Systolic Blood Pressure, Sacubitril/Valsartan, and Cardiovascular Outcomes in Heart Failure with Preserved Ejection Fraction: PARAGON-HF

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ABSTRACT (word count = 299)

Background: Guidelines recommend targeting systolic blood pressure (SBP)<130 mmHg in heart failure with preserved ejection fraction (HFpEF) with limited data.

Objectives: To assess whether BP lowering is associated with clinical benefit, and whether the treatment effects of sacubitril/valsartan on outcomes are related to BP lowering, particularly among women who derive greater benefit from sacubitril/valsartan.

Methods: We analyzed 4,795 participants from the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial. We related baseline and time-updated, mean achieved SBP quartiles (<120, 120-129, 130-139, ≥140 mmHg) to the primary outcome (CV death and total HF hospitalization), its components, myocardial infarction or stroke, and a renal composite outcome. At the 16-week visit, we assessed the relationship between SBP change and Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). We analyzed whether the BP lowering effects of sacubitril/valsartan accounted for its treatment effects.

Results: Average age was 73±8 years and 52% were women. After multivariable adjustment, baseline and mean achieved SBP 120-129mmHg demonstrated the lowest risk for all outcomes. Sacubitril/valsartan reduced SBP by 5.2 (95%CI: 4.4, 6.0) mmHg compared with valsartan at 4-weeks, which was not modified by baseline SBP. However, sacubitril/valsartan reduced SBP more in women (6.3 mmHg) than men (4.0 mmHg) (interaction p=0.005). Change in SBP was directly associated with change in NT-proBNP (p<0.001) but not KCCQ-OSS (p=0.40). The association between sacubitril/valsartan and the primary outcome was not modified by baseline

SBP (interaction p=0.50) and was similar when adjusting for time-updated SBP, irrespective of sex.

Conclusions: Baseline and mean achieved SBP of 120-129 mmHg identified the lowest risk HFpEF patients. Baseline SBP did not modify the treatment effect of sacubitril/valsartan and the BP lowering effects of sacubitril/valsartan did not account for its effects on outcomes, irrespective of sex.

Keywords: heart failure with preserved ejection fraction; heart failure hospitalization; sacubitril/valsartan; blood pressure

CONDENSED ABSTRACT (word count = 100).

Guidelines recommend targeting SBP<130mmHg in HFpEF, but the clinical benefits of, and influence of sacubitril/valsartan on, BP lowering are unknown. In PARAGON-HF, baseline and mean achieved SBP 120-129mmHg was associated with the lowest risk for adverse outcomes. Sacubitril/valsartan reduced SBP by 5.2mmHg compared with valsartan. The associations between sacubitril/valsartan and outcomes were not modified by baseline SBP and was similar when adjusting for time-updated SBP. In sum, SBP 120-129 mmHg identified the lowest risk patients, supporting current guidelines. Baseline SBP did not modify the treatment effect of sacubitril/valsartan and the BP lowering effects of sacubitril/valsartan did not account for its effects on outcomes.

ACRONYMS AND ABBREVIATIONS

eGFR, estimated glomerular filtration rate

HFpEF, heart failure with preserved ejection fraction

KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire overall summary score

NT-proBNP, N-terminal pro B-type natriuretic peptide

PARAGON-HF, Prospective Comparison of Angiotensin receptor–neprilysin inhibitor with Angiotensin-receptor blockers Global Outcomes in HF with Preserved Ejection Fraction

PARAMOUNT, Prospective comparison of ARNi with ARB on Management Of heart failUre with preserved ejectioN fracTion

SBP, systolic blood pressure

SPRINT, Systolic Blood Pressure Intervention Trial

TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

INTRODUCTION

Few therapeutic options exist in treating patients with heart failure with preserved ejection fraction (HFpEF), and accordingly, treatment has generally focused on optimizing management of comorbidities (1-4). Hypertension is very common in HFpEF, is thought to play an etiologic role, and because it leads to left ventricular hypertrophy, diastolic dysfunction, abnormal ventricular arterial coupling, and end organ damage, it has been conjectured that blood pressure control could relate to improvement in outcomes (5-7). In fact, professional society guidelines have recommended targeting a systolic blood pressure (SBP) of less than 130 mmHg in HFpEF (8,9). However, there is limited evidence to support this recommendation, particularly since the Systolic Blood Pressure Intervention Trial (SPRINT), which demonstrated that intensive versus standard BP control improved cardiovascular outcomes, excluded patients with symptomatic HF (10). In addition, while several agents that lower BP have been studied in clinical trials of HFpEF (1-3,11,12), a dedicated trial using BP targets has not been performed in this population. Further, a substudy of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Americas did not identify a significant relationship between SBP quartiles and cardiovascular outcomes, and blood pressure reduction did not explain the potential beneficial effects of spironolactone (13).

Thus, the extent to which SBP control influences clinical outcomes remains unclear. In addition, whether BP reduction is associated with clinical benefit (reflected by quality of life and cardiovascular outcomes) is of significant interest. Moreover, the relationship between BP reduction and biomarkers in HFpEF is not well established. The Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial is the largest

randomized study in HFpEF to date (12), and whether the anti-hypertensive effects of sacubitril/valsartan mediate its effects on outcomes, particularly among women and those with lower EF given significant effect modification observed in these subgroups, is unknown (14,15).

In this study, we assessed the prognostic role of baseline SBP and mean achieved SBP in patients with HFpEF enrolled in PARAGON-HF, the relationship between SBP lowering with biomarker and clinical outcomes, and whether the SBP lowering effect of sacubitril-valsartan related to its treatment effects. We hypothesized that the relationship between SBP and outcomes would be J-shaped (13), and the SBP lowering effect of sacubitril-valsartan would not be responsible for its treatment effects.

METHODS

PARAGON-HF study design

The design of the PARAGON-HF study has been described in detail previously (5). Briefly, PARAGON-HF was an international, randomized, double blind, parallel group, actively-controlled, 2-arm event-driven trial comparing the efficacy and safety of sacubitril/valsartan versus valsartan in patients with HFpEF. PARAGON-HF enrolled patients with signs and symptoms of heart failure (New York Heart Association class II–IV), left ventricular EF ≥45%, increased plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (degree of elevation depending on history of HF hospitalization within 9 months and presence or absence of atrial fibrillation on screening electrocardiogram), evidence of structural heart disease (increased left atrial size or left ventricular hypertrophy), and diuretic therapy within 30 days. Before randomization, patients entered sequential single-blind run-in periods ensuring that both treatments were tolerated at half the target doses. The primary endpoint for the trial was

cardiovascular death and total (first and recurrent) HF hospitalizations. The study was approved by institutional review boards at individual study sites, and all patients signed written informed consent.

Key exclusion criteria included prior left ventricular EF <40%, and SBP <110 or ≥180 mm Hg. Patients with SBP >150 mm Hg were excluded unless they were receiving at least 3 antihypertensive medications at screening. In addition, participants were excluded with estimated glomerular filtration rates (eGFR) <30 ml/min/1.73 m2 as calculated by the Modification in Diet in Renal Disease formula at visit 1. Detailed exclusion criteria are listed elsewhere (5). For the present study, we excluded 1 participant with missing SBP at baseline and 26 participants enrolled from a site closed for violations of Good Clinical Practice.

Study Outcomes

Endpoints studied in this analysis include the primary composite outcome of total (first and recurrent) hospitalizations for HF and death from cardiovascular causes, total HF hospitalizations, cardiovascular death, myocardial infarction or stroke, all-cause mortality, and a renal composite outcome (decrease in the eGFR of ≥50%, development of end-stage renal disease, or death due to renal failure and doubling of serum creatinine). For safety assessment, we analyzed dose reduction or discontinuation. Among a subgroup of participants with available data, we also assessed the relationship of the change in SBP to several endpoints included at the 16-week visit. These included quality of life assessed using the overall summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ-OSS) (scores range from 0 to 100, with higher scores indicating better health status) (16), NT-proBNP, and high-sensitivity troponin T.

Statistical analysis

Baseline characteristics grouped by quartiles (<120, 120-129, 130-139, ≥140 mmHg) of baseline SBP were described using means±SD and medians and interquartile ranges or percentages as appropriate for the levels of measurement and distributions of the variables. These quartiles also approximated clinical guideline thresholds for classification and treatment of hypertension (9). The SBP quartiles were compared using ANOVA for continuous variables and chi-squared tests (or Fisher's exact test when appropriate) for categorical variables.

The association between baseline SBP quartiles and the efficacy and safety outcomes were assessed using crude and multivariable-adjusted Cox regression, using the 2nd quartile (120-129mmHg) as the referent group (with the lowest event rate), given a J-shaped relationship observed. In a complementary analysis using restricted cubic splines, we examined the continuous association between SBP and all outcomes. Four knots placed at the 5th, 35th, 65th, and 95th percentiles were used for all outcomes except the renal composite outcome, which was analyzed linearly. Multivariable models adjusted for covariates used in a previous analysis of SBP in HFpEF, including region, atrial fibrillation, creatinine, diabetes mellitus, New York Heart Association class, heart rate, sex, age, race, current smoking, peripheral vascular disease, number of anti-hypertensive medications, and treatment group (model 1) (13). We additionally adjusted for diastolic blood pressure in model 2. We repeated these analyses using mean SBP as a time-updated covariate, which was updated at each BP ascertainment to represent the average observed blood pressure up to that time point (17).

We next determined the valsartan-adjusted change in SBP from baseline to the 4-week visit overall and by SBP quartile. Four weeks was selected as this was the time at which maximal SBP change occurred in the trial (12). Interaction terms between treatment and both gender and

EF (modeled continuously) were tested (14,15). We subsequently assessed the relationships between change in SBP (expressed per 10 mmHg reduction) from baseline to the 16 and 48-week visits with KCCQ-OSS score, log transformed NT-proBNP, and log transformed high-sensitivity troponin T. An interaction term between treatment and continuous SBP was tested.

To understand whether SBP reduction related to the treatment effect of sacubitril/valsartan, we generated Cox models assessing the relationship between treatment assignment and outcomes adjusting for baseline SBP and time-updated SBP (which was updated at each study visit). Interaction analyses were performed to determine whether sex or EF (modeled continuously) modified these relationships. We assessed the primary outcome, recurrent HF hospitalization, and the renal composite outcome since these outcomes were most strongly associated with a treatment effect (12). Analyses were performed using STATA version 14, and a two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of the 4,795 participants meeting study inclusion criteria stratified by quartiles of SBP are shown in **Table 1**. The mean baseline BP was 131±15 / 74±11 mmHg. The average age was 73±8 years, 52% were women, and 82% were white. Higher SBP quartile was associated with higher diastolic BP, proportionately more people of white race, higher body mass index, lower heart rate, less frequent atrial fibrillation, more frequent diabetes mellitus, higher eGFR, and lower NT-proBNP ($p<0.05$ for all comparisons).

In crude analyses of the efficacy outcomes, using quartile 2 (120-129mmHg) as the referent quartile, both the lowest and highest quartiles had a higher risk of the primary outcome

(**Table 2**). However, after multivariable adjustment, only the highest quartile was independently associated with elevated risk for the primary outcome (HR 1.54, 95% CI 1.24, 1.91), which was driven by a greater risk in total HF hospitalizations (HR 1.63, 95% CI 1.28, 2.09). Quartile 2 demonstrated the lowest risk for myocardial infarction or stroke, with greater risk observed in each of the other 3 quartiles after multivariable adjustment. Risk for the renal composite outcome increased in a graded fashion with increasing SBP quartile, while the risk for drug discontinuation was elevated at both the lowest and highest SBP quartiles after adjustment. Thus, quartile 2 demonstrated the lowest risk for all studied outcomes.

In a complementary analysis modeling SBP as a continuous variable, a J-shaped relationship was observed between SBP and the primary outcome (as well as the other cardiovascular outcomes) (**Figure 1)**; $p<0.05$ for overall relationship and for non-linearity). Baseline SBP did not modify the relationship between sacubitril/valsartan and the primary outcome (interaction $p=0.50$) or any other outcome ($p>0.20$ for all interaction terms).

To understand the relationship between change in BP and subsequent risk, we analyzed the relationship between time-updated, mean achieved SBP for all study outcomes, using quartile 2 (120-129mmHg) as the referent arm (**Table 3**) (17). Similar to the baseline SBP analysis, quartile 4 was associated with higher risks of the primary outcome and recurrent HF hospitalization after multivariable adjustment. In contrast, compared to quartile 2, quartile 1 was associated with a higher risk of mortality (HR 1.29, 95% CI 1.04, 1.62), and both quartiles 3 and 4 were associated with a higher risk of myocardial infarction or stroke as well as the renal composite outcome. Therefore quartile 2 was again associated with the lowest risk for all outcomes.

During the run-in period, SBP decreased 5.5 (95% CI 5.1, 6.0) mmHg. After randomization, sacubitril/valsartan further reduced SBP by a maximum of 5.2 (95% CI 4.4, 6.0) mmHg, when compared with valsartan, by the 4-week visit (**Table 4**). Sacubitril/valsartan had a similar BP lowering effect across the 4 SBP baseline quartiles at the 4-week visit (interaction p=0.61) (**Table 4** and **CENTRAL ILLUSTRATION**). However, during follow-up, the difference in SBP among the treatment arms in the highest quartile diminished over time. In addition, the distribution of time-updated, mean achieved SBP quartile for the entire cohort is shown at randomization, 16 weeks, and 48 weeks by treatment arm in **Figure 3**, demonstrating a greater distribution of participants in lower SBP categories in the sacubitril/valsartan arm compared to the valsartan arm**;** this distribution is also shown in **Supplementary Table 1** among those with baseline SBP ≥130 mmHg.

We noted significant effect modification by gender for the SBP lowering effect of sacubitril/valsartan, such that sacubitril/valsartan reduced SBP at the 4-week visit more in women (6.3 mmHg, 95% CI 5.2, 7.4 mmHg) than in men (4.0 mmHg, 95% CI 2.9, 5.1 mmHg) (interaction p=0.005), which was driven by higher SBP among women in the valsartan arm (**Figure 4**). A marginal treatment effect by EF was observed (interaction p=0.08), such that sacubitril/valsartan reduced SBP more in with EF>57% (5.8 mmHg, 95% CI 4.6, 7.0 mmHg) than in those with EF≤57% (4.6 mmHg, 95% CI 3.6, 5.7 mmHg).

In a mechanistic analysis, we assessed the relationship between change in SBP between baseline to the 16 and 48-week visits with quality of life (KCCQ-OSS) and biomarkers (NT-proBNP and high-sensitivity troponin T) (**Table 5**). Change in SBP was not associated with change in KCCQ-OSS or high-sensitivity troponin T after multivariable adjusted analysis. Change in SBP was associated with a modest change in log transformed NT-proBNP after

multivariable (-3.8% per 10 mmHg lowering in SBP, p<0.001) analysis at 16 weeks, which was similar at 48 weeks (-2.1% per 10 mmHg lowering in SBP, p=0.027).

To determine whether the treatment effects of sacubitril/valsartan were mediated by BP reduction, we performed Cox regression adjusting for baseline SBP and time-updated SBP for the primary outcome, recurrent HF hospitalization, and the renal composite outcome. As shown in **Table 6**, adjustment had little effect on the hazard ratios for any endpoint. Further, analyses were consistent regardless of sex (interaction p=0.49) or EF (continuous interaction p=0.80).

DISCUSSION

In patients with HFpEF, both baseline and time-updated, mean achieved SBP 120-129 mmHg independently identified patients at the lowest risk for cardiovascular and renal outcomes prespecified in PARAGON-HF. Change in SBP related to change in NT-proBNP, though not with quality of life. Sacubitril/valsartan reduced SBP by a maximum of 5.2 mmHg, compared with valsartan, by the 4-week visit; this effect was consistently observed across baseline SBP quartiles, though the BP lowering effect was greater in women than men. However, the treatment effect of sacubitril/valsartan was not modified by baseline SBP and was independent of change in SBP, irrespective of sex. Our analyses provide new insight into the relationship of baseline, and mean achieved, SBP and outcomes in HFpEF, and further suggest that SBP reduction with sacubitril/valsartan is not responsible for its treatment benefits in HFpEF in both women and men.

A lack of a relationship between SBP quartiles and outcomes in HFpEF was shown in a TOPCAT analysis restricted to the Americas, though when SBP was analyzed continuously, a J-shaped relationship was observed (13). This difference in SBP quartile findings relative to the

current study may simply relate to the significantly larger sample size in PARAGON. Additionally, in a post-hoc analysis of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, a randomized trial of sacubitril/valsartan in HF and reduced EF, the relationship between SBP and several outcomes was also noted to be J-shaped (18). Low SBP in HFpEF could be causally related to worse outcomes, but might also signify a sicker patient population with confounding conditions, supported by attenuation of the association between lower SBP and worse outcomes after the multivariable adjustment which included comorbidities and other variables predictive of higher risk. For example, there was a higher percentage of patients with atrial fibrillation or flutter in the lowest SBP quartile, as demonstrated in another HFpEF analysis (13), which could reflect greater use of therapies for rate control that additionally lower SBP or loss of atrial contraction that could also reduce BP.

The anti-hypertensive properties of sacubitril/valsartan in HFpEF in PARAGON-HF are similar to findings observed in HF with reduced EF. Vasodilators including sacubitril/valsartan in PARADIGM-HF (though not hydralazine and nitrates), reduce SBP across the baseline SBP range (18-21). Similar to these former studies in HFrEF, the beneficial effects of the therapies tested were independent of baseline SBP or change in SBP in PARAGON-HF. Among HFpEF patients, the BP lowering of sacubitril-valsartan in PARAGON-HF is similar in magnitude to spironolactone in TOPCAT (13). Compared specifically to studies of sacubitril-valsartan in other settings, the magnitude of BP reduction observed in PARAGON-HF was greater than that seen in mild to moderate hypertension (22) and acutely decompensated HFrEF (23), but similar to chronic kidney disease (24), HFrEF (18), and the phase II trial of sacubitril-valsartan in HFpEF (25). Interestingly, women achieved greater SBP reduction than men, which was driven by worse

BP control with valsartan and equivalent BP control with sacubitril/valsartan compared to men. This differential gender effect does not appear to be observed in other cardiovascular conditions for which valsartan has been studied (26). However, the BP lowering effect still failed to explain the beneficial treatment effect of sacubitril/valsartan observed in women (14). In addition, a marginal treatment interaction by EF was observed, such that those with lower baseline EF had less BP reduction. It is possible the physiology in these participants behave more similarly to HFrEF, whereby some vasodilators may increase cardiac output, attenuating the BP lowering effects of therapy (19,21).

In a mechanistic analysis, we assessed the change in SBP with change in biomarkers and quality of life. Change in SBP was associated with change in NT-proBNP, but not high-sensitivity troponin T or quality of life. Interestingly, the phase II trial of ARNI in HFpEF did not identify a significant relationship between change in BP and change in NT-proBNP (25). Our findings of a modest relationship may relate to larger sample or larger range of SBP allowed for study entry in PARAGON-HF. The lack of change with other high sensitivity troponin T and quality of life could reflect a longer time course needed to achieve these findings.

As a result of the SPRINT Trial, professional society guidelines have recommended an SBP goal <130 mmHg (8). Notably, SPRINT excluded patients with prevalent HF. Our analysis shows that a mean achieved SBP of 120-129 mmHg was associated with the lowest risk for all study outcomes, supporting the current recommendation for blood pressure management. Given the observational nature of this analysis, a randomized trial of achieved SBP targets in HFpEF would be useful to confirm these findings.

Interestingly, the SBP reduction of sacubitril/valsartan in PARAGON-HF did not account for the treatment effect of sacubitril/valsartan (irrespective of sex), similar to findings of

spironolactone in HFpEF (13). It is possible that the time course needed for BP reduction to reflect in the treatment effect could be much longer, since a longer duration of BP control may improve arterial stiffness, diastolic function, or cardiac remodeling. In addition, greater SBP control in the valsartan arm over time, particularly evident in the highest quartile, may have diminished the relevance of SBP reduction to the treatment effect. The Prospective comparison of ARNI with ARB on Management of HFpEF (PARAMOUNT) trial also demonstrated the independence of sacubitril/valsartan BP lowering with left atrial size and NYHA class (25). In addition, in HFrEF, sacubitril/valsartan did not affect central aortic stiffening compared to enalapril (27). These data suggest that the potential benefits of sacubitril/valsartan in HFpEF are likely multifactorial and go beyond its hemodynamic effects on blood pressure. Sacubitril/valsartan, for instance, increases availability of natriuretic peptides and a number of other vasoactive peptides which induce diuresis, natriuresis, and improve myocardial relaxation (5). Sacubitril/valsartan also specifically improves left atrial remodeling, a strong predictor of adverse events in HFpEF (28).

There are some limitations of the study. Ambulatory BP monitoring, rather than office BPs, may provide a more accurate assessment of BP as well as the treatment effect of sacubitril/valsartan. A previous analysis of sacubitril/valsartan in hypertension showed a significant reduction in ambulatory BP (29), but its relationship to outcomes was not studied. In addition, the specific inclusion/exclusion criteria for blood pressure in PARAGON-HF may limit generalizability to a broad HFpEF population. Finally, although PARAGON-HF is the largest trial in HFpEF to date, we may have been underpowered to detect more subtle relationships of SBP quartiles with some outcomes, particularly in subgroups.

In summary, baseline and mean achieved SBP of 120-129 mmHg was associated with the lowest risk of adverse outcomes after multivariable adjustment. Lowering SBP was associated with a modest reduction in NT-proBNP, however without relationship to quality of life. Sacubitril/valsartan consistently reduced SBP across baseline SBP quartiles by 5.2 mmHg, an effect greater in women than men at the 4-week visit compared to valsartan. though BP reduction failed to account for its treatment effects on cardiovascular outcomes irrespective of sex. The potential benefits of sacubitril/valsartan in HFpEF may thus be mediated through other mechanisms.

PERSPECTIVES

Competency in Medical Knowledge: In patients with heart failure with preserved ejection fraction (HFpEF), a systolic blood pressure (SBP) of 120-129 mmHg identified the lowest risk participants. Sacubitril/valsartan lowers blood pressure by ~5 mmHg compared to valsartan in HFpEF, an effect greater among women than men.

Competency in Patient Care: Our findings support current professional society guidelines for targeting SBP<130 mmHg in patients with HFpEF and reinforce the current focus toward optimal BP management in HFpEF. Women may derive a greater SBP lowering effect with sacubitril/valsartan compared to valsartan.

Translational Outlook: Since SBP lowering failed to explain the treatment effects of sacubitril/valsartan, future research into mechanisms of potential benefit are needed.

DISCLOSURES

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FIGURE LEGENDS

Figure 1:

Title: ***Relationship between Baseline Continuous Systolic Blood Pressure and Efficacy and Safety Outcomes***

Caption: Incidence rates for the primary endpoint, cardiovascular death, total heart failure hospitalization, all-cause death, myocardial infarction or stroke, a renal composite outcome, and study drug dose reduction or discontinuation among all patients according to systolic blood pressure at baseline. Sacubitril/valsartan shown in red, and valsartan depicted in blue. The interrupted lines are 95% confidence limits. MI, myocardial infarction; p-yrs, person-years.

Figure 2 (CENTRAL ILLUSTRATION):

Title: ***Treatment effects of systolic blood pressure over time by baseline systolic blood pressure quartile .***

Caption: Systolic blood pressure during follow-up for valsartan (blue) and sacubitril/valsartan (red) treated patients shown separately for each systolic blood pressure quartile at baseline. Visits are truncated after week 216. Bars represent 95% confidence interval. SBP, systolic blood pressure.

Figure 3:

Title: ***Stacked bar graphs of time-updated, mean achieved systolic blood pressure quartile over time by treatment group.***

Caption: Percent of participants in each time-updated, mean achieved systolic blood pressure quartile at randomization, 16-week, and 48-week visits by treatment randomization to valsartan or sacubitril/valsartan. Systolic blood pressure expressed in mmHg.

Figure 4:

Title: ***Systolic blood pressure over time by treatment arm and gender.***

Caption: Women (maroon) had higher blood pressure than men (navy) on valsartan treatment, but there was no gender difference in patients randomized to sacubitril/valsartan. Visits are truncated after week 216. Bars represent 95% confidence interval. SBP, systolic blood pressure.

TABLE 1. Baseline Clinical Characteristics by Systolic Blood Pressure Quartile

	SBP<120 mmHg N=1146	**120≤SBP<129 mmHg N=1105**	**130≤SBP<139 mmHg N=1155**	**SBP≥140 mmHg N=1389**	**P-value for trend**
SBP (mmHg)	112 ± 5	124 ± 3	133 ± 3	149 ± 10	
DBP (mmHg)	67 ± 9	73 ± 9	76 ± 9	79 ± 11	<0.001
Pulse pressure (mmHg)	44 ± 9	50 ± 10	57 ± 9	70 ± 14	<0.001
Randomization to sacubitril/valsartan, n (%)	584 (51.0%)	537 (48.6%)	582 (50.4%)	704 (50.7%)	0.86
Age, years	73 ± 9	73 ± 8	72 ± 8	73 ± 8	0.52
Female sex, n (%)	574 (50.1%)	554 (50.1%)	610 (52.8%)	741 (53.3%)	0.05
White race, n (%)	879 (76.7%)	913 (82.6%)	942 (81.6%)	1173 (84.4%)	<0.001
NYHA, n (%)					0.18
I	33 (2.9 %)	33 (3.0 %)	23 (2.0 %)	48 (3.5 %)	

II	877 (76.6%)	851 (77.0%)	889 (77.0%)	1088 (78.3%)	
III	229 (20.0%)	219 (19.8%)	235 (20.4%)	249 (17.9%)	
IV	6 (0.5 %)	2 (0.2 %)	7 (0.6 %)	4 (0.3 %)	
Geographic region, n (%)					0.33
Asia-Pacific or other	238 (20.8%)	163 (14.8%)	173 (15.0%)	188 (13.5%)	
Central Europe	274 (23.9%)	392 (35.5%)	502 (43.5%)	547 (39.4%)	
Latin America	91 (7.9 %)	92 (8.3 %)	94 (8.1 %)	93 (6.7 %)	
North America	209 (18.2%)	124 (11.2%)	100 (8.7 %)	126 (9.1 %)	
Western Europe	334 (29.1%)	334 (30.2%)	286 (24.8%)	435 (31.3%)	
KCCQ-OSS	70.6 ± 19.5	71.8 ± 18.6	71.6 ± 19.1	71.6 ± 18.7	0.26
Physical Characteristics					
Body mass index (kg/m^2)	29.9 ± 5.2	30.1 ± 4.9	30.3 ± 5.0	30.5 ± 4.9	0.001
Heart rate (beats/min)	71.4 ± 12.8	70.8 ± 12.3	70.4 ± 11.7	69.5 ± 12.2	<0.001

Comorbidities, n (%)					
Hypertension	1038 (90.6%)	1053 (95.3%)	1122 (97.1%)	1370 (98.6%)	<0.001
Hospitalization for HF	546 (47.6%)	526 (47.6%)	577 (50.0%)	657 (47.3%)	0.91
Atrial fibrillation or flutter	480 (41.9%)	394 (35.8%)	346 (30.1%)	332 (24.0%)	<0.001
Diabetes mellitus	424 (37.0%)	461 (41.7%)	507 (43.9%)	669 (48.2%)	<0.001
Myocardial infarction	261 (22.8%)	241 (21.8%)	265 (22.9%)	316 (22.8%)	0.84
Stroke	112 (9.8 %)	116 (10.5%)	133 (11.5%)	147 (10.6%)	0.42
Current smoker	90 (7.9 %)	78 (7.1 %)	87 (7.6 %)	98 (7.1 %)	0.55
Medication Use, n (%)					
ACE-I and/or ARB at screening	921 (80.4%)	948 (85.8%)	1006 (87.1%)	1264 (91.0%)	<0.001
Beta-blocker	907 (79.1%)	886 (80.2%)	931 (80.6%)	1096 (78.9%)	0.89
Calcium channel blocker	275 (24.0%)	368 (33.3%)	414 (35.8%)	583 (42.0%)	<0.001
Diuretic	1088 (94.9%)	1062 (96.1%)	1114 (96.5%)	1320 (95.0%)	0.92

Mineralocorticoid antagonist	340 (29.7%)	305 (27.6%)	304 (26.3%)	290 (20.9%)	<0.001
Laboratory Testing					
Estimated glomerular filtration rate (mL/min/1.78 m^2)	60 ± 18	62 ± 19	64 ± 19	64 ± 20	< 0.001
Hemoglobin (mg/dL)	13.5 ± 1.6	13.5 ± 1.5	13.5 ± 1.6	13.5 ± 1.6	0.97
NT-proBNP (pg/mL)*	1028 [544, 1680]	918 [466, 1598]	852 [432, 1660]	790 [446, 1556]	<0.001
LV Ejection Fraction	58 ± 8	58 ± 8	57 ± 8	58 ± 8	0.16

*Presented as median [25^{th}-75^{th} percentile] since values are skewed.

NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

TABLE 2. Event Rates and Crude and Adjusted Hazard Ratios for Efficacy and Safety Outcomes by Baseline Systolic Blood Pressure Quartile

Efficacy outcomes, n (%)	**SBP<120 mmHg N=1146**	**120≤SBP<129 mmHg N=1105**	**130≤SBP<139 mmHg N=1155**	**SBP≥140 mmHg N=1389**
Composite endpoint				
• Event rate and 95% CI (per 100 person-years)	15.2 (13.2, 17.6)	11.4 (9.7, 13.5)	12.2 (10.6, 14.1)	15.6 (13.6, 17.8)
• Crude model HR (95% CI)	1.34 (1.08, 1.67)	Ref	1.07 (0.86, 1.34)	1.37 (1.10, 1.69)
• Multivariable adjusted model 1 HR (95% CI)	1.18 (0.94, 1.47)	Ref	1.17 (0.94, 1.46)	1.43 (1.16, 1.77)
• Multivariable adjusted model 2 HR (95% CI)	1.11 (0.89, 1.39)	Ref	1.21 (0.98, 1.51)	1.54 (1.24, 1.91)
Cardiovascular mortality				
• Event rate and 95% CI (per 100 person-years)	3.5 (2.9, 4.3)	2.6 (2.1, 3.3)	3.0 (2.5, 3.6)	2.9 (2.4, 3.4)

• Crude model HR (95% CI)	1.35 (1.02, 1.79)	Ref	1.13 (0.85, 1.51)	1.08 (0.82, 1.43)
• Multivariable adjusted model HR (95% CI)	1.24 (0.93, 1.65)	Ref	1.16 (0.87, 1.55)	1.17 (0.88, 1.55)
• Multivariable adjusted model 2 HR (95% CI)	1.18 (0.88, 1.58)	Ref	1.19 (0.89, 1.60)	1.23 (0.92, 1.65)
Recurrent HF hospitalization				
• Event rate and 95% CI (per 100 person-years)	11.7 (9.9, 13.8)	8.8 (7.2, 10.6)	9.2 (7.8, 10.9)	12.7 (10.9, 14.8)
• Crude model HR (95% CI)	1.34 (1.04, 1.72)	Ref	1.06 (0.82, 1.36)	1.45 (1.14, 1.86)
• Multivariable adjusted model HR (95% CI)	1.17 (0.91, 1.51)	Ref	1.18 (0.91, 1.51)	1.51 (1.18, 1.92)
• Multivariable adjusted model 2 HR (95% CI)	1.10 (0.85, 1.42)	Ref	1.22 (0.95, 1.57)	1.63 (1.28, 2.09)
Myocardial infarction or stroke				

• Event rate and 95% CI (per 100 person-years)	3.3 (2.7, 4.0)	1.9 (1.5, 2.5)	3.0 (2.5, 3.7)	3.7 (3.1, 4.3)
• Crude model HR (95% CI)	1.70 (1.24, 2.33)	Ref	1.56 (1.31, 2.15)	1.88 (1.39, 2.54)
• Multivariable adjusted model HR (95% CI)	1.53 (1.10, 2.12)	Ref	1.66 (1.20, 2.30)	1.98 (1.45, 2.70)
• Multivariable adjusted model 2 HR (95% CI)	1.54 (1.10, 2.15)	Ref	1.66 (1.20, 2.30)	1.97 (1.43, 2.70)
All-cause mortality				
• Event rate and 95% CI (per 100 person-years)	5.8 (5.1, 6.7)	5.0 (4.3, 5.8)	4.5 (3.9, 5.3)	4.7 (4.1, 5.4)
• Crude model HR (95% CI)	1.19 (0.96, 1.46)	Ref	0.91 (0.73, 1.14)	0.93 (0.76, 1.15)
• Multivariable adjusted model HR (95% CI)	1.12 (0.90, 1.39)	Ref	0.95 (0.76, 1.19)	1.00 (0.80, 1.23)
• Multivariable adjusted model 2 HR (95% CI)	1.07 (0.86, 1.33)	Ref	0.97 (0.78, 1.22)	1.05 (0.84, 1.31)

Renal composite outcome				
• Event rate and 95% CI (per 100 person-years)	0.3 (0.2, 0.6)	0.5 (0.3, 0.8)	0.8 (0.5, 1.1)	1.1 (0.9, 1.5)
• Crude model HR (95% CI)	0.67 (0.30, 1.49)	Ref	1.67 (0.88, 3.15)	2.44 (1.37, 4.38)
• Multivariable adjusted model HR (95% CI)	0.63 (0.28, 1.41)	Ref	1.74 (0.92, 3.29)	2.47 (1.37, 4.43)
• Multivariable adjusted model 2 HR (95% CI)	0.60 (0.27, 1.37)	Ref	1.77 (0.93, 3.36)	2.58 (1.42, 4.71)
Drug discontinuation				
• Event rate and 95% CI (per 100 person-years)	11.8 (10.6, 13.1)	8.8 (7.8, 10.0)	8.7 (7.8, 9.9)	10.7 (9.7, 11.8)
• Crude model HR (95% CI)	1.34 (1.14, 1.57)	Ref	0.99 (0.83, 1.18)	1.21 (1.03, 1.42)
• Multivariable adjusted model HR (95% CI)	1.27 (1.08, 1.50)	Ref	1.04 (0.87, 1.23)	1.23 (1.04, 1.45)

• Multivariable adjusted model 2 HR (95% CI)	1.28 (1.09, 1.52)	Ref	1.03 (0.87, 1.23)	1.22 (1.03, 1.44)

HR, hazard ratio; CI, confidence interval; HF, heart failure.

Model 1 covariates include region, atrial fibrillation, creatinine, diabetes mellitus, New York Heart Association class, heart rate, sex, age, race, current smoking, number of anti-hypertensive medications, and treatment group.

Model 2 includes model 1 covariates and additionally adjusts for diastolic blood pressure.

TABLE 3. Event Rates and Crude and Adjusted Hazard Ratios for Efficacy and Safety Outcomes by Time-Updated Mean Achieved Systolic Blood Pressure Quartile

Efficacy outcomes, n (%)	**SBP<120 mmHg**	**120≤SBP<129 mmHg**	**130≤SBP<139 mmHg**	**SBP≥140 mmHg**
Composite endpoint				
• Events/person-years	397/2564	474/3776	499/4013	532/3494
• Event rate and 95% CI (per 100 person-years)	15.5 (14.0, 17.1)	12.6 (11.5, 13.7)	12.4 (11.4, 13.6)	15.2 (14.0, 16.6)
• Crude model HR (95% CI)	1.25 (1.04, 1.42)	Ref	0.99 (0.87, 1.12)	1.22 (1.07, 1.38)
• Multivariable adjusted model 1 HR (95% CI)	1.10 (0.96, 1.27)	Ref	1.05 (0.92, 1.19)	1.24 (1.10, 1.41)
• Multivariable adjusted model 2 HR (95% CI)	1.07 (0.93, 1.23)	Ref	1.07 (0.94, 1.22)	1.30 (1.14, 1.47)
Cardiovascular mortality				
• Events/person-years	89/2559	112/3780	117/4015	98/3505

• Event rate and 95% CI (per 100 person-years)	3.5 (2.8, 4.3)	3.0 (2.5, 3.6)	2.9 (2.4, 3.5)	2.8 (2.3, 3.4)
• Crude model HR (95% CI)	1.20 (0.91, 1.58)	Ref	0.98 (0.76, 1.27)	0.95 (0.72, 1.24)
• Multivariable adjusted model HR (95% CI)	1.15 (0.86, 1.53)	Ref	1.01 (0.78, 1.31)	1.01 (0.77, 1.34)
• Multivariable adjusted model 2 HR (95% CI)	1.12 (0.84, 1.50)	Ref	1.03 (0.79, 1.34)	1.05 (0.79, 1.39)
Recurrent HF hospitalization				
• Events/person-years	312/2564	356/3776	385/4013	433/3494
• Event rate and 95% CI (per 100 person-years)	12.2 (10.9, 13.6)	9.4 (8.5, 10.5)	9.6 (8.7, 10.6)	12.4 (11.3, 13.6)
• Crude model HR (95% CI)	1.30 (1.12, 1.51)	Ref	1.02 (0.88, 1.18)	1.32 (1.14, 1.51)
• Multivariable adjusted model HR (95% CI)	1.13 (0.97, 1.32)	Ref	1.09 (0.94, 1.26)	1.33 (1.15, 1.54)

• Multivariable adjusted model 2 HR (95% CI)	1.09 (0.94, 1.28)	Ref	1.11 (0.96, 1.29)	1.39 (1.20, 1.60)
Myocardial infarction or stroke				
• Events/person-years	78/2467	84/3647	116/3857	125/3318
• Event rate and 95% CI (per 100 person-years)	3.2 (2.5, 3.9)	2.3 (1.9, 2.9)	3.0 (2.5, 3.6)	3.8 (3.2, 4.5)
• Crude model HR (95% CI)	1.33 (0.98, 1.82)	Ref	1.31 (0.98, 1.73)	1.62 (1.23, 2.14)
• Multivariable adjusted model HR (95% CI)	1.21 (0.87, 1.66)	Ref	1.39 (1.05, 1.85	1.70 (1.28, 2.25)
• Multivariable adjusted model 2 HR (95% CI)	1.21 (0.88, 1.69)	Ref	1.39 (1.04, 1.84)	1.68 (1.26, 2.24)
All-cause mortality				
• Events/person-years	161/2559	179/3780	180/4015	170/3505
• Event rate and 95% CI (per 100 person-years)	6.3 (5.4, 7.3)	4.7 (4.1, 5.5)	4.5 (3.9, 5.2)	4.9 (4.2, 5.6)

• Crude model HR (95% CI)	1.38 (1.11, 1.71)	Ref	0.94 (0.77, 1.16)	1.03 (0.84, 1.27)
• Multivariable adjusted model HR (95% CI)	1.33 (1.07, 1.66)	Ref	0.95 (0.77, 1.17)	1.07 (0.87, 1.33)
• Multivariable adjusted model 2 HR (95% CI)	1.29 (1.04, 1.62)	Ref	0.97 (0.79, 1.20)	1.11 (0.89, 1.38)
Renal composite outcome				
• Events/person-years	13/2543	17/3762	34/3979	33/3467
• Event rate and 95% CI (per 100 person-years)	0.5 (0.3 0.9)	0.5 (0.3, 0.7)	0.9 (0.6, 1.2)	1.0 (0.7, 1.3)
• Crude model HR (95% CI)	1.19 (0.58, 2.46)	Ref	1.89 (1.06, 3.38)	2.15 (1.20, 3.38)
• Multivariable adjusted model HR (95% CI)	1.26 (0.60, 2.61)	Ref	1.91 (1.06, 3.43)	1.95 (1.08, 3.54)
• Multivariable adjusted model 2 HR (95% CI)	1.30 (0.62, 2.71)	Ref	1.87 (1.04, 3.38)	1.87 (1.02, 3.43)
Drug discontinuation				

• Events/person-years	274/2261	318/3412	315/3584	327/3046
• Event rate and 95% CI (per 100 person-years)	12.1 (10.8, 13.6)	9.3 (8.3, 10.4)	8.8 (7.9, 9.8)	10.7 (9.6, 12.0)
• Crude model HR (95% CI)	1.29 (1.10, 1.52)	Ref	0.94 (0.81, 1.10)	1.14 (0.98, 1.33)
• Multivariable adjusted model HR (95% CI)	1.20 (1.02, 1.41)	Ref	0.96 (0.82, 11.3)	1.09 (0.93, 1.28)
• Multivariable adjusted model 2 HR (95% CI)	1.21 (1.02, 1.43)	Ref	0.96 (0.82, 1.12)	1.08 (0.92, 1.27)

HR, hazard ratio; CI, confidence interval; HF, heart failure.

Time-updated, mean achieved systolic blood pressure uses average SBP as a time-updated covariate, which is updated at each BP ascertainment to represent the average observed blood pressure up to that time point.

Model 1 covariates include region, atrial fibrillation, creatinine, diabetes mellitus, New York Heart Association class, heart rate, sex, age, race, current smoking, number of anti-hypertensive medications, and treatment group.

Model 2 includes model 1 covariates and additionally adjusts for diastolic blood pressure.

TABLE 4. Valsartan-adjusted Change in Systolic Blood Pressure at the 4 Week Visit by Treatment Arm

Baseline Systolic Blood Pressure Group	Sacubitril/Valsartan Arm (N=2379)	Valsartan Arm (N=2366)	Treatment Effect of Sacubitril/valsartan vs. Valsartan	
	4-week Change in SBP (95% CI)	4-week Change in SBP (95% CI)	4-week Change in SBP (95% CI)	P-value
All Patients	-1.8 (-2.4, -1.2)	+3.4 (+2.8, +4.1)	-5.2 (-6.0, -4.4)	<0.001
SBP < 120 mmHg	+5.5 (+4.4, +6.6)	+10.7 (+9.5, +11.9)	-5.3 (-6.9, -3.6)	<0.001
120 mmHg ≤ SBP <129 mmHg	+1.4 (+0.3, +2.5)	+6.3 (+5.2, +7.4)	-4.9 (-6.5, -3.3)	<0.001
130 mmHg ≤ SBP < 139 mmHg	-3.8 (-4.9, -2.7)	+1.3 (+0.1, +2.4)	-5.1 (-6.7, -3.5)	<0.001
SBP ≥ 140 mmHg	-8.5 (-9.6, -7.4)	-3.1 (-4.3, -2.0)	-5.4 (-7.0, -3.9)	<0.001

SBP, systolic blood pressure.

Analyses adjust for baseline blood pressure.

TABLE 5. Relationship between Change in Systolic Blood Pressure and Changes in Quality of Life and Biomarkers from Baseline to the 16 and 48-Week Visit.

	Total N	Change in Parameter per 10 mmHg Reduction in Systolic Blood Pressure from Baseline to the 16-Week Visit Fully-adjusted Model Beta-coefficient (95% CI)*^	P for treatment interaction	Change in Parameter per 10 mmHg Reduction in Systolic Blood Pressure from Baseline to the 48-Week Visit Fully-adjusted Model Beta-coefficient (95% CI)*^	P for treatment interaction
Quality of Life					
• **KCCQ-OSS (change in score)**	4507	+0.1 (-0.2, +0.4), p=0.40	0.10	+0.1 (-0.3, +0.3), p=0.92	0.30
Biomarkers					
• **NT-proBNP (% change)**	3222	-3.8% (-5.4%, -2.2%), p<0.001	0.75	-2.1% (-3.8%, -0.2%), p=0.027	0.72

• **High-sensitivity troponin T (% change)**	1205	+0.9% (-0.3%, +2.0%), p=0.13	0.98	+1.0% (-0.4%, +2.4%), p=0.16	0.98

CI, confidence interval; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score.

*Expressed as change in the parameter (KCCQ-OSS, NT-proBNP, or high-sensitivity troponin T) per 10 mmHg decrease in systolic blood pressure from baseline to the specified visit (16 or 48 week visit). All analyses controlled for and baseline blood pressure.

^ Additionally adjusted for baseline covariates including region, atrial fibrillation, creatinine, diabetes mellitus, New York Heart Association class, heart rate, sex, age, race, current smoking, number of anti-hypertensive medications, and treatment group.

Table 6. Effect of Change in Systolic Blood Pressure on Treatment Effect of Sacubitril/valsartan

Efficacy outcomes	Unadjusted Hazard Ratio Sacubitril/Valsartan vs. Valsartan (95% CI)	P-value	Multivariable-Adjusted Hazard Sacubitril/Valsartan vs. Valsartan (95% CI)*	P-value
Composite endpoint	0.87 (0.75, 1.01)	0.058	0.87 (0.75, 1.00)	0.056
Recurrent HF hospitalization	0.85 (0.72, 1.00)	0.051	0.85 (0.72, 1.01)	0.059
Renal composite outcome	0.50 (0.33, 0.77)	0.001	0.52 (0.34, 0.79)	0.002

CI, confidence interval; HF, heart failure.

*Adjusted for baseline systolic blood pressure and time-updated systolic blood pressure.