Effects of sacubitril/valsartan versus valsartan on renal function in patients with and without diabetes and heart failure with preserved ejection fraction: insights from PARAGON-HF

Alexander Peikert[1], Muthiah Vaduganathan[1], Finnian Mc Causland[2],
Brian L. Claggett[1], Safia Chatur[1], Milton Packer[3], Marc A. Pfeffer[1], Faiez Zannad[4],
Martin P. Lefkowitz[5], Burkert Pieske[6,7], Hans-Dirk Düngen[6,7], John J.V. McMurray[8],
and Scott D. Solomon[1]*

[1]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Baylor Heart and Vascular Hospital, Baylor University Medical Center, Dallas, TX, USA; [4]University of Nancy, Nancy, France; [5]Novartis, East Hanover, NJ, USA; [6]Department of Internal Medicine and Cardiology, Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany; [7]DZHK (German Center for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; and [8]New British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

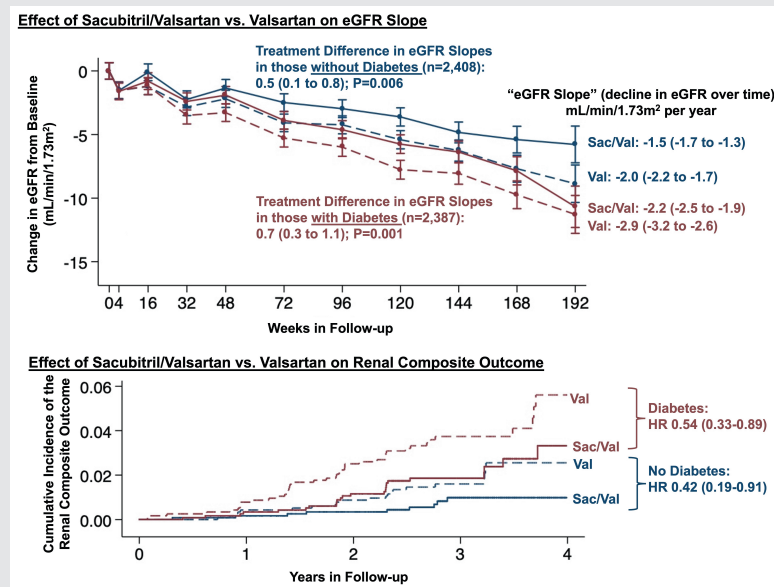|	
Aims	Diabetes is associated with a faster rate of renal function decline in patients with heart failure (HF). Sacubitril/valsartan attenuates the deterioration of renal function to a greater extent in patients with diabetes and HF with reduced ejection fraction compared with renin–angiotensin system inhibitors alone. We assessed whether the same may be true in HF with preserved ejection fraction (HFpEF).
Methods and results	In the PARAGON-HF trial in patients with HF and left ventricular ejection fraction of $\geq 45\%$ ($n = 4796$), we characterized the effects of sacubitril/valsartan on changes in estimated glomerular filtration rate (eGFR) over a period of 192 weeks, and on the pre-specified renal composite outcome (eGFR reduction of $\geq 50\%$, end-stage renal disease, or death attributable to renal causes) in patients with ($n = 2388$) and without diabetes ($n = 2408$). The decline in eGFR was greater in patients with diabetes than in those without (-2.6 vs. -1.7 ml/min/1.73 m^2 per year, $p < 0.001$), regardless of treatment assignment. Sacubitril/valsartan attenuated decline in eGFR similarly in patients with (-2.2 vs. -2.9 ml/min/1.73 m^2 per year, $p = 0.001$) and without diabetes (-1.5 vs. -2.0 ml/min/1.73 m^2 per year, $p = 0.006$) ($p_{interaction}$ for difference in eGFR slopes $= 0.40$). Compared with valsartan, sacubitril/valsartan reduced the renal composite outcome similarly in patients without diabetes (hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.19–0.91) and those with diabetes (HR 0.54, 95% CI 0.33–0.89; $p_{interaction} = 0.59$), as well as across a range of baseline glycated haemoglobin ($p_{interaction} = 0.71$).
Conclusion	Sacubitril/valsartan, compared with valsartan, attenuates the decline of eGFR and reduces clinically relevant kidney events similarly among patients with HFpEF with and without diabetes.

*Corresponding author. Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA. Tel: +1 857 307-1960, Fax: +1 857 307-1944, Email: ssolomon@rics.bwh.harvard.edu

Graphical Abstract

Effect of Sacubitril/Valsartan vs. Valsartan on eGFR Slope

Treatment Difference in eGFR Slopes in those without Diabetes (n=2,408): 0.5 (0.1 to 0.8); P=0.006

"eGFR Slope" (decline in eGFR over time) mL/min/1.73m² per year

Sac/Val: -1.5 (-1.7 to -1.3)
Val: -2.0 (-2.2 to -1.7)

Treatment Difference in eGFR Slopes in those with Diabetes (n=2,387): 0.7 (0.3 to 1.1); P=0.001

Sac/Val: -2.2 (-2.5 to -1.9)
Val: -2.9 (-3.2 to -2.6)

Effect of Sacubitril/Valsartan vs. Valsartan on Renal Composite Outcome

Diabetes: HR 0.54 (0.33-0.89)
No Diabetes: HR 0.42 (0.19-0.91)

Treatment effect of sacubitril/valsartan (Sac/Val) on changes in estimated glomerular filtration rate (eGFR) over time and the renal composite outcome in patients with and without diabetes. Adjusted means for eGFR over a period of 192 weeks were obtained from repeated-measures mixed-effect models. Error bars indicate 95% confidence intervals. eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation. Estimates of the probability of a first occurrence of the renal composite outcome (eGFR reduction of ≥50% relative to baseline, development of end-stage renal disease, or death attributable to renal causes) were obtained from Kaplan–Meier failure analyses. HR, hazard ratio.

Introduction

Diabetes commonly coexists with heart failure with preserved ejection fraction (HFpEF) and is a major risk factor for micro- and macrovascular disease.[1–4] Patients with heart failure (HF) and coexistent diabetes experience more than a two-fold faster rate of decline in renal function, whereby renal impairment is associated with adverse cardiovascular events and increased mortality.[5–7]

Prior studies have demonstrated that cardio-protective therapies may have different effects on renal function depending on diabetes status and HF subtype. For instance, the sodium–glucose cotransporter 2 (SGLT2) inhibitors have recently been shown to reduce the long-term decline in estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease (CKD), with the treatment benefit appearing to be greater in patients with diabetes.[8] Although renin–angiotensin system (RAS) inhibitors substantially improve cardiovascular outcomes in patients with HF, they are associated with mild short-term worsening of renal function, while they may provide long-term benefits attenuating the progression of proteinuric CKD in patients with diabetes.[6,9,10] In

the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, simultaneous neprilysin inhibition combined with RAS blockade slowed the decline of eGFR in patients with HF and reduced ejection fraction (HFrEF), with a greater treatment benefit observed in patients with diabetes.[11] However, in patients with HFpEF, RAS inhibition alone appeared to worsen renal function with less robust cardiovascular benefits compared to patients with HFrEF.[12] Whether neprilysin inhibition combined with RAS blockade may reduce the deterioration of renal function in patients with HFpEF and diabetes remains unclear.

The PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) compared the effects of simultaneous angiotensin receptor–neprilysin inhibition through sacubitril/valsartan with valsartan in patients with HFpEF.[13] The trial provides the opportunity to assess changes in renal function over time and treatment effects of neprilysin inhibition in patients with HFpEF with and without diabetes in a global setting. In this post-hoc analysis, we report the effects of neprilysin inhibition on changes in renal function and the occurrence of clinically relevant kidney events

in HFpEF across the glycaemic spectrum, including those with comorbid diabetes.

Methods

Study design and patients

The trial design and primary results of PARAGON-HF have been reported previously.[13,14] In brief, PARAGON-HF was a randomized, double-blind comparison of sacubitril/valsartan with valsartan in patients aged ≥50 years with chronic HF, New York Heart Association functional class II to IV symptoms, preserved left ventricular ejection fraction (≥45%), features of structural heart disease (left ventricular hypertrophy or left atrial enlargement), diuretic therapy within 30 days and elevated plasma B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide concentrations. Key exclusion criteria included an eGFR of <30 ml/min/1.73 m^2 at screening or <25 ml/min/1.73 m^2 at randomization, an eGFR decrease >35% between screening and randomization, systolic blood pressure <110 mmHg at screening or <100 mmHg at randomization, and serum potassium >5.2 mmol/L at screening or >5.4 mmol/L at randomization. The study complies with the Declaration of Helsinki, the local ethics committees at all participating sites approved the study protocol, and each participant provided written informed consent. The trial is registered in ClinicalTrials.gov with the number NCT01920711.

Definition of diabetic status

Previously known diagnoses of diabetes were recorded as part of the case report forms. In addition, glycated haemoglobin (HbA1c) was determined in all patients at baseline. Patients with either a known diagnosis of diabetes or a baseline HbA1c of ≥6.5% were defined as having diabetes in accordance with the International Diabetes Expert Committee criteria of the International Diabetes Federation.[15]

Assessments of renal outcomes

For evaluating the effects of neprilysin inhibition on changes in renal function in patients with diabetes, eGFR was determined at randomization, at 4, 16, 32, and 48 weeks after randomization and every 24 weeks thereafter up to week 192. As per the protocol, the 2009 Chronic Kidney Disease Epidemiology Collaboration formula was applied to calculate eGFR.[16]

To assess the occurrence of clinically relevant kidney events, this analysis used the renal composite outcome pre-specified as a key secondary outcome in PARAGON-HF, i.e. either a decrease in eGFR of ≥50% from baseline, the development of end-stage renal disease, or death due to renal disease (online supplementary *Table S1*). In addition to the pre-specified renal composite outcome, the effect of sacubitril/valsartan on the composite of either ≥40% decline in eGFR relative to baseline, development of end-stage renal disease, or death attributable to renal causes was analysed to reflect the recommendations from the scientific workshop of the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency.[17] Declines in eGFR by ≥50% and ≥40% from baseline were determined by two consecutive post-baseline central laboratory measurements separated >30 days. End-stage renal disease was defined as either initiation of dialysis continuing for ≥30 days without known recovery of renal function, initiation of dialysis with

death before 30 days, a drop in eGFR from baseline to a value <15 ml/min/1.73 m^2 on two consecutive central laboratory measurements separated by ≥30 days, or occurrence of kidney transplantation.

Statistical analysis

Normally distributed data are reported as mean (± standard deviation), non-normally distributed data as median (interquartile range), and categorical variables as frequencies and percentages. All analyses were performed applying an intention to treat approach. Differences between baseline characteristics of patients with and without diabetes were assessed using Student's *t*-test, Wilcoxon rank sum test, or χ^2 test.

Changes in eGFR over time were examined by repeated-measures mixed-effect models. All available data at randomization, at 4, 16, 32, and 48, and every 24 weeks after randomization, up to week 192 were included, with no imputation for missing data. The model was adjusted for randomized treatment, time, and the interaction between randomized treatment and time as fixed effects, with patient-level random intercepts and slopes with respect to time since randomization. Slopes of eGFR change per year were assessed in patients with and without diabetes for both treatment groups. To identify whether treatment effects on eGFR changes over time varied between patients with and those without diabetes, interaction testing was performed. In addition, exploratory models were adjusted for time-dependent changes in systolic blood pressure.

The hazard ratio (HR) for occurrence of the renal composite outcome was estimated by Cox proportional hazard models, stratified according to geographic region. Kaplan−Meier failure curves were used to illustrate estimates of the probability of a first occurrence of the renal composite outcome. Treatment-by-diabetes interaction was tested to determine differences in treatment effects on renal composite outcomes between patients with and without diabetes. We further assessed event rates for the renal composite outcome across the spectrum of HbA1c and eGFR at baseline by Poisson regression using restricted cubic splines with three knots for each of the analyses.

P-values of <0.05 were considered statistically significant. Statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, USA).

Results

The PARAGON-HF trial enrolled a total of 4822 patients with HFpEF across 788 sites in 43 countries. Overall, 4796 patients were validly randomized, 26 patients were excluded because they were enrolled from a site closed due to Good Clinical Practice violations. A total of 2062 patients (43.0%) had a known diagnosis of diabetes at screening, while 326 (6.8%) without prior diagnosis were additionally found to have a HbA1c ≥6.5% at randomization. Thus, 2388 (49.8%) of the randomized patients were reported to have diabetes, while 2408 (50.2%) did not.

Patient characteristics

At baseline, patients were categorized by diabetes status (*Table 1*). Patients with diabetes were more likely to be younger, male, have a history of hypertension, myocardial infarction, ischaemic aetiology and HF hospitalizations, compared to patients without

Table 1 Baseline characteristics

Characteristic	Patients without diabetes (n = 2408)	Patients with diabetes (n = 2388)	p-value
Age, years	73.4 ± 8.5	72.0 ± 8.3	<0.001
Female sex, n (%)	1301 (54.0)	1178 (49.3)	0.001
Race, n (%)			0.06
Asian	291 (12.1)	316 (13.2)	
Black	41 (1.7)	61 (2.6)	
Other	88 (3.7)	92 (3.9)	
White	1988 (82.6)	1919 (80.4)	
Region, n (%)			0.003
Asia-Pacific/other	364 (15.1)	398 (16.7)	
Central Europe	828 (34.4)	887 (37.1)	
Latin America	213 (8.8)	157 (6.6)	
North America	256 (10.6)	303 (12.7)	
Western Europe	747 (31.0)	643 (26.9)	
NYHA class, n (%)			0.05
I	58 (2.4)	79 (3.3)	
II	1910 (79.4)	1796 (75.2)	
III	430 (17.9)	502 (21.0)	
IV	9 (0.4)	10 (0.4)	
HF duration, n (%)			0.5
0−3 months	411 (17.1)	362 (15.2)	
3−6 months	328 (13.6)	258 (10.8)	
6−12 months	318 (13.2)	298 (12.5)	
1−2 years	339 (14.1)	340 (14.3)	
2−5 years	464 (19.3)	529 (22.2)	
>5 years	543 (22.6)	594 (24.9)	
Non-ischaemic aetiology, n (%)	1665 (69.1)	1408 (58.9)	<0.001
Prior HF hospitalization, n (%)	1058 (43.9)	1248 (52.3)	<0.001
LVEF, %	57.8 ± 7.9	57.2 ± 7.9	0.007
SBP, mmHg	129.5 ± 15.4	131.7 ± 15.5	<0.001
Heart rate, bpm	69.5 ± 12.2	71.4 ± 12.3	<0.001
BMI, kg/m^2	29.4 ± 5.0	31.1 ± 4.9	<0.001
HbA1c, %	5.8 ± 0.4	7.3 ± 1.5	<0.001
eGFR, ml/min/1.73 m^2 (full range)	63.0 ± 18.3 (21.9−147.3)	62.2 ± 19.9 (20.3−166.8)	0.2
Serum creatinine, mg/dl	1.07 ± 0.28	1.11 ± 0.33	<0.001
NT-proBNP, without AF, pg/ml, median (IQR)	603 (377−1034)	596 (382−1075)	0.9
NT-proBNP with AF, pg/ml, median (IQR)	1601 (1166−2357)	1577 (1174−2197)	0.5
Medical history, n (%)			
Myocardial infarction	446 (18.5)	637 (26.7)	<0.001
Atrial flutter/fibrillation	784 (32.6)	768 (32.3)	0.8
Hypertension	2275 (94.5)	2309 (96.7)	<0.001
Current smoking	186 (7.8)	167 (7.0)	0.3
Stroke	236 (9.8)	272 (11.4)	0.08
COPD	320 (13.3)	350 (14.7)	0.4
Medications, n (%)			
Diuretics	2295 (95.3)	2290 (95.9)	0.3
ACE inhibitor/ARB	2070 (86.0)	2069 (86.6)	0.5
Beta-blocker	1860 (77.2)	1961 (82.1)	<0.001
MRA	618 (25.7)	621 (26.0)	0.8
Antiplatelets	257 (10.7)	378 (15.8)	<0.001
Insulin	1 (0.1)	656 (27.5)	−
Oral hypoglycaemic agents	6 (0.2)	1476 (61.8)	−
GLP-1 receptor agonist	0 (0.0)	20 (0.8)	−

Plus−minus values are mean ± standard deviation.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP; N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.
p-values are reported for differences between patients with and those without diabetes.

Table 2 Rate of decline from baseline in estimated glomerular filtration rate (ml/min/1.73 m² per year)

	All patients	Patients without diabetes	Patients with diabetes
All patients	−2.1 (−2.3 to −2.0)	−1.7 (−1.9 to −1.5)	−2.6 (−2.8 to −2.3)
Valsartan	−2.4 (−2.6 to −2.2)	−2.0 (−2.2 to −1.7)	−2.9 (−3.2 to −2.6)
Sacubitril/valsartan	−1.8 (−2.0 to −1.6)	−1.5 (−1.7 to −1.3)	−2.2 (−2.5 to −1.9)
Difference (95% CI) *p*-value	0.6 (0.3 to 0.9) *p* < 0.001	0.5 (0.1 to 0.8) *p* = 0.006	0.7 (0.3 to 1.1) *p* = 0.001

CI, confidence interval.
P-values are reported for differences in estimated glomerular filtration rate change between patients treated with valsartan and patients treated with sacubitril/valsartan.

diabetes. In addition, patients with diabetes had a higher body mass index, heart rate, systolic blood pressure and serum creatinine, compared to those without diabetes. Compared to those without diabetes, patients with diabetes showed more severe HF symptoms and had a slightly lower left ventricular ejection fraction, whereas N-terminal pro-B-type natriuretic peptide levels were similar. Beta-blockers and antiplatelet agents were prescribed more frequently among patients with diabetes, but the use of diuretics, RAS inhibitors, and mineralocorticoid receptor antagonists did not differ between patients with and without diabetes. There were no significant differences in eGFR at baseline between patients with (62.2 ± 19.9 ml/min/1.73 m²) and without diabetes (63.0 ± 18.3 ml/min/1.73 m²).

Change in estimated glomerular filtration rate over time in patients with and without diabetes

During the follow-up period between randomization and trial completion, the mean decline of eGFR for both treatment groups combined was −2.1 ml/min/1.73 m² per year (95% confidence interval [CI] −2.3 to −2.0; *Table 2*). In the overall study population, patients with diabetes experienced a more rapid decline of eGFR than those without (−2.6 vs. −1.7 ml/min/1.73 m² per year, *p* < 0.001; *Table 2*). Among patients with diabetes, those treated with sacubitril/valsartan experienced a slower decline of eGFR over time, compared with those treated with valsartan (−2.2 vs. −2.9 ml/min/1.73 m² per year, *p* = 0.001; *Figure 1*, *Table 2*). Similarly, in patients without diabetes, treatment with sacubitril/valsartan attenuated the eGFR decline, compared with valsartan (−1.5 vs. −2.0 ml/min/1.73 m² per year, *p* = 0.006; *Figure 1*, *Table 2*). The difference in eGFR change between patients treated with sacubitril/valsartan and valsartan was similar in those with (0.7 ml/min/1.73 m² per year, 95% CI 0.3 to 1.1) and without diabetes (0.5 ml/min/1.73 m² per year, 95% CI 0.1 to 0.8; *p*ₐₒₓ... $p_{\text{interaction}}$ for difference in eGFR slopes = 0.40; *Figure 1*, *Table 2*). Additional adjustment for systolic blood pressure changes during follow-up did not affect treatment effect estimates on eGFR decline in patients with (adjusted mean difference 0.7 ml/min/1.73 m² per year, 95% CI 0.3 to 1.1) and without diabetes (adjusted mean difference 0.4 ml/min/1.73 m² per year, 95% CI 0.1 to 0.8, $p_{\text{interaction}}$ for difference in eGFR slopes = 0.38).

Pre-specified renal composite outcomes according to diabetes status

The pre-specified renal composite outcome occurred in 2.8% (*n* = 67) of patients with and 1.2% (*n* = 30) of patients without diabetes. Patients with diabetes had an over two-fold increased risk for the renal composite outcome, compared to those without diabetes (HR 2.37, 95% CI 1.54−3.63, *p* < 0.001). Compared with valsartan, sacubitril/valsartan reduced the renal composite outcome to a similar extent in patients with (HR 0.54, 95% CI 0.33−0.89) and those without diabetes (HR 0.42, 95% CI 0.19−0.91; $p_{\text{interaction}}$ = 0.59; *Figure 2*, *Table 3*). The majority of events among the renal composite outcome were declines in eGFR ≥50% relative to baseline, with a similar treatment effect observed in patients with (HR 0.48, 95% CI 0.28−0.82) and without diabetes (HR 0.34, 95% CI 0.15−0.82; $p_{\text{interaction}}$ = 0.50; *Table 3*). Rates of progression to end-stage renal disease were similarly reduced by sacubitril/valsartan compared with valsartan in patients with (HR 0.71, 95% CI 0.22−2.27) and without diabetes (HR 0.39, 95% CI 0.08−2.01; $p_{\text{interaction}}$ = 0.58; *Table 3*). Death attributable to renal causes occurred in one patient with diabetes treated with valsartan and in one patient without diabetes treated with sacubitril/valsartan. Sacubitril/valsartan equally attenuated the endpoint of ≥40% decline in eGFR relative to baseline and the composite outcome of either a ≥40% decline in eGFR relative to baseline, progression to end-stage renal disease, or death attributable to renal causes among patients with and without diabetes (*Table 3*).

The treatment effect of sacubitril/valsartan compared with valsartan for the renal composite endpoint did not differ across a range of baseline HbA1c ($p_{\text{interaction}}$ = 0.71; *Figure 3*) and baseline eGFR ($p_{\text{interaction}}$ = 0.99; *Figure 4*).

Discussion

In this post-hoc analysis of the PARAGON-HF trial, patients with HFpEF and coexisting diabetes experienced a steeper decline in eGFR than those without diabetes. Patients with diabetes experienced a greater than two-fold increased risk for the renal composite outcome compared to those without diabetes. Sacubitril/valsartan similarly attenuated this decline of eGFR among patients with and without diabetes. The occurrence of renal composite outcomes was reduced by sacubitril/valsartan to a similar extent in patients with and without diabetes (*Graphical Abstract*).

Change in eGFR over 192 weeks
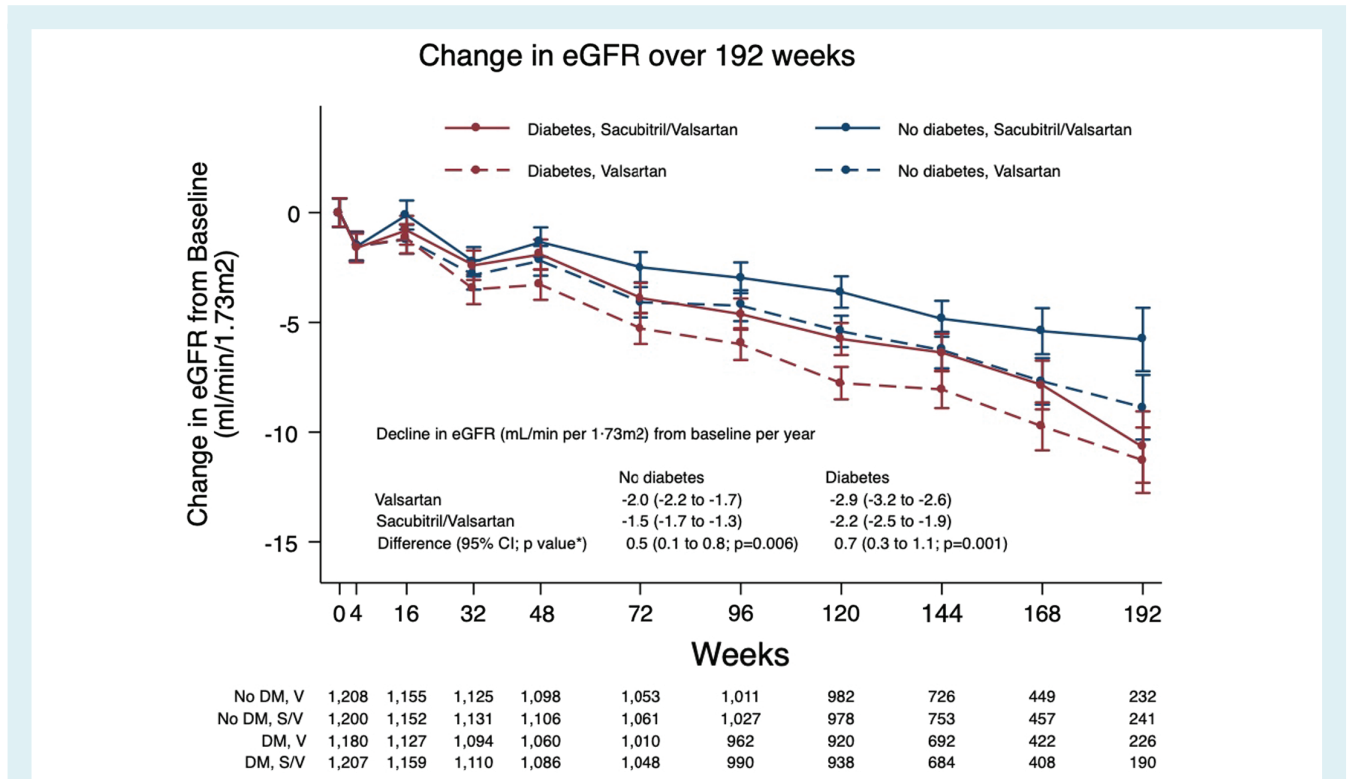
Figure 1 Change in estimated glomerular filtration rate (eGFR) over time in patients with and without diabetes. Adjusted means for eGFR over a period of 192 weeks were obtained from repeated-measures mixed-effect models. Error bars indicate 95% confidence intervals. eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation. Numbers of available measurements at each time point per arm are displayed below. *P-values are reported for differences in eGFR change between patients treated with valsartan (V) and patients treated with sacubitril/valsartan (S/V). DM, diabetes mellitus.
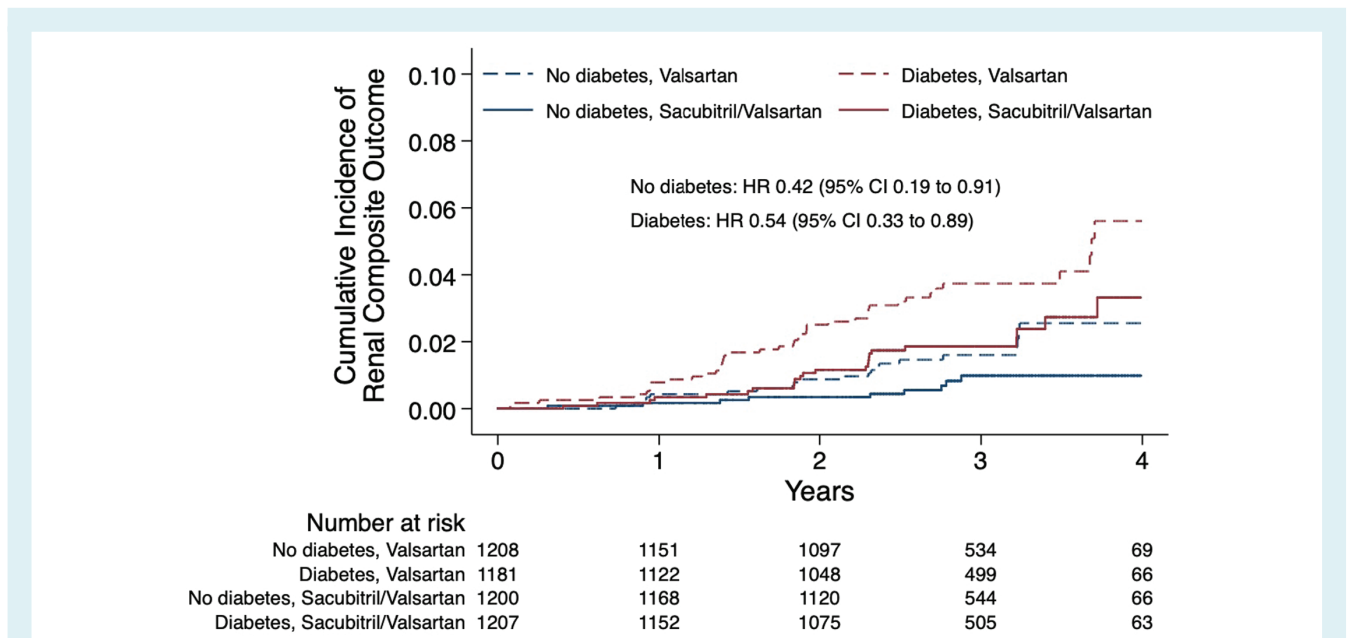
Figure 2 Kaplan−Meier analysis of the renal composite outcome by diabetes status. Estimates of the probability of a first occurrence of the renal composite outcome (estimated glomerular filtration rate reduction of ≥50% relative to baseline, development of end-stage renal disease, or death attributable to renal causes) obtained from Kaplan−Meier failure analyses. CI, confidence interval; HR, hazard ratio.

Table 3 Renal composite outcome and its individual components

Outcome	Patients without diabetes			Patients with diabetes			$p_{interaction}$
	Valsartan ($n = 1208$)	Sacubitril/ valsartan ($n = 1181$)	Hazard ratio (95% CI)	Valsartan ($n = 1200$)	Sacubitril/ valsartan ($n = 1207$)	Hazard ratio (95% CI)	
Renal composite outcome[a]	21 (1.7%)	9 (0.8%)	0.42 (0.19−0.91)	43 (3.6%)	24 (2.0%)	0.54 (0.33−0.89)	0.59
≥50% decline in eGFR	20 (1.7%)	7 (0.6%)	0.34 (0.15−0.82)	40 (3.4%)	20 (1.7%)	0.48 (0.28−0.82)	0.50
End-stage renal disease	5 (0.4%)	2 (0.2%)	0.39 (0.08−2.01)	7 (0.6%)	5 (0.4%)	0.71 (0.22−2.27)	0.58
Death from renal causes	0 (0.0%)	1 (0.1%)	−	1 (0.1%)	0 (0.0%)	−	−
Renal composite outcome[b]	55 (4.6%)	24 (2.0%)	0.42 (0.26−0.68)	91 (7.7%)	64 (5.3%)	0.68 (0.50−0.94)	0.10
≥40% decline in eGFR	54 (4.5%)	22 (1.8%)	0.40 (0.24−0.65)	88 (7.5%)	60 (5.0%)	0.66 (0.48−0.91)	0.09

CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2).
$p_{interaction}$ values are reported for treatment group differences between patients with and without diabetes.
[a]Defined as either a ≥50% decline in eGFR relative to baseline, development of end-stage renal disease, or death attributable to renal causes.
[b]Defined as either a ≥40% decline in eGFR relative to baseline, development of end-stage renal disease, or death attributable to renal causes.
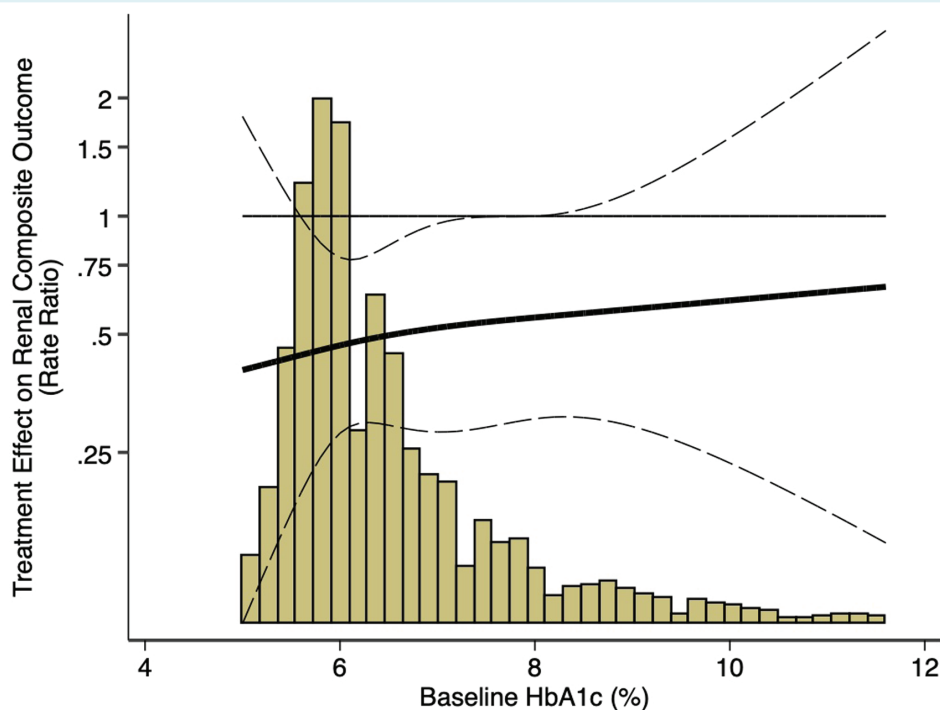
Figure 3 Treatment effect of sacubitril/valsartan, compared with valsartan, on the renal composite outcome (estimated glomerular filtration rate reduction of ≥50% relative to baseline, development of end-stage renal disease, or death attributable to renal causes) across a range of baseline glycated haemoglobin (HbA1c). Estimated rate ratios and 95% confidence intervals were obtained from negative binomial regression models with HbA1c expressed via restricted cubic spline.

We found greater rates of mean decline in eGFR in PARAGON-HF than those observed in PARADIGM-HF.[18] Except for ejection fraction, both trials had comparable designs in terms of eligibility criteria, run-in periods, active comparators, and end-point assessment, nevertheless the included patient populations differed markedly.[13,19] PARAGON-HF enrolled a older population with notably higher proportion of patients with coexisting diabetes, although the faster rate of eGFR decline compared with PARADIGM-HF appeared in both patients with and without diabetes.[4,11]

As expected, patients with diabetes showed a greater decrease in eGFR than those without diabetes, a finding that has been seen in many studies and cohorts. The effects of cardio-protective therapies on decline in renal function, however, have varied by diabetes status. In the DAPA-CKD trial (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease),
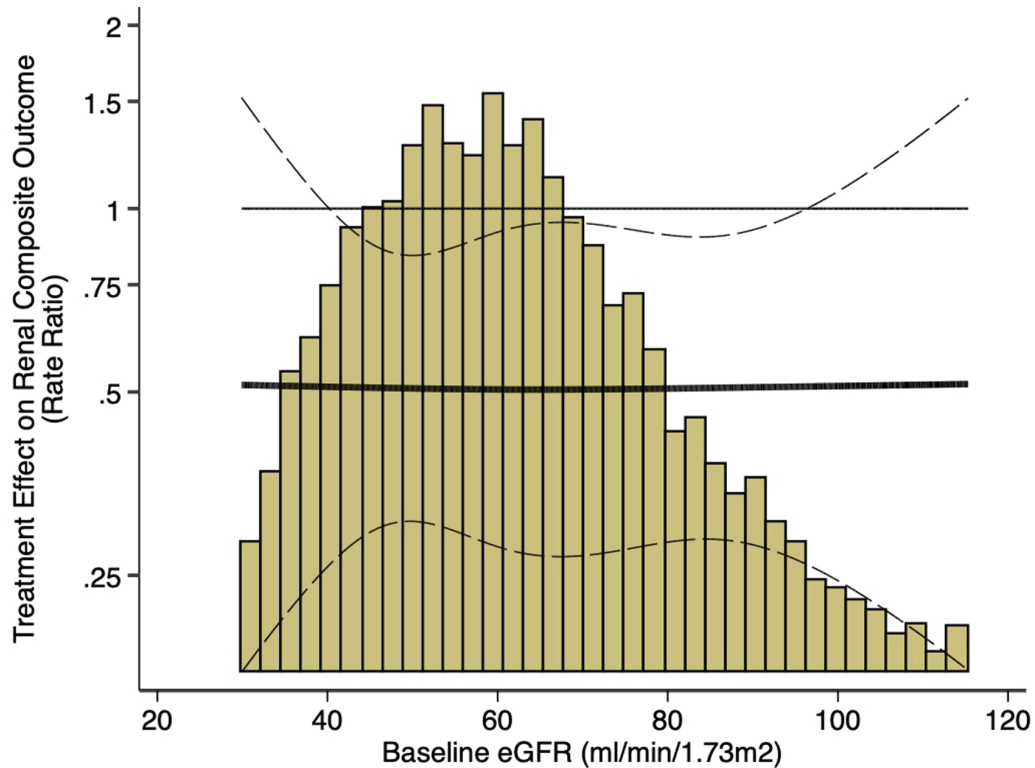
Figure 4 Treatment effect of sacubitril/valsartan, compared with valsartan, on the renal composite outcome (estimated glomerular filtration rate reduction [eGFR] of ≥50% relative to baseline, development of end-stage renal disease, or death attributable to renal causes) across a range of baseline eGFR. Estimated rate ratios and 95% confidence intervals were obtained from negative binomial regression models with baseline eGFR expressed via restricted cubic spline.

SGLT2 inhibition with dapagliflozin slowed the eGFR decline and reduced albuminuria to a greater extent in proteinuric CKD patients with diabetes compared to those without.[8,20] Moreover, in comparison with enalapril, treatment with sacubitril/valsartan attenuated the deterioration of eGFR to a greater extent in patients with HFrEF and diabetes than in patients without diabetes in PARADIGM-HF.[11] In PARAGON-HF, sacubitril/valsartan slowed the rate of eGFR decline similarly in patients with and without diabetes. Although no statistical interaction between treatment effects of sacubitril/valsartan on the decline in eGFR and diabetes status was detectable in PARAGON-HF, the absolute magnitudes of treatment benefits of sacubitril/valsartan in PARAGON-HF appeared comparable to those observed in PARADIGM-HF among patients with (0.7 vs. 0.6 ml/min/1.73 m² per year) and without diabetes (0.5 vs. 0.3 ml/min/1.73 m² per year).[11] Possible reasons for the differences in findings compared to PARADIGM-HF may include that PARADIGM-HF enrolled almost twice as many patients than PARAGON-HF (n = 8399 vs. n = 4796), resulting in greater statistical power to detect differences between patients with and without diabetes.[11,19] Alternatively, differences in patient characteristics may have contributed to the differential response of patients with diabetes compared to PARADIGM-HF. Patients with HFpEF are known to have heterogeneous phenotypes, which raises the possibility of differential treatment effects.[13,21] Notably, compared with the participants of PARADIGM-HF, those enrolled in PARAGON-HF were more likely to be female, tended to be older, had more often a history of hypertension and higher baseline systolic blood pressure.[13,19] Moreover, among patients with diabetes, the use of insulin was more frequent in PARAGON-HF than in PARADIGM-HF (27.5% vs.19.0%), suggesting that PARAGON-HF possibly enrolled a considerably higher proportion of severely affected diabetes patients.[22]

Therapeutic benefits of simultaneous angiotensin receptor–neprilysin inhibition on renal function are likely to be mediated by several complementary pathways, although the underlying mechanisms are complex and not entirely understood. Potential mechanisms of neprilysin inhibition may include favourable effects on constrictive tubuloglomerular feedback (TGF) through increased cyclic guanosine monophosphate levels.[23,24] Experimentally, neprilysin inhibition increases intraglomerular capillary pressure by raising plasma concentrations of active natriuretic peptides, leading to enhanced eGFR.[25–27] On the other hand, RAS inhibition alone is known to frequently result in a decrease in eGFR by limiting glomerular autoregulation.[28] Unlike other drugs with inhibitory effects on TGF, no acute decline in eGFR throughout the initiation was observed with sacubitril/valsartan in PARAGON-HF, PARAMOUNT and PARADIGM-HF.[18,29,30] Possible acute effects

on eGFR may not be completely reflected due to the run-in phase. Nevertheless, it is likely that the neprilysin component of sacubitril/valsartan may counteract the decline in eGFR induced by RAS inhibition and attenuate the deterioration in renal function compared with valsartan alone. Aside from its benefits on the decline of glomerular function, it is important to consider that sacubitril/valsartan led to increased urinary albumin excretion in patients with and without diabetes in PARADIGM-HF.[11] Patients with diabetes often experience increased intraglomerular pressures associated with glomerular hyperfiltration, progressive albuminuria, and declining GFR.[31] Despite the presumed opposing glomerular effects and the worsening of albuminuria described in association with sacubitril/valsartan, similar renal benefits were observed in patients with and without diabetes in this study. Thus, it can be assumed that beyond its glomerular effects, sacubitril/valsartan may mediate additional beneficial non-haemodynamic effects through reducing inflammation and renal fibrosis.[32–34]

Limitations

There are several limitations that should be noted in the context of this study. The PARAGON-HF trial was not powered to evaluate differences in eGFR decline and renal composite outcomes in patients with and without diabetes. Type of diabetes (either type 1 or 2) was not separately captured in case report forms, preventing separate consideration in our analyses. While the renal composite outcome was a pre-defined secondary endpoint in PARAGON-HF, the observed number of renal composite outcome events in patients with and without diabetes was relatively small, limiting the results to an exploratory nature. In addition, PARAGON-HF did not include patients with advanced kidney disease precluding conclusions in this population. Serum creatinine was not further determined after the end of the study, precluding conclusions about eGFR trajectory during the post-treatment interval after discontinuation of study medication. In contrast to PARADIGM-HF, no urine albumin/creatinine ratio was measured in PARAGON-HF. Urinary protein measurement at baseline was solely determined by dipstick without additional laboratory testing in PARAGON-HF, precluding specific analysis of albuminuria.

Conclusion

In patients with HFpEF, treatment with sacubitril/valsartan attenuated the decline in eGFR and reduced clinically relevant renal events among those with and without diabetes, compared with valsartan. The treatment effects on renal function did not differ between patients with and without diabetes. Sacubitril/valsartan represents a potential treatment option for patients with HFpEF and diabetes at risk for or with mild to moderate CKD.

Supplementary Information

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

Funding

Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent.

References

1. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve trial (Irbesartan in Heart Failure with Preserved Ejection Fraction). *Circulation*. 2017;**135**:724–35.

2. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong JJ, Anavekar N, et al. Baseline characteristics of patients with heart failure and preserved ejection fraction in the PARAGON-HF trial. *Circ Heart Fail*. 2018;**11**:e004962.

3. Lacey B, Herrington WG, Preiss D, Lewington S, Armitage J. The role of emerging risk factors in cardiovascular outcomes. *Curr Atheroscler Rep*. 2017;**19**:28.

4. Jackson AM, Rørth R, Liu J, Kristensen SL, Anand IS, Claggett BL, et al.; PARAGON-HF Committees and Investigators. Diabetes and pre-diabetes in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2022;**24**:497–509.

5. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation*. 2021;**143**:298–309.

6. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;**35**:455–69.

7. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol*. 2013;**24**:302–8.

8. Heerspink HJL, Jongs N, Chertow GM, Langkilde AM, McMurray J, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;**9**:743–54.

9. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;**345**:851–60.

10. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;**345**:861–9.

11. Packer M, Claggett B, Lefkowitz MP, McMurray JJV, Rouleau JL, Solomon SD, et al. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol*. 2018;**6**:547–54.

12. Damman K, Solomon SD, Pfeffer MA, Swedberg K, Yusuf S, Young JB, et al. Worsening renal function and outcome in heart failure patients with reduced and preserved ejection fraction and the impact of angiotensin receptor blocker treatment: data from the CHARM-study programme. *Eur J Heart Fail*. 2016;**18**:1508–17.

13. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al.; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;**381**:1609–20.

14. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. *JACC Heart Fail*. 2017;**5**:471–82.

15. International Diabetes Federation. *IDF Diabetes Atlas*. 9th edition. Brussels, Belgium; 2019. Available at: https://www.diabetesatlas.org.

16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;**150**:604–12.

17. Levey AS, Gansevoort RT, Coresh J, Inker LA, Heerspink HL, Grams ME, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis*. 2020;**75**:84–104.

18. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail*. 2018;**6**:489–98.

19. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;**371**:993–1004.

20. Jongs N, Greene T, Chertow GM, McMurray J, Langkilde AM, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;**9**:755–66.

21. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;**131**:269–79.

22. Seferovic JP, Claggett B, Seidelmann SB, Seely EW, Packer M, Zile MR, et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol*. 2017;**5**:333–40.

23. Lessa LM, Carraro-Lacroix LR, Crajoinas RO, Bezerra CN, Dariolli R, Girardi ACC, et al. Mechanisms underlying the inhibitory effects of uroguanylin on NHE3 transport activity in renal proximal tubule. *Am J Physiol Renal Physiol*. 2012;**303**:F1399–408.

24. Thomson SC, Deng A. Cyclic GMP mediates influence of macula densa nitric oxide over tubuloglomerular feedback. *Kidney Blood Press Res*. 2003;**26**:10–8.

25. Marin-Grez M, Fleming JT, Steinhausen M. Atrial natriuretic peptide causes pre-glomerular vasodilatation and post-glomerular vasoconstriction in rat kidney. *Nature*. 1986;**324**:473–6.

26. Pham I, Sediame S, Maistre G, Roudot-Thoraval F, Chabrier PE, Carayon A, et al. Renal and vascular effects of C-type and atrial natriuretic peptides in humans. *Am J Physiol*. 1997;**273**:R1457–64.

27. Mangiafico S, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett JC. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *Eur Heart J*. 2013;**34**:886–893c.

28. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. *Eur Heart J*. 2012;**33**:2135–42.

29. Mc Causland FR, Lefkowitz MP, Claggett B, Anavekar NS, Senni M, Gori M, et al. Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. *Circulation*. 2020;**142**:1236–45.

30. Voors AA, Gori M, Liu LC, Claggett B, Zile MR, Pieske B, et al.; PARAMOUNT Investigators. Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2015;**17**:510–7.

31. Hallow KM, Gebremichael Y, Helmlinger G, Vallon V. Primary proximal tubule hyperreabsorption and impaired tubular transport counterregulation determine glomerular hyperfiltration in diabetes: a modeling analysis. *Am J Physiol Renal Physiol*. 2017;**312**:F819–35.

32. Myakala K, Jones BA, Wang XX, Levi M. Sacubitril/valsartan treatment has differential effects in modulating diabetic kidney disease in. *Am J Physiol Renal Physiol*. 2021;**320**:F1133–51.

33. Jing W, Vaziri ND, Nunes A, Suematsu Y, Farzaneh T, Khazaeli M, et al. LCZ696 (sacubitril/valsartan) ameliorates oxidative stress, inflammation, fibrosis and improves renal function beyond angiotensin receptor blockade in CKD. *Am J Transl Res*. 2017;**9**:5473–84.

34. Cunningham JW, Claggett BL, O'Meara E, Prescott MF, Pfeffer MA, Shah SJ, et al. Effect of sacubitril/valsartan on biomarkers of extracellular matrix regulation in patients with HFpEF. *J Am Coll Cardiol*. 2020;**76**:503–14.