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CLINICAL RESEARCH

Cardiovascular and Renal Outcomes of Mineralocorticoid Receptor Antagonist Use in PARAGON-HF

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ABSTRACT

OBJECTIVES This study sought to evaluate the efficacy and safety of sacubitril/valsartan in patients with heart failure with preserved ejection fraction (HFpEF) according to background mineralocorticoid receptor antagonist (MRA) therapy.

BACKGROUND Current guidelines recommend consideration of MRAs in selected patients with HFpEF. This study assessed cardiovascular outcomes, renal outcomes, and safety of sacubitril/valsartan compared with valsartan in patients with HFpEF according to background MRA treatment.

METHODS PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction) randomized 4,796 patients with HFpEF to sacubitril/valsartan or valsartan. In a pre-specified subgroup analysis, the effect of sacubitril/valsartan versus valsartan was evaluated according to baseline MRA use on the primary study composite of total heart failure hospitalizations and cardiovascular death using semiparametric proportional rates methods, as well as the renal composite of ≥50% decrease in estimated glomerular filtration rate, development of end-stage renal disease, or death from renal causes using Cox proportional hazards regression models. Annual decline in estimated glomerular filtration rate was analyzed with repeated-measures mixed-effect models. Key safety outcomes included incidence of hypotension, hyperkalemia, and elevations in serum creatinine above predefined thresholds.

RESULTS Patients treated with MRAs at baseline (n = 1,239, 26%), compared with MRA nonusers (n = 3,557, 74%), were younger (72 vs. 73 years), more often male (52% vs. 47%), had lower left ventricular ejection fraction (57% vs. 58%), and a higher proportion of prior HF hospitalization (59% vs. 44%) (all $p < 0.001$). Efficacy of sacubitril/valsartan compared with valsartan with regard to the primary cardiovascular (for MRA users: rate ratio: 0.73; 95% confidence interval [CI]: 0.56 to 0.95; vs. for MRA nonusers: rate ratio: 0.94; 95% CI: 0.79 to 1.11; $p_{interaction} = 0.11$) and renal endpoints (for MRA users: hazard ratio: 0.31; 95% CI: 0.13 to 0.76; vs. for MRA non-users: HR: 0.59; 95% CI: 0.36 to 0.95; $p_{interaction} = 0.21$) did not significantly vary by baseline MRA use. The incidence of key safety outcomes including hypotension and severe hyperkalemia ($K > 6.0$ mmol/l) did not vary by baseline MRA use. However, annual decline in estimated glomerular filtration rate was less with the combination of MRA and sacubitril/valsartan (for MRA users: absolute difference favoring sacubitril/valsartan: +1.2 ml/min/1.73 m^2 per year; 95% CI: 0.6 to 1.7; vs. for MRA nonusers: +0.4; 95% CI: 0.1 to 0.7; $p_{interaction} = 0.01$).

CONCLUSIONS Clinical efficacy of sacubitril/valsartan compared with valsartan with regard to predefined cardiorenal composite outcomes in PARAGON-HF was consistent in patients treated and not treated with MRA at baseline. Addition of sacubitril/valsartan rather than valsartan alone to MRA appears to be associated with a lesser decline in renal function and no increase in severe hyperkalemia. These data support possible added value of combination treatment with sacubitril/valsartan and MRA in patients with HFpEF. (Prospective Comparison of ARNI [angiotensin receptor -neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction [PARAGON-HF]; NCT01920711) (J Am Coll Cardiol HF 2021;9:13–24) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CV = cardiovascular

eGFR = estimated glomerular filtration rate

ESRD = end-stage renal disease

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HHF = hospitalization for heart failure

HR = hazard ratio

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

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

NYHA = New York Heart Association

OR = odds ratio

For patients with heart failure with preserved ejection fraction (HFpEF) evidence-based therapies are limited, and management focuses on treatment of congestion and comorbid conditions. In addition to angiotensin II receptor blockers, current guidelines recommend consideration of mineralocorticoid receptor (MRAs) in selected patients with HFpEF (1). Moreover, because resistant hypertension is common in HFpEF, spironolactone is often used for blood pressure control in this population (2,3).

In the PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor -neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction) trial, treatment with sacubitril/valsartan compared with valsartan was associated with a modest reduction in total heart failure hospitalizations (HHFs) and cardiovascular (CV) death, though this result was of borderline statistical significance (4). Sacubitril/valsartan was associated with a significant reduction in the pre-specified renal composite of ≥50% decrease in estimated glomerular filtration rate (eGFR), development of end-stage renal disease (ESRD) or death from renal causes (4). The efficacy and safety of sacubitril/valsartan and MRAs in combination for patients with HFpEF, has not been explored. In a pre-specified subgroup analysis of PARAGON-HF, we examined CV and renal effects as well as safety of sacubitril/valsartan according to baseline MRA use.

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METHODS

STUDY DESIGN AND POPULATION. The design and primary results of PARAGON-HF have been previously reported (4,5). Briefly, patients ≥50 years were eligible if they had symptomatic heart failure (New York Heart Association [NYHA] functional classes II to IV), preserved left ventricular ejection fraction ([LVEF] ≥45%), structural heart disease, need for diuretics, and elevated natriuretic peptides. Exclusion criteria included any prior LVEF <40%, acute decompensated heart failure at screening, symptomatic hypotension (or systolic blood pressure <100 mm Hg at screening), eGFR <30 ml/min/1.73 m^2, or serum potassium >5.2 mmol/l at screening. MRA use was permitted at the discretion of the treating physician.

The ethics committee at each participating site approved the study protocol, and participants provided written, informed consent.

PROCEDURES. Serum potassium and creatinine were measured at screening, during the run-in period, at randomization, 1 month and 4 months following randomization, and in 4-month intervals thereafter. eGFR was calculated by MDRD (Modification in Diet in Renal Disease) formula (6). N-terminal pro-B-type natriuretic peptide (NT-proBNP) and urinary cyclic guanosine monophosphate were measured prior to randomization and at 1 year from frozen venous samples using Roche proBNP II assay (Roche Diagnostics GmbH, Mannheim, Germany) and from first void urine using enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, Minnesota).

PRE-SPECIFIED CLINICAL ENDPOINTS. The primary endpoint was a composite of total (first and recurrent) HHF and CV death. Secondary outcomes included change in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and NYHA functional class from baseline to 8 months, the renal composite (≥50% decrease in eGFR, development of ESRD, or death from renal failure), and all-cause death. In an exploratory analysis, a cardiorenal composite, defined as first HHF, CV death, ≥50% decrease in eGFR, development of ESRD, or death from renal failure, was evaluated. Changes in renal function, measured as the slope of annual decline in eGFR, were assessed. Hypotension (systolic blood pressure <100 mm Hg), elevations in serum creatinine (≥2.0 mg/dl, ≥2.5 mg/dl, and ≥3.0 mg/dl),

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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hyperkalemia (potassium >5.5 mmol/l), severe hyperkalemia (potassium >6.0 mmol/l), and angioedema were recorded as safety outcomes.

In the present study, effects of sacubitril/valsartan compared with valsartan were analyzed according to baseline MRA treatment as a pre-specified subgroup analysis.

STATISTICAL ANALYSIS. Data are presented as mean ± SD when distributed normally, median (interquartile range) for skewed distributions, and frequency (percentage) for categorical variables. Baseline characteristics of MRA users and nonusers were compared with the Student's *t*-test, Mann-Whitney *U* test, and Pearson chi-square test where appropriate.

In both MRA users and nonusers, the effect of treatment assignment on the primary outcome as well as total HHFs was evaluated using semiparametric proportional rates methods of Lin et al. (7), stratified by geographic region. The primary outcome, its components, the renal composite, all-cause mortality, and the cardiorenal composite were also analyzed using Cox regression in a time-to-first-event analysis. Cumulative total events (first and recurrent) were graphically displayed with Nelson-Aalen curves and first events with Kaplan-Meier curves.

Sensitivity analyses were performed using time-updated rather than baseline MRA treatment, which was assessed at randomization; 6 months; and 1, 2, and 3 years. In an exploratory analysis, effects of treatment assignment in MRA users and nonusers, stratified by median LVEF of 57%, were evaluated.

A repeated measures proportional cumulative odds model was used to examine treatment effect on changes in NYHA functional class and KCCQ-CSS from baseline to 8 months, and a mixed-effect logistic responder analysis for treatment effect on improvement of ≥5 points in KCCQ-CSS from baseline to 8 months.

Changes in blood pressure and weight from baseline to 8 months, and changes in NT-proBNP, soluble suppression of tumorigenesis 2, and urinary cyclic guanosine monophosphate from baseline to 1 year were assessed with repeated measures analysis of covariance with the corresponding baseline value included as a covariate and after log-transformation of skewed variables.

Temporal changes in eGFR, estimated by MDRD formula, were assessed by repeated-measures mixed-effect modeling using patient-level random intercept terms and slopes. Treatment, time, and assigned treatment × time interaction terms were included as fixed effects. Time was modeled linearly. To calculate the slope of annual eGFR decline, all available data were used without imputation for missing values. In a complementary analysis for the slope of eGFR decline, eGFR was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (8). Analyses were adjusted for geographic region and for differences in baseline characteristics between MRA users and nonusers including age, sex, race, systolic blood pressure, body mass index, tobacco use, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, ischemic etiology of HF, prior HHF, NYHA functional class, LVEF, diuretic use, NT-proBNP (log-transformed), and eGFR. Models were furthermore adjusted for changes in: 1) systolic blood pressure; 2) mean arterial blood pressure; or 3) weight over time, respectively. Because MRA use could change during the study, sensitivity analyses were performed in which patients were censored at the time of change in MRA status and in which MRA use was updated over time.

The effects of treatment assignment, according to baseline MRA treatment, on incidence of hypokalemia (potassium <3.5 mmol/l), hyperkalemia (potassium >5.5 mmol/l), and severe hyperkalemia (potassium >6.0 mmol/l) were analyzed using Cox regression.

A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed using STATA version 14.2 (Stata Corp., College Station, Texas).

RESULTS

Of the 4,769 randomized patients, 1,239 (26.0%) were taking MRA at baseline and 3,557 (74.0%) were not. Spironolactone was the most common MRA, prescribed in 87% of patients (Supplemental Table S1). Compared with patients not prescribed MRA at baseline, MRA users were younger, more male, and more likely to have ischemic heart disease and atrial fibrillation. MRA users had more advanced NYHA functional class, higher levels of NT-proBNP, lower LVEF, and more commonly had been hospitalized for HF prior to enrollment (all $p < 0.001$). Baseline renal function was similar in both groups (**Table 1**).

In the sacubitril/valsartan arm, the proportion of patients prescribed MRA at baseline was slightly lower (24.6%) compared with in the valsartan arm (27.1%; $p = 0.05$). Within MRA subgroups, baseline characteristics among those assigned to sacubitril/valsartan versus valsartan were well balanced (Supplemental Table S2).

CARDIOVASCULAR OUTCOMES. Rates of the primary composite CV outcome and its components according to treatment assignment, stratified by

TABLE 1 Baseline Characteristics by Baseline MRA Use

	No MRA (n = 3,557)	MRA (n = 1,239)	p Value
Age, yrs	73.1 ± 8.4	71.7 ± 8.5	<0.001
Female	1,889 (53.1)	590 (47.6)	<0.001
Race			<0.001
Caucasian	2,944 (82.8)	963 (77.7)	
Black	82 (2.3)	20 (1.6)	
Asian	379 (10.7)	228 (18.4)	
Other	152 (4.2)	28 (2.3)	
Geographic region			<0.001
North America	462 (13.0)	97 (7.8)	
Latin America	284 (8.0)	86 (6.9)	
Western Europe	1,111 (31.2)	279 (22.5)	
Central Europe	1,214 (34.1)	501 (40.4)	
Asia-Pacific or other	486 (13.7)	276 (22.3)	
Systolic blood pressure, mm Hg	131.3 ± 15.6	128.5 ± 14.7	<0.001
Diastolic blood pressure mm Hg	74.4 ± 10.5	73.9 ± 10.7	0.15
Pulse pressure, mm Hg	56.8 ± 14.9	54.5 ± 13.8	<0.001
Heart rate, beats/min	70.3 ± 12.1	70.8 ± 12.8	0.18
Body mass index, kg/m^2	30.2 ± 5.0	30.2 ± 5.1	0.95
LVEF, %	57.8 ± 7.7	56.7 ± 8.2	<0.001
MAGGIC score	20.2 ± 5.6	19.9 ± 5.6	0.18
NYHA functional class			<0.001
I	111 (3.1)	26 (2.1)	
II	2,789 (78.5)	917 (74.0)	
III	645 (18.1)	287 (23.2)	
IV	10 (0.3)	9 (0.7)	
KCCQ			
Clinical summary score	72.2 ± 18.9	72.5 ± 19.4	0.65
Overall summary score	71.6 ± 18.8	70.9 ± 19.4	0.28
HHF	1,576 (44.3)	730 (58.9)	<0.001
Time since prior HHF			<0.001
≤30 days since HHF	436 (12.3)	186 (15.0)	
31–90 days since HHF	392 (11.0)	163 (13.2)	
91–180 days since HHF	295 (8.3)	140 (11.3)	
>6 months since HHF	453 (21.7)	241 (19.5)	
No prior HHF	1,981 (55.7)	509 (41.1)	
Medical history			
Hypertension	3,421 (96.2)	1,163 (93.9)	<0.001
Hyperlipidemia	2,216 (62.5)	683 (55.3)	<0.001
Diabetes	1,543 (43.4)	519 (41.9)	0.36
Atrial fibrillation or flutter	1,092 (30.8)	460 (37.2)	<0.001
Stroke	370 (10.4)	138 (11.2)	0.47
Myocardial infarction	794 (22.3)	289 (23.3)	0.47
Ischemic etiology of heart failure	1,243 (35.0)	480 (38.7)	0.02
Tobacco use (current or former)	1,361 (38.5)	493 (39.9)	0.39

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MRA use are illustrated in **Figure 1**. Overall, the event rate for the primary outcome was 15.4 per 100 patient-years (95% confidence interval [CI]: 14.1 to 16.7) in MRA users and 13.2 per 100 patient-years (95% CI: 12.5 to 13.9) in MRA nonusers. Rates of the individual components of the primary outcome, total HHF and CV death, were higher among MRA users than nonusers. The treatment effect of sacubitril/valsartan, compared with valsartan, on the primary CV outcome was not significantly different in MRA users (rate ratio: 0.73; 95% CI: 0.56 to 0.95) and nonusers (rate ratio: 0.94; 95% CI: 0.79 to 1.11; $p_{interaction} = 0.11$) (**Table 2, Central Illustration**).

In both MRA users and nonusers, the treatment effect of sacubitril/valsartan relative to valsartan was not significantly different for either total HHF or CV death (**Table 2**). Sensitivity analyses using time-updated rather than baseline MRA treatment or stratified by median LVEF of 57% yielded similar results (Supplemental Tables S3 and S4).

There was no significant difference in the between group change from baseline to 8 months in NYHA functional class or KCCQ-CSS among MRA users and nonusers (Supplemental Table S5).

RENAL OUTCOMES. Overall, the incidence of the study renal composite, defined as ≥50% decrease in eGFR, development of ESRD, or death from renal failure, was 0.8 per 100 patient-years (95% CI: 0.5 to 1.1) among MRA users and 0.7 per 100 patient-years (95% CI: 0.5 to 0.9) among MRA nonusers. Regardless of baseline MRA use, the incidence of the renal composite was significantly lower with sacubitril/valsartan than with valsartan, in both MRA users (hazard ratio [HR]: 0.59; 95% CI: 0.36 to 0.95) and nonusers (HR: 0.31; 95% CI: 0.13 to 0.76; $p_{interaction} = 0.21$) (**Table 2**).

Incidence of a combined cardiorenal composite endpoint, defined as first HHF, CV death, ≥50% decrease in eGFR, development of ESRD, or death from renal failure, was 10.6 per 100 patient-years (95% CI: 9.5 to 11.8) in MRA users and 8.5 per 100 patient-years (95% CI: 7.9 to 9.1) in MRA nonusers. The treatment effect of sacubitril/valsartan, compared with that of valsartan, on the cardiorenal composite endpoint was not significantly different between MRA users and nonusers ($p_{interaction} = 0.15$).

In MRA nonusers, the slope of eGFR decline was less with sacubitril/valsartan (−2.0 ml/min/1.73 m^2 per year; 95% CI: −2.2 to −1.7) than with valsartan (−2.4 ml/min/1.73 m^2 per year; 95% CI: −2.6 to −2.1). In MRA users, the slope of eGFR decline was also significantly less with sacubitril/valsartan (−1.4 ml/min/1.73 m^2 per year; 95% CI: −1.8 to −1.0) than with valsartan (−2.6 ml/min/1.73 m^2 per year; 95% CI: −3.0 to −2.2). Attenuation of eGFR decline with sacubitril/valsartan was greater in MRA users than in nonusers, with an adjusted mean difference in favor of sacubitril/valsartan of 1.2 ml/min/1.73 m^2 per year (95% CI: 0.6 to 1.7) in MRA users and 0.4 ml/min/1.73 m^2 per year (95% CI: 0.1 to 0.7) in MRA nonusers ($p_{interaction} = 0.01$) (**Figure 2**). These differences persisted after multivariate adjustment and adjustment for changes in systolic blood pressure, mean arterial

pressure, or weight over time (Figure 2). Sensitivity analyses using time-updated MRA treatment or stratified by median LVEF yielded similar results (Supplemental Table S6).

Over 3 years, MRA use slightly increased from 26% to 28%, with 13% new initiation and 28% discontinuation of MRA treatment during follow-up (Supplemental Figure S1). MRA therapy was initiated in 13% of patients randomized to sacubitril/valsartan and 12% of those randomized to valsartan (odds ratio [OR]: 1.02; 95% CI: 0.76 to 1.37). Among patients prescribed MRA at baseline, 74% in the sacubitril/valsartan arm and 70% in the valsartan arm remained on MRA therapy by 3 years (OR: 1.24; 95% CI: 0.85 to 1.80) (Supplemental Table S7 and Supplemental Figure S2). In sensitivity analyses restricted to the on-treatment population, censoring patients at the time of change in MRA status, annual eGFR decline was significantly less with sacubitril/valsartan than with valsartan in MRA users but not in nonusers ($p_{interaction}$ = 0.001) (Supplemental Table S8). A complementary analysis using the CKD-EPI, rather than the MDRD equation, yielded similar results (Supplemental Table S8).

CHANGES IN BLOOD PRESSURE, WEIGHT, AND NATRIURETIC PEPTIDES. Reductions in systolic and diastolic blood pressures from baseline to 8 months and decreases in NT-proBNP and soluble suppression of tumorigenesis 2 from baseline to 1 year were greater with sacubitril/valsartan than with valsartan regardless of MRA use (all $p_{interaction}$ > 0.4). Weight changes from baseline to 8 months did not differ significantly between sacubitril/valsartan and valsartan within the subgroups defined by MRA use (Supplemental Tables S5 and S9).

SAFETY. Irrespective of MRA use, hypotension occurred more frequently in the sacubitril/valsartan arm versus the valsartan arm. Risk of elevations in serum creatinine, defined as serum creatinine ≥2.0 mg/dl, ≥2.5 mg/dl, and ≥3.0 mg/dl, was not increased by sacubitril/valsartan compared with valsartan. Study drug discontinuation rates were similar between treatment arms regardless of baseline MRA use. Reasons for study drug discontinuation are displayed in Supplemental Table S10. Differences in other adverse events between sacubitril/valsartan and valsartan did not differ by MRA therapy (Table 3).

Overall, incidence of hyperkalemia (potassium >5.5 mmol/l) was higher among MRA users than nonusers (7.1 vs. 4.7 per 100 patient-years; HR: 1.51; 95% CI: 1.28 to 1.77) during follow-up. Incidence of severe hyperkalemia (potassium >6.0 mmol/l) did not differ significantly between MRA users and nonusers (1.6 vs. 1.2 per 100 patient-years; HR: 1.33; 95% CI: 0.97 to 1.83). Regardless of MRA use, rates of hyperkalemia and severe hyperkalemia did not differ significantly between sacubitril/valsartan and valsartan ($p_{interaction}$ >0.30) (Table 4).

In the overall study population, incidence of hypokalemia (potassium <3.5 mmol/l) was not significantly different between MRA users and nonusers (2.8 vs. 2.7 per 100 patient-years; HR: 1.04; 95% CI: 0.82 to 1.31). Within MRA subgroups, incidence of hypokalemia did not differ significantly by treatment allocation (Table 4).

TABLE 1 Continued

	No MRA (n = 3,557)	MRA (n = 1,239)	p Value
Treatment at randomization			
Mineralocorticoid receptor antagonist			N/A
Spironolactone		1,082 (87.3)	
Eplerenone		128 (10.3)	
Potassium canrenoate		16 (1.3)	
Canrenone		13 (1.1)	
Sacubitril/valsartan	1,815 (51.0)	592 (47.8)	0.05
ACE inhibitor or ARB	3,066 (86.2)	1,073 (86.6)	0.72
Diuretic	3,346 (94.1)	1,239 (100.0)	<0.001
Beta-blocker	2,818 (79.2)	1,003 (81.0)	0.19
Digoxin	308 (8.7)	142 (11.5)	0.004
Statin	2,280 (64.1)	775 (62.6)	0.33
Antiplatelet	461 (13.0)	174 (14.0)	0.33
Anticoagulant	1,117 (31.4)	434 (35.0)	0.02
Serologies (baseline)			
Serum creatinine, mg/dl	1.1 ± 0.3	1.1 ± 0.3	0.07
eGFR, ml/min/1.73 m^2	62.7 ± 19.1	62.3 ± 19.1	0.58
Potassium, mmol/l	4.5 ± 0.4	4.6 ± 0.5	<0.001
NT-proBNP, pg/ml	877.0 (451.0, 1,566.0)	1,025.0 (518.0, 1,764.0)	<0.001
Hemoglobin, g/dl	13.5 ± 1.6	13.6 ± 1.6	0.26

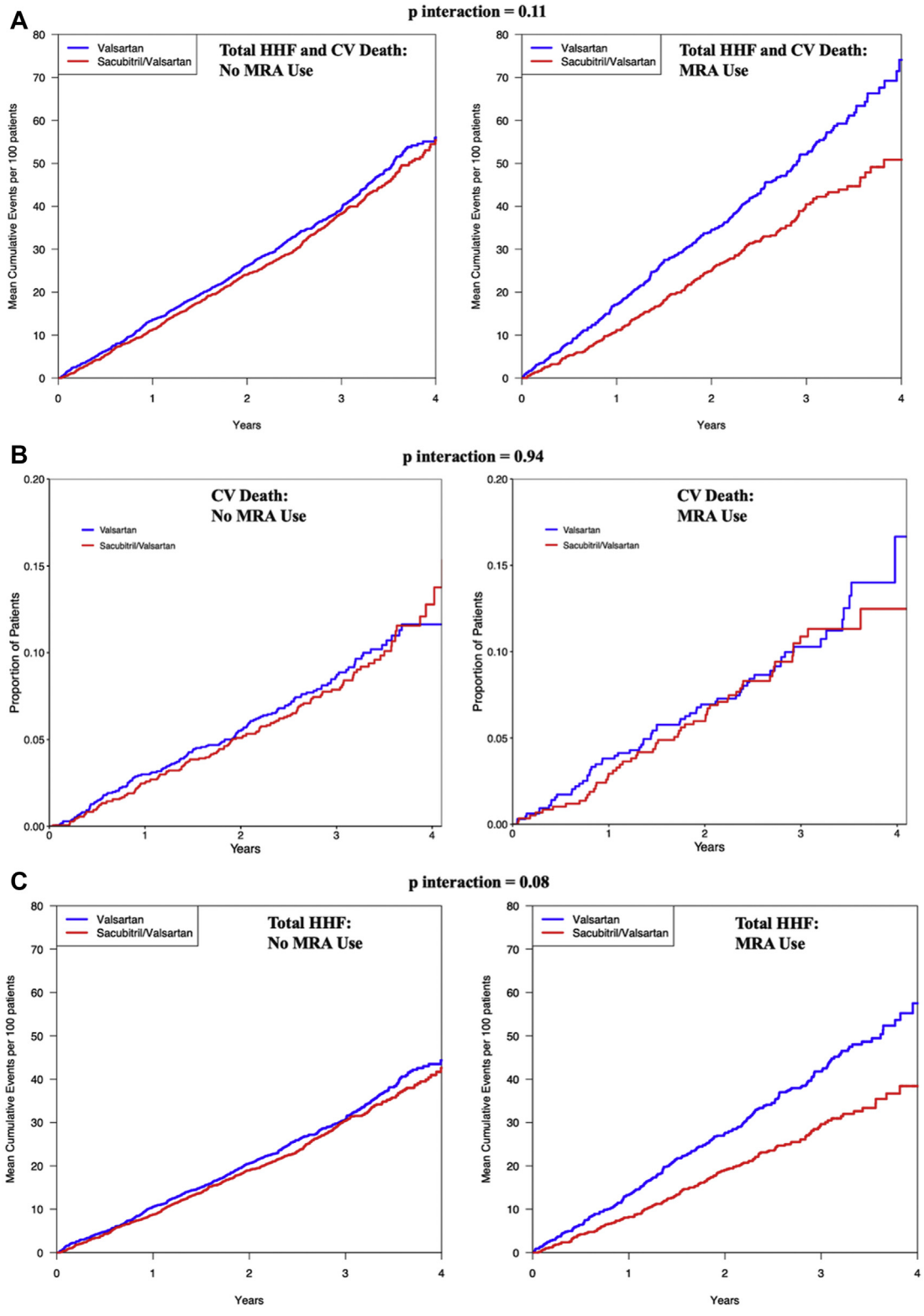
Values are mean ± SD, n (%), or median (interquartile range). Race was self-reported.

ACE inhibitor = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; eGFR = estimated glomerular filtration rate; HHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; MRA = mineralocorticoid receptor antagonist; N/A = not available; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

DISCUSSION

In this pre-specified subgroup analysis of PARAGON-HF, we examined efficacy and safety of sacubitril/valsartan compared with that of valsartan in the context of MRA therapy and found that the treatment effect of sacubitril/valsartan relative to valsartan did not differ among subgroups defined by MRA use. Treatment with sacubitril/valsartan was associated with a reduction in the study renal composite, irrespective of baseline MRA therapy. However, in an analysis of change in renal function estimated as the slope of eGFR decline, the benefit of sacubitril/

FIGURE 1 Time-to-Event Curves for the Primary Composite and Its Components, According to Baseline MRA Use



(A) Nelson-Aalen curves for total hospitalizations for heart failure (HHFs) and cardiovascular (CV) death, (B) Kaplan-Meier curves for CV death, and **(C)** Nelson-Aalen curves for total HHF are shown. MRA = mineralocorticoid receptor antagonist.

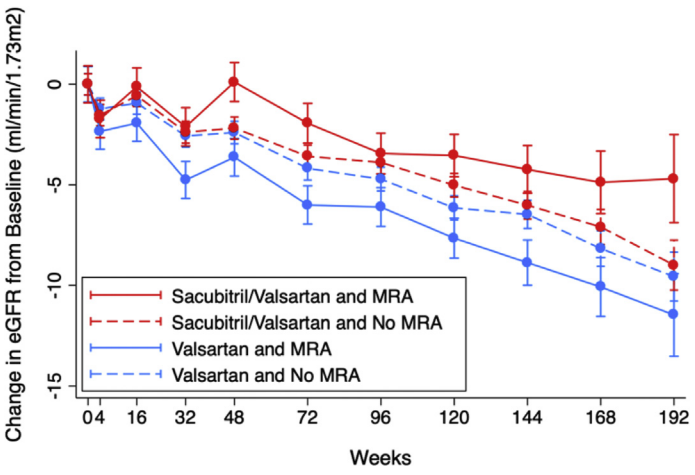
TABLE 2 Primary and Secondary Outcomes According to Baseline MRA Use

	No MRA Use					MRA Use						
	All (n = 3,557)	Valsartan (n = 1,742)	Sacubitril/ Valsartan (n = 1,815)	Rate Ratio	p Value	All (n = 1,239)	Valsartan (n = 647)	Sacubitril/ Valsartan (n = 592)	Rate Ratio	p Value	Interaction Unadjusted	p Value Adjusted*
Primary composite outcome												
Events (in patients)	1,358 (761)	682 (377)	676 (384)			545 (322)	327 (180)	218 (142)				
Event rate	13.2 (12.5–13.9)	13.6 (12.6–14.6)	12.8 (11.9–13.8)	0.94 (0.79–1.11)	0.46	15.4 (14.1–16.7)	17.6 (15.8–19.6)	12.9 (11.3–14.7)	0.73 (0.56–0.95)	0.02	0.11	0.23
Total HHFs												
Events (in patients)	1,063 (583)	535 (283)	528 (300)			424 (255)	262 (150)	162 (105)				
Event rate	10.3 (9.7–11.0)	10.6 (9.8–11.6)	10.0 (9.2–10.9)	0.93 (0.76–1.13)	0.47	11.9 (10.9–13.1)	14.1 (12.5–15.9)	9.6 (8.2–11.2)	0.68 (0.50–0.91)	0.01	0.08	0.12
CV death												
Events	295	147	148			121	65	56				
Incidence rate	2.9 (2.6–3.2)	2.9 (2.5–3.4)	2.8 (2.4–3.3)	0.96 (0.77–1.21)	0.74	3.4 (2.8–4.1)	3.5 (2.7–4.5)	3.3 (2.5–4.3)	0.95 (0.661.36)	0.78	0.94	0.52
All-cause death												
Events	503	253	250			188	96	92				
Incidence rate	4.9 (4.5–5.3)	5.0 (4.4–5.7)	4.7 (4.2–5.4)	0.94 (0.79–1.12)	0.51	5.3 (4.6–6.1)	5.2 (4.2–6.3)	5.4 (4.4–6.7)	1.06 (0.79–1.41)	0.73	0.52	0.24
First HHF or CV death												
Events	761	377	384			322	180	142				
Incidence rate	8.1 (7.5–8.7)	8.2 (7.4–9.1)	7.9 (7.2–8.8)	0.96 (0.83–1.1)	0.54	10.1 (9.0–11.2)	10.1 (9.4–12.6)	9.2 (7.8–10.8)	0.84 (0.68–1.05)	0.12	0.33	0.63
First HHF, urgent HF visit, or CV death												
Events	790	395	395			337	190	147				
Incidence rate	8.4 (7.9–9.0)	8.7 (7.8–9.6)	8.2 (7.4–9.0)	0.94 (0.81–1.08)	0.35	10.6 (9.5–11.8)	11.6 (10.1–13.4)	9.6 (8.1–11.2)	0.82 (0.66–1.02)	0.07	0.31	0.60
First HHF												
Events	583	283	300			255	150	105				
Incidence rate	6.2 (5.7–6.7)	6.2 (5.5–6.9)	6.2 (5.6–6.9)	0.99 (0.84–1.16)	0.9	8.0 (7.1–9.0)	9.1 (7.7–10.6)	6.8 (5.6–8.2)	0.74 (0.58–0.95)	0.02	0.06	0.12
Renal composite												
Events	70	43	27			27	21	6				
Incidence rate	0.7 (0.5–0.9)	0.9 (0.6–1.2)	0.5 (0.4–0.8)	0.59 (0.36–0.95)	0.03	0.8 (0.5–1.1)	1.1 (0.7–1.8)	0.4 (0.2–0.8)	0.31 (0.13–0.76)	0.01	0.21	0.33
Decline in eGFR >50%												
Events	62	41	21			25	19	6				
Incidence rate	0.6 (0.5–0.8)	0.8 (0.6–1.1)	0.4 (0.3–0.3)	0.48 (0.28–0.82)	0.007	0.7 (0.5–1.0)	1.0 (0.7–1.6)	0.4 (0.2–0.8)	0.34 (0.14–0.85)	0.02	0.51	0.71
Cardiorenal composite												
Events	798	400	398			337	195	142				
Incidence rate	8.5 (7.9–9.1)	8.8 (7.9–9.7)	8.3 (7.5–9.1)	0.93 (0.81–1.07)	0.31	10.6 (9.5–11.8)	11.9 (10.3–13.7)	9.2 (7.8–10.8)	0.77 (0.62–0.96)	0.02	0.15	0.38
New onset AF												
Events	206	96	110			56	29	27				
Incidence rate	2.1 (1.8–2.4)	2.0 (1.6–2.4)	2.2 (1.8–2.6)	1.10 (0.83–1.44)	0.51	1.6 (1.2–2.1)	1.6 (1.1–2.3)	1.6 (1.1–2.4)	1.01 (0.60–1.71)	0.96	0.79	0.93
Myocardial infarction												
Events	163	80	83			62	31	31				
Incidence rate	1.6 (1.3–1.9)	1.6 (1.3–2.0)	1.6 (1.3–2.0)	0.98 (0.72–1.33)	0.89	1.8 (1.4–2.3)	1.7 (1.2–2.4)	1.9 (1.3–2.7)	1.08 (0.66–1.77)	0.76	0.72	0.73
Myocardial infarction or stroke												
Events	291	143	148			112	57	55				
Incidence rate	2.9 (2.6–3.3)	3.0 (2.5–3.5)	2.9 (2.5–3.4)	0.98 (0.78–1.24)	0.88	3.3 (2.8–4.0)	3.2 (2.5–4.2)	3.4 (2.6–4.5)	1.05 (0.73–1.52)	0.79	0.76	0.77

Values are n and rates (95% CI). Incidence rates denote number of events per 100 patient-years. The primary composite outcome consists of total HHF and CV death. The renal composite is defined as ≥50% decrease in eGFR (by MDRD formula) from baseline, development of end-stage renal disease, or death from renal failure. The cardiorenal composite is defined as first HHF, CV death, ≥50% decrease in eGFR from baseline, development of end-stage renal disease, or death from renal failure. *Adjusted for sex, sex-sacubitril/valsartan interaction, LVEF, LVEF-sacubitril/valsartan interaction, age, race, systolic blood pressure, body mass index, tobacco use, hypertension, hyperlipidemia, diabetes mellitus, AF, ischemic etiology of HF, prior HHF, NYHA functional class, baseline NT-proBNP (log-transformed), eGFR, and diuretic use.

AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; MDRD = Modification in Diet in Renal Disease; other abbreviations as in Table 1.

FIGURE 2 Change in eGFR Over Time in Patients With and Without Baseline MRA Use According to Treatment Assignment



Annual decline in estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2 per year), calculated by MDRD (Modification in Diet in Renal Disease) formula, with 95% confidence interval. Model adjusted for age, sex, race, geographic region, systolic blood pressure, hypertension, diabetes mellitus, atrial fibrillation, ischemic etiology of heart failure, prior hospitalization for heart failure, left ventricular ejection fraction, New York Heart Association functional class, baseline N-terminal pro-B-type natriuretic peptide (log-transformed), diuretic, calcium channel blocker, and digoxin use.

valsartan appeared greater in MRA users than in nonusers. Risk of adverse events, including hyperkalemia and elevations in serum creatinine, was not higher with the combination of sacubitril/valsartan and MRA than with valsartan and MRA or either study treatment in MRA nonusers. Incidence of hypokalemia was similar with sacubitril/valsartan and valsartan regardless of MRA therapy.

In the absence of targeted therapies, MRAs and angiotensin II receptor blockers currently remain the only guideline-recommended pharmacological treatment for selected patients with HFpEF (1,9). Nevertheless, as in heart failure with reduced ejection fraction (HFrEF), MRAs are underprescribed, frequently out of fear of hyperkalemia and worsening renal function (10–12). In PARAGON-HF, MRA use was modest and varied significantly across geographic regions, with lower use in North America and Western Europe. Recruitment predated the 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America update on the 2013 HF guidelines, which may partially explain low use in North America. Notably, the clinical profile of MRA users, with greater age, lower LVEF, higher NYHA functional class, higher levels of natriuretic peptides, more recent HHF, and greater diuretic needs, is reflective of a high-risk population, supported by overall higher CV event rates in MRA users versus nonusers.

In this paper, we demonstrate that addition of sacubitril/valsartan to MRA therapy is not only safe but is also associated with lower incidence of the renal composite. Safety of combined sacubitril/valsartan and MRA therapy in patients with HFrEF was shown in a secondary analysis of PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting -Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial). In PARADIGM-HF, sacubitril/valsartan was associated with lower incidence of severe hyperkalemia (potassium >6.0 mmol/l) relative to enalapril in MRA users only (13). Lower overall incidence of hyperkalemia in PARAGON-HF compared with in PARADIGM-HF may in part account for the observed differences. We extend the observations from PARADIGM-HF to older patients with HFpEF, demonstrating no significant disturbances in potassium homeostasis and, despite more hypotension in the sacubitril/valsartan arm, no increased risk of worsening renal function with sacubitril/valsartan added to MRA therapy.

In addition to this favorable safety profile, clinical efficacy of sacubitril/valsartan with regard to predefined CV and renal composite outcomes was consistent regardless of background MRA use. Nevertheless, overall MRA users experienced higher rates of CV events than MRA nonusers did, which is reflective of a higher risk profile. In patients on MRAs, CV event rates were lower with sacubitril/valsartan than with valsartan, driven by differences in HHFs, although no significant heterogeneity of treatment effect for sacubitril/valsartan and MRA use was observed. MRA users in PARAGON-HF had lower LVEF and more commonly had been hospitalized for HF prior to enrollment, both factors that may alter treatment response to sacubitril/valsartan (14,15). Yet treatment effects of sacubitril/valsartan and MRA on CV and renal endpoints were not modified by LVEF.

Consistent with our findings, studies of sacubitril/valsartan in HFrEF and HFpEF demonstrated less decline in eGFR with sacubitril/valsartan compared with decline when using inhibitors of the renin-angiotensin system alone (4,16–18). In the present study, beneficial effects of sacubitril/valsartan versus those of valsartan with regard to the renal composite were consistent in MRA users and nonusers. Low incidence of the renal composite may have left the present study underpowered to detect significant differences between MRA users and nonusers with study treatment. Attenuation of the rate of decline in

TABLE 3 Adverse Events During Study Follow-Up According to Baseline MRA Use and Treatment Assignment

	No MRA Use				MRA Use				
	All (n = 3,557)	Valsartan (n = 1,742)	Sacubitril/Valsartan (n = 1,815)	p Value	All (n = 1,239)	Valsartan (n = 647)	Sacubitril/Valsartan (n = 592)	p Value	Interaction p Value
Hypotension (SBP <100 mm Hg)	443 (12.5)	174 (10.0)	269 (14.8)	<0.001	194 (15.7)	83 (12.8)	111 (18.8)	0.004	0.96* 0.89†
Elevated serum creatinine, mg/dl									
≥2.0	429 (12.1)	233 (13.4)	196 (10.8)	0.02	160 (12.9)	95 (14.7)	65 (11.0)	0.05	0.94* 0.85†
≥2.5	154 (4.3)	80 (4.6)	74 (4.1)	0.45	52 (4.2)	29 (4.5)	23 (3.9)	0.60	0.85* 0.69†
≥3.0	57 (1.6)	27 (1.5)	30 (1.7)	0.81	21 (1.7)	13 (2.0)	8 (1.4)	0.37	0.44* 0.55†
Angioedema	13 (0.4)	3 (0.2)	10 (0.6)	0.06	5 (0.4)	1 (0.2)	4 (0.7)	0.15	0.81* 0.87†
Discontinuation of study drug	490 (13.8)	246 (14.1)	244 (13.4)	0.56	174 (14.0)	92 (14.2)	82 (13.9)	0.85	0.86* 0.64†

Values are n (%). *Model adjusted for region. †Model adjusted for age, sex, race, SBP, hypertension, diabetes mellitus, AF, ischemic etiology of HF, prior HHF, LVEF, NYHA functional class, baseline NT-proBNP (log-transformed), eGFR, diuretic use and region. For elevations in serum creatinine, baseline serum creatinine levels were included.

Abbreviations as in Table 1.

eGFR was greatest with sacubitril/valsartan and MRA use, suggesting potential synergistic effects of these two agents.

Spironolactone was the most commonly prescribed MRA in PARAGON-HF. In animal models, spironolactone reached higher renal than cardiac tissue concentrations compared with eplerenone (19). Future studies are needed to investigate whether potential renoprotective effects of MRA and sacubitril/valsartan combination therapy observed in PARAGON-HF are specific to spironolactone as it concentrates in the kidneys or whether those effects extend to all MRAs.

MRA use was not randomized in PARAGON-HF, and thus our findings could be influenced by selection bias or confounding. Nevertheless, neprilysin/renin-angiotensin system inhibition has been consistently shown to reduce decline in eGFR in clinical trials of HF and in preclinical trials reduced proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis compared with renin-angiotensin system inhibition alone (20,21). MRAs in turn are known to reduce albuminuria in patients with chronic kidney disease (22). Mechanistically possible additive diuretic, vasodilatory, and antifibrotic effects of sacubitril/valsartan and MRA could lend biological plausibility to observed differences of eGFR decline. Although changes in natriuretic peptides or weight, as markers of decongestion, did not modify the rate of eGFR decline, enhanced diuresis mediated by combined sacubitril/valsartan and MRA therapy, or lower diuretic needs may have helped preserve renal function by relieving venous congestion and improving forward flow (23,24). Sacubitril/valsartan has been shown to reduce aldosterone levels in patients with HFrEF relative to enalapril but whether enhanced aldosterone suppression by sacubitril/valsartan and MRA combination therapy reduces myocardial and renal fibrosis to a greater extent is unclear (25). Substantial heterogeneity

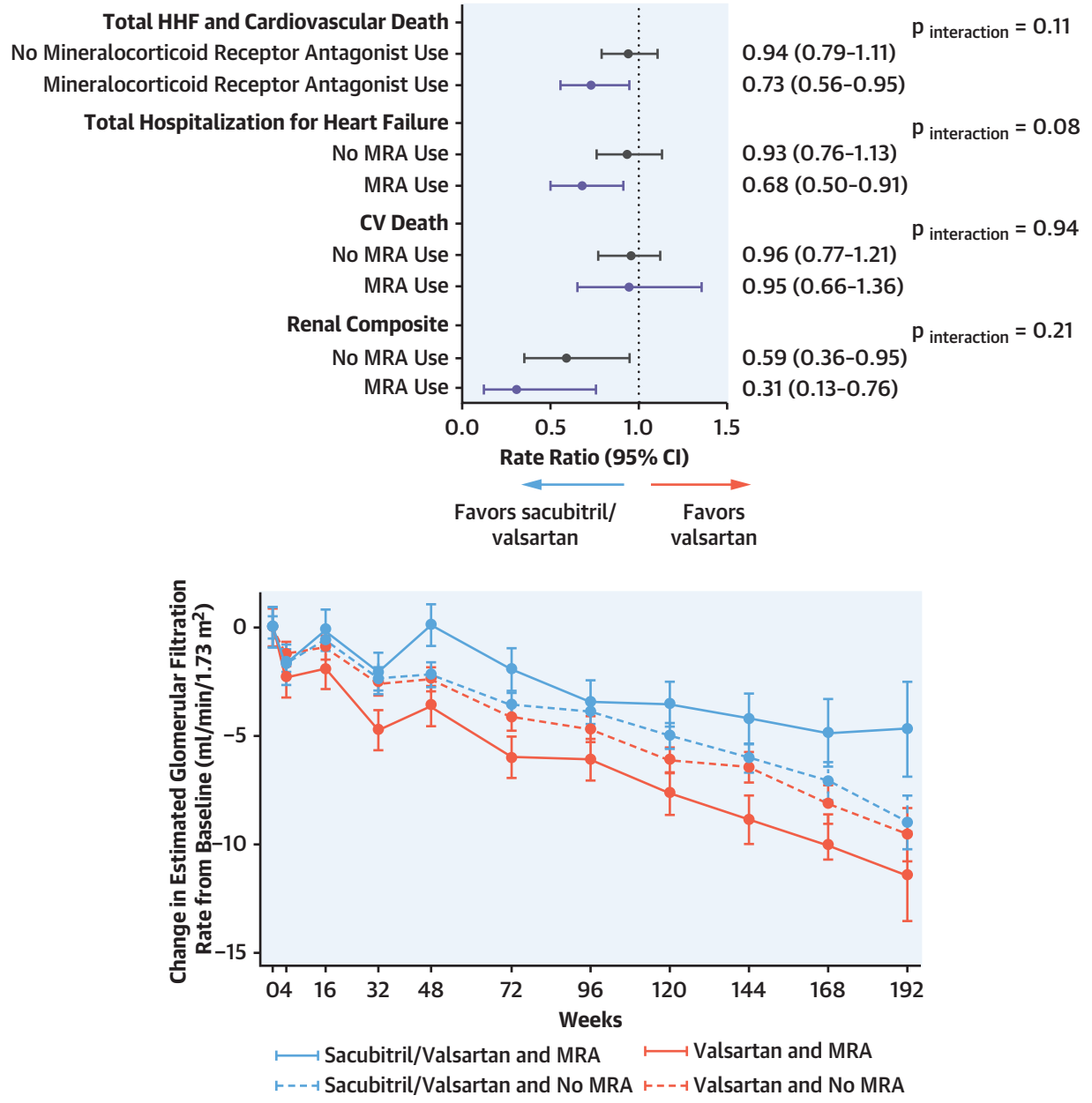
TABLE 4 Incidence of Hyper- and Hypokalemia in MRA Users and Nonusers Throughout Follow-Up by Treatment Assignment

	All	Incidence	Valsartan	Incidence	Sacubitril/Valsartan	Incidence	HR (95% CI)	p Value
No MRA use								
Hyperkalemia	451 (12.7)	4.7	241 (13.8)	5.2	210 (11.6)	4.2	0.83 (0.69–0.99)	0.04
Severe hyperkalemia	121 (3.4)	1.2	71 (4.1)	1.4	50 (2.8)	1.0	0.67 (0.47–0.96)	0.03
Hypokalemia	264 (7.4)	2.7	125 (7.2)	2.6	139 (7.7)	2.8	1.06 (0.83–1.35)	0.65
MRA use								
Hyperkalemia	226 (18.2)	7.1	120 (18.5)	7.3	106 (17.9)	7.0	0.96 (0.74–1.24)	0.75
Severe hyperkalemia	55 (4.4)	1.6	30 (4.6)	1.7	25 (4.2)	1.5	0.92 (0.54–1.55)	0.74
Hypokalemia	94 (7.6)	2.8	42 (6.5)	2.3	52 (8.8)	3.3	1.40 (0.93–2.11)	0.10

Values are n (%), unless otherwise indicated. Incidence per 100 patient-years. Hyperkalemia is defined as potassium >5.5 mmol/l, severe hyperkalemia as >6.0 mmol/l, and hypokalemia as <3.5 mmol/l. For sacubitril/valsartan and baseline MRA use for hyperkalemia, $p_{interaction} = 0.35$; for severe hyperkalemia, $p_{interaction} = 0.34$; and for hypokalemia, $p_{interaction} = 0.26$.

HR = hazard ratio; other abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION **Treatment Effect of Sacubitril/Valsartan Relative to Valsartan According to Background MRA Therapy**



Jering, K.S. et al. J Am Coll Cardiol HF. 2021;9(1):13-24.

Forest plot of treatment effects of sacubitril/valsartan relative to those of valsartan on the primary composite endpoint of total hospitalization for heart failure (HHF) and cardiovascular (CV) death; its individual components; and the renal composite endpoint of ≥50% decrease in estimated glomerular filtration rate (eGFR), development of end-stage renal disease, or death from renal causes, according to baseline mineralocorticoid receptor antagonist (MRA) use. Change in eGFR (ml/min/1.73 m^2) from baseline during follow-up, according to treatment assignment and baseline MRA use. **Error bars** denote 95% confidence interval (CI).

among patients diagnosed with HFpEF may further explain differences in treatment response whereby MRA use simply identifies patients with more congestion and more advanced HF at risk for clinical events who may respond more favorably to therapy.

STUDY LIMITATIONS. Because MRA use in PARAGON-HF was not randomized, selection bias and confounding by indication may influence the results. History of MRA intolerance prior to enrollment was not collected. Some participants may not have been prescribed MRAs because they had failed prior MRA administrations, and it is possible that these patients were at higher risk of developing worsening renal function. Use of sodium glucose cotransporter-2 inhibitors was not captured given their relative novelty at the time of study design. Any imbalance in their use across treatment arms and MRA subgroups could have differentially affected renal function over time.

CONCLUSIONS

Addition of sacubitril/valsartan to MRA treatment appears safe and does not augment rates of worsening renal function or hyperkalemia. Clinical efficacy of sacubitril/valsartan with regard to predefined cardiovascular and renal composite outcomes is consistent regardless of background MRA use. In addition, sacubitril/valsartan attenuates eGFR decline over time relative to valsartan, with larger effect size in patients on MRA therapy. These data suggest possible added value of combination treatment with sacubitril/valsartan and MRA in patients with HFpEF.

AUTHOR DISCLOSURES

The PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction) study was funded by Novartis. Dr. Jering has received support from the National Institutes of Health (Training Grant 5-T32 HL007604). Dr. Zannad has received fees for serving on Steering Committees from AstraZeneca, Janssen, Bayer, Boston Scientific, CVRx, and Boehringer Ingelheim; has received consulting fees from Amgen, Vifor Pharma-Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, and Merck; has received consulting fees from AstraZeneca; and was a founder of Cardiovascular Clinical Trialists. Dr. Claggett has received consultancy fees from Boehringer Ingelheim, Gilead, AOBiome, Amgen, Novartis, MyoKardia, and Corvia. Mc Causland is supported by National Institute of Diabetes and Digestive and Kidney Diseases grants U01DK096189, R03DK122240, and K23DK102511. Dr. Ferreira has received consultancy fees from Boehringer Ingelheim. Dr. Desai has received research grant support from AstraZeneca, Alnylam, and Novartis; and has received consulting fees and/or honoraria from Abbott, AstraZeneca, Alnylam, Boehringer-Ingelheim, Boston Scientific, Biofourmis, Corvidia, DalCor Pharma, Novartis, Relypsa, and Regeneron. Dr. Barkoudah has received research support from the National Institutes of Health/National Heart, Lung, and Blood Institute, Bristol Myers Squibb, and Janssen; has received payments made to Brigham and Women's Hospital for performing clinical endpoints; has received Advisory Board fees from Bristol Myers Squibb, Janssen, Novartis, Pfizer, and Portola; and has received travel expenses from Alexion. Dr. McMurray has served as an executive committee member and coprincipal investigator of ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure) and coprincipal investigator of the PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) and PARAGON-HF trials and his employer, Glasgow University, has been paid by Novartis for his time spent in these roles; has received travel expenses from Novartis, AstraZeneca, Cardiorentis, Amgen, Theracos, AbbVie, GlaxoSmithKline, Vifor-Fresenius, and Kings College Hospital; has been a member of a Steering Committee and Endpoint Committee for Cardiorentis; has been a member of a Steering Committee for Amgen, Oxford University/Bayer, AbbVie, DalCor Pharma, GlaxoSmithKline, Vifor-Fresenius, Kidney Research United Kingdom; has been a member of the Data Safety Monitoring Board for Pfizer and Merck; and has been a member of an Executive Committee for Novartis. Dr. Pfeffer has received grants from Novartis; and has received personal fees for consulting from AstraZeneca, DalCor, GlaxoSmithKline, Novo Nordisk, Sanofi, Jazz Pharmaceuticals, MyoKardia, Servier, Takeda, and Corvidia. Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos Therapeutics, Gilead, GlaxoSmithKline, Ionis Pharmaceuticals, Lone Star Heart, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Sanofi Pasteur, and Theracos; and has consulted for Akros, Alnylam, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardior, Corvia, Cytokinetics, Gilead, GlaxoSmithKline, Ironwood, Merck, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion Pharmaceuticals, AOBiome, Janssen, Cardiac Dimensions, and Tenaya Therapeutics. Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, Respicardia, Sanofi Pasteur, Theracos; and has consulted for Abbott, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GlaxoSmithKline, Ironwood, Lilly, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, and Moderna.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Clinical efficacy of sacubitril/valsartan compared with that of valsartan is consistent in patients treated and those not treated with MRA. Addition of sacubitril/valsartan to MRA therapy is safe and attenuates decline in renal function over time.

TRANSLATIONAL OUTLOOK: These data suggest a possible synergistic effect of sacubitril/valsartan and MRA on renal function and provide a rationale for future studies to elucidate underlying mechanisms.

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KEY WORDS clinical outcomes, heart failure with preserved ejection fraction, mineralocorticoid receptor antagonists, renal outcomes, sacubitril/valsartan

APPENDIX For supplemental figures and tables, please see the online version of this paper.