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Serum uric acid, influence of sacubitril–valsartan, and cardiovascular outcomes in heart failure with preserved ejection fraction: PARAGON-HF

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Aims

This study aimed to determine the prognostic value of serum uric acid (SUA) on outcomes in heart failure (HF) with preserved ejection fraction (HFpEF), and whether sacubitril–valsartan reduces SUA and use of SUA-related therapies.

Methods and results

We analysed 4795 participants from 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 related baseline hyperuricaemia (using age and gender adjusted assay definitions) to the primary outcome [cardiovascular (CV) death and total HF hospitalizations]. We assessed the associations between changes in SUA and Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS) and other cardiac biomarkers from baseline to 4 months. We simultaneously adjusted for baseline and time-updated SUA to determine whether lowering SUA was associated with clinical benefit. The mean ($\pm$ standard deviation) age of patients was 73 ± 8 years and 52% were women. After multivariable adjustment, hyperuricaemia was associated with increased risk for the primary outcome [rate ratio 1.61, 95% confidence interval (CI) 1.37–1.90]. The treatment effect of sacubitril–valsartan for the primary endpoint was not significantly modified by hyperuricaemia (P -value for interaction = 0.14). Sacubitril–valsartan reduced SUA by 0.38 mg/dL (95% CI 0.31–0.45) compared with valsartan at 4 months, with greater effect in those with elevated SUA vs. normal SUA (-0.51 mg/dL vs. -0.32 mg/dL) (P -value for 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.

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Conclusions

Serum uric acid independently predicted adverse outcomes in HFpEF. Sacubitril–valsartan reduced SUA and the initiation of related therapy compared with valsartan. Reductions in SUA were associated with improved outcomes.

Keywords

Heart failure with preserved ejection fraction • Heart failure hospitalization • Sacubitril–valsartan • Uric acid • Quality of life

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. 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 and oxidative stress.⁹ 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 function¹³ and worsening metabolic phenotype.¹⁴ As 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 ejection fraction (HFrEF).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 HF [New York Heart Association (NYHA) classes II–IV], left ventricular ejection fraction (LVEF) $\geq 45\%$, 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 tolerable 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 LVEF of $<40\%$, an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m², and systolic blood pressure (SBP) <110 mmHg or ≥ 180 mmHg. Patients with SBP >150 mmHg were excluded unless they were receiving at least three antihypertensive medications at screening. Detailed exclusion criteria are listed elsewhere.¹⁵ We excluded one participant with missing SUA at baseline.

Serum uric acid measurement and therapies

Measurement of SUA was performed through a central laboratory at screening, during run-in, at randomization, and at weeks 16 and 48, then annually. Each SUA measurement was converted from $\mu\text{mol/L}$ to mg/dL by dividing it 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; these limits were used to define hyperuricaemia for this analysis.⁶ We classified any pre-existing use of SUA-related therapies (xanthine oxidase inhibitors, uricosuric agents and colchicine) at baseline, as well as the initiation of such treatments during follow-up. The management of SUA-related therapies was left to the discretion of the treating physician.

Study outcomes

Endpoints examined in this analysis include the primary composite outcome of total HF hospitalizations and death from cardiovascular (CV) causes, total HF hospitalizations, CV death, myocardial infarction or stroke, all-cause mortality, and a renal composite outcome (defined as a reduction of $\geq 50\%$ in eGFR, development of end-stage renal disease, or death caused by renal failure). In a subgroup of participants for whom data were available, we also assessed the relationships between the change in SUA from baseline (randomization) to 4 months with changes in several other variables also measured at the baseline and 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 SBP,¹⁸ eGFR, haemoglobin A1c, high-sensitivity (hs) 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 the presence or absence of hyperuricaemia were described using mean $\pm$ standard deviation (SD) values, medians and 25th–75th 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 tests when appropriate) for categorical variables.

The associations between baseline hyperuricaemia 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 (HR) was used for time-to-first-event outcomes. In a complementary analysis using

restricted cubic splines, the continuous association between SUA and all outcomes was examined. Four knots were used for all outcomes. Multivariable models were adjusted for covariates used in an analysis of SUA and sacubitril–valsartan in HFrEF [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, SBP, heart rate, ejection fraction, NYHA class, history of HF hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index (BMI), prior myocardial infarction, prior stroke, eGFR, haemoglobin, sodium, albumin, randomized treatment, diuretic use and NT-proBNP.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 ejection fraction 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 analyse the relationship between the 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 baseline to 4 months with changes in KCCQ-OSS score, eGFR, haemoglobin A1c, SBP, log-transformed NT-proBNP, log-transformed hs 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 lowered SUA was associated with reductions 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 14.0 (StataCorp LLC, College Station, TX, USA). A two-sided *P*-value of <0.05 was considered to indicate a difference of statistical significance.

Results

Baseline characteristics

The baseline characteristics of the 4795 participants meeting study inclusion criteria stratified by hyperuricaemia status are shown in Table 1. The mean $\pm$ SD baseline SUA level was 6.6 ± 1.9 mg/dL and 1264 (26%) subjects had hyperuricaemia. Hyperuricaemia was associated with higher age, higher NYHA class, shorter duration of HF, lower KCCQ-OSS score, lower blood pressure, higher BMI, lower eGFR and higher NT-proBNP, as well as with higher proportions of atrial fibrillation, diabetes mellitus and diuretic use. Hyperuricaemic participants less frequently used anti-hypertensive agents and xanthine oxidase inhibitors.

Association of serum uric acid with cardiovascular outcomes

In crude analyses, hyperuricaemia 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, hyperuricaemia was independently associated with elevated risk for the primary outcome [rate ratio 1.61, 95% confidence interval (CI) 1.37–1.90], total HF hospitalization (rate ratio 1.61, 95% CI 1.34–1.94), CV 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 the 675 participants using xanthine oxidase inhibitors, uricosuric agents and colchicine at baseline were excluded (Supplementary material online, Table S1).

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 an SUA value of <6 mg/dL did not demonstrate an elevated risk for outcomes, whereas those with SUA above 6 mg/dL generally did (Supplementary material online, Table S2). The treatment effect of sacubitril–valsartan did not differ significantly by baseline SUA group (categorical interaction *P* = 0.14 for primary outcome), except for the renal composite outcome (HR 0.18, 95% CI 0.06–0.51 for hyperuricaemia vs. HR 0.66, 95% CI 0.41–1.06 for normal SUA; categorical interaction *P* = 0.029) (Supplementary material online, Table S3).

Effect of treatment on serum uric acid (SUA) levels and SUA-related therapy initiation

During the run-in period, SUA decreased by 0.16 mg/dL (95% CI 0.12–0.19) (Figure 2). After randomization, sacubitril–valsartan further reduced SUA by 0.38 mg/dL (95% CI 0.31–0.45; *P* < 0.001) in comparison with valsartan, by the 16-week visit (Figure 2; Supplementary material online, Table S4). 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 0.30 to 0.45) or thiazide (0.38, 95% CI 0.30 to 0.45) diuretic use at these time-points minimally impacted the treatment effect. The SUA-lowering effect of sacubitril–valsartan was larger among those with baseline hyperuricaemia (0.51 mg/dL, 95% CI 0.32–0.69) than those without (0.32 mg/dL, 95% CI 0.24–0.40) (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 ejection fraction.

Serum uric acid-related therapies (xanthine oxidase inhibitors, uricosuric agents and colchicine) were initiated in 229 (9.5%) participants in the sacubitril–valsartan arm and 318 (13.3%) participants in the valsartan arm (Table 3), corresponding to an absolute reduction in therapy of 3.8%. 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 29%, 62% and 35% reductions in xanthine oxidase inhibitors, uricosuric agents and colchicine, respectively (*P* < 0.05 for all comparisons).

Table 1 Baseline clinical characteristics by presence of hyperuricaemia

	Normal SUA levels (n = 3531)	Elevated SUA levels (n = 1264)	P-value
SUA, mg/dL, mean $\pm$ SD	5.8 $\pm$ 1.2	9.0 $\pm$ 1.3	
Randomization to sacubitril–valsartan, n (%)	1766 (50.0)	641 (50.7)	0.67
Age, years, mean $\pm$ SD	72.5 $\pm$ 8.5	73.3 $\pm$ 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 class, 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 $\pm$ 18.8	70.5 $\pm$ 19.4	0.041
HF duration, days ^a	564 (154–1813)	493 (148–1520)	0.011
Average number of alcoholic drinks per day, mean $\pm$ SD	1.4 $\pm$ 1.6	1.4 $\pm$ 1.6	0.99
Physical characteristics, mean $\pm$ SD			
Systolic blood pressure, mmHg	131 $\pm$ 15	129 $\pm$ 16	<0.001
Diastolic blood pressure, mmHg	75 $\pm$ 10	73 $\pm$ 11	<0.001
Body mass index, kg/m ²	30.0 $\pm$ 5.0	30.9 $\pm$ 5.0	<0.001
Heart rate, b.p.m.	70.2 $\pm$ 12.0	71.0 $\pm$ 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)	0.20
Current smoker	273 (7.8)	80 (6.4)	0.10
Medication use, n (%)			
ACEI 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			
eGFR, mL/min/1.78 m ² , mean $\pm$ SD	66 $\pm$ 19	53 $\pm$ 15	<0.001
Haemoglobin A1c, %, mean $\pm$ SD	6.5 $\pm$ 1.3	6.7 $\pm$ 1.3	<0.001
Haemoglobin, mg/dL, mean $\pm$ SD	13.5 $\pm$ 1.5	13.4 $\pm$ 1.6	0.003
Sodium, mEq/L, mean $\pm$ SD	141 $\pm$ 3	141 $\pm$ 3	0.36
Albumin, g/dL, mean $\pm$ SD	4.2 $\pm$ 0.3	4.2 $\pm$ 0.3	0.89
NT-proBNP, pg/mL ^a	836 (451–1522)	1110 (527–1849)	<0.001
Ejection fraction, mean $\pm$ SD	58 $\pm$ 8	58 $\pm$ 8	0.64

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SUA, serum uric acid.

^aPresented as median (25th–75th percentile) as values are skewed.

Table 2 Event rates and crude and adjusted hazard ratios for efficacy outcomes by baseline serum uric acid

Efficacy outcomes	Normal SUA levels (n = 3531)	Elevated SUA levels (n = 1264)	P-value
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)	<0.001
Multivariable adjusted model rate ratio (95% CI)	Ref	1.61 (1.37–1.90)	<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)	<0.001
Multivariable adjusted model HR (95% CI)	Ref	1.58 (1.26–1.98)	<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)	<0.001
Multivariable adjusted model rate ratio (95% CI)	Ref	1.61 (1.34–1.94)	<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)	0.018
Multivariable adjusted model HR (95% CI)	Ref	1.08 (0.86–1.35)	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)	<0.001
Multivariable adjusted model HR (95% CI)	Ref	1.42 (1.18–1.69)	<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)	0.99
Multivariable adjusted model HR (95% CI)	Ref	1.08 (0.64–1.82)	0.78

CI, confidence interval; HF, heart failure; HR, hazard ratio; SUA, serum uric acid.

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, haemoglobin, sodium, albumin, randomized treatment, diuretic use and N-terminal pro brain natriuretic peptide.

Relationships between changes in serum uric acid and clinical characteristics and laboratory values

In a mechanistic analysis, we assessed the relationships between change in SUA between randomization and the 4-month visit and clinical characteristics and biomarkers (Supplementary material online, Table S5). After multivariable adjustment, reduction in SUA was independently associated with a decrease in haemoglobin A1c and hs troponin T, as well as an increase in KCCQ-OSS, SBP, eGFR, and urinary cGMP to creatinine ratio. These relationships were not modified by treatment assignment.

Assessment of reducing serum uric acid 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 material online, Table S6). Time-updated SUA was generally a stronger predictor of outcomes, even after adjusting for baseline SUA.

Discussion

In HFpEF, hyperuricaemia was common (26%) and independently identified patients at elevated risk for CV 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 hyperuricaemia (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 the

Figure 1 Relationship between baseline continuous serum uric acid (SUA) and outcomes by treatment arm. Incidence rates are shown for the primary endpoint, cardiovascular death, heart failure hospitalization (HFH), all-cause death, myocardial infarction (MI) or stroke, and a renal composite outcome, among all patients according to SUA at baseline using restricted cubic splines (4 knots). The interrupted lines are 95% confidence limits.

initiation of each class of therapy during follow-up. Reduction in SUA was associated with improvements in quality of life, several biomarkers and CV outcomes. Our analyses provide novel insights into the relationships between SUA and outcomes in HFpEF therapeutic effect of sacubitril-valsartan in reducing SUA compared to valsartan, and characterization of SUA as a modifiable risk factor.

Our results are complementary to those of several studies in subjects with HFREF.^{2–6,11} Specifically, in PARADIGM-HF, a randomized trial of sacubitril-valsartan vs. enalapril, 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 with 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 that achieved by primary treatment strategies aimed at reducing SUA.^{3,4} Therefore, sacubitril-valsartan

should not be considered as a primary treatment for hyperuricaemia.

Limited data are available regarding the relationships 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 CV events.^{1,25} Our analysis extends 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 although 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 the use of uricosuric agents most, which is perhaps explained by

clinician measurements of higher urinary uric acid excretion in sacubitril–valsartan-treated patients with subsequent less rationale to initiate a uricosuric agent. Finally, lower diuretic requirements in the sacubitril–valsartan arm (as observed in PARADIGM-HF) may lower SUA levels, although adjusting for the use of diuretics at these times had minimal impact on the treatment effect.²⁸ The consistent reductions in SUA in patient subgroups defined 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-hyperuricaemic therapies may be relevant to reducing polypharmacy in HFpEF. Notably, our study design isolates the effect of sacubitril, and whereas other angiotensin receptor blockers, such as losartan, have been shown to have uricosuric effects, valsartan may have a neutral impact on SUA.²⁹ The lack of a placebo arm in PARAGON-HF prohibits

the determination of 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 relationships between change in SUA and changes in clinical and laboratory variables. Reducing SUA was independently associated with improved quality of life and higher SBP. The importance of the latter relationship is unclear, as this finding may relate to changing blood pressure medications, which can effect both SUA levels and SBP. In addition, reducing SUA was associated with better renal function and a 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 hyperuricaemia have been explored in several clinical trials in HFpEF, with overall disappointing results.^{3,4,30,31} However, no trial in HFpEF has been published. Given the potential importance of SUA in mediating adverse pathophysiologies relevant in HFpEF (e.g. hypertension, insulin resistance, and endothelial dysfunction), the reduction of SUA may be a novel treatment target in HFpEF.^{2,8,12,13} This is further suggested in our analysis demonstrating that a reduction in SUA was associated with improved outcomes, even after adjusting for baseline SUA. Importantly, however, this may also reflect an epiphenomenon and a dedicated clinical trial of SUA reduction in HFpEF is required to confirm these findings.

Our study has some limitations. Despite comprehensive multivariable adjustment, residual confounding may have influenced some of our results. In addition, the specific inclusion and exclusion criteria in PARAGON-HF may limit its generalizability to a broad HFpEF population. The strengths of our study include its large sample size and number of events, the comprehensive determination of SUA and related therapies during follow-up at numerous visits,

Table 3 Serum uric acid-related therapy initiation during follow-up by treatment arm

	Sacubitril–valsartan arm, n (%)	Valsartan arm, n (%)	Odds ratio (95% CI) Sacubitril–valsartan vs. valsartan	P-value
Combinations of treatment				
Any SUA-related therapy ^a	229 (9.5)	318 (13.3)	0.68 (0.57–0.82)	<0.001
SUA-lowering therapy ^b	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.

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

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

and mechanistic analyses to elucidate the potential mechanisms of action of SUA reduction and the lowering of adverse events.

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

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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