

Renal Effects and Associated Outcomes During Angiotensin-Nepriylsin Inhibition in Heart Failure



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ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the renal effects of sacubitril/valsartan in patients with heart failure and reduced ejection fraction.

BACKGROUND Renal function is frequently impaired in patients with heart failure with reduced ejection fraction and may deteriorate further after blockade of the renin-angiotensin system.

METHODS In the PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, 8,399 patients with heart failure with reduced ejection fraction were randomized to treatment with sacubitril/valsartan or enalapril. The estimated glomerular filtration rate (eGFR) was available for all patients, and the urinary albumin/creatinine ratio (UACR) was available in 1872 patients, at screening, randomization, and at fixed time intervals during follow-up. We evaluated the effect of study treatment on change in eGFR and UACR, and on renal and cardiovascular outcomes, according to eGFR and UACR.

RESULTS At screening, the eGFR was 70 ± 20 ml/min/1.73 m² and 2,745 patients (33%) had chronic kidney disease; the median UACR was 1.0 mg/mmol (interquartile range [IQR]: 0.4 to 3.2 mg/mmol) and 24% had an increased UACR. The decrease in eGFR during follow-up was less with sacubitril/valsartan compared with enalapril (-1.61 ml/min/1.73 m²/year; [95% confidence interval: -1.77 to -1.44 ml/min/1.73 m²/year] vs. -2.04 ml/min/1.73 m²/year [95% CI: -2.21 to -1.88 ml/min/1.73 m²/year]; $p < 0.001$) despite a greater increase in UACR with sacubitril/valsartan than with enalapril (1.20 mg/mmol [95% CI: 1.04 to 1.36 mg/mmol] vs. 0.90 mg/mmol [95% CI: 0.77 to 1.03 mg/mmol]; $p < 0.001$). The effect of sacubitril/valsartan on cardiovascular death or heart failure hospitalization was not modified by eGFR, UACR (p interaction = 0.70 and 0.34, respectively), or by change in UACR (p interaction = 0.38).

CONCLUSIONS Compared with enalapril, sacubitril/valsartan led to a slower rate of decrease in the eGFR and improved cardiovascular outcomes, even in patients with chronic kidney disease, despite causing a modest increase in UACR. (J Am Coll Cardiol HF 2018;6:489–98) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CKD = chronic kidney disease

eGFR = estimated glomerular
filtration rate

HFrEF = heart failure with
reduced ejection fraction

HR = hazard ratio

RAAS = renin-angiotensin-
aldosterone system

IQR = interquartile range

UACR = urinary albumin/
creatinine ratio

Renin-angiotensin-aldosterone system (RAAS) inhibition is the cornerstone of treatment of patients with heart failure with reduced ejection fraction (HFrEF) (1). Furthermore, in patients without diabetes and nephropathy, RAAS inhibition reduces urinary albumin excretion and slows progression to end-stage renal disease (2,3). However, the use of RAAS inhibitors may be limited by an increase in serum creatinine, often resulting in treatment discontinuation (1). This move is especially disadvantageous in HFrEF patients with chronic kidney disease (CKD) who are at particularly high risk of adverse outcomes, and have the greatest absolute risk reduction with RAAS inhibition (4).

SEE PAGE 499

Recently, the combined angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan (formerly known as LCZ696), was shown to reduce the risk of death and hospital admission, compared with enalapril, in patients with HFrEF (5). However, sacubitril/valsartan did not reduce the pre-specified composite renal endpoint of a decrease in the estimated glomerular filtration rate (eGFR) of $\geq 50\%$, or by >30 ml/min/1.73 m² from baseline (and to <60 ml/min/1.73 m²), or progression to end-stage renal disease. Moreover, sacubitril/valsartan is known to increase the urinary albumin/creatinine ratio (UACR) in patients with heart failure and preserved ejection fraction (6). Given the importance of kidney function in patients with HFrEF, and the potential interactions between eGFR, UACR, and the effect of therapy in HFrEF, we conducted a comprehensive analysis of the PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial. We describe the effects of sacubitril/valsartan and enalapril on eGFR and UACR and the relationship between changes in eGFR and UACR and cardiovascular and renal outcomes, according to treatment assignment (5,7).

METHODS

The design and results of PARADIGM-HF have been reported elsewhere (5,7). The trial received local

ethics committee approval and all patients gave written, informed consent. Briefly, patients in New York Heart Association functional classes II to IV with an ejection fraction of $\leq 40\%$, and elevated levels of plasma B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide were enrolled. Patients were required to be treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker in a dose equivalent to at least enalapril 10 mg/day for at least 4 weeks before screening, along with a stable dose of beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist (if indicated). Exclusion criteria included symptomatic hypotension (or a systolic blood pressure <100 mm Hg at screening or <95 mm Hg at random treatment assignment), an eGFR of <30 ml/min/1.73 m² at screening or random treatment assignment (or a decrease $>25\%$ [amended to $>35\%$] between screening and random treatment assignment), and hyperkalemia (serum potassium >5.2 mmol/l at screening or >5.4 mmol/l at random treatment assignment).

On trial entry, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment was discontinued, and patients entered sequential single-blind run in phases (enalapril for 2 weeks, followed by sacubitril/valsartan for 4 to 6 weeks, with uptitration). Patients tolerating both drugs were then randomly assigned to double-blind treatment in a 1:1 ratio with either enalapril 10 mg or sacubitril/valsartan 97/103 mg twice daily.

ESTIMATION OF eGFR AND UACR. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (8) with creatinine traceable to isotope dilution mass spectrometry. The glomerular filtration rate was estimated at screening, random treatment assignment, at 2, 4, and 8 weeks, and 4 months after random treatment assignment; and every 4 months thereafter. By protocol, in a subset of patients, urinary albumin and creatinine concentrations, measured in spot urine samples (transferred at ambient temperature to a central laboratory for immediate analysis), were used to calculate the UACR. Urinary albumin was analyzed using the Roche Tinaquant chemiluminescent immunoassay. The UACR was determined at screening, random treatment assignment, and at 1 and 8 months after random

including PARADIGM-HF and lectures, advisory boards, and other meetings related to PARADIGM-HF and sacubitril/valsartan. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Damman and Gori contributed equally to this work and are joint first authors. Drs. Solomon and McMurray contributed equally to this work and are joint senior authors.

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treatment assignment. Normoalbuminuria was defined as a UACR of <3.5 mg/mmol, microalbuminuria as a UACR between 3.5 and 35 mg/mmol, and macroalbuminuria as a UACR of ≥ 35 mg/mmol.

PRE-SPECIFIED TRIAL OUTCOMES. The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure. In this analysis, we also report the individual components of the composite endpoint, and all-cause mortality. The pre-specified renal endpoint was time to first occurrence of any of: 1) a 50% decline in eGFR relative to baseline; 2) >30 ml/min/1.73 m² decline in eGFR relative to baseline to <60 ml/min/1.73 m²; or 3) reaching end-stage renal disease.

ADDITIONAL RENAL OUTCOMES. In post hoc analyses for the present study, we examined the more conventional renal composite outcome of either a 50% decrease in the eGFR from baseline or reaching end-stage renal disease, in addition to the pre-specified renal outcome described above.

The differential effect of sacubitril/valsartan on the primary outcome in the subgroups of patients with and without CKD (eGFR <60 ml/min/1.73 m²) at baseline was a pre-specified subgroup analysis. A pre-specified exploratory outcome was to test whether sacubitril/valsartan was superior to enalapril in slowing the rate of decrease in the eGFR.

STATISTICAL ANALYSIS. Data are reported as mean \pm SD when normally distributed, as median and interquartile ranges (IQRs) or 95% confidence intervals (CIs) when the distribution was skewed and as frequencies and percentages for categorical variables. The Student *t* test, Mann-Whitney *U*, or chi-square tests were used to determine significant differences between baseline variables for patients with and without CKD or albuminuria. Changes in eGFR and blood pressure over time was calculated by repeated analysis mixed effect modeling using unstructured covariance. Covariates that were used as fixed effects included the region where the patient was included in the trial, treatment, visit and treatment \times visit interaction, with random intercept and slope on individual patient level. Time was modeled linearly. We defined UACR worsening as a change in the UACR to a more advanced clinical category (normoalbuminuria/microalbuminuria/macroalbuminuria) at either month 1 or month 8. We also used the alternative definition of a 25% UACR increase (9). Quantile regression estimated the median UACR level at each available study visit, along with corresponding 95% CI. The relationship between the UACR at 1 month after random treatment assignment and the subsequent incidence of the primary endpoint was analyzed using Poisson regression, with log-transformed UACR as the exposure variable.

For the renal and clinical endpoints we used Cox proportional hazard models to estimate hazard ratios (HRs) with 95% CIs, and we tested for interactions between the treatment effect of sacubitril/valsartan on cardiovascular death or heart failure hospitalization and CKD or albuminuria status at screening or UACR worsening at follow-up. We also assessed the relationship between UACR values at 1 month after random treatment assignment and the risk of subsequent cardiovascular death or hospitalization for heart failure, according to treatment assignment. A 2-tailed *p* value of <0.05 was considered significant. Statistical analyses were performed using STATA (version 12.0, Stata Corp., College Station, Texas).

RESULTS

The mean age was 64 ± 11 years, 22% of participants were female, and the mean ejection fraction was $29 \pm 6\%$. At screening, the mean eGFR was 70 ± 20 ml/min/1.73 m² and a total of 2,745 patients (33%) had CKD. In the subset of 1,872 patients with a screening UACR measurement, the median UACR was 1.0 mg/mmol (IQR: 0.4 to 3.2 mg/mmol) and a total of 441 patients (24%) had microalbuminuria or macroalbuminuria. **Table 1** shows the other baseline characteristics of the study participants, including differences between patients with and without CKD, and those with and without microalbuminuria or macroalbuminuria at screening.

CHANGE IN BLOOD PRESSURE. During the run-in phase of the study, both systolic (-7.0 mm Hg; 95% CI: -7.5 to -6.6 mm Hg) and diastolic blood pressure (-4.2 mm Hg; 95% CI: -4.6 to -3.9 mm Hg) decreased in the entire study population. After 8 months of treatment, the decrease in systolic (-3.6 mm Hg; 95% CI: -4.1 to -3.1 mm Hg), and diastolic blood pressure (-2.5 mm Hg; 95% CI: -2.8 to -2.2 mm Hg) in patients assigned to enalapril was significantly smaller than the decrease in systolic (-6.7 mm Hg; 95% CI: -7.2 to -6.2 mm Hg), and diastolic blood pressure (-4.0 mm Hg; 95% CI: -4.3 to -3.6 mm Hg) in those assigned to sacubitril/valsartan (all interaction *p* < 0.001).

CHANGE IN eGFR. The eGFR decreased by 10.2 ml/min/1.73 m² (95% CI: 12.1 to 8.3 ml/min/1.73 m²) in patients assigned to enalapril between screening and end of follow-up and by 7.8 ml/min/1.73 m² (95% CI: 9.6 to 6.0 ml/min/1.73 m²) in those assigned to sacubitril/valsartan (**Figure 1A**, **Online Figure 1**). The rate of decrease in the eGFR was less with sacubitril/valsartan compared with enalapril: -1.61 ml/min/1.73 m²/year (95% CI: -1.77 to -1.44 ml/min/1.73 m²/year) compared with -2.04 ml/min/1.73 m²/year (95% CI: -2.21 to -1.88 ml/min/1.73 m²/year; *p* < 0.001). This finding was

TABLE 1 Baseline Characteristics According to CKD and Albuminuria Status at Screening

	No CKD (eGFR ≥ 60 ml/min/1.73 m ²)	CKD (eGFR < 60 ml/min/1.73 m ²)	p Value	No Albuminuria (UACR < 3.5 mg/mmol)	Albuminuria* (UACR ≥ 3.5 mg/mmol)	p Value
n (%)	5,654 (67)	2,745 (33)		1,431 (76)	441 (24)	
Age (yrs)	61 \pm 11	70 \pm 9	<0.001	67 \pm 10	68 \pm 10	0.040
Males (%)	79.4	75.7	<0.001	80.1	83.9	0.074
Ethnicity (%)			<0.001			0.099
White	62.6	73.1		95.5	93.4	
Black	6.2	2.8		2.8	4.3	
Asian	20.0	13.7		0.1	0.7	
Other	11.2	10.4		1.6	1.6	
SBP (mm Hg)	128 \pm 17	129 \pm 17	0.027	122 \pm 15	127 \pm 16	<0.001
DBP (mm Hg)	78 \pm 10	76 \pm 11	<0.001	73 \pm 10	75 \pm 11	0.008
Heart rate (beats/min)	73 \pm 12	71 \pm 12	<0.001	71 \pm 12	73 \pm 12	0.010
Weight (kg)	81 \pm 20	80 \pm 18	0.12	87 \pm 18	90 \pm 20	0.006
Creatinine (mg/dl) [†]	0.97 (0.85-1.09)	1.37 (1.26-1.54)	<0.001	1.07 (0.93-1.28)	1.14 (0.95-1.41)	<0.001
eGFR (ml/min/1.73 m ²)	81 \pm 14	49 \pm 8	<0.001	68 \pm 18	65 \pm 19	0.007
UACR (mg/mmol)	1.0 (0.5-3.2)	1.6 (0.5-5.1)	<0.001	0.8 (0.35-2.0)	7.55 (2.55-21.8)	<0.001
Ischemic etiology (%)	57	66	<0.001	64	66	0.28
LVEF (%)	29 \pm 6	30 \pm 6	0.077	30 \pm 6	30 \pm 6	0.73
BNP (pmol/l) [‡]	58 (33-108)	80 (45-154)	<0.001	60 (35-109)	97 (49-177)	<0.001
NT-proBNP (pmol/l) [§]	90 (53-163)	143 (82-256)	<0.001	99 (58-177)	146 (78-271)	<0.001
NYHA functional class I/II/III/IV	4.9/72.0/22.4/0.7	4.1/67.7/27.5/0.7	<0.001	3/73/23/1	1/71/27/1	0.056
KCCQ	78 (61-90)	74 (57-87)	<0.001	76 (61-89)	75 (54-87)	0.026
Medical history (%)						
Hypertension	67	78	<0.001	75	86	<0.001
Diabetes	32	39	<0.001	34	55	<0.001
Atrial fibrillation	33	44	<0.001	46	55	0.002
Prior HF hospitalization	63	63	0.97	59	63	0.097
Myocardial infarction	40	50	<0.001	49	49	0.81
Stroke	7	11	<0.001	10	12	0.19
Medical therapy (%)						
Prior ACE inhibitor	79	75	<0.001	82	75	0.002
Prior ARB	21	26	<0.001	19	26	0.001
Diuretic agents	78	85	<0.001	81	84	0.13
Digoxin	31	28	<0.001	22	23	0.58
Beta-blocker	93	92	0.12	96	94	0.25
MRA	58	52	<0.001	45	43	0.40
ICD (including CRT-D)	13	19	<0.001	29	25	0.10
CRT	5	10	<0.001	10	13	0.17

Values are n (%), mean \pm SD, %, or median (interquartile ranges), unless otherwise noted. *Microalbuminuria or macroalbuminuria. [†]For μ mol/l multiply by 88.4. [‡]To convert to pg/ml, multiply by 4.545. [§]To convert to pg/ml, multiply by 8.457.

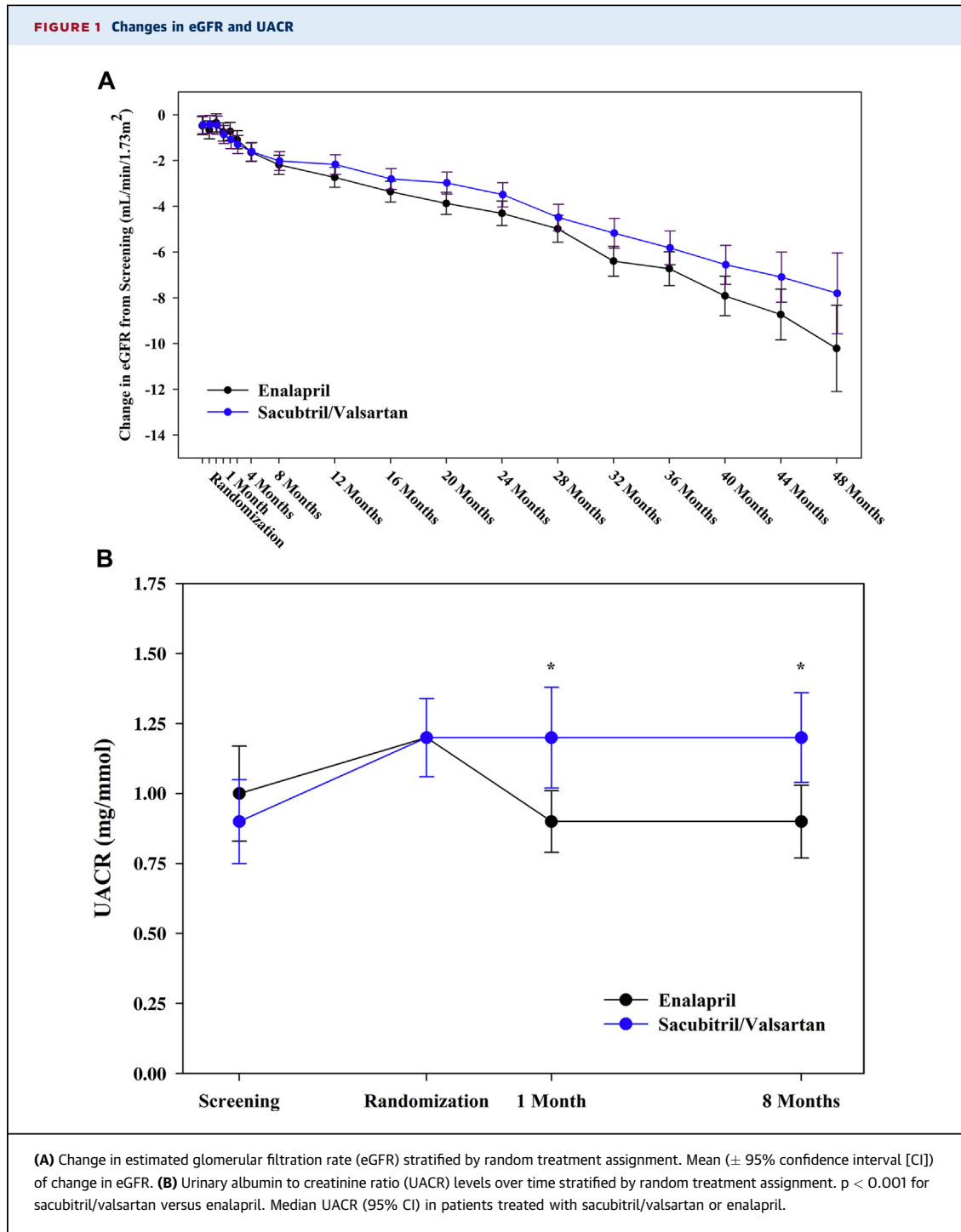
ACE = angiotensin-converting enzyme; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MRA = magnetic resonance angiography; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; UACR = urinary albumin creatinine ratio.

similar in patients with and without CKD at screening (p for interaction = 0.54) (Table 1, Online Table 1).

CREATININE SAFETY THRESHOLDS. In the trial overall, 188 patients in the enalapril group (4.5%) and 139 in the sacubitril/valsartan group (3.3%) had a serum creatinine of ≥ 2.5 mg/dl during follow-up (odds ratio: 0.73; 95% CI: 0.59 to 0.92; p = 0.007) and 83 (2.0%) and 63 (1.5%), respectively, had a serum creatinine of ≥ 3.0 mg/dl (odds ratio: 0.76; 95% CI: 0.55 to 1.06; p = 0.10). Among patients with CKD at screening

(n = 2,745), 251 (9.0%) had a serum creatinine of ≥ 2.5 mg/dl during follow-up and 101 (3.7%) had a serum creatinine of ≥ 3.0 mg/dl; these numbers were 76 (1.3%) and 45 (0.8%), respectively, in patients without CKD. The between-treatment differences were similar in patients with and without CKD at screening.

CHANGE IN UACR. The UACR increased in the period between screening and random treatment assignment, from a median of 1.0 mg/mmol (IQR:



0.4 to 3.2 mg/mmol) to 1.2 mg/mmol (IQR: 0.5 to 4.0 mg/mmol; $p < 0.001$). After random assignment, the UACR remained increased in patients assigned to sacubitril/valsartan, but returned to the screening level in patients assigned to enalapril (Figure 1B). The UACR was significantly higher at 1 and 8 months after treatment assignment in the sacubitril/

valsartan group compared with the enalapril group ($p < 0.001$ at both time points).

An increase in the UACR category was more common in patients assigned to sacubitril/valsartan (19%) compared with enalapril (16%; $p = 0.08$). Compared with enalapril, UACR worsening with sacubitril/valsartan was mainly driven by a shift from

TABLE 2 Effect of Sacubitril/Valsartan on Renal and Cardiovascular Endpoints Stratified by Baseline CKD Status

	All Patients (N = 8,399)				CKD (n = 2,745) (eGFR < 60 ml/min/1.73 m ²)			No CKD (n = 5,654) (eGFR ≥ 60 ml/min/1.73 m ²)			p Value Interaction
	Sacubitril/ Valsartan (n = 4,187)	Enalapril (n = 4,212)	HR (95% CI)	p Value	Sacubitril/ Valsartan (n = 1,333)	Enalapril (n = 1,412)	HR (95% CI)	Sacubitril/ Valsartan (n = 2,854)	Enalapril (n = 2,800)	HR (95% CI)	
Renal endpoints											
Prespecified composite renal outcome (first event)	94 (2.2)	108 (2.6)	0.86 (0.65-1.13)	0.29	22 (1.7)	36 (2.6)	0.64 (0.37-1.08)	72 (2.5)	72 (2.6)	0.97 (0.70-1.34)	0.19
≥50% decrease in eGFR*	32 (0.8)	42 (1.0)	0.75 (0.48-1.19)	0.23	12 (0.9)	17 (1.2)	0.73 (0.35-1.54)	20 (0.7)	25 (0.9)	0.77 (0.43-1.39)	0.92
>30 ml/min/1.73 m ² decrease in eGFR to <60 ml/min/1.73 m ² *	77 (1.8)	69 (1.6)	1.11 (0.80-1.53)	0.54	10 (0.8)	17 (1.2)	0.62 (0.28-1.35)	67 (2.4)	52 (1.9)	1.25 (0.87-1.79)	0.11
ESRD*	8 (0.2)	16 (0.4)	0.50 (0.21-1.16)	0.11	6 (0.5)	9 (0.6)	0.70 (0.25-1.95)	2 (0.1)	7 (0.3)	0.28 (0.06-1.32)	0.33
Post hoc composite renal outcome (≥50% reduction in eGFR or ESRD) (first event)	37 (0.9)	58 (1.4)	0.63 (0.42-0.95)	0.028	16 (1.2)	26 (1.8)	0.64 (0.34-1.19)	21 (0.7)	32 (1.1)	0.63 (0.36-1.10)	0.97
Cardiovascular endpoints											
CV death or HF hospitalization*	914 (22)	1,117 (27)	0.80 (0.73-0.87)	<0.001	358 (27)	465 (33)	0.79 (0.69-0.90)	556 (19)	652 (23)	0.81 (0.73-0.91)	0.70
CV death	558 (13)	693 (17)	0.80 (0.71-0.89)	<0.001	211 (16)	291 (21)	0.76 (0.63-0.90)	347 (12)	402 (14)	0.84 (0.72-0.96)	0.39
HF hospitalization	537 (13)	658 (16)	0.79 (0.71-0.89)	<0.001	223 (17)	288 (20)	0.79 (0.67-0.95)	314 (11)	370 (13)	0.81 (0.70-0.94)	0.83
All-cause mortality	711 (17)	835 (20)	0.84 (0.76-0.93)	<0.001	269 (20)	354 (25)	0.79 (0.68-0.93)	442 (15)	481 (17)	0.89 (0.78-1.01)	0.27

Values are n (%) unless otherwise noted. *First event contributing to composite.
CI = confidence interval; CV = cardiovascular; ESRD = end-stage renal disease (defined as start of permanent dialysis or renal transplantation); HF = heart failure; other abbreviations as in [Table 1](#).

normoalbuminuria to microalbuminuria at 1 month of follow-up, but this difference was not significant at 8 months after randomization ([Online Figure 2](#)). An increase of ≥25% in the UACR at 1 and 8 months was more common in the sacubitril/valsartan group (46% and 51% of patients, respectively), compared with the enalapril group (39% and 39%; $p = 0.004$ and $p < 0.001$, respectively).

RELATIONSHIP BETWEEN CHANGE IN UACR AND eGFR. In patients experiencing an increase of ≥25% in the UACR, sacubitril/valsartan was associated with a slower rate of decline in eGFR compared with enalapril, although there was no difference between treatments in patients experiencing no change or a decrease in UACR ([Online Table 1](#)).

RENAL OUTCOMES. The incidence of the pre-specified renal outcome did not differ significantly between patients with or without CKD at screening and did not differ between treatment groups, either overall or by baseline CKD status ([Table 2](#)). A post hoc analysis of a conventional renal composite outcome (end-stage renal disease or a ≥50% decrease in the eGFR from baseline) showed that this occurred significantly less frequently in patients assigned to sacubitril/valsartan overall (HR: 0.63; 95% CI: 0.42 to 0.95; $p = 0.028$), and in both

the CKD and no-CKD subgroups (p for interaction = 0.97).

The incidence of the pre-specified renal outcome was higher in patients with microalbuminuria or macroalbuminuria at screening, but did not differ between treatment groups, either overall or by baseline albuminuria status, although all these analyses were based on small numbers of events ([Table 3](#)).

Worsening of UACR category was associated with a higher risk of the pre-specified composite renal endpoint in the enalapril arm (HR: 4.21; 95% CI: 1.66 to 10.68), but not in the sacubitril/valsartan arm (HR: 0.50; 95% CI: 0.07 to 3.77; $p = 0.06$ for interaction). Similarly, a 25% increase in the UACR was associated with a higher risk of the renal composite endpoint in the enalapril arm (HR: 2.53; 95% CI: 1.09 to 5.84), but not in the sacubitril/valsartan arm (HR: 0.28; 95% CI: 0.08 to 1.01; $p = 0.005$ for interaction).

CARDIOVASCULAR ENDPOINTS. Among patients with CKD, 823 individuals (30%) experienced the primary outcome during follow-up, compared with 1,208 (21%) of those without CKD ([Table 2](#)). The relative risk reduction with sacubitril/valsartan, compared with enalapril, was similar in patients with

TABLE 3 Effect of Sacubitril/Valsartan on Renal and Cardiovascular Endpoints Stratified for Albuminuria

	Albuminuria (n = 441) (UACR ≥3.5 mg/mmol)			No Albuminuria (n = 1,431) (UACR <3.5 mg/mmol)			p Value Interaction
	Sacubitril/ Valsartan (n = 226)	Enalapril (n = 215)	HR (95% CI)	Sacubitril/ Valsartan (n = 734)	Enalapril (n = 697)	HR (95% CI)	
Renal endpoints							
Prespecified composite renal outcome (first event)	10 (4.4)	11 (5.1)	0.94 (0.40-2.21)	11 (1.5)	19 (2.7)	0.54 (0.26-1.14)	0.35
≥50% decrease in eGFR*	4 (1.8)	2 (0.9)	2.05 (0.38-11.2)	5 (0.7)	6 (0.9)	0.79 (0.24-2.59)	0.36
>30 ml/min/1.73 m ² decrease in eGFR to <60 ml/min/1.73 m ² *	8 (3.5)	8 (3.7)	1.02 (0.38-2.72)	9 (1.2)	15 (2.2)	0.56 (0.24-1.29)	0.36
ESRD*	1 (0.4)	2 (0.9)	0.56 (0.05-6.17)	1 (0.1)	2 (0.3)	0.47 (0.04-5.18)	0.93
Post hoc composite renal outcome (≥50% reduction in eGFR or ESRD) (first event)	4 (1.8)	4 (1.9)	1.05 (0.26-4.21)	5 (0.7)	8 (1.2)	0.59 (0.19-1.80)	0.52
Cardiovascular endpoints							
CV death or HF hospitalization*	68 (30)	70 (33)	0.94 (0.67-1.31)	133 (18)	158 (23)	0.77 (0.61-0.97)	0.34
CV death	37 (16)	33 (15)	1.12 (0.70-1.80)	74 (10)	79 (11)	0.88 (0.64-1.21)	0.39
HF hospitalization	45 (20)	49 (23)	0.88 (0.59-1.32)	78 (11)	105 (15)	0.68 (0.51-0.91)	0.30
All-cause mortality	53 (24)	46 (21)	1.15 (0.78-1.71)	112 (15)	103 (15)	1.02 (0.78-1.33)	0.61

Values are n (%) unless otherwise noted. *First event contributing to composite.
 Abbreviations as in Tables 1 and 2.

CKD (HR: 0.79; 95% CI: 0.69 to 0.90) and without CKD (HR: 0.81; 95% CI: 0.73 to 0.91; p for interaction = 0.70) (Figure 2A), but the absolute risk reduction was greater in patients with CKD (3.7 vs. 2.1 fewer patients per 100 patient-years). The benefit of sacubitril/valsartan over enalapril was consistent across the components of the primary endpoint, and for all-cause mortality, in patients with and without CKD, and for any stages of CKD, including stage 3b CKD (Online Table 2).

Among patients with microalbuminuria or macroalbuminuria at screening, 138 individuals (31%) experienced the primary outcome during follow-up, compared with 291 (20%) of those without with microalbuminuria or macroalbuminuria (Table 3). The HR for the primary endpoint with sacubitril/valsartan, compared with enalapril, in patients with microalbuminuria or macroalbuminuria was 0.94 (95% CI: 0.67 to 1.31) and was 0.81 (95% CI: 0.73 to 0.91) in those without microalbuminuria or macroalbuminuria (p for interaction = 0.71).

Higher UACR values at 30 days after random treatment assignment were associated with a higher incidence of the primary outcome in both treatment groups (Figure 2B). However, for any level of UACR at this time, the incidence of the primary outcome was lower in the sacubitril/valsartan group compared with the enalapril group. The benefits of sacubitril/valsartan therapy over enalapril were maintained

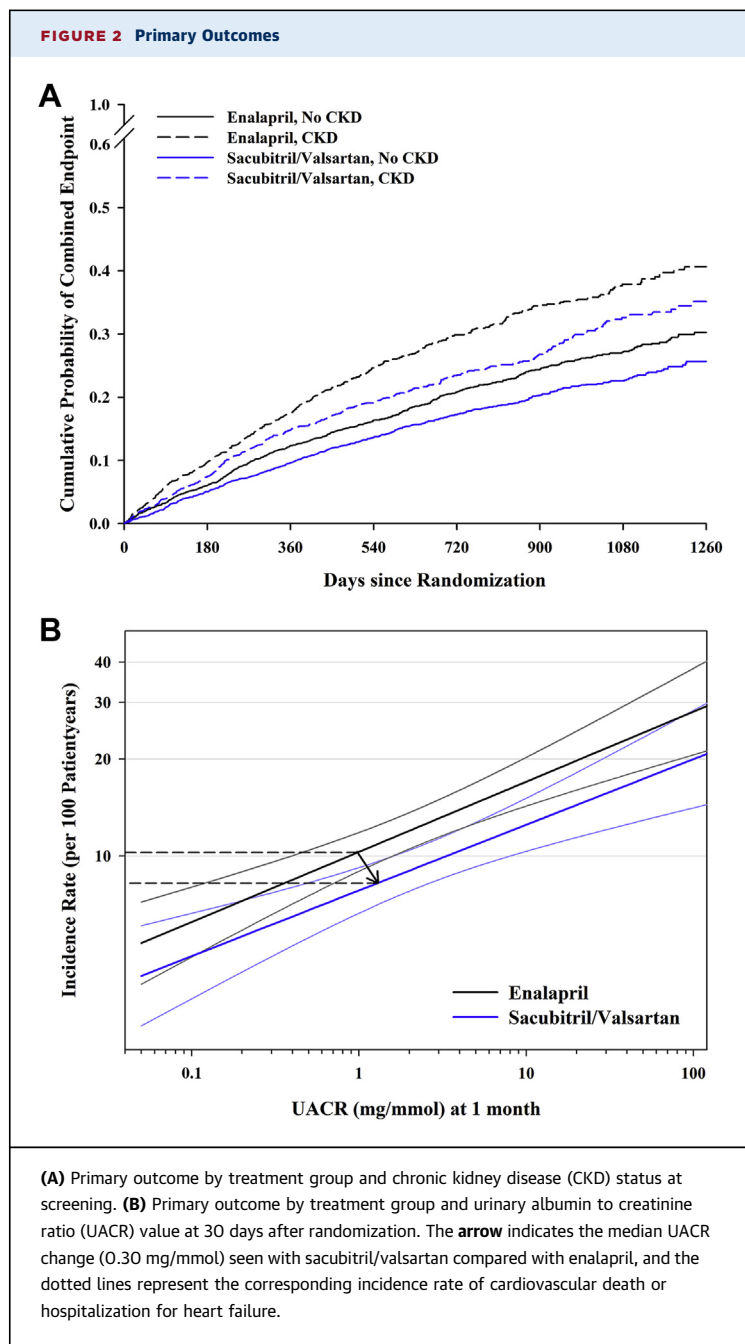
independently from UACR increase or decrease at 1 month after randomization as compared with pre-run-in (Online Figure 3).

STUDY DRUG TOLERABILITY

STUDY DRUG DISCONTINUATION. The study drug was discontinued for reasons other than death in 833 patients (19.8%) in the enalapril group and 746 patients (17.8%) in the sacubitril/valsartan group (HR: 0.89; 95% CI: 0.80 to 0.98; p = 0.016). The number of patients stopping study drug because of a renal adverse effect was 59 (1.4%) and 29 (0.7%), respectively (HR: 0.49; 95% CI: 0.31 to 0.76; p = 0.002).

In patients without CKD at screening, the study drug was discontinued for reasons other than death in 478 patients (17%) in the enalapril group and 422 patients (15%) in the sacubitril/valsartan group (HR: 0.84; 95% CI: 0.74 to 0.96; p = 0.010). The number of patients stopping the study drug in those with CKD was 355 (25%) and 324 (24%), respectively (HR: 0.97; 95% CI: 0.84 to 1.13; p = 0.72; p for interaction = 0.18).

In patients without CKD, the study drug was discontinued for renal reasons in 23 patients (0.82%) in the enalapril group and 14 patients (0.49%) in the sacubitril/valsartan group (HR: 0.59; 95% CI: 0.30 to 1.15; p = 0.12). The number of patients stopping the study drug for renal reasons in those with CKD was 36 (2.6%) and 15 (1.1%), respectively (HR: 0.43;



95% CI: 0.24 to 0.80; $p = 0.008$; p for interaction = 0.52).

DISCUSSION

We found that sacubitril/valsartan, compared with enalapril, slowed the rate of decrease in the eGFR and had favorable effects on cardiovascular and renal outcomes in HFrEF patients with and without

CKD and in those with and without microalbuminuria or macroalbuminuria. These renal and cardiovascular benefits were observed even though sacubitril/valsartan increased the UACR compared with enalapril.

It was notable in the present study that the beneficial effect of sacubitril/valsartan on eGFR occurred despite a decrease in arterial pressure, a hemodynamic change usually leading to a decrease in the eGFR when it occurs in the setting of RAAS blockade. Our findings are supported by a smaller study in patients with heart failure and preserved ejection fraction in which the decrease in the eGFR from baseline to 36 weeks was less in patients treated with sacubitril/valsartan than in those treated with valsartan (6). Similarly, in older studies in patients with HFrEF using the dual neprilysin angiotensin-converting enzyme inhibitor omapatrilat, the incidence of renal adverse events was lower than in those receiving enalapril or lisinopril (10,11). In those studies, the decrease in blood pressure was also greater in patients receiving a neprilysin inhibitor in addition to a RAAS blocker, compared with a RAAS blocker alone.

Early studies with neprilysin inhibitors (either given alone or combined with a RAAS blocker) reported mixed effects on renal hemodynamics, showing either no change or a decrease in renal perfusion (12-15). Neprilysin inhibition is associated with an increase in atrial natriuretic peptide levels and natriuresis, but also a decrease in intraglomerular pressures (12,16). The mechanisms of relative preservation of eGFR with sacubitril/valsartan are therefore not clear, and might also just reflect improvement in heart failure status.

We also looked at whether the slower rate of decrease in the eGFR with sacubitril/valsartan translated into decreases in end-stage renal disease or large decreases in eGFR. The pre-specified composite renal endpoint in PARADIGM-HF included 3 components: 1) a $\geq 50\%$ decrease in the eGFR from baseline; 2) a >30 ml/min/1.73 m² decrease in the eGFR from baseline (and to <60 ml/min/1.73 m²); or 3) reaching end-stage renal disease. The first and third components of this composite (which together represent a more conventional renal endpoint used frequently in large clinical trials) (2,17,18) were decreased by sacubitril/valsartan compared with enalapril, although the second was not. The favorable effects of sacubitril/valsartan, compared with enalapril, on eGFR and these renal outcomes were similar in patients with baseline CKD, compared with those without CKD,

which is potentially important therapeutically because conventional RAAS blockers are often withheld or withdrawn in patients with heart failure and renal dysfunction (19).

We also found that sacubitril/valsartan increased UACR compared with enalapril. Greater urinary albumin excretion has been associated with a more rapid worsening of renal function in patients with CKD (although it is not known whether this is also true in HFrEF) (20,21). However, the finding of an increase in the UACR with neprilysin inhibition is consistent with the effects of infused natriuretic peptides and earlier observations from a smaller study with sacubitril/valsartan in patients with heart failure and preserved ejection fraction (6,22). Of note, we observed the usual association between a higher UACR and deteriorating renal function in the enalapril-treated patients, in contradistinction to those in the sacubitril/valsartan group, who had more favorable renal outcomes. It is likely that the rapid onset and modest increase in UACR seen with sacubitril/valsartan, and that stabilizes after few weeks of treatment, reflects a distinct, and probably acute intrarenal hemodynamic effect, likely due to the actions of natriuretic peptides (and possibly other vasoactive substances catalyzed by neprilysin). The possibilities include one or more of an increase in glomerular endothelial permeability and hydraulic conductivity, a direct effect on mesangial cells, or alterations in renal arteriolar tone (22-26).

The effect observed with sacubitril/valsartan on renal outcomes, including UACR and eGFR was found in addition to the effects on cardiovascular outcome. The cardiovascular benefits of sacubitril/valsartan over enalapril were also consistent in patients with and without CKD and in those with and without microalbuminuria and macroalbuminuria.

STUDY LIMITATIONS. This post hoc study has several limitations. First, we examined several renal outcomes in addition to those pre-specified. Therefore, our analyses should be treated with caution and considered only as hypothesis generating. Our data were derived from a randomized, controlled trial and the patients enrolled were not fully representative of all patients with HFrEF because of the trial-specific inclusion and exclusion criteria. UACR measurements were obtained in only a subset of mainly white

participants and there were few renal outcomes among these patients.

CONCLUSIONS

Compared with enalapril, sacubitril/valsartan led to a slower rate of decrease in the eGFR and improved renal and cardiovascular outcomes, even in patients with CKD, despite causing a modest increase in UACR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Despite often causing a decrease in the eGFR, renin-angiotensin system inhibitors improve cardiovascular outcomes in patients with HFrEF. In the present study, adding a neprilysin inhibitor to a RAAS blocker improved cardiovascular outcomes further. The relative risk reduction in cardiovascular events was similar in patients with and without CKD or albuminuria at baseline and the renal safety profile of sacubitril/valsartan was more favorable than that of enalapril. Moreover, eGFR decreased less in patients receiving neprilysin inhibition in addition to a RAAS blocker, compared with a RAAS blocker alone. Sacubitril/valsartan was associated with a modest increase in the UACR, which stabilized over time and did not modify the beneficial effect of treatment. Whereas an increase in UACR was associated with worse renal outcomes in patients treated with enalapril, this was not the case with sacubitril/valsartan. These findings highlight that, despite causing a small increase in the UACR, sacubitril/valsartan had a favorable renal and cardiovascular safety profile, and was associated with significant reduction of cardiovascular events, in patients with and without CKD or albuminuria.

TRANSLATIONAL OUTLOOK: The pathophysiologic mechanisms underlying these potentially clinically important benefits of sacubitril/valsartan on renal function, despite causing a small increase in UACR remain uncertain. The renal mechanisms of action of neprilysin inhibition in heart failure (and possibly other conditions) merit further investigation.

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