Angiotensin-Neprilysin Inhibition and Renal Outcomes in Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Background

In patients with heart failure, chronic kidney disease (CKD) is common and associated with a higher risk of renal events than in patients without CKD. We assessed the renal effects of angiotensin/neprilysin inhibition in patients with heart failure and preserved ejection fraction (HFpEF) enrolled in PARAGON-HF.

Methods

In this randomized, double-blind, event-driven trial, we assigned 4,822 patients with HFpEF to receive sacubitril/valsartan (n=2419) or valsartan (n=2403). Herein we present the results of the pre-specified renal composite outcome (time to first occurrence of either: ≥50% reduction in eGFR, end-stage renal disease, or death from renal causes), the individual components of this composite, and the influence of therapy on eGFR slope.

Results

At randomization, eGFR was 63±19 ml/min/1.73m^2. At study closure, the composite renal outcome occurred in 33 patients (1.4%) assigned to sacubitril/valsartan and 64 patients (2.7%) assigned to valsartan (hazard ratio [HR], 0.50; 95%CI, 0.33 to 0.77; P=0.001). The treatment effect on the composite renal endpoint did not differ according to the baseline eGFR (<60 vs ≥

60 ml/min/1.73 m^2 (P-interaction=0.92). The decline in eGFR was less for sacubitril/valsartan compared with valsartan (-1.8 [95%CI, -2.0 to -1.6] vs. -2.4 [95%CI, -2.6 to -2.2] ml/min/1.73m^2/year).

Conclusions

In patients with HFpEF, sacubitril/valsartan reduced the risk of renal events, and slowed decline in eGFR, compared with valsartan.

Trial Registration

(Funded by Novartis; PARAGON-HF ClinicalTrials.gov number, NCT01920711.)

CLINICAL PERSPECTIVE

What Is New?

- In this prespecified analysis of patients with heart failure with preserved ejection fraction enrolled in PARAGON-HF, sacubitril/valsartan reduced the occurrence of the renal composite outcome (≥50% reduction in eGFR, end-stage renal disease, or death from renal causes) compared with valsartan.
- Sacubitril/valsartan attenuated the decline in estimated glomerular filtration rate over the course of the study, independent of changes in blood pressure, compared with valsartan.

What Are the Clinical Implications?

- Therapeutic benefits of sacubitril/valsartan with respect to renal outcomes are observed among patients with heart failure with preserved ejection fraction and appear to be similar across baseline kidney function.
- Sacubitril/valsartan may represent an important therapeutic option to slow kidney function decline in patients with heart failure with preserved ejection fraction.

INTRODUCTION

Chronic kidney disease (CKD) is a common comorbid condition in patients with heart failure, and is associated with a higher risk for adverse cardiovascular (CV) events, compared to heart failure patients without CKD.[1–3] Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of heart failure cases, and includes features of diastolic dysfunction, vascular stiffness and abnormalities in systolic function.[4,5] Inhibitors of the renin-angiotensin system (RAS) are known to reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF),[6–9] and to slow the progression of proteinuric CKD in patients with diabetes.[10–12] However, in patients with HFpEF, RAS inhibition has not demonstrated conclusive benefit in reducing mortality or adverse renal outcomes.[13–16]

The addition of neprilysin inhibition to RAS blockade offers an alternative approach to target abnormal neurohormonal signaling in heart failure by augmenting the endogenous vasoactive peptide system, including the biologically active natriuretic peptides, while simultaneously blocking the renin-angiotensin system. In patients with heart failure and reduced ejection fraction (HFrEF) enrolled in the PARADIGM-HF trial, sacubitril/valsartan has been shown to reduce the risk of CV death and HF hospitalization,[17] and to result in a slower rate of estimated glomerular filtration rate (eGFR) decline,[18] compared with enalapril. Similar patterns of benefit in slowing eGFR decline were noted in a phase 2 trial of sacubitril/valsartan in HFpEF, compared with valsartan.[19]

The PARAGON-HF trial compared sacubitril/valsartan with valsartan in patients with HFpEF, and demonstrated a 13% reduction (rate ratio 0.87; 95%CI 0.75 to 1.01) in total heart failure hospitalizations and CV death.[20] Here, we report the results of the prespecified secondary renal outcome (composite of either a ≥50% reduction in eGFR relative to baseline, development of end-stage renal disease, or death from renal causes), the effect of study treatment on change in eGFR, and the effect of treatment on renal outcomes according to baseline renal function.

METHODS

Data Sharing

The sponsor of this trial is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described.[21]

Trial design and oversight

The design and methods of the PARAGON-HF trial have been described previously.[20,22] Local ethics committees approved the trial and all patients provided written, informed consent. The executive committee designed and oversaw the conduct of the trial and data analysis in collaboration with the sponsor, Novartis. A full copy of the trial protocol is available with this article. The trial was reviewed by an independent data and safety monitoring committee. Data were collected, managed, and analyzed by the sponsor according to a predefined statistical analysis plan. An independent academic statistician replicated the primary analyses. The first author wrote the first draft of the present manuscript. All authors submitted revisions and made the collective decision to submit the present manuscript for publication.

Study Patients

Briefly, the PARAGON-HF study population included patients aged ≥50 years, left ventricular ejection fraction ≥45% by echocardiography with features of structural heart disease defined by left ventricular hypertrophy and/or left atrial enlargement, on maintenance diuretic therapy and with elevated plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NTproBNP) concentrations. Notable exclusion criteria included: symptomatic hypotension (or a systolic blood pressure <110 mm Hg at screening or <100 mm Hg at random treatment assignment); an eGFR of <30 ml/min/1.73 m^2 at screening or <25 ml/min/1.73 m^2 at randomization, or a decrease >35% in eGFR between screening and randomization; and hyperkalemia (serum potassium >5.2 mmol/l at screening or >5.4 mmol/l at random treatment assignment).

Definition of Primary and Secondary Outcomes

The primary outcome of the PARAGON-HF trial was a composite of CV death and total (first and recurrent) heart failure hospitalizations. The composite renal outcome was a prespecified key secondary outcome, defined as either: 1) ≥50% decline in eGFR relative to baseline; 2) development of end-stage renal disease; or 3) death due to renal causes (See supplementary Table 1 for renal endpoint definitions).

Post Hoc Assessments of Renal Outcomes

We conducted post-hoc analyses to examine for the effect of sacubitril/valsartan (versus valsartan) on the individual components of the renal composite endpoint. In addition, we examined for a differential effect of sacubitril/valsartan on the renal outcome, according to the baseline eGFR (eGFR at randomization, modeled as a continuous variable). A prespecified exploratory outcome was to examine if sacubitril/valsartan resulted in a slower rate of decline in eGFR, compared with valsartan. For these analyses, the eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, with creatinine traceable to isotope dilution mass spectrometry, using data from randomization, at 4, 16, 32, and 48 weeks, and every 24 weeks thereafter until week 192.

Renal Safety and Laboratory Assessments

We conducted safety analyses to examine for a differential effect of sacubitril/valsartan for the incidence of at least one adverse event, at least one serious adverse event, study drug discontinuation for adverse and serious adverse events, hyperkalemia, elevations in serum creatinine, and symptomatic hypotension, according to the baseline eGFR (<60 versus ≥60 ml/min/1.73 m^2).

Statistical Analyses

We report data as mean (+/-SD) when normally distributed, as median (25^{th}-75^{th} percentile) when non-normally distributed, and as frequencies and percentages for categorical variables. We used the Student t-test, Wilcoxon Rank Sum, or chi-

square tests to determine differences between baseline variables for patients according to the baseline (eGFR <60 versus ≥60 ml/min/1.73 m^2, respectively), according to data distribution.

We used an intention-to-treat approach to perform analyses in patients who had received at least one dose of study drug. For the renal endpoints we used Cox proportional hazard models to estimate hazard ratios (HRs) with 95% CIs, stratified according to geographic region. We tested for interactions between the treatment effect of sacubitril/valsartan and baseline eGFR, age, sex, and ejection fraction on the renal outcomes. Data from patients who did not have an event were censored on the last day they were known to be free of the outcome.

We assessed for changes in eGFR over time with repeated measures mixed effect models, using available data from randomization, at 4, 16, 32, and 48 weeks, and every 24 weeks thereafter, until week 192. We adjusted for treatment assignment, trial visit, and the interaction between treatment assignment and visit. Intercepts and slopes over time were allowed to vary randomly between patients by inclusion of patient and time as random effects. As sacubitril/valsartan resulted in a lower mean blood pressure compared with valsartan, in exploratory models, we adjusted for time-updated measurements of systolic blood pressure.

All analyses were performed at the nominal alpha level of 0.05 without correction for multiple hypothesis testing. No formal power calculations were performed *a priori* for renal secondary or exploratory outcomes. Statistical

analyses were performed using STATA (version 14.0, Stata Corp., College Station, Texas).

RESULTS

Patients

A total of 4822 patients were randomized, with 4796 included in the efficacy analysis (26 patients were excluded as they were enrolled at a site that was closed for violations of Good Clinical Practice; Figure 1). At baseline, the mean eGFR was 63±19 ml/min/1.73 m^2 and 47% of patients had an eGFR < 60 ml/min/1.73 m^2. The patients were categorized according to the eGFR at baseline (<60 versus ≥60 ml/min/1.73m^2) and had similar characteristics according to treatment assignment within these sub-groups (Table 1). Overall, at baseline, patients with eGFR < 60 ml/min/1.73 m^2 (mean 47± 8 ml/min/1.73 m^2) were more likely to be older, female, have a history of diabetes, atrial fibrillation or prior stroke, to be taking a diuretic, and have marginally higher ejection fraction and NTproBNP; they were less likely to be taking an ACEi or ARB, and had lower systolic blood pressure (Supplementary Table 2). The mean eGFR was 77± 14 ml/min/1.73 m^2 in those with baseline eGFR ≥ 60 ml/min/1.73 m^2.

Prespecified Renal Outcomes

The composite renal outcome occurred in 33 of the 2407 patients (1.4%) in the sabubitril/valsartan group and 64 of the 2389 patients (2.7%) in the valsartan group, with a risk reduction of 50% (HR 0.50, 95%CI 0.33-0.77; P=0.001; Fig. 2). The 4-year risk of experiencing the renal composite outcome was 2.1% in the

sacubitril/valsartan group and 4.1% in the valsartan group, corresponding to a number needed to treat of 51 (28, 220) over this time period.

The treatment effect from an on-treatment analysis were similar to the intention-to-treat approach (HR 0.45; 95%CI 0.28 to 0.74). The treatment effect on the composite renal endpoint did not differ according to the baseline eGFR (<60 vs ≥ 60 ml/min/1.73 m^2; P-interaction=0.92; Table 2). Furthermore, there was no evidence for effect modification according to age (P-interaction=0.41), sex (P-interaction=0.90), or ejection fraction (P-interaction=0.31).

The overall result from the renal composite outcome was driven by the individual component of ≥50% reduction in eGFR from baseline, which occurred in 27 of the 2407 patients (1.1%) in the sacubitril/valsartan group and 60 of the 2389 patients (2.5%) of the valsartan group (HR 0.44, 95%CI 0.28-0.69). The development of ESRD occurred in 7 of 2407 patients (0.3%) in the sacubitril/valsartan group and in 12 of 2377 patients (0.5%) in the valsartan group (HR 0.58, 95%CI 0.23-1.47). There were 2 deaths from renal disease, with one occurring in the sacubitril/valsartan group and one in the valsartan group. The treatment effects on the individual components of the renal composite outcome did not differ according to the baseline eGFR (Table 2).

Renal Function over Time

From randomization through the end of study, the mean decline in eGFR was -2.0 (95%CI -2.2 to -1.9) ml/min/1.73 m^2 per year for the sacubitril/valsartan

group, compared with -2.7 (95%CI -2.8 to -2.5) ml/min/1.73 m^2 per year for the valsartan group, with an adjusted mean difference of 0.6 (95%CI 0.4 to 0.9; P<0.001) ml/min/1.73 m^2 per year (Fig. 3). Treatment effect estimates were similar after additional adjustment for changes in systolic blood pressure during the study (adjusted mean difference 0.6 (95%CI 0.3 to 0.8; P<0.001) ml/min/1.73 m^2 per year.

Safety and Adverse Events

Overall, adverse events requiring study drug discontinuation and serious adverse events, and permanent discontinuation due to renal impairment were more common among those with baseline eGFR < 60 ml/min/1.73 m^2 (versus eGFR ≥ 60 ml/min/1.73 m^2). Patients with baseline eGFR < 60 ml/min/1.73 m^2 assigned to the sacubitril/valsartan group had more hypotensive events, fewer episodes of elevated serum creatinine above 2 mg/dL, and no difference in the frequency of hyperkalemic events. Patients with baseline eGFR ≥ 60 ml/min/1.73 m^2 assigned to the sacubitril/valsartan group had fewer episodes of serum creatinine ≥ 2 mg/dl or hyperkalemia ≥6 mmol/L, compared with the valsartan group (Supplementary Table 3).

DISCUSSION

Among patients with HFpEF in the PARAGON-HF trial, sacubitril/valsartan resulted in lower rates of the renal composite outcome than valsartan. This result was driven mainly by a lower incidence of ≥50% decline in eGFR relative to baseline and was consistent across sub-groups of baseline eGFR (< 60 and ≥ 60 ml/min/1.73m^2). Patients in the sacubitril/valsartan group also had a lower overall rate of decline in eGFR, compared with those in the valsartan group.

There have been suggestions of renal benefit with combined angiotensin and neprilysin inhibition in prior studies of patients with heart failure. For example, in the OVERTURE trial there were fewer adverse events of renal impairment with omapatrilat (versus enalapril) in patients with NYHA class II-IV heart failure or LVEF≤30%.[23] In the PARADIGM-HF trial, while a significant decrease in the prespecified renal composite endpoint (end-stage renal disease, or decrease in eGFR of ≥50%, or a decrease of more than 30 ml/min/1.73 m^2 from randomization to less than 60 ml/min/1.73 m^2) was not observed, a post hoc analysis examining the effect of sacubitril/valsartan on the more conventional composite of end-stage renal disease or ≥50% decline in eGFR did show a decreased risk (HR 0.63; 95% CI 0.42 – 0.95), while the rate of decline in eGFR was also lower.[18] Overall, these results suggest beneficial renal effects for combined angiotensin/neprilysin inhibition in patients with heart failure across the spectrum of ejection fraction.

The renal benefits we observed in PARAGON-HF and PARADIGM-HF were not observed in the HARP-III trial, a relatively small trial which compared sacubitril/valsartan with irbesartan in 414 patients with CKD (eGFR 20-60 ml/min/1.73 m^2) of various etiologies. HARP-III observed no significant difference between groups in the primary outcome of measured eGFR at 12 months.[24] Of note, compared with participants of PARAGON-HF, those in HARP-III tended to be younger, predominantly male, had higher blood pressure, more advanced CKD and higher levels of proteinuria, and a very low prevalence of self-reported heart failure and diuretic use. These differences in patient characteristics, the smaller sample size, the much shorter duration of follow up, and the inclusion of a heterogenous group of CKD etiologies in HARP-III, may explain the discrepant results in renal outcomes between the two studies.

Sacubitril/valsartan lowered systolic blood pressure to a greater extent than valsartan in PARAGON-HF and was associated with a higher frequency of hypotensive events. Despite these differences, the occurrence of adverse renal events was lower with sacubitril/valsartan. Indeed, in additional analyses that adjusted for changes in systolic blood pressure, there still appeared to be benefit for sacubitril/valsartan in terms of a lower rate of decline in eGFR during the course of the study. These findings suggest that the beneficial renal effects are independent of blood pressure lowering.

The activation of several neurohormonal pathways in heart failure, including the renin-angiotensin system and the counter-regulatory natriuretic

peptide system, have important consequences for renal hemodynamics. Micropuncture studies in rodent models of heart failure have reported higher glomerular capillary pressures compared with controls, which are lowered with angiotensin converting enzyme (ACE) blockade.[25] Furthermore, omapatrilat (an inhibitor of both ACE and neprilysin) appeared to result in further reduction of intra-glomerular pressure, compared with enalapril.[26] However, the clinical relevance of these observations is uncertain, as several post-hoc analyses of randomized trials in heart failure have not found evidence for longer-term preservation of renal function (and potentially even accelerated decline) with the use of RAS inhibitors, versus placebo. [27–31] Similarly, trials of beta-blocker therapy in heart failure have also failed to result in renal benefits,[32] suggesting that optimization of cardiac function alone is not enough to attenuate renal function decline in heart failure. While it could be debated if the renal benefit we observed is reflective of less ARB effect with sacubitril/valsartan than single-agent valsartan, pharmacokinetic studies suggest bioequivalence in ARB dosing with the respective sacubitril/valsartan formulation.[33] Furthermore, similar renal benefits were observed in PARADIGM-HF, compared with enalapril, suggesting the renal benefits are not limited to differences in the hemodynamic effects of ARBs. Thus, our present findings suggest that simultaneous inhibition of the renin-angiotensin and neprilysin systems has opposing effects on the determinants of glomerular function. Additionally, it is likely that several non-hemodynamic pathways are also affected by combined angiotensin/neprilysin

inhibition, with some evidence suggesting an anti-inflammatory role for neprilysin inhibition (beyond that of RAS inhibitors alone) in terms of reducing biomarkers of renal fibrosis and inflammation.[34,35]

It is important to view these results in the context of recent therapeutic advances with sodium-glucose cotransporter 2 (SGLT2) inhibitors which have been shown to have long-term renal benefit in patients with T2DM, compared with placebo.[36–40] While the mean difference in eGFR decline in our analyses was 0.7 ml/min/1.73m^2/year, compared with 1.5 ml/min/1.73m^2/year in CREDENCE, there were major differences in the study design, including the specific recruitment of individuals with CKD (without requirement for HFpEF) and use of placebo-control in CREDENCE,[36] as well as different mechanisms of action and blood pressure lowering effects. In contrast to the initial decline in eGFR observed over the first few months of SGLT2 inhibitor therapy compared with placebo, we noted some minor fluctuations in eGFR until the 32-week measurement, perhaps reflective of titration of study medication dosing. Despite this, we still found significant attenuation of eGFR decline for sacubitril/valsartan over the course of follow-up, in both intention-to-treat and on-treatment analyses. Longer term renal outcome data with SGLT2 inhibitors in the specific setting of heart failure is limited to date.[41]

There are some limitations to the present analyses. Although the composite renal outcome was a key prespecified secondary outcome of PARAGON-HF, the trial was not primarily powered for analyses of the individual

renal components, nor for assessment of differences in eGFR decline. Urine albumin/creatinine ratio was not measured during the course of this study, limiting our ability to compare with PARADIGM-HF where, although CV benefits were maintained, modest increases in microalbuminuria were noted with sacubitril/valsartan, compared with enalapril. PARAGON-HF excluded patients with more advanced kidney disease (eGFR <30 ml/min/1.73 m^2) and had a modest proportion of non-Caucasians, thereby limiting generalizability of our findings to such populations.

In summary, in patients with HFpEF enrolled in the PARAGON-HF trial, treatment with sacubitril/valsartan resulted in fewer adverse renal events and slower decline in eGFR, despite a higher frequency of hypotensive events. Notably, these renal benefits appear to extend across the spectrum of baseline renal function, providing an important therapeutic option to slow renal function decline in patients with heart failure.

Table 1. Characteristics of the Patients at Baseline, According to the Estimated Glomerular Filtration Rate (eGFR) and Randomized Treatment Assignment.[a]

Characteristic	Patients with eGFR <60 ml/min/1.73m^2		Patients with eGFR ≥60 ml/min/1.73m^2	
	Valsartan (N=1,177)	Sacubitril/Valsartan (N=1,164)	Valsartan (N=1,211)	Sacubitril/Valsartan (N=1,243)
Age, yrs	75.2 ± 7.6	74.9 ± 7.6	70.4 ± 8.8	70.7 ± 8.5
Female, no. (%)	645 (54.8)	675 (58.0)	593 (49.0)	566 (45.5)
Race, no. (%)				
Asian	141 (12.0)	132 (11.3)	168 (13.9)	165 (13.3)
Black	23 (2.0)	23 (2.0)	27 (2.2)	29 (2.3)
Other	40 (3.4)	42 (3.6)	45 (3.7)	53 (4.3)
White	973 (82.7)	967 (83.1)	971 (80.2)	996 (80.1)
Geographic Region, no. (%)				
North America	175 (14.9)	176 (15.1)	96 (7.9)	112 (9.0)
Latin America	87 (7.4)	88 (7.6)	92 (7.6)	103 (8.3)
Western Europe	370 (31.4)	387 (33.2)	320 (26.4)	312 (25.1)
Central Europe	360 (30.6)	349 (30.0)	499 (41.2)	507 (40.8)
Asia-Pacific or other	185 (15.7)	164 (14.1)	204 (16.9)	209 (16.8)
Systolic blood pressure, mmHg	130.0 ± 15.8	129.2 ± 16.1	131.2 ± 14.9	131.7 ± 14.9
Heart rate, beats/min	70.0 ± 12.3	70.7 ± 12.5	70.6 ± 12.1	70.5 ± 12.1
Body-mass index[c]	30.3 ± 5.0	30.4 ± 4.9	30.3 ± 5.2	30.0 ± 4.9

Serum creatinine, mg/dL [d]	1.3 ± 0.3	1.3 ± 0.3	0.9 ± 0.2	0.9 ± 0.2
Estimated glomerular filtration rate, mL/min/1.73 m^2	47 ± 8	47 ± 8	77 ± 15	77 ± 14
Clinical features of heart failure				
Ischemic Cause, no. (%)	403 (34.2)	416 (35.8)	421 (34.8)	483 (38.9)
Left ventricular ejection fraction, %	57.8 ± 7.7	58.2 ± 7.8	57.2 ± 8.2	57.0 ± 7.8
Median NT-proBNP (25^{th}-75^{th} percentile), pg/mL	1025 [522 – 1854]	1060 [556 - 1809]	780 [400 - 1464]	764 [414 - 1407]
NYHA Classification, no. (%)				
I	34 (2.9)	33 (2.8)	30 (2.5)	40 (3.2)
II	892 (75.8)	884 (76.0)	947 (78.2)	982 (79.1)
III	246 (20.9)	244 (21.0)	228 (18.8)	214 (17.2)
IV	5 (0.4)	2 (0.2)	6 (0.5)	6 (0.5)
Medical History, no. (%)				
Hypertension	1128 (95.8)	1118 (96.0)	1151 (95.0)	1186 (95.4)
Diabetes	537 (45.6)	512 (44.0)	478 (39.5)	534 (43.0)
Atrial Fibrillation or	413 (35.3)	405 (34.9)	364 (30.1)	370 (29.8)

flutter				
Stroke	138 (11.8)	148 (12.7)	104 (8.6)	118 (9.5)
Hospitalization for heart failure	592 (50.3)	549 (47.2%)	579 (47.8)	586 (47.1)
Myocardial infarction	258 (21.9)	265 (22.8%)	264 (21.8)	296 (23.8)
Treatment, no. (%)				
Diuretic at randomization	1142 (97.0)	1121 (96.3)	1148 (94.8)	1173 (94.4)
ACE inhibitor or ARB at screening	1002 (85.1)	983 (84.5)	1063 (87.8)	1091 (87.8)
Mineralocorticoid-receptor antagonist at randomization	317 (26.9)	285 (24.5)	330 (27.3)	307 (24.7)
Beta-blocker at randomization	918 (78.0)	926 (79.6)	980 (80.9)	996 (80.1)

[a] Plus-minus values are mean +/- SD. There were no significant differences between the study groups except with respect to ischemia as a primary cause of heart failure in patients with eGFR ≥60 ml/min/1.73 m^2 (P=0.04).

[b] The GFR at baseline was estimated according to the four-variable Modification of Diet in Renal Disease formula. Data on eGFR at baseline was not available for one patient in the Valsartan group.

[c] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[d] This characteristic was measured at the randomization visit instead of the screening visit.

NYHA, New York Heart Association; BMI, Body Mass Index; ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blocker

Table 2. Renal Outcomes

Outcome	Valsartan	Sacubitril/Valsartan	Hazard Ratio (95% CI)
Overall	**(n=2389)**	**(n=2407)**	
Renal Composite, no. (%)	64 (2.7)	33 (1.4)	0.50 (0.33-0.77)
>50% decline in eGFR	60 (2.5)	27 (1.1)	0.44 (0.28-0.69)
End-stage renal disease	12 (0.5)	7 (0.3)	0.58 (0.23-1.47)
Death from renal causes	1 (0.04)	1 (0.04)	–
Patients with baseline eGFR < 60 ml/min/1.73m^2	**(n=1177)**	**(n=1164)**	
Renal Composite, no. (%)	32 (2.7)	16 (1.4)	0.50 (0.28-0.92)
>50% decline in eGFR	28 (2.4)	11 (1.0)	0.39 (0.20-0.79)
End-stage renal disease	12 (1.0)	6 (0.5)	0.51 (0.19-1.35)
Death from renal causes	1 (0.04)	1 (0.04)	–
Patients with baseline eGFR ≥60 ml/min/1.73m^2	**(n=1211)**	**(n=1243)**	
Renal Composite, no. (%)	32 (2.6)	17 (1.4)	0.51 (0.29-0.93)
>50% decline in eGFR	32 (2.6)	16 (1.3)	0.48 (0.27-0.88)
End-stage renal disease	0 (0.0)	1 (0.1)	–
Death from renal causes	0 (0.0)	0 (0.0)	–

Figure 1. Consort Flow Diagram

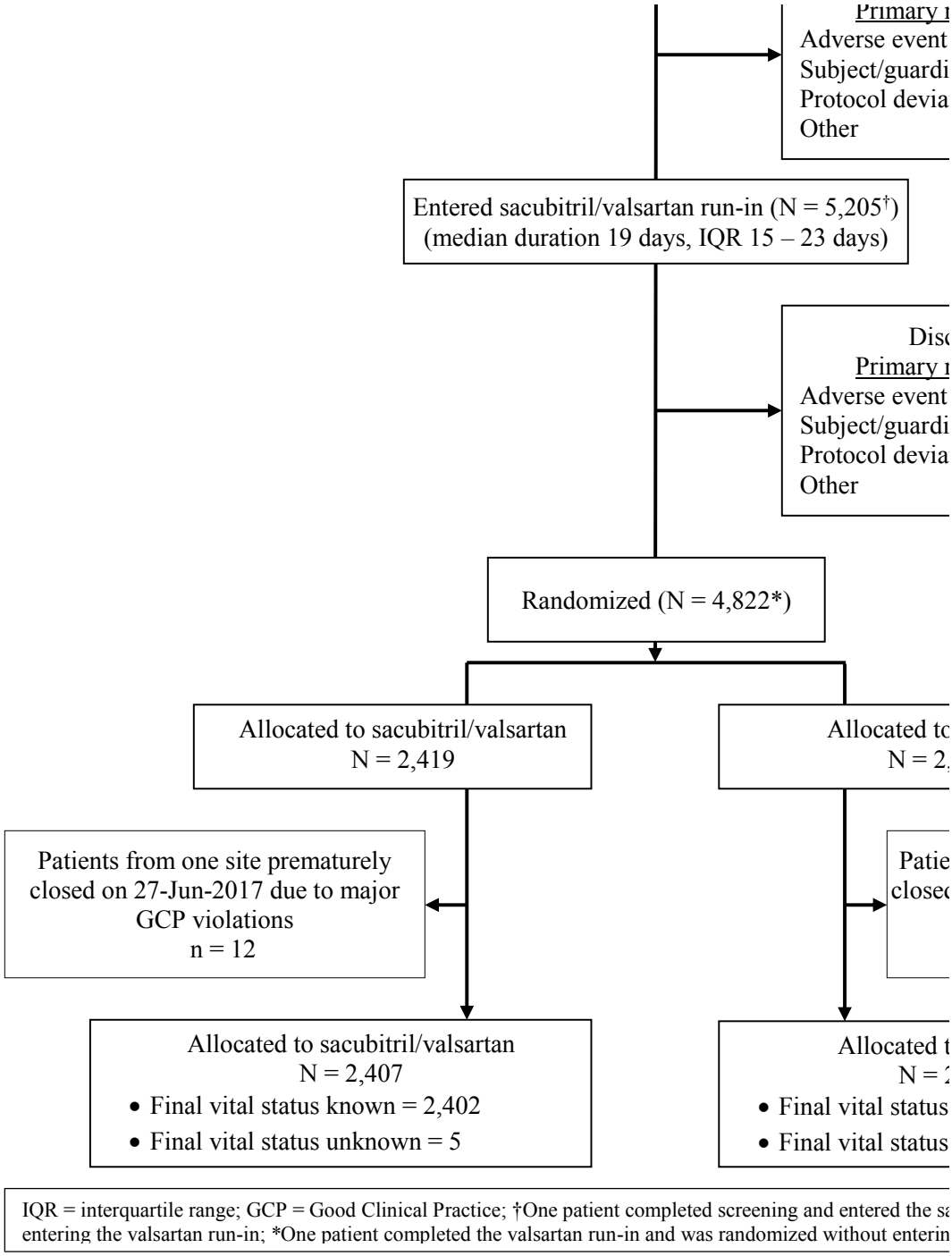
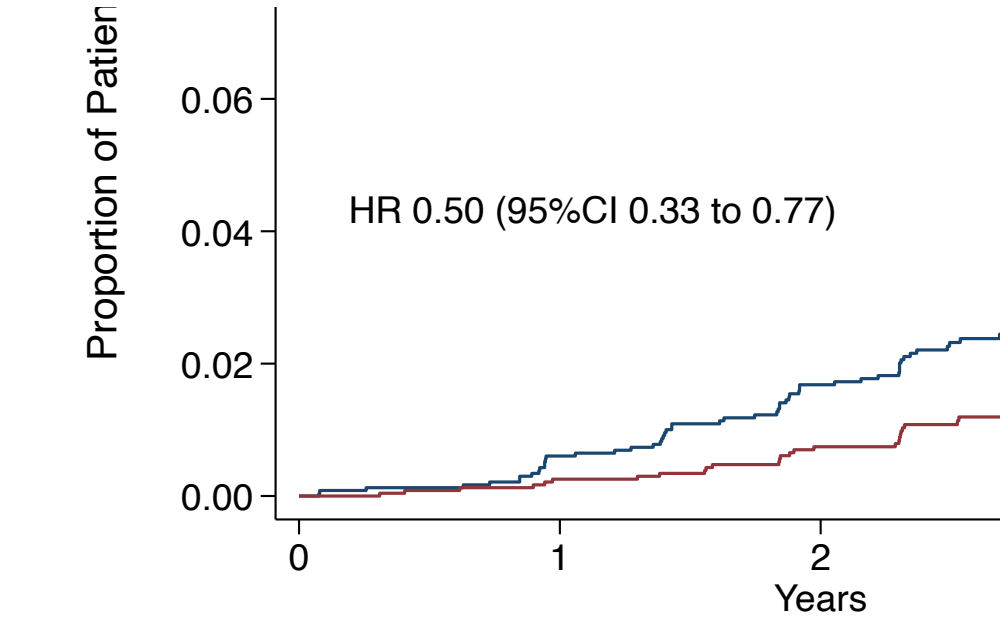


Figure 2. Kaplan-Meier Analysis of Renal Outcomes

Shown are estimates of the probability of a first occurrence of a prespecified renal composite outcome of either a ≥50% reduction in eGFR relative to baseline, attainment of end-stage renal disease, or death due to renal causes among patients who received at least one dose of either sacubitril/valsartan or valsartan.

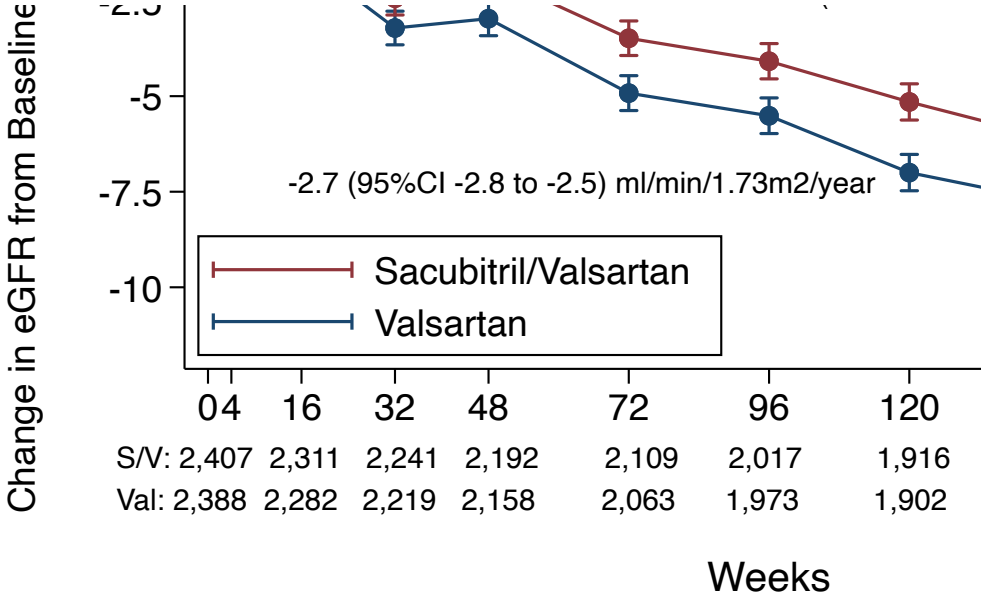


Number at risk

valsartan	2389	2273	2145
sacubitril/valsartan	2407	2320	2195

Figure 3. Change in renal function over time

Shown are the adjusted means for the estimated glomerular filtration rate (eGFR) over a period of 192 weeks among patients who received at least one dose of either sacubitril/valsartan or valsartan. The I bars indicate 95% confidence intervals. The eGFR was calculated according to the creatinine formula developed by the Chronic Kidney Disease Epidemiology Collaboration study. This panel is based on a mixed-model, repeated measures analysis in patients who received at least one dose of study drug and had a baseline and post-baseline measurement. The number of measurements available at each timepoint per arm are presented below the x-axis.


Change in eGFR from Baseline
-5
-7.5
-10
-2.7 (95%CI -2.8 to -2.5) ml/min/1.73m2/year
Sacubitril/Valsartan
Valsartan
0 4 16 32 48 72 96 120
S/V: 2,407 2,311 2,241 2,192 2,109 2,017 1,916
Val: 2,388 2,282 2,219 2,158 2,063 1,973 1,902
Weeks

Supplementary Table 1. Prespecified Renal Endpoint Definitions

Endpoint	Criteria
End-stage renal disease	One of the following: a) Initiation of dialysis (e.g., hemodialysis, peritoneal dialysis, or continuous veno-venous hemodialysis), continuing for ≥ 30 days without known recovery of renal function, Sites were queried to provide evidence of continuation of dialysis for over 90 days. b) Initiation of dialysis with death before 30 days (excludes dialysis events associated with acute kidney injury with death before 30 days) c) A drop in eGFR from baseline (randomization, i.e. Visit 199/201) to a value <15 mL/min/1.73m2 on two consecutive central laboratory measurements separated by ≥ 30 days. This event was identified programmatically by the sponsor d) Occurrence of kidney transplantation
Worsening Renal Function	Sustained reduction in estimated GFR (eGFR) by 50% from baseline (Randomization, Visit 199/201) as determined by 2 consecutive post-baseline central

	laboratory measurements separated by > 30 days. This event was identified programmatically by the sponsor.
Death from Renal Causes	Death occurring from complications of renal failure (e.g. hyperkalemia, uremia, acidosis) after a patient refuses or a physician withholds renal replacement therapy (i.e. initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. Such events were adjudicated as renal death only when another cause of death was not adjudicated.

Supplementary Table 2. Characteristics of the Patients at Baseline According to the Estimated Glomerular Filtration Rate (eGFR).[a]

Characteristic	Patients with eGFR <60 ml/min/1.73m^2 (n=2341)	Patients with eGFR ≥60 ml/min/1.73m^2 (n=2454)
Age, yrs	75.0 ± 7.6	70.6 ± 8.6
Female, no. (%)	1320 (56.4)	1159 (47.2)
Race, no. (%)		
Asian	273 (11.7)	333 (13.6)
Black	46 (2.0)	56 (2.3)
Other	82 (3.5)	98 (4.0)
White	1940 (82.9)	1967 (80.2)
Geographic Region, no. (%)		
North America	351 (15.0)	208 (8.5)
Latin America	175 (7.5)	195 (8.0)
Western Europe	757 (32.3)	632 (25.8)
Central Europe	709 (30.3)	1006 (41.0)
Asia-Pacific or other	349 (14.9)	413 (16.8)
Systolic blood pressure, mmHg	129.6 ± 16.0	131.5 ± 14.9
Heart rate, beats/min	70.3 ± 12.4	70.5 ± 12.1
Body-mass index[c]	30.3 ± 4.9	30.1 ± 5.1
Serum creatinine, mg/dL [d]	1.3 ± 0.3	0.9 ± 0.2
Estimated glomerular filtration rate, mL/min/1.73 m^2	47 ± 8	77 ± 14
Clinical features of heart failure		
Ischemic Cause, no. (%)	819 (35.0)	904 (36.8)
Left ventricular ejection fraction, %	58.0 ± 7.8	57.1 ± 8.0
Median NT-proBNP (25th-75th percentile), pg/mL	1040 [541 – 1820]	770 [409 - 1438]

NYHA Classification, no. (%)		
I	67 (2.9)	70 (2.9)
II	1776 (75.9)	1929 (78.6)
III	490 (20.9)	442 (18.0)
IV	7 (0.3)	12 (0.5)
Medical History, no. (%)		
Hypertension	2246 (95.9)	2337 (95.2)
Diabetes	1049 (44.8)	1012 (41.2)
Atrial Fibrillation or flutter	818 (35.1)	734 (30.0)
Stroke	286 (12.3)	222 (9.1)
Hospitalization for hearth failure	1141 (48.7)	1165 (47.5%)
Myocardial infarction	523 (22.3)	560 (22.8%)
Treatment, no. (%)		
Diuretic at randomization	2263 (96.7)	2321 (94.6)
ACE inhibitor or ARB at screening	1985 (84.8)	2154 (87.8)
Mineralocorticoid-receptor antagonist at randomization	602 (25.7)	637 (26.0)
Beta-blocker at randomization	1844 (78.8)	1976 (80.5)
Randomized to Sacubitril/Valsartan, no. (%)	1164 (49.7)	1243 (50.7)

[a] Plus-minus values are mean +/- SD. There were significant differences between the study groups with respect to age, sex, region, systolic blood pressure, creatinine, eGFR, ejection fraction, NTproBNP, diabetes mellitus, atrial fibrillation, stroke, diuretics, and ACEi/ARB use.

[b] The GFR at baseline was estimated according to the four-variable Modification of Diet in Renal Disease formula. Data on eGFR at baseline was not available for one patient in the Valsartan group.

[c] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[d] This characteristic was measured at the randomization visit instead of the screening visit.

NYHA, New York Heart Association; BMI, Body Mass Index; ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blocker

Supplementary Table 3. Key Adverse Events [a]

Characteristic	Patients with eGFR <60 ml/min/1.73m^2		Patients with eGFR ≥60 ml/min/1.73m^2	
	Valsartan (N=1177)	Sacubitril/ Valsartan (N=1164)	Valsartan (N=1211)	Sacubitril/ Valsartan (N=1243)
≥1 Adverse event, no. (%)	1138 (96.7)	1126 (96.7)	1151 (95.0)	1170 (94.1)
Adverse event requiring study drug discontinuation, no. (%)	327 (27.8)	279 (24.0)	192 (15.9)	213 (17.1)
≥1 Serious adverse event, no. (%)	759 (64.5)	750 (64.4)	654 (54.0)	672 (54.1)
Serious adverse event requiring study drug discontinuation, no. (%)	209 (17.8)	171 (14.7)	129 (10.7)	155 (12.5)
Permanent treatment discontinuation due to renal impairment, no. (%)	68 (5.8)	57 (4.9)	22 (1.8)	13 (1.0)
Hypotension with SBP <100 mm Hg, no. (%)	125 (10.6)	219 (18.8)	132 (10.9)	161 (13.0)
Elevated Serum Creatinine, no.				

(%)				
≥2.0 mg/dl	274 (23.3)	231 (19.8)	54 (4.5)	30 (2.4)
≥2.5 mg/dl	96 (8.2)	86 (7.4)	13 (1.1)	11 (0.9)
≥3.0 mg/dl	34 (2.9)	32 (2.7)	6 (0.5)	6 (0.5)
Hyperkalemia				
>5.5 mmol/L	212 (18.0)	183 (15.7)	149 (12.3)	133 (10.7)
>6 mmol/L	55 (4.7)	50 (4.3)	46 (3.8)	25 (2.0)

[a] Shown are the results of prespecified safety events at any time after randomization for patients who received at least one dose of study drug (includes events that occurred during treatment or within 7 days of last receipt of study drug). In those with eGFR < 60 ml/min/1.73 m^2 there were more hypotension events in the sacubitril/valsartan group (P<0.001), fewer events of serum creatinine ≥2 mg/dl (P=0.04), fewer adverse events requiring study drug discontinuation (P=0.04) and fewer serious adverse events requiring study drug discontinuation (P=0.04). In those with eGFR ≥ 60 ml/min/1.73 m^2 there were significantly fewer events of serum creatinine ≥ 2 mg/dl (P=0.005) and hyperkalemia ≥6 mmol/L (P=0.01).

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