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ORIGINAL INVESTIGATIONS

Variation in Renal Function Following Transition to Sacubitril/Valsartan in Patients With Heart Failure

Safia Chatur, MD,[a] Brian L. Claggett, PhD,[a] Finnian R. McCausland, MD,[b] Jean Rouleau, MD,[c] Michael R. Zile, MD,[d] Milton Packer, MD,[e] Marc A. Pfeffer, MD, PhD,[a] Martin Lefkowitz, MD,[f] John J.V. McMurray, MD,[g] Scott D. Solomon, MD,[a] Muthiah Vaduganathan, MD, MPH[a]

ABSTRACT

BACKGROUND Some patients with heart failure may experience transient changes in kidney function upon transition to sacubitril/valsartan. Whether such changes portend adverse outcomes or influence long-term treatment benefits with sacubitril/valsartan continuation is unknown.

OBJECTIVES This investigation aimed to evaluate the association between the occurrence of moderate estimated glomerular filtration rate (eGFR) decline (>15%) after initial exposure to sacubitril/valsartan and subsequent cardiovascular outcomes and its treatment benefits in PARADIGM-HF and PARAGON-HF.

METHODS In sequential run-in phases, patients were titrated to enalapril 10 mg twice daily and then sacubitril/valsartan 97 mg/103 mg twice daily (in PARADIGM-HF) or valsartan 80 mg twice daily and then sacubitril/valsartan 49 mg/51 mg twice daily (in PARAGON-HF).

RESULTS Among randomized participants, 11% in PARADIGM-HF and 10% in PARAGON-HF experienced eGFR decline (>15%) during sacubitril/valsartan run-in. eGFR partially recovered (from nadir to postrandomization week 16) regardless of sacubitril/valsartan continuation or switch to renin-angiotensin system inhibitor (RASi) postrandomization. Initial eGFR decline was not consistently associated with clinical outcomes in either trial. Treatment benefits of sacubitril/valsartan vs RASi on primary outcomes were similar irrespective of run-in eGFR decline in PARADIGM-HF (eGFR decline, HR: 0.69; 95% CI: 0.53-0.90; and no eGFR decline, HR: 0.80; 95% CI: 0.73-0.88; $P_{interaction} = 0.32$) and PARAGON-HF (eGFR decline, rate ratio [RR]: 0.84; 95% CI: 0.52-1.36 and no eGFR decline, RR: 0.87; 95% CI: 0.75-1.02, $P_{interaction} = 0.92$). The treatment effect of sacubitril/valsartan remained consistent across a range of eGFR declines.

CONCLUSIONS Moderate eGFR decline when transitioning from RASi to sacubitril/valsartan is not consistently associated with adverse outcomes, and its long-term benefits are retained in heart failure across a broad range of eGFR declines. Early eGFR changes should not deter continuation of sacubitril/valsartan or stall uptitration. (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF]; NCT01920711; Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitors with Angiotensin-Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF]; NCT01035255) (J Am Coll Cardiol 2023;81:1443-1455) © 2023 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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From the [a]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [b]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [c]Institut de Cardiologie de Montréal, Université de Montréal, Montréal, Québec, Canada; [d]Medical University of South Carolina and the Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, South Carolina, USA; [e]Baylor University Medical Center, Dallas, Texas, USA; [f]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; and the [g]BHF Cardiovascular Research Centre, University of Glasgow, United Kingdom.

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

NYHA = New York Heart Association

RASi = renin-angiotensin system inhibitor

SGLT2i = sodium-glucose cotransporter-2 inhibitor

Although renal impairment is an important adverse prognostic indicator in patients with heart failure (HF),[1] many therapies used in the management of HF, such as renin-angiotensin system inhibitors (RASis), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2is) may result in early declines in estimated glomerular filtration rate (eGFR). Such declines are thought to reflect intraglomerular hemodynamic alterations[2,3] and mechanisms of tubuloglomerular feedback[4] as opposed to intrinsic kidney injury. Moreover, although some of these drugs have demonstrated renal protective effects, renal dysfunction remains a common clinical concern and may prompt premature discontinuation of the drug.[5] Understanding the heterogeneity in response to declines in renal function early after starting HF therapies is therefore important.

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Sacubitril/valsartan significantly reduced the risk of cardiovascular death or HF hospitalization in PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitors with Angiotensin-Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure)[6] and led to a modest but nonsignificant reduction in the composite of total HF hospitalizations and cardiovascular (CV) death in PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction).[7] Furthermore, sacubitril/valsartan attenuated the rate of eGFR decline and resulted in improved kidney outcomes in both HF with reduced ejection fraction (HFrEF)[8] and HF with preserved ejection fraction (HFpEF).[9] Expert consensus statements suggest that moderate declines in eGFR of up to 15% to 20%[2] on initiation of sacubitril/valsartan may be expected. However, there is limited evidence on the prognostic significance of the early eGFR decline on transition from RASi to sacubitril/valsartan and its influence on the long-term treatment benefits of sacubitril/valsartan. How these effects may differ in patients according to HF phenotype (HFrEF vs HFpEF) is also unknown.

In this post hoc analysis of the PARADIGM-HF and PARAGON-HF trials, we describe the frequency and predictors of early declines in eGFR on transition from RASi to sacubitril/valsartan treatment as well as the prognostic significance and relative treatment benefits according to its occurrence in patients with HFrEF and HFpEF.

METHODS

STUDY DESIGN. The trial designs and results of both PARADIGM-HF and PARAGON-HF have been previously reported.[6,7] Both were double-blind, active-controlled randomized trials that compared sacubitril/valsartan vs enalapril (PARADIGM-HF) or valsartan (PARAGON-HF). PARADIGM-HF enrolled patients ≥18 years with left ventricular ejection fraction ≤40% and elevated natriuretic peptides or hospitalization for HF within 12 months. PARAGON-HF included patients ≥50 years of age with symptomatic HF (New York Heart Association [NYHA] functional class II-IV), preserved ejection fraction (left ventricular ejection fraction ≥45%), evidence of structural heart disease, elevated natriuretic peptides, and at least intermittent use of diuretics. Exclusion criteria were similar between trials and included symptomatic hypotension or systolic blood pressure (SBP) <100 mm Hg, eGFR <30 mL/min/1.73 m^2, or serum potassium >5.2 mmol/L assessed at the time of screening. For each trial, ethics committees at each study site approved the study protocol, and written informed consent was provided by study participants.

RUN-IN EPOCH. The run-in design and flow have been previously described for both PARADIGM-HF[10] and PARAGON-HF[11] and are summarized in **Figure 1**. In brief, patients were randomized following sequential run-in phases during which they were first titrated to 10 mg twice daily enalapril and then 97 mg/103 mg twice daily sacubitril/valsartan (PARADIGM-HF) or 80 mg twice daily valsartan and then 49 mg/51 mg twice daily sacubitril/valsartan (PARAGON-HF). Patients were excluded during the run-in phase if eGFR declined to <30 mL/min/1.73 m^2 (PARADIGM-HF) or <25 mL/min/1.73 m^2 (PARAGON-HF) or by >35% between screening and randomization.

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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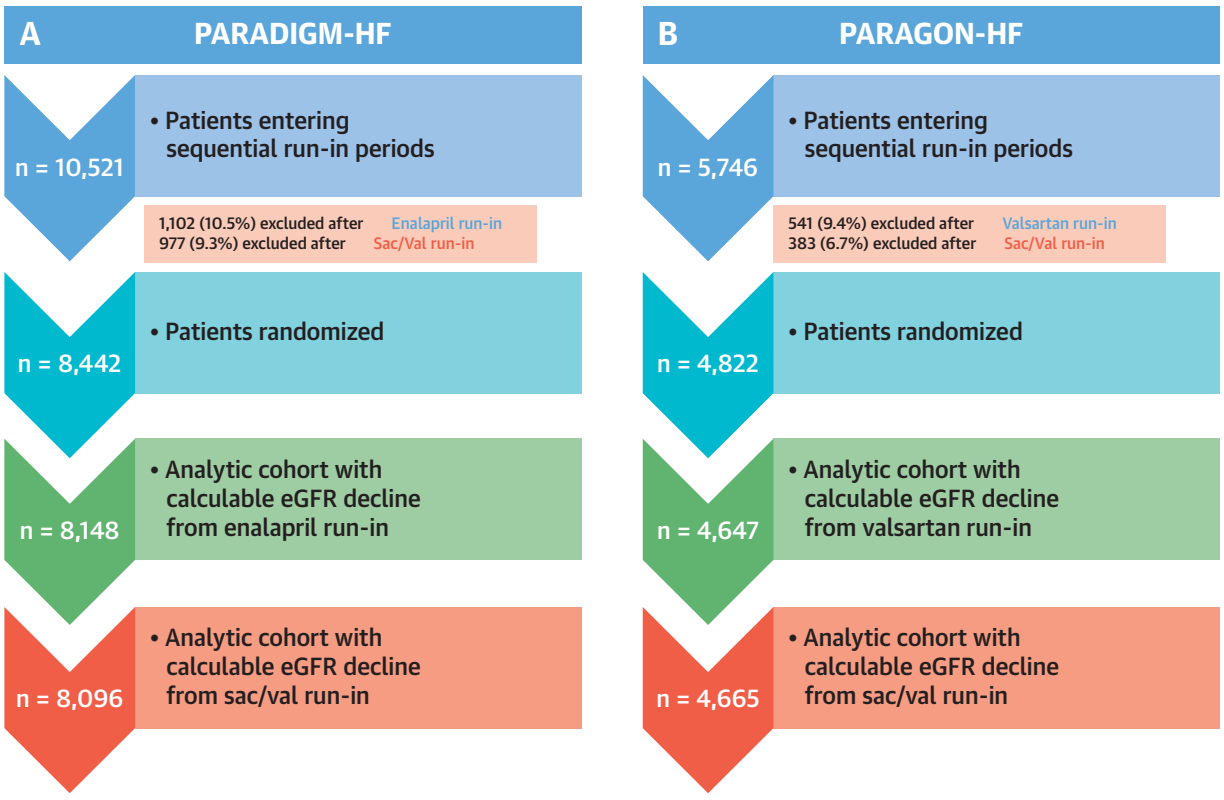
FIGURE 1 Flow Diagram and Patient Selection



Presented here are the total patients entering sequential run-in periods, total number of patients randomized, and the analytic cohorts for the renin angiotensin system inhibitor (RASi) run-in and for the sacubitril/valsartan (sac/val) run-in periods in PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitors with Angiotensin-Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure) **(A)** and PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) **(B)**. The RASi comparator was enalapril in PARADIGM-HF and valsartan in PARAGON-HF. eGFR = estimated glomerular filtration rate.

CLINICAL ENDPOINTS. The primary endpoint was the composite of cardiovascular death or first HF hospitalization in PARADIGM-HF and total (first and recurrent) HF hospitalizations and death from CV causes in PARAGON-HF. Time to death from any cause was a secondary outcome in both trials. Safety outcomes included the occurrence of hypotension (SBP <90 mm Hg, PARADIGM-HF; <100 mm Hg, PARAGON-HF), elevations in serum creatinine (≥2.0 mg/dL, ≥2.5 mg/dL, and ≥3.0 mg/dL), hyperkalemia, and drug discontinuation.

STATISTICAL ANALYSIS

eGFR decline was defined as a deterioration of >15% occurring during the RASi or sacubitril-valsartan run-in periods, which would be beyond expectations based on expert consensus.[2] The eGFR decline during the RASi period was calculated by comparing the eGFR at screening with the eGFR obtained at the time of the study visit corresponding to the end of the RASi run-in period. The eGFR decline during the sacubitril/valsartan run-in period was calculated by comparing eGFR at the beginning of the sacubitril/valsartan run-in period with the eGFR obtained at the study visit immediately following initial sacubitril/valsartan run-in. All patients with calculable eGFR declines were included in this analysis. Baseline patient characteristics were compared according to the occurrence of sacubitril/valsartan run-in eGFR decline. Data are reported as mean ± SD, median (IQR) for skewed distributions, and frequency (%) for categorical variables. Student's *t*-tests and chi-square tests were used when appropriate.

Kidney function was evaluated during the run-in period; at randomization; and 2 weeks, 4 weeks,

8 weeks, and 16 weeks (PARADIGM-HF) and 4 weeks and 16 weeks (PARAGON-HF), followed by 4-month intervals thereafter. eGFR was calculated by the Modification in Diet and Renal Disease (MDRD) formula. Temporal changes in eGFR were analyzed from sacubitril/valsartan run-in through trial follow-up to assess recovery in kidney function. Median percent recovery in eGFR from nadir decline to post-randomization week 16 was calculated.

Logistic regression models were used to identify predictors of the occurrence of a run-in eGFR decline with sacubitril/valsartan in the entire screened population. All baseline patient characteristics were considered in univariable models. Covariates that were significant in univariable models at a $P < 0.10$ or deemed clinically relevant were then entered into multivariable models. In PARADIGM-HF, covariates included age, sex, race, SBP, heart rate, randomization eGFR, EF, NYHA class, history of hypertension, diabetes, atrial fibrillation, previous history of HF hospitalization, previous myocardial infarction (MI), N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), and background HF medical therapies. In PARAGON-HF, covariates included sex, age, race, SBP, eGFR, EF, NYHA functional class, history of hypertension, diabetes, previous HF hospitalization, and background HF medical therapies.

We assessed the association between the occurrence of both eGFR decline with RASi (enalapril, PARADIGM-HF or valsartan, PARAGON-HF) and eGFR decline on transition to sacubitril/valsartan and subsequent cardiovascular outcomes as well as the treatment effects of sacubitril/valsartan. Run-in changes in eGFR were assessed categorically (>15% decline) and continuously using restricted cubic spline models. Time-to-first events analyses were performed using Cox proportional hazards models. Proportional hazards assumptions were assessed using Schoenfeld residuals. Recurrent events were analyzed using semiparametric proportional rates methods of Lin et al.[12] All models assessing the associations between eGFR decline and subsequent cardiovascular outcomes were adjusted for clinically relevant covariates: randomization eGFR, age, sex, NT-proBNP, NYHA class, EF, SBP, previous hospitalization for HF, ischemic cardiomyopathy, and diabetes. The association between run-in eGFR decline and safety outcomes was analyzed using logistic regression.

All analyses were carried out using STATA version 17 (LLC StataCorp). A P value of <0.05 was considered to be statistically significant.

RESULTS

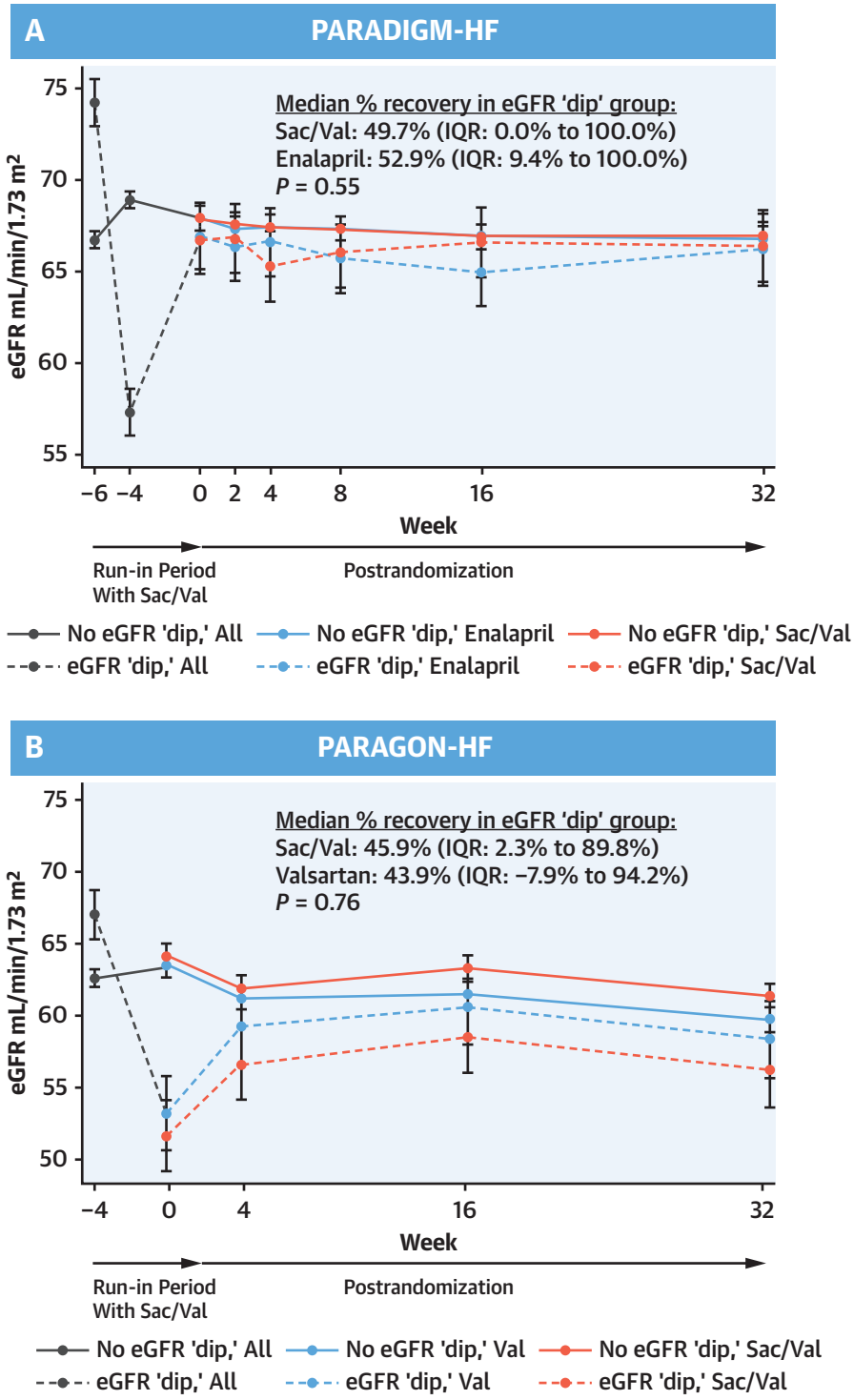
Study discontinuations during sequential run-in periods have previously been described.[10,11] Few participants were excluded because of substantial changes in kidney function during sequential run-in phases (n = 354 [3%] in PARADIGM-HF and n = 153 [3%] in PARAGON-HF). Among participants who proceeded to randomization, the median (IQR) eGFR change for the entire sequential run-in period (RASi followed by sacubitril/valsartan) was −0.6 mL/min/1.73 m^2 (IQR: −6.9 to 5.7 mL/min/1.73 m^2) in PARADIGM-HF and −1.5 mL/min/1.73 m^2 (IQR: −6.8 to 4.1 mL/min/1.73 m^2) in PARAGON-HF.

EARLY eGFR DECLINE WITH RASi. Participants were initially exposed to RASi run-in at target doses of enalapril (in PARADIGM-HF) and half-target doses of valsartan (in PARAGON-HF). The median eGFR change was −0.6 mL/min/1.73 m^2 (IQR: −6.2 to 5.1 mL/min/1.73 m^2) during the enalapril run-in period in PARADIGM HF and −1.3 mL/min/1.73 m^2 (IQR: −5.9 to 3.2 mL/min/1.73 m^2) during the valsartan run-in period in PARAGON-HF. RASi run-in eGFR decline was calculable in 8,148 (97%) in PARADIGM-HF and 4,647 (97%) in PARAGON-HF (Figure 1). In PARADIGM-HF, 49% of patients did not experience eGFR decline following enalapril run-in, 38% experienced a decline of ≤15%, whereas 13% experienced an eGFR decline of >15%. In PARAGON-HF, 48% of patients did not experience eGFR decline following valsartan run-in, 39% experienced declines of ≤15%, whereas 13% of patients experienced eGFR declines of >15%.

FREQUENCY OF EARLY eGFR DECLINES WITH SACUBITRIL/VALSARTAN TRANSITION. Participants were subsequently exposed to sacubitril/valsartan run-in at target dose (in PARADIGM-HF) and half-target dose (in PARAGON-HF). The median (IQR) eGFR change during the sacubitril/valsartan run-in period was 0.0 mL/min/1.73 m^2 (IQR: −5.5 to 5.2 mL/min/1.73 m^2) in PARADIGM-HF and −0.6 mL/min/1.73 m^2 (IQR: −5.1 to 3.8 mL/min/1.73 m^2) in PARAGON-HF. Sacubitril/valsartan run-in eGFR decline was calculable in 8,096 (96%) patients in PARADIGM-HF and 4,665 (97%) patients in PARAGON-HF (Figure 1). In PARADIGM-HF, 52% of patients experienced no eGFR decline, 37% experienced an eGFR decline of ≤15%, and 11% experienced an eGFR decline of >15%. In PARAGON-HF, 48% of patients experienced no eGFR decline, 42% experienced declines of ≤15%, and 10% experienced declines of >15%.

Regardless of the occurrence of eGFR decline, no significant net differences in diuretic dose

FIGURE 2 **Average eGFR Over Time According to eGFR Decline and Treatment**



Temporal changes in eGFR were analyzed from sacubitril/valsartan run-in through trial follow-up to assess recovery in kidney function in PARADIGM-HF **(A)** and PARAGON-HF **(B)**. Median percent recovery in eGFR from nadir decline to postrandomization week 16 is presented in patients according to the occurrence of sacubitril/valsartan run-in eGFR decline. eGFR was observed to partially recover (from nadir to postrandomization week 16) regardless of sacubitril/valsartan continuation or switch to renin angiotensin system inhibitor (RASi) postrandomization. 'All' = all study patients entering the run-in period; 'dip' = eGFR decline following initiation of sacubitril/valsartan; other abbreviations as in Figure 1.

TABLE 1 Association Between Sac/Val Run-In eGFR Decline and Subsequent Outcomes in PARADIGM-HF

	No eGFR Decline[a] (n = 7,177)	eGFR Decline[a] (n = 919)	*P* Value
First HFH or CV death			
Event rate (per 100 person-years)	11.75 (11.2-12.33)	11.93 (10.44-13.67)	
HR	1.01 (0.87-1.16)		0.94
Adjusted HR	0.98 (0.85-1.13)		0.78
First HFH			
Event rate (per 100 person-years)	6.91 (6.50-7.36)	6.72 (5.63-8.06)	
HR	0.96 (0.80-1.15)		0.67
Adjusted HR	0.95 (0.78-1.15)		0.59
CV death			
Event rate (per 100 person-years)	6.74 (6.35-7.16)	7.00 (5.95-8.28)	
HR	1.04 (0.87-1.24)		0.67
Adjusted HR	0.98 (0.82-1.18)		0.86
All-cause mortality			
Event rate (per 100 person-years)	8.28 (7.85-8.74)	8.64 (7.46-10.05)	
HR	1.05 (0.89-1.23)		0.57
Adjusted HR	1.01 (0.85-1.18)		0.95

Time-to-first events analyses were performed using Cox proportional hazards models. All models were adjusted for clinically relevant covariates: randomization eGFR, age, sex, N terminal pro-hormone of B-type natriuretic peptide, New York Heart Association functional class, ejection fraction, systolic blood pressure, previous heart failure hospitalization, ischemic cardiomyopathy, and diabetes. [a]96% of patients with calculable eGFR decline.

CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HFH = heart failure hospitalization.

(furosemide dose equivalents) were observed in either PARADIGM-HF (net change −0.35% [−2.2 to 1.5]; $P = 0.71$) or PARAGON-HF (net change +0.88% [−1.8% to 3.6%]; $P = 0.52$) during the sacubitril/valsartan run-in periods.

Of those patients that experienced >15% eGFR decline during the RASi run-in period, only 46 patients in PARADIGM-HF and 18 patients in PARAGON-HF also experienced >15% eGFR decline during the subsequent sacubitril/valsartan run-in period.

RECOVERY OF eGFR AFTER INITIAL DIP FOLLOWING SACUBITRIL/VALSARTAN INITIATION. Among patients remaining in the study following sacubitril/valsartan run-in, a partial recovery in eGFR was observed regardless of whether patients continued on sacubitril/valsartan or were switched to RASi after randomization (**Figure 2**). The median (IQR) percent recovery (from nadir to postrandomization week 16) among patients experiencing run-in eGFR decline and subsequently randomized to sacubitril/valsartan vs RASi was 49.7% (0.0% to 100.0%) vs 52.9% (IQR: 9.4% to 100.0%) ($P = 0.55$) in PARADIGM-HF and 45.9% (IQR: 2.3% to 89.8%) vs 43.9% (IQR: −7.9% to 94.2%) ($P = 0.76$) in PARAGON-HF (**Figure 2**).

BASELINE CHARACTERISTICS AND PREDICTORS OF eGFR DECLINE. In both trials, patients experiencing sacubitril/valsartan run-in eGFR decline were more often women and patients who experienced more severe symptoms of HF. In PARADIGM-HF, Black and Asian patients less frequently experienced run-in eGFR decline. In PARAGON-HF, those patients experiencing run-in eGFR decline had a higher ejection fraction and lower baseline SBPs. Kidney function at screening was similar between groups in both trials (Supplemental Table 1). In multivariable models, more severe HF functional class remained significantly associated with the occurrence of eGFR decline in both trials. In addition, SBP, history of hypertension, and female sex were identified as predictors of eGFR decline in PARAGON-HF (Supplemental Table 2).

ASSOCIATION OF RASi eGFR DECLINE WITH SUBSEQUENT LONG-TERM CLINICAL OUTCOMES. Median follow-up in PARADIGM-HF was 27 months, and in PARAGON-HF, median follow-up was 35 months. eGFR decline, when receiving enalapril in PARADIGM-HF or valsartan in PARAGON-HF, was not consistently associated with risk of subsequent outcomes (Supplemental Table 3).

RELATIVE BENEFITS OF SACUBITRIL/VALSARTAN ACCORDING TO THE OCCURRENCE OF PRERANDOMIZATION eGFR DECLINE DURING THE RASi RUN-IN PERIOD. The treatment effect of sacubitril/valsartan relative to RASi on clinical outcomes was consistent regardless of whether or not patients experienced eGFR decline during the RASi run-in period (Supplemental Table 4).

ASSOCIATION OF SACUBITRIL/VALSARTAN eGFR DECLINE WITH SUBSEQUENT LONG-TERM CLINICAL OUTCOMES. eGFR decline when receiving sacubitril/valsartan was not significantly associated with the development of the primary composite outcome in PARADIGM-HF (HR: 1.01; 95% CI: 0.87-1.16; $P = 0.94$) (**Table 1**). In PARAGON-HF, event rates of the primary composite outcome were numerically higher although not statistically significant (rate ratio [RR]: 1.26; 95% CI: 0.98-1.61; $P = 0.07$) (**Table 2**). Adjustment for clinically relevant covariates did not meaningfully alter these associations. When sacubitril/valsartan run-in eGFR decline was analyzed as a continuous variable, there was no clear linear association between a wide range of eGFR changes and the incidence of the primary composite (time to first events) in PARADIGM-HF and PARAGON-HF (**Figure 3**).

RELATIVE BENEFITS OF SACUBITRIL/VALSARTAN ACCORDING TO THE OCCURRENCE OF PRERANDOMIZATION eGFR DECLINE DURING THE SACUBITRIL/VALSARTAN RUN-IN PERIOD. The treatment effect of sacubitril/valsartan relative to RASi on the primary composite outcome was consistent regardless of

whether or not patients experienced eGFR decline in both PARADIGM-HF (eGFR decline, HR: 0.69; 95% CI: 0.53-0.90 and no eGFR decline, HR: 0.80; 95% CI: 0.73-0.88; $P_{interaction} = 0.32$) and PARAGON-HF (eGFR decline, RR: 0.84; 95%: 0.52-1.36 and no eGFR decline, RR: 0.87; 95% CI: 0.75-1.02; $P_{interaction} = 0.92$) (Tables 3 and 4). The treatment benefit of sacubitril/valsartan vs RASi remained consistent across a range of run-in eGFR declines when analyzed as a continuous variable (Central Illustration).

ADVERSE EVENTS IN FOLLOW-UP. In both PARADIGM-HF and PARAGON-HF, the treatment effect on safety outcomes and rates of drug discontinuation were similar whether or not patients experienced eGFR decline during the sacubitril/valsartan run-in period (Supplemental Table 5).

SENSITIVITY ANALYSES. In analyses of association between early eGFR decline and subsequent outcomes, as well as the relative treatment benefits of sacubitril/valsartan, some statistically significant violations of proportional hazards assumption were detected. To address these issues, alternative models were constructed stratifying for covariates with nonproportional effects and partitioning follow-up time. These alternative models upheld the proportional hazards assumption, and overall findings did not qualitatively change (Supplemental Tables 6 to 9).

TABLE 2 Association Between Sac/Val Run-In eGFR Decline and Subsequent Outcomes in PARAGON-HF

	No eGFR Decline[a] (n = 4,204)	eGFR Decline[a] (n = 461)	*P* Value
Total HFH + CV death			
Event rate (per 100 person-years)	13.33 (12.24-14.30)	17.54 (13.88-22.49)	
RR	1.26 (0.98-1.61)		0.07
Adjusted RR	1.28 (0.99-1.65)		0.06
Total HFH			
Event rate (per 100 person-years)	10.36 (9.50-11.34)	13.66 (10.36-18.38)	
RR	1.23 (0.93-1.65)		0.15
Adjusted RR	1.27 (0.95-1.71)		0.11
First HFH + CV death			
Event rate (per 100 person-years)	8.28 (7.77-8.85)	10.79 (9.05-12.95)	
HR	1.26 (1.05-1.52)		0.015
Adjusted HR	1.24 (1.02-1.52)		0.032
First HFH			
Event rate (per 100 person-years)	6.48 (6.03-6.98)	6.69 (10.09)	
HR	1.21 (0.97-1.50)		0.08
Adjusted HR	1.19 (0.95-1.50)		0.13
CV death			
Event rate (per 100 person-years)	2.85 (2.57-3.17)	3.88 (2.96-5.17)	
HR	1.26 (1.01-1.83)		0.045
Adjusted HR	1.30 (0.96-1.77)		0.09
All-cause mortality			
Event rate (per 100 person-years)	4.79 (4.43-5.20)	6.05 (4.88-7.58)	
HR	1.27 (1.00-1.60)		0.05
Adjusted HR	1.22(0.95-1.55)		0.12

Time-to-first events analyses were performed using Cox proportional hazards models. Recurrent events were analyzed using semi-parametric proportional rates methods of Lin et al.[12] All models were adjusted for clinically relevant covariates: randomization eGFR, age, sex, N terminal pro-hormone of B-type natriuretic peptide, New York Heart Association functional class, ejection fraction, systolic blood pressure, previous heart failure hospitalization, ischemic cardiomyopathy, and diabetes. [a]97% with calculable eGFR decline.

Abbreviations as in Table 1.

DISCUSSION

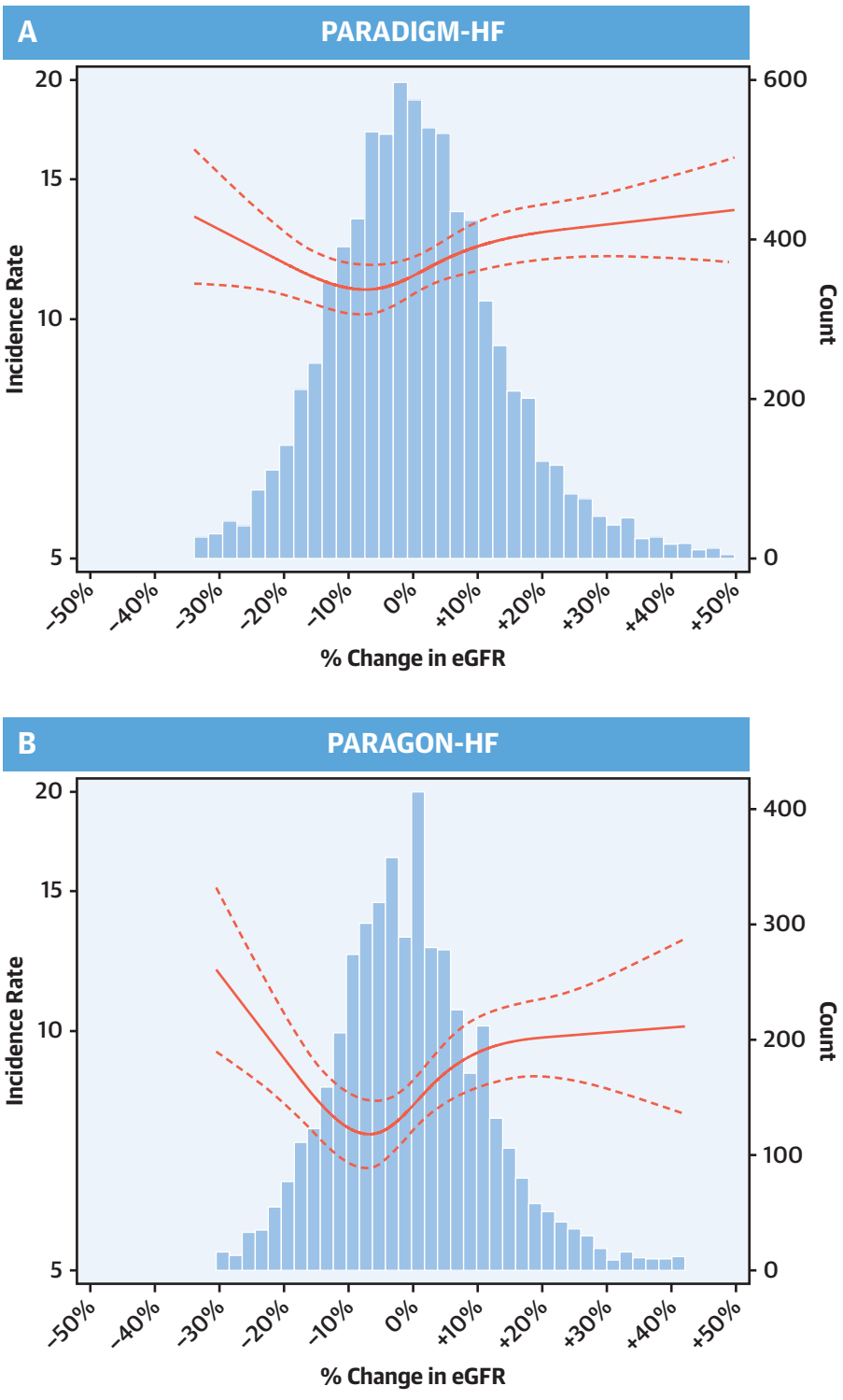
In this post hoc analysis of both the PARADIGM-HF and PARAGON-HF trials, we found that eGFR decline on transition from treatment with RASi to sacubitril/valsartan was variable but usually small and partially recoverable in most patients. Moderate eGFR decline with transition to sacubitril/valsartan was not consistently associated with subsequent adverse outcomes. The treatment benefit and safety profile of sacubitril/valsartan was consistent regardless of the occurrence of initial eGFR decline. Taken together, these data suggest that early moderate reductions in eGFR should not deter sacubitril/valsartan continuation or uptitration.

Most patients in these 2 large HF trial experiences had little to no change in eGFR upon initial exposure to sacubitril/valsartan. Moderate early eGFR declines occurred in only 1 in 10 participants. Compared with patients with HFrEF, eGFR declines on initiation of sacubitril/valsartan occurred slightly more frequently in patients with HFpEF but were less severe when they did occur. This may reflect slightly different dosing regimens in the run-in period of both trials. Importantly, eGFR decline was at least partially recoverable in most patients and did not appear hampered by continuation or uptitration of sacubitril/valsartan. Recovery occurred quickly—within weeks—in patients with HFrEF and HFpEF. These data help to inform the timeline over which recovery may be expected.

The exact mechanisms underlying the initial decline in eGFR on sacubitril/valsartan exposure are poorly understood. Sacubitril/valsartan is associated with a decrease in systemic arterial pressure, which may lead to a transient initial reduction in eGFR.[6,7] Changes may be driven by both the RASi component of the sacubitril/valsartan combination in addition to other neprilysin-mediated effects.[8] Although some studies demonstrate no change in renal perfusion with inhibition of neprilysin, others report increased natriuresis and reduced intraglomerular pressures.[8]

The large variability in the between-patient renal response to sacubitril/valsartan is consistent with the postinitiation renal response to RASi, MRA, and SGLT2i.[13-17] In the current study, the multivariable

FIGURE 3 **Incidence Rates of the Primary Composite Outcome by eGFR Decline**



eGFR decline was analyzed continuously using restricted cubic spline models. No clear linear association was observed between a wide range of eGFR changes and the incidence of the primary composite (time to first events) in PARADIGM-HF **(A)** and PARAGON-HF **(B)**. % Change in eGFR = during sacubitril/valsartan run-in period; other abbreviations as in Figure 1. eGFR = estimated glomerular filtration rate; Sac/Val = sacubitril/valsartan.

TABLE 3 Relative Treatment Benefits by the Occurrence of eGFR Decline in PARADIGM-HF

	No eGFR Decline[a] (n = 7,177)		eGFR Decline[a] (n = 919)		
	Enalapril (n = 3,579)	Sac/val (n = 3,598)	Enalapril (n = 472)	Sac/Val (n = 447)	*P* Interaction
Primary composite outcome					
N	948	782	130	92	
Event rate (per 100 person-years)	13.08 (12.27-13.96)	10.46 (9.74-11.23)	14.24 (11.93-17.08)	9.70 (7.93-11.96)	
HR	0.80 (0.73-0.88)		0.69 (0.53-0.90)		0.32
First HF hospitalization					
N	557	461	77	48	
Event rate (per 100 person-years)	7.69 (7.07-8.37)	6.16 (5.63-6.77)	8.44 (6.74-10.67)	5.06 (3.83-6.82)	
HR	0.80 (0.70-0.90)		0.61 (0.42-0.88)		0.19
CV death					
N	589	478	81	60	
Event rate (per 100 person-years)	7.50 (6.92-8.13)	5.99 (5.48-6.65)	7.99 (6.43-10.01)	6.00 (4.70-7.77)	
HR	0.80 (0.71-0.90)		0.75 (0.53-1.04)		0.68
All-cause death					
N	708	603	95	79	
Event rate (per 100 person-years)	9.01 (8.38-9.70)	7.56 (6.99-8.19)	9.37 (7.66-11.55)	7.90 (6.38-9.87)	
HR	0.84 (0.75-0.94)		0.84 (0.62-1.13)		0.99

Time-to-first events analyses were performed using Cox proportional hazards models. Consistent treatment benefits were observed irrespective of the occurrence of moderate eGFR decline on transition to sacubitril/valsartan. [a]96% of patients with calculable eGFR decline.

Sac/Val = sacubitril/valsartan; other abbreviations as in Table 1.

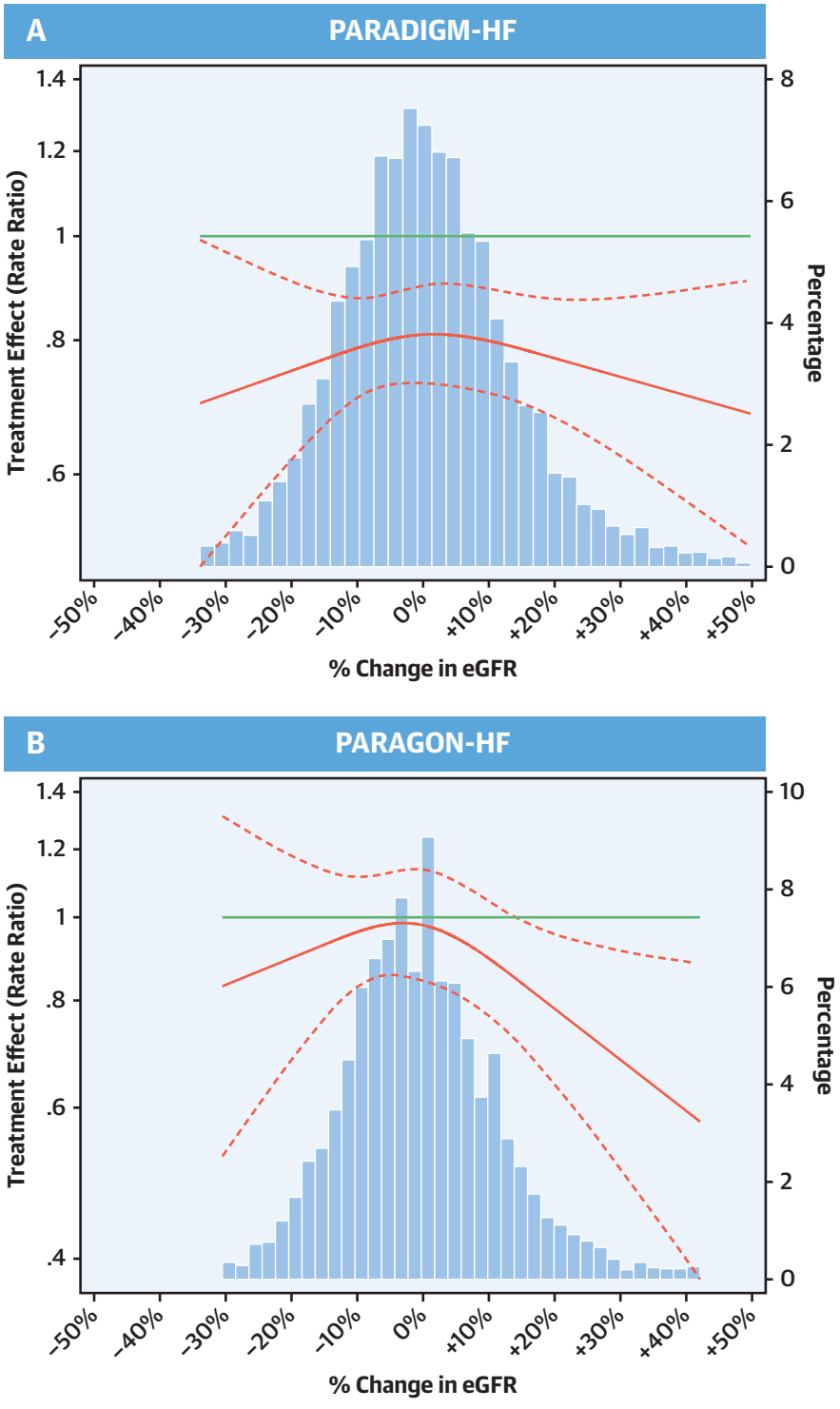
TABLE 4 Relative Treatment Benefits by the Occurrence of eGFR Decline in PARAGON-HF

	No eGFR Decline[a] (n = 4,204)		eGFR Decline[a] (n = 461)		
	Valsartan	Sac/Val	Valsartan	Sac/Val	*P* Interaction
Total HFH + CV death					
N	854	757	122	104	
Event rate (per 100 person-years)	14.02 (12.56-15.70)	12.4 (11.18-13.84)	19.4 (14.28-27.03)	15.75 (10.96-23.47)	
RR	0.87 (0.75-1.02)		0.84 (0.52-1.36)		0.92
Total HFH					
N	677	586	96	80	
Event rate (per 100 person years)	11.11 (9.80-12.66)	9.62 (8.54-10.87)	15.27 (10.70-22.58)	12.12 (7.80-19.89)	
RR	0.85 (0.71-1.01)		0.84 (0.48-1.48)		0.96
First HFH or CV death					
N	477	447	65	59	
Event rate (per 100 person-years)	8.61 (7.87-9.43)	7.97 (7.27-8.76)	11.66 (9.15-15.02)	9.98 (7.73-13.04)	
HR	0.92 (0.80-1.04)		0.86 (0.60-1.22)		0.76
First HFH					
N	374	349	51	43	
Event rate (per 100 person-years)	6.75 (6.10-7.49)	6.22 (5.61-6.92)	9.12 (6.98-12.18)	7.27 (5.40-9.97)	
HR	0.91 (0.78-1.05)		0.81 (0.54-1.21)		0.60
CV death					
N	177	171	26	24	
Event rate (per 100 person-years)	2.90 (2.51-3.37)	2.80 (2.42-3.26)	4.13 (2.84-6.22)	3.63 (2.46-5.56)	
HR	0.96 (0.78-1.19)		0.84 (0.48-1.47)		0.81
All-cause mortality					
N	299	286	38	40	
Event rate (per 100 person-years)	4.90 (4.39-5.55)	4.69 (4.19-5.27)	6.04 (4.44-8.39)	6.05 (4.49-8.33)	
HR	0.95 (0.81-1.12)		0.98 (0.63-1.53)		0.78

Time-to-first events analyses were performed using Cox proportional hazards models. Recurrent events were analyzed using semiparametric proportional rates methods of Lin et al.[12] Consistent treatment benefits were observed irrespective of the occurrence of moderate eGFR decline on transition to sacubitril/valsartan. [a]97% with calculable eGFR decline.

Abbreviations as in Tables 1 and 3.

CENTRAL ILLUSTRATION **Treatment Effect on the Primary Composite Outcome by Estimated Glomerular Filtration Rate Change**



Chatur S, et al. J Am Coll Cardiol. 2023;81(15):1443–1455.

Estimated glomerular filtration rate (eGFR) change was analyzed continuously using restricted cubic spline models. The treatment benefit of sacubitril/valsartan vs renin-angiotensin system inhibitor remained consistent across a range of sacubitril/valsartan run-in eGFR declines when analyzed as a continuous variable in both PARADIGM-HF **(A)** and PARAGON-HF **(B)**.

analysis identified more severe HF symptoms to be a predictor of early eGFR decline, which may reflect an overall diminished renal reserve caused by reduced kidney filtration and altered glomerular barrier and tubular function among patients with more severe HF.[18] In addition, blood pressure and female sex were significantly associated with eGFR decline in patients with HFpEF. Altered ventricular-arterial coupling associated with hypertension may make such patients less tolerant to unfavorable hemodynamic changes, even if transient.[19] Also, women appear to have greater impairment in measures of ventricular-arterial stiffening.[20] This appears to be particularly important in patients with HFpEF, who have an inherent tendency to greater preload dependence.[21] More frequent early eGFR declines with sacubitril/valsartan in women with HFpEF may represent a potentially addressable perceived barrier to optimization of HF guideline-directed medical therapy (GDMT) in women. This is especially important, as women were found to derive greater benefits from sacubitril/valsartan relative to valsartan in PARAGON-HF.[22]

Renal impairment is an established indicator of poor prognosis in patients with HF and is associated with reduced survival.[1,23] Understanding whether short-term changes in renal function induced by pharmacotherapy with proven benefit also portend poor prognosis has important clinical implications. We found, however, that early post-sacubitril/valsartan transition eGFR declines were not consistently associated with adverse prognoses across all evaluated cardiovascular outcomes. This is consistent with studies of SGLT2i-related eGFR declines that are either not prognostic[14] or even associated with improved clinical outcomes.[13]

Postinitiation reductions in eGFR are a commonly cited reason for the premature discontinuation of beneficial HF therapies. However, in both PARADIGM-HF and PARAGON-HF, treatment benefits of sacubitril/valsartan were maintained irrespective of the occurrence of eGFR decline. In addition, rates of discontinuation caused by serious adverse events were similar regardless of the occurrence of run-in eGFR decline.

In clinical practice, previous demonstrated tolerance to RASi is often used as a potential predictor of tolerance to sacubitril/valsartan. In this analysis, relatively few patients who developed moderate eGFR decline with RASi also developed moderate eGFR decline on transition to sacubitril/valsartan. Moreover, the relative treatment benefits of sacubitril/valsartan were found to be consistent irrespective of the occurrence of eGFR decline with RASi. These data suggest that poor renal responses of moderate severity with RASi alone should not dissuade trial of sacubitril/valsartan, as treatment benefits appear to be preserved even in these circumstances.

STUDY LIMITATIONS. First, the analyses of the safety and efficacy of sacubitril/valsartan vs RASi according to the occurrence of eGFR decline were not prespecified and should be considered hypothesis generating. Second, patients were excluded during the run-in phase if eGFR declined to <30 mL/min/1.73 m^2 (PARADIGM-HF) or <25 mL/min/1.73 m^2 (PARAGON-HF) or by >35% between screening and randomization limiting conclusions regarding more extreme eGFR reduction; however, the frequency of such run-in exclusion was infrequent. Third, patients with severe chronic kidney disease (eGFR <30 mL/min/1.73 m^2) were excluded in both PARADIGM-HF and PARAGON-HF; therefore, these findings may not apply to this population. Fourth, the run-in design, consisting of 2 sequential run-in periods of RASi followed by sacubitril/valsartan, may have selected for a more tolerant population and may underestimate the risk of eGFR decline after transition to sacubitril/valsartan. Fifth, early eGFR declines to sacubitril/valsartan exposure might represent natural variation in eGFR rather than necessarily reflecting a direct pharmacologic renal response. Similarly, subsequent postrandomization "recovery" might reflect regression to the mean. Finally, run-in eGFR data were not available for all patients.

CONCLUSIONS

The occurrence of eGFR decline on transition from treatment with RASi to sacubitril/valsartan is highly variable, usually mild, and partially recoverable in most patients. Moderate eGFR declines with transition to sacubitril/valsartan do not appear to portend adverse prognostic significance consistently. Moreover, the treatment benefits of sacubitril/valsartan vs RASi remains apparent across a range of acute early eGFR declines. Taken together, early treatment-related eGFR changes with sacubitril/valsartan should not deter its continuation or stall uptitration.

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ADDRESS FOR CORRESPONDENCE: Prof Scott D. Solomon, Brigham and Women's Hospital, Harvard Medical School, Department of Medicine, Cardiovascular Division, 75 Francis Street, Boston, Massachusetts 02115, USA. E-mail: ssolomon@rics.bwh.harvard.edu. Twitter: @safchat, @UoGHeartFailure, @scottdsolomon, @mvaduganathan.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with heart failure, sacubitril/valsartan is beneficial across a wide range of early post-transition eGFR declines.

TRANSLATIONAL OUTLOOK: Additional research is needed to fully characterize the pathophysiological factors that mediate an early decline in eGFR after transition to sacubitril/valsartan in patients with HF.

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KEY WORDS heart failure, kidney function, sacubitril/valsartan

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

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