27.7)	569 (24.6)	274 (23.5)	295 (25.6)	-

Data are presented as number (%).

Hypotension is defined as systolic blood pressure below 100 mmHg.

* Model stratified by or adjusted for region

† Model adjusted for age, heart rate, systolic blood pressure, body mass index, N-terminal pro-B-type natriuretic peptide level (log), estimated glomerular filtration rate, New York Heart Association functional class, left ventricular ejection fraction, prior heart failure hospitalization, myocardial infarction, diabetes, smoking, atrial fibrillation and region

For creatinine, the multivariable model included baseline creatinine rather than estimated glomerular filtration rate.

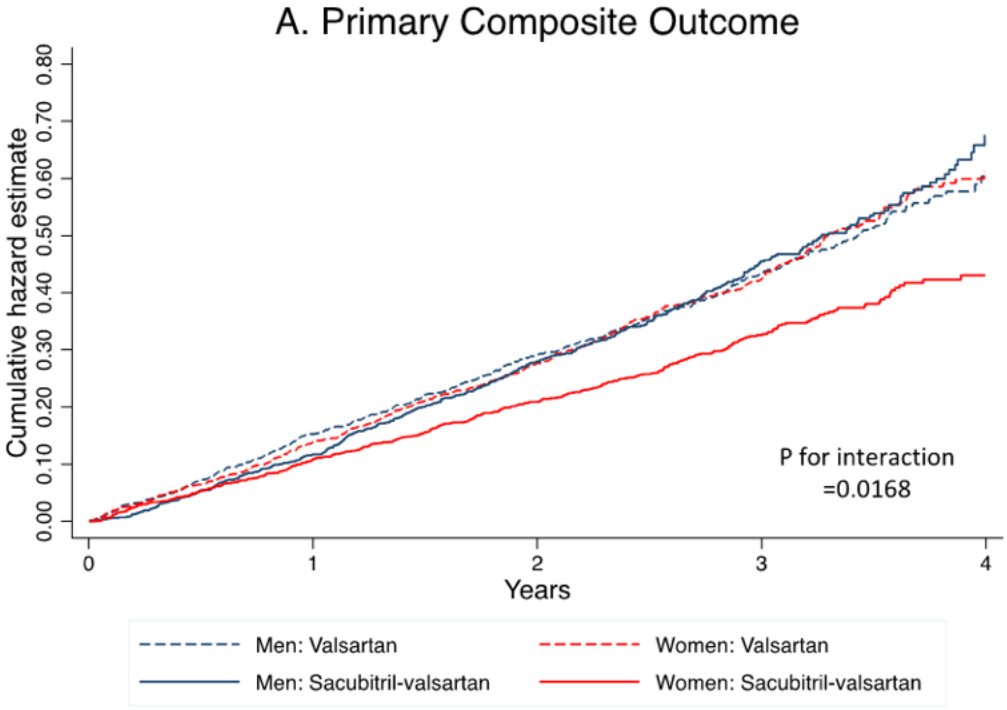
For potassium, the multivariable model also included baseline potassium.

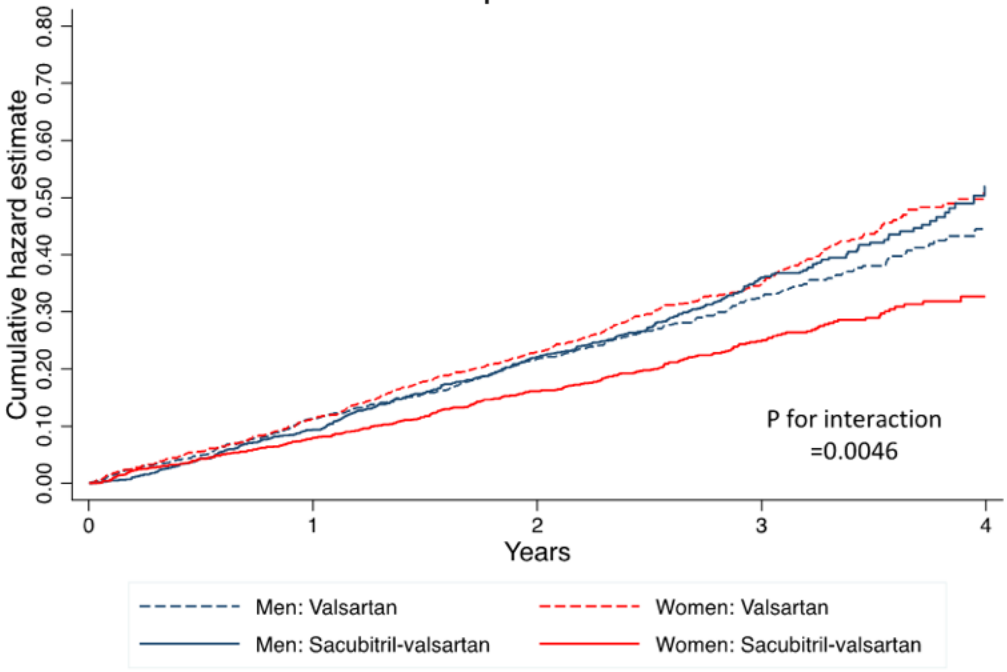
Figure 1. Cumulative hazard estimate for the primary composite outcome and total hospitalizations for heart failure (first and repeat) according to sex and treatment in PARAGON-HF.

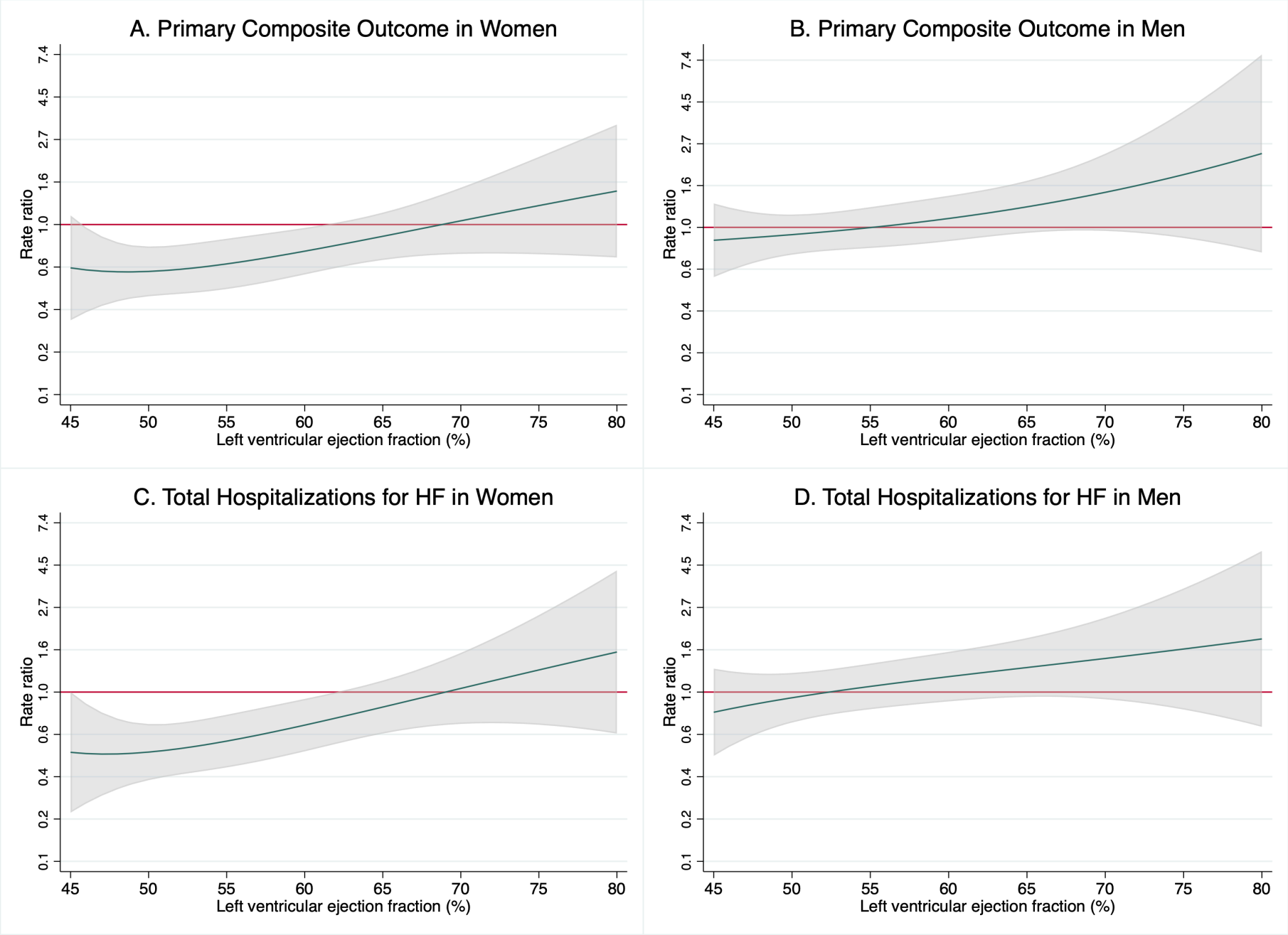
A. Cumulative hazard estimate for the primary composite outcome. B. Cumulative hazard estimate for total hospitalizations (first and repeat).

Figure 2. Treatment effect in women and men in PARAGON-HF according to left ventricular ejection fraction.

A. Treatment effect on the primary composite outcome in women. B. Treatment effect on the primary composite outcome in men. C. Treatment effect on total hospitalizations for heart failure in women. D. Treatment effect on total hospitalizations for heart failure in men. Rate ratios and 95% confidence intervals shown.


A. Primary Composite Outcome
Cumulative hazard estimate
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0
1
2
3
4
Years
P for interaction
=0.0168
Men: Valsartan
Women: Valsartan
Men: Sacubitril-valsartan
Women: Sacubitril-valsartan


B. Total Hospitalizations for HF
Cumulative hazard estimate
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0
1
2
3
4
Years
P for interaction
=0.0046
Men: Valsartan
Women: Valsartan
Men: Sacubitril-valsartan
Women: Sacubitril-valsartan


A. Primary Composite Outcome in Women
B. Primary Composite Outcome in Men
C. Total Hospitalizations for HF in Women
D. Total Hospitalizations for HF in Men
Rate ratio
0.1
0.2
0.4
0.6
1.0
1.6
2.7
4.5
7.4
45
50
55
60
65
70
75
80
Left ventricular ejection fraction (%)