Serum Uric Acid, Influence of Sacubitril/Valsartan, and Cardiovascular Outcomes in Heart Failure with Preserved Ejection Fraction: PARAGON-HF

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ABSTRACT (word count = 244)

Aims: To determine the prognostic value of serum uric acid (SUA) on outcomes in heart failure with preserved ejection fraction (HFpEF), and whether sacubitril/valsartan reduces SUA and SUA-related therapies.

Methods and Results: We analyzed 4,795 participants from PARAGON-HF. We related baseline hyperuricemia (using assay definitions) to the primary outcome (CV death and total HF hospitalization). Between baseline and 4 months, we assessed the association between changes in SUA and Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) and other cardiac biomarkers. We simultaneously adjusted for baseline and time-updated SUA to determine whether lowering SUA was associated with clinical benefit. Average age was 73±8 years and 52% were women. After multivariable adjustment, hyperuricemia was associated with increased risk for the primary outcome (rate ratio 1.61, 95%CI 1.37, 1.90). The treatment effect of sacubitril/valsartan for the primary endpoint was not significantly modified by hyperuricemia (p-interaction=0.14). Sacubitril/valsartan reduced SUA -0.38 mg/dL (95%CI: -0.45, -0.31) compared with valsartan at 4 months, with greater effect in those with elevated SUA vs. normal SUA (-0.51 vs. -0.32 mg/dL) (p-interaction=0.031). Sacubitril/valsartan reduced the odds of initiating SUA-related treatments by 32% during follow-up ($p<0.001$). After multivariable adjustment, change in SUA was inversely associated with change in KCCQ-OSS and directly associated with high-sensitivity Troponin T ($p<0.05$). Time-updated SUA was a stronger predictor of adverse outcomes than baseline SUA.

Conclusions: SUA independently predicted adverse outcomes in HFpEF. Sacubitril/valsartan reduced SUA and related therapy initiation compared to valsartan. Reducing SUA was associated with improved outcomes.

Keywords: heart failure with preserved ejection fraction; heart failure hospitalization; sacubitril/valsartan; uric acid

ACRONYMS AND ABBREVIATIONS

eGFR, estimated glomerular filtration rate

HFpEF, heart failure with preserved ejection fraction

HFrEF, heart failure with reduced ejection fraction

KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire overall summary score

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

PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

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

SUA, serum uric acid

INTRODUCTION

Elevated serum uric acid (SUA) is common in patients with heart failure (HF).[1-6] SUA is the terminal product of purine nucleotide metabolism by the enzyme xanthine oxidase, and SUA levels therefore reflect enzymatic activity, but also purine ingestion and renal excretion. Elevated SUA is a marker of inflammatory cytokine activation,[7] insulin resistance,[8] oxidative stress,[9] and endothelial dysfunction.[2] In addition, SUA may directly contribute to worsening HF outcomes by impairing endothelial function,[2] altering myocardial energetics,[10, 11] elevating blood pressure,[12] reducing renal function,[13] and worsening metabolic phenotype.[14] Since many of these pathways may contribute to the pathogenesis of HF with preserved ejection fraction (HFpEF), we sought to explore the prognostic contribution of SUA and the relationship between SUA reduction and clinical outcomes in 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. We further sought to assess whether sacubitril/valsartan reduces SUA in HFpEF, as it modestly does in HF with reduced EF.[6]

METHODS

PARAGON-HF study design

The design and primary results of the PARAGON-HF study have been described previously.[15, 16] Briefly, PARAGON-HF was an international, randomized, double blind, actively-controlled event-driven trial comparing the efficacy and safety of sacubitril/valsartan with valsartan in patients with HFpEF. PARAGON-HF included 4796 validly randomized 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), evidence of structural heart disease, and diuretic therapy within 30 days. All patients entered sequential single-blind run-in periods prior to randomization to ensure that both treatments were tolerated at half the target doses. 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%, estimated glomerular filtration rates (eGFR) <30 ml/min/1.73 m^2, 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. Detailed exclusion criteria are listed elsewhere.[15]

Serum uric acid measurement and therapies

Measurement of SUA was pre-specified to be performed through a central laboratory at screening, during run-in, at randomization, and weeks 16, 48, and then annually. SUA was converted from μmol/L to mg/dL by dividing by 59.48. The upper limit of normal for the SUA assay used was 8.0 mg/dL for men and 7.3 mg/dL for women aged 66–90 years, and 6.9 mg/dL for women aged 18–65 years, which was used to define hyperuricemia for this analysis.[6] We excluded 1 participant with missing SUA at baseline. We classified pre-existing use of SUA-related therapies (xanthine oxidase inhibitors, uricosuric agents, and colchicine) at baseline as well as initiation of such treatments during follow-up. The management of SUA-related therapies was left to the discretion of the treating physicians.

Study Outcomes

Endpoints examined in this analysis include the primary composite outcome of total 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 (defined as a reduction of 50% or more in eGFR, development of end-stage renal disease, or death caused by renal failure). Among a subgroup of participants with available data, we also assessed the relationship of the change in SUA from baseline (randomization) to 4 months with change in several other variables also measured at the baseline and the 4-month visits. 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),[17] systolic blood pressure,[18] eGFR, hemoglobin A1c, high-sensitivity troponin T, NT-proBNP, and the urinary cyclic guanosine monophosphate (cGMP) to creatinine ratio. cGMP is a secondary messenger associated with natriuretic peptide activity, which is augmented by sacubitril/valsartan.[19]

Statistical analysis

Baseline characteristics grouped by presence or absence of hyperuricemia were described using means±SD and medians and 25^{th}-75^{th} percentiles or percentages as appropriate for the levels of measurement and distributions of the variables. SUA groups were compared using t-tests for continuous variables (or nonparametric equivalent when appropriate) and chi-squared tests (or Fisher's exact test when appropriate) for categorical variables.

The associations between baseline hyperuricemia and outcomes that included recurrent events (primary outcome and total HF hospitalizations) were assessed using the semiparametric proportional rates method of Lin in unadjusted and adjusted models to calculate rate ratios.[20] Cox regression to calculate hazard ratios was used for time-to-first event outcomes. In a complementary analysis using restricted cubic splines, we examined the continuous association

between SUA and all outcomes. Four knots were used for all outcomes. Multivariable models adjusted for covariates used in an analysis of SUA and sacubitril/valsartan in HF with reduced EF [Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)]. These covariates included age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, New York Heart Association class, history of HF hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, estimated glomerular filtration rate, hemoglobin, sodium, albumin, randomized treatment, diuretic use, and N-terminal pro brain natriuretic peptide.[6] We tested interaction terms between treatment and both dichotomized and continuous SUA levels with each outcome.

We next compared SUA changes from baseline to 4 months between treatment groups using linear regression, adjusting for the baseline SUA level. Interaction terms between treatment and baseline SUA group, eGFR, use of SUA-lowering therapies, gender, and EF were tested.[21, 22] To understand whether the treatment effect of sacubitril/valsartan on SUA was related to change in renal function or diuretic use, we also adjusted for baseline and 4-month eGFR level as well as loop and thiazide diuretic use. In addition, we used logistic regression to analyze the relationship between initiation of SUA-related therapies during follow-up and treatment assignment.

We subsequently assessed the relationships between change in SUA (expressed per 1 mg/dL reduction) from the baseline to 4 months with changes in KCCQ-OSS score, eGFR, hemoglobin A1c, systolic blood pressure, log transformed NT-proBNP, log transformed high-sensitivity troponin T, and log transformed urinary cGMP to creatinine ratio. Multivariable adjusted analyses employed the same covariates used in the outcomes analyses. An interaction term between treatment and continuous SUA was tested.

Finally, we assessed whether SUA lowering was associated with reduction in outcomes by simultaneously entering baseline and time-updated SUA into semiparametric or Cox models as appropriate with all outcomes, as employed previously.[23, 24] Analyses were performed using STATA version 14 (STATA Corp, College Station, TX), 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 hyperuricemia status are shown in **Table 1**. The mean baseline SUA level was 6.6±1.9 mg/dL, and 1264 (26%) had hyperuricemia. Hyperuricemia was associated with higher age, higher NYHA class, shorter duration of HF, lower KCCQ-OSS score, lower blood pressure, higher body mass index, lower eGFR, and higher NT-proBNP as well as higher proportion of atrial fibrillation, diabetes mellitus, and diuretic use. Hyperuricemic participants less frequently used anti-hypertensive agents and xanthine oxidase inhibitors.

Association of SUA with cardiovascular outcomes

In crude analyses, hyperuricemia was associated with an increased risk for all examined outcomes, except for the renal composite outcome (which had the fewest number of events) (**Table 2**). After comprehensive multivariable adjustment, hyperuricemia was independently associated with elevated risk for the primary outcome (rate ratio 1.61, 95% CI 1.37-1.90), total HF hospitalization (rate ratio 1.61, 95% CI 1.34-1.94), cardiovascular death (HR 1.58, 95% CI 1.26-1.98), and all-cause mortality (HR 1.42, 95% CI 1.18-1.69). These findings were similar

when excluding 675 participants using xanthine oxide inhibitors, uricosuric agents, and colchicine at baseline (**Supplementary Table 1**).

In a complementary analysis using SUA as a continuous variable, a sharp increase in the risk for most outcomes (apart from the renal outcome) was observed near a baseline SUA value of 6 mg/dL (**Figure 1)**. Relative to an SUA level of 6 mg/dL, participants with a value <6 mg/dL did not demonstrate an elevated risk for outcomes, while those above 6 mg/dL generally did (**Supplementary Table 2**). The treatment effect of sacubitril/valsartan was not significantly different by baseline SUA group for all outcomes (categorical interaction p=0.14 for primary outcome), except for the renal composite outcome (HR 0.18, 95%CI 0.06, 0.51 for hyperuricemia vs. HR 0.66, 95%CI 0.41, 1.06 for normal SUA; categorical interaction p=0.029) (**Supplementary Table 3**).

Effect of treatment on SUA levels and SUA-related therapy initiation

During the run-in period, SUA decreased by 0.16 (95% CI 0.12, 0.19) mg/dL (**Figure 2**). After randomization, sacubitril/valsartan further reduced SUA 0.38 (95% CI 0.31, 0.45, p<0.001) mg/dL, when compared with valsartan, by the 16-week visit (**Supplementary Table 4 and Figure 2**). Adjusting for the change in eGFR only modestly decreased the treatment effect [0.34, 95% (CI 0.28, 0.41)], and adjusting for loop (-0.38, 95%CI -0.45, -0.30) or thiazide (-0.38, 95%CI -0.45, -0.30) diuretic use at these timepoints minimally impacted the treatment effect. The SUA lowering effect of sacubitril/valsartan was larger among those with baseline hyperuricemia (0.51, 95%CI 0.32, 0.69 mg/dL) than those without (0.32, 95%CI 0.24, 0.40 mg/dL) (interaction p=0.031). There were no treatment interactions for the SUA lowering effect

of sacubitril/valsartan by eGFR, use of SUA-lowering therapies (xanthine oxidase inhibitors or uricosuric agents), gender, or EF.

SUA-related therapies (xanthine oxidase inhibitors, uricosuric agents, and colchicine) were initiated in 229 (9.5%) participants in the sacubitril/valsartan and 318 (13.3%) participants in the valsartan arm (**Table 3**), corresponding to an absolute reduction in therapy of 3.8% and a number needed to treat of 26. Sacubitril/valsartan reduced the odds of SUA-related therapy initiation by 32% (odds ratio 0.68, 95%CI 0.57, 0.82, $p<0.001$). Similarly, sacubitril/valsartan reduced SUA-lowering therapy (xanthine oxidase inhibitors or uricosuric agents) by an absolute value of 3.3%, corresponding to a 31% relative reduction (odds ratio 0.69, 95%CI 0.57, 0.83, $p<0.001$). Sacubitril/valsartan was associated with a 29%, 62%, 35% reduction in xanthine oxidase inhibitors, uricosuric agents, and colchicine, respectively ($p<0.02$ for all comparisons).

Relationship between changes in SUA and clinical characteristics and laboratory values

In a mechanistic analysis, we assessed the relationship between change in SUA between randomization to the 4-month visit with clinical characteristics and biomarkers (**Supplementary Table 5**). After multivariable adjustment, reduction in SUA was independently associated with a decrease in hemoglobin A1c and high-sensitivity troponin T, as well as an increase in KCCQ-OSS, systolic blood pressure, eGFR, and urinary cGMP to creatinine ratio. These relationships were not modified by treatment assignment.

Assessment of reducing SUA and clinical benefit

Finally, to assess whether reducing SUA was associated with clinical benefit and is a modifiable risk factor, we simultaneously adjusted for baseline and time-updated SUA

(**Supplementary Table 6**). Time-updated SUA was a stronger predictor of outcomes, even after adjusting for baseline SUA.

DISCUSSION

In HFpEF, hyperuricemia is common (26%) and independently identified patients at elevated risk for cardiovascular outcomes prespecified in PARAGON-HF. We identified an increase in most outcomes above an SUA value of 6 mg/dL. The treatment effect of sacubitril/valsartan was not modified by SUA for the primary outcome but was greater for renal outcome. Sacubitril/valsartan reduced SUA by 0.38 mg/dL, compared with valsartan, an effect greater in those with hyperuricemia (0.51 mg/dL). Sacubitril/valsartan reduced the odds of initiating any SUA-related therapy (xanthine oxidase inhibitors, uricosuric agents, and colchicine) by 32%, and also individually reduced initiation of each class during follow-up. Reduction in SUA was associated with improvements in quality of life, several biomarkers, and cardiovascular outcomes. Our analyses provide novel insight into the relationship of SUA and outcomes in HFpEF, therapeutic effect of sacubitril/valsartan in reducing SUA compared to valsartan, and that SUA is a modifiable risk factor.

Our results are complementary to several studies in HFrEF.[2-6, 11] Specifically, in PARADIGM-HF, a randomized trial of sacubitril/valsartan vs. enalapril in HFrEF, the average SUA value at randomization (6.9 mg/dL) was similar to that observed in PARAGON-HF (6.6 mg/dL). In PARADIGM-HF, baseline SUA was also independently associated with adverse events, and sacubitril/valsartan reduced SUA by 0.26 mg/dL over 4 months compared to enalapril.[6] It is noteworthy that the comparators in these trials are different (enalapril and valsartan); the comparator arm in PARAGON-HF (valsartan) allowed us to isolate the direct

contribution of neprilysin inhibition in reducing SUA. The modest reduction in SUA achieved with sacubitril/valsartan, however, is significantly less than primary treatment strategies aimed at reducing SUA.[3, 4] Therefore, sacubitril/valsartan should not be considered a primary treatment for hyperuricaemia.

Limited data are available regarding the relationship of SUA in HFpEF.[1, 25, 26] Outpatient studies have demonstrated that elevated SUA is associated with greater arterial stiffness, adverse biomarker profiles, and worse exercise capacity.[1, 26] Further, elevated SUA identified inpatients and outpatients at higher risk for cardiovascular events.[1, 25] Our analysis goes beyond these findings in a larger, international cohort of HFpEF patients with several adjudicated outcomes, showing potential mechanisms associated with SUA reduction, the SUA-lowering effect of sacubitril/valsartan, and that reduction in SUA was associated with improved outcomes.

Sacubitril/valsartan may reduce SUA by several mechanisms. Sacubitril/valsartan appears to slow the decline of renal function,[16] though adjusting for the change in eGFR only modestly affected the treatment effect estimate. In addition, a dual inhibitor of angiotensin converting enzyme and neprilysin (MDL 100 240) was shown to have uricosuric effects.[27] This mechanism would be concordant with our finding that sacubitril/valsartan lowers use of uricosuric agents the most, perhaps explained by clinician measurement of higher urinary UA excretion in sacubitril/valsartan-treated patients with subsequent less pathophysiologic rationale to start a uricosuric agent. Finally, lower diuretic requirements in the sacubitril/valsartan arm (as observed in PARADIGM-HF) might lower SUA levels, though adjusting for use of diuretics at these times had minimal impact on the treatment effect.[28] The consistent reductions in SUA in patient subgroups by sex and LVEF demonstrate that SUA reduction does not explain the

outcome heterogeneity observed in these patient subgroups with sacubitril/valsartan compared with valsartan.[21, 22]

The related reduction in initiating anti-hypeuricemic therapies may be relevant to reduce polypharmacy in HFpEF. Notably, our study design isolates the effect of sacubitril, and while other angiotensin receptor blockers, such as losartan, have been shown to have uricosuric effects, valsartan specifically has been shown to have neutral impact on SUA.[29] The lack of a placebo arm in PARAGON-HF prohibits determining whether the increase in SUA levels in the valsartan arm is the result of natural disease progression or a valsartan effect in HFpEF. However, the rise in SUA after the run-in period (which included sacubitril/valsartan) among participants randomized to valsartan produced SUA levels overall similar to the screening values.

In a mechanistic analysis, we assessed the change in SUA with change in clinical and laboratory variables. Reducing SUA was independently associated with improved quality of life and higher systolic blood pressure. The importance of the latter relationship is unclear, as this finding may relate to changing blood pressure medications, which might change SUA levels and systolic blood pressure. In addition, reducing SUA was associated with better renal function and higher urinary cGMP to creatinine ratio (reflecting natriuretic peptide activity), both of which are augmented by sacubitril/valsartan.[16, 19] Of course, however, SUA levels are intricately related to renal function, and therefore causality cannot be inferred.

Xanthine oxidase inhibitors and other treatments for hyperuricemia have been explored in several clinical trials of HFrEF, with overall disappointing results.[3, 4, 30, 31] However, no trial has been published in HFpEF. Given the potential importance of serum uric acid mediating adverse pathophysiologies relevant in HFpEF (hypertension, insulin resistance, endothelial dysfunction, and renal impairment, for example), reducing SUA may be a novel treatment target in HFpEF.[2, 8,

[12, 13] This is further suggested in our analysis, showing that a reduction in SUA was associated with improved outcomes, even after adjusting for baseline SUA. Importantly, however, this could also reflect an epiphenomenon and a dedicated clinical trial of SUA reduction in HFpEF would be needed to confirm these findings.

There are some limitations of our study. Despite comprehensive multivariable adjustment, residual confounding may still influence some of our results. In addition, the specific inclusion/exclusion criteria in PARAGON-HF may limit generalizability to a broad HFpEF population. Strengths of our study include the large sample size and number of events, comprehensive determination of SUA and related therapies during follow-up at numerous visits, and mechanistic analyses to understand potential mechanism of action of SUA reduction and lowering adverse events.

In summary, baseline hyperuricemia was associated with an increased risk for several cardiovascular outcomes after comprehensive multivariable adjustment. Sacubitril/valsartan reduced SUA and initiation of related therapies. Lowering SUA was associated with a modest increase in quality of life, salutary changes in biomarkers, and a reduced risk of adverse events, and dedicated clinical trials would be helpful to confirm these observational findings. These data suggest that SUA may be a relevant therapeutic target in HFpEF.

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FIGURE LEGENDS

Figure 1:

Title: ***Relationship between Baseline Continuous Serum Uric Acid and Outcomes by Treatment Arm***

Caption: Incidence rates for the primary endpoint, cardiovascular death, HFH, all-cause death, myocardial infarction or stroke, and a renal composite outcome, among all patients according to serum uric acid at baseline using restricted cubic spline (4 knots). The interrupted lines are 95% confidence limits. HFH, heart failure hospitalization, MI, myocardial infarction; p-yrs, person-years.

Figure 2:

Title: ***Serum Uric Acid Levels over Time by Treatment Arm***

Caption: The effect of study drug on serum uric acid levels is shown over study visits where serum uric acid was pre-specified to be collected (truncated after the week 144 visit) with 95% confidence intervals delineated. Serum uric acid concentrations for the two run-in periods were analyzed at the end of the run-in.

TABLE 1. Baseline Clinical Characteristics by Presence of Hyperuricemia

	Normal Serum Uric Acid Levels N=3531	Elevated Serum Uric Acid Levels N=1264	P-value
Serum uric acid (mg/dl)	5.8 ± 1.2	9.0 ± 1.3	
Randomization to sacubitril/valsartan, n (%)	1766 (50.0%)	641 (50.7%)	0.67
Age, years	72.5 ± 8.5	73.3 ± 8.3	0.003
Women, n (%)	1827 (51.7%)	652 (51.6%)	0.92
White race, n (%)	2895 (82.0%)	1012 (80.1%)	0.13
NYHA, n (%)			0.001
I	99 (2.8 %)	38 (3.0 %)	
II	2774 (78.6%)	931 (73.7%)	
III	646 (18.3%)	286 (22.6%)	
IV	11 (0.3 %)	8 (0.6 %)	
Geographic region, n (%)			<0.001
Asia-Pacific or other	527 (14.9%)	235 (18.6%)	
Central Europe	1398 (39.6%)	317 (25.1%)	
Latin America	284 (8.0 %)	86 (6.8 %)	
North America	376 (10.6%)	183 (14.5%)	
Western Europe	946 (26.8%)	443 (35.0%)	
KCCQ-OSS	71.8 ± 18.8	70.5 ± 19.4	0.041
Heart failure duration (days)*	564 [154, 1813]	493 [148, 1520]	0.011
Average number of alcohol drinks (per	1.4 ± 1.6	1.4 ± 1.6	0.99

day)			
Physical Characteristics			
Systolic blood pressure (mmHg)	131 ± 15	129 ± 16	<0.001
Diastolic blood pressure (mmHg)	75 ± 10	73 ± 11	<0.001
Body mass index (kg/m^2)	30.0 ± 5.0	30.9 ± 5.0	<0.001
Heart rate (beats/min)	70.2 ± 12.0	71.0 ± 12.9	0.038
Comorbidities, n (%)			
Hypertension	3377 (95.6%)	1206 (95.4%)	0.74
Hospitalization for HF	1595 (45.2%)	711 (56.2%)	<0.001
Atrial fibrillation or flutter	1040 (29.6%)	512 (40.6%)	<0.001
Diabetes mellitus	1465 (41.5%)	596 (47.2%)	<0.001
Myocardial infarction	815 (23.1%)	268 (21.2%)	0.17
Stroke	362 (10.3%)	146 (11.6%)	0.2
Current smoker	273 (7.8 %)	80 (6.4 %)	0.1
Medication Use, n (%)			
ACE-I and/or ARB at screening	3076 (87.1%)	1063 (84.1%)	0.007
Beta-blocker	2803 (79.4%)	1017 (80.5%)	0.41
Calcium channel blocker	1240 (35.1%)	400 (31.6%)	0.026
Diuretic	3342 (94.6%)	1242 (98.3%)	<0.001
Mineralocorticoid antagonist	891 (25.2%)	348 (27.5%)	0.11
Xanthine oxidase inhibitor	530 (15.0%)	117 (9.3 %)	<0.001
Uricosuric agent	9 (0.3 %)	4 (0.3 %)	0.72

Colchicine	21 (0.6 %)	21 (1.7 %)	<0.001
Laboratory Testing			
Estimated glomerular filtration rate (mL/min/1.78 m^2)	66 ± 19	53 ± 15	<0.001
Hemoglobin A1c (%)	6.5 ± 1.3	6.7 ± 1.3	<0.001
Hemoglobin (mg/dL)	13.5 ± 1.5	13.4 ± 1.6	0.003
Sodium (mEq/L)	141 ± 3	141 ± 3	0.36
Albumin	4.2 ± 0.3	4.2 ± 0.3	0.89
NT-proBNP (pg/mL)*	836 [451 , 1522]	1110 [527 , 1849]	<0.001
Ejection Fraction	58 ± 8	58 ± 8	0.64

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

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

TABLE 2. Event Rates and Crude and Adjusted Hazard Ratios for Efficacy Outcomes by Baseline Serum Uric Acid

Efficacy outcomes, n (%)	**Normal Serum Uric Acid Levels N=3531**	**Elevated Serum Uric Acid Levels N=1264**
Composite endpoint		
• Events	1128	774
• Event rate and 95% CI (per 100 person-years)	11.0 (10.1, 12.1)	21.6 (19.0, 24.6)
• Crude model rate ratio (95% CI)	Ref	1.97 (1.69, 2.31), p<0.001
• Multivariable adjusted model rate ratio (95% CI)	Ref	1.61 (1.37, 1.90), p<0.001
Cardiovascular mortality		
• Events	261	155
• Event rate and 95% CI (per 100 person-years)	2.5 (2.2, 2.9)	4.3 (3.7, 5.1)
• Crude model HR (95% CI)	Ref	1.71 (1.40, 2.09), p<0.001
• Multivariable adjusted model HR (95% CI)	Ref	1.58 (1.26, 1.98), p<0.001
Total HF hospitalizations		
• Events	867	619
• Event rate and 95% CI (per 100 person-years)	8.4 (7.7, 9.3)	17.3 (14.9, 20.1)
• Crude model rate ratio (95% CI)	Ref	2.05 (1.72, 2.45) , p<0.001
• Multivariable adjusted model rate ratio (95% CI)	Ref	1.61 (1.34, 1.94) , p<0.001
Myocardial infarction or stroke		
• Events	278	125

• Event rate and 95% CI (per 100 person-years)	2.8 (2.5, 3.2)	3.6 (3.1, 4.3)
• Crude model HR (95% CI)	Ref	1.29 (1.04, 1.59), p=0.018
• Multivariable adjusted model HR (95% CI)	Ref	1.08 (0.86, 1.35), p=0.51
All-cause mortality		
• Events	448	242
• Event rate and 95% CI (per 100 person-years)	4.4 (4.0, 4.8)	6.8 (6.0, 7.7)
• Crude model HR (95% CI)	Ref	1.56 (1.33, 1.82), p<0.001
• Multivariable adjusted model HR (95% CI)	Ref	1.42 (1.18, 1.69), p<0.001
Renal composite		
• Events	72	25
• Event rate and 95% CI (per 100 person-years)	0.7 (0.6, 0.9)	0.7 (0.5, 1.0)
• Crude model HR (95% CI)	Ref	1.00 (0.64, 1.58), p=0.99
• Multivariable adjusted model HR (95% CI)	Ref	1.08 (0.64, 1.82), p=0.78

HR, hazard ratio; CI, confidence interval; HF, heart failure.
Covariates used for adjustment include age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, New York Heart Association class, history of HF hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, estimated glomerular filtration rate, hemoglobin, sodium, albumin, randomized treatment, diuretic use, and N-terminal pro brain natriuretic peptide.

TABLE 3. New Serum Uric Acid Related Therapy Initiation During Follow-up by Treatment Arm

	Sacubitril/Valsartan (n, %)	Valsartan (n, %)	Odds Ratio (95% CI) Sacubitril/Valsartan vs. Valsartan	P-value
Combinations of treatment				
Any SUA-Related Therapy*	229 (9.5%)	318 (13.3%)	0.68 (0.57, 0.82)	<0.001
SUA-Lowering Therapy^	206 (8.6%)	285 (11.9%)	0.69 (0.57, 0.83)	<0.001
Individual treatments				
Xanthine Oxidase Inhibitors	202 (8.4%)	270 (11.3%)	0.71 (0.59, 0.87)	0.001
Uricosuric Agents	8 (0.3%)	21 (0.9%)	0.38 (0.17, 0.85)	0.019
Colchicine	60 (2.5%)	90 (3.8%)	0.65 (0.47, 0.91)	0.012

CI, confidence interval, SUA, serum uric acid.

*Includes xanthine oxidase inhibitors, uricosuric agents, and colchicine. Participants are counted only once if multiple therapies are initiated.

^Includes xanthine oxidase inhibitors and uricosuric agents. Participants are counted only once if multiple therapies are initiated.

Figure 1.

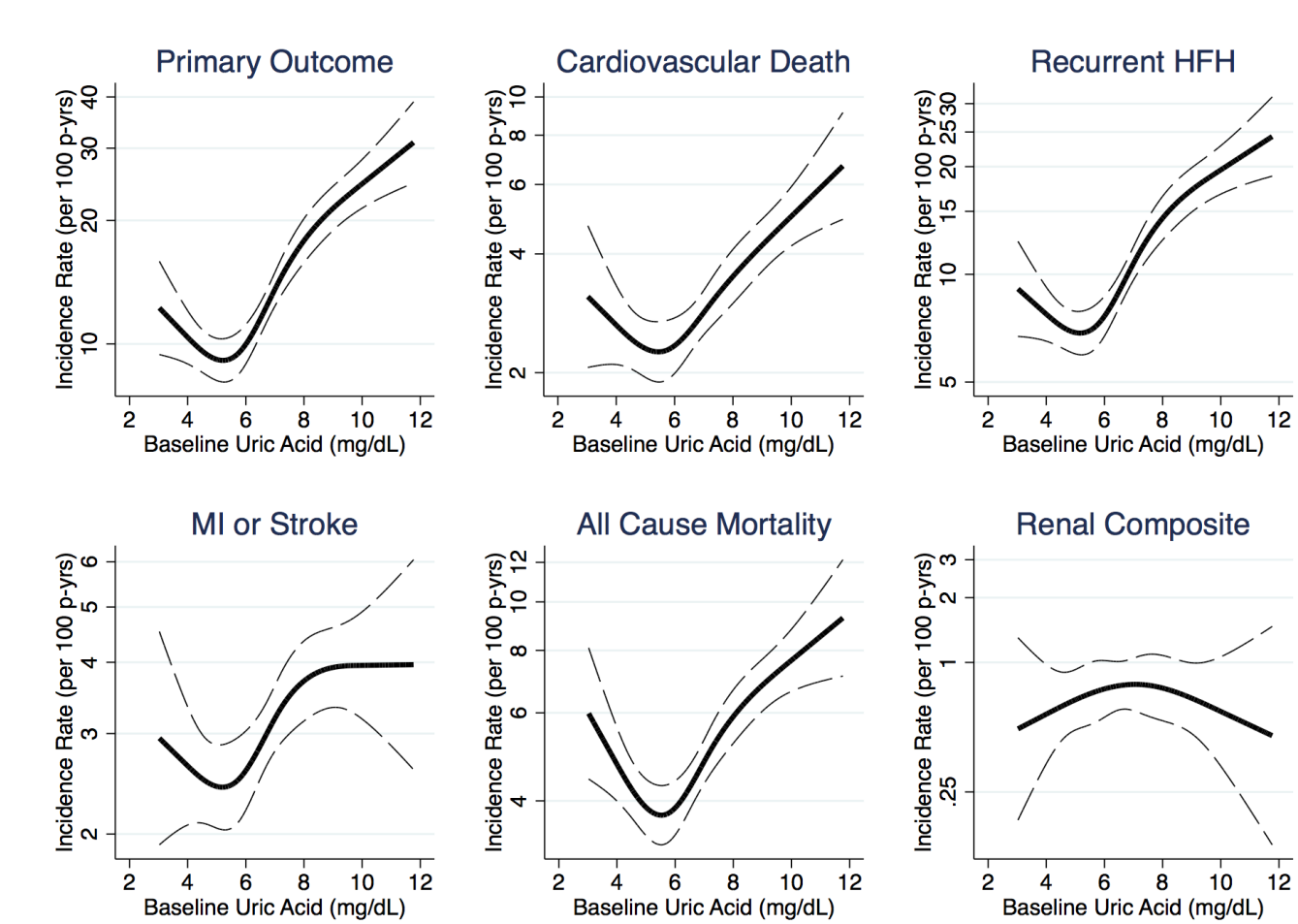

Figure 2.