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RESEARCH ARTICLE

Longitudinal trajectories in renal function before and after heart failure hospitalization among patients with heart failure with preserved ejection fraction in the PARAGON-HF trial

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Aims Worsening renal function may impact long-term outcomes in heart failure (HF). However, little is known about the longitudinal trajectories in renal function in relation to HF hospitalization or how this high-risk clinical event impacts renal outcomes.

Methods and results In PARAGON-HF, we evaluated the association between recency of prior HF hospitalization (occurring pre-randomization) and subsequent first renal composite outcome: (i) time to ≥50% decline in estimated glomerular filtration rate (eGFR); (ii) development of end-stage renal disease; or (iii) death attributable to renal causes. A total of 2306 (48.1%) patients had a history of prior HF hospitalization. Incident rates of the renal outcome were highest in those most recently hospitalized and decreased with longer time from last hospitalization. Treatment effect on the renal outcome of sacubitril/valsartan versus valsartan was similar between patients with (hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.24–0.76) and without (HR 0.63; 95% CI: 0.33–1.18; $p_{interaction} = 0.39$) a prior history of HF hospitalization and appeared consistent regardless of timing of prior hospitalization for HF ($p_{interaction} = 0.39$). Serial eGFR measurements leading up to and after a HF hospitalization (occurring during the study period) and estimated eGFR trajectories using repeated measures regression models with restricted cubic splines were also examined. Patients experiencing a post-randomization HF hospitalization had a significant decline in eGFR prior to hospitalization while patients without HF hospitalization experienced a relatively stable eGFR trajectory ($p < 0.001$). A change in the rate of decline of eGFR trajectory was observed 12 months preceding a HF hospitalization, and continued in the post-discharge window to 12 months following hospitalization.

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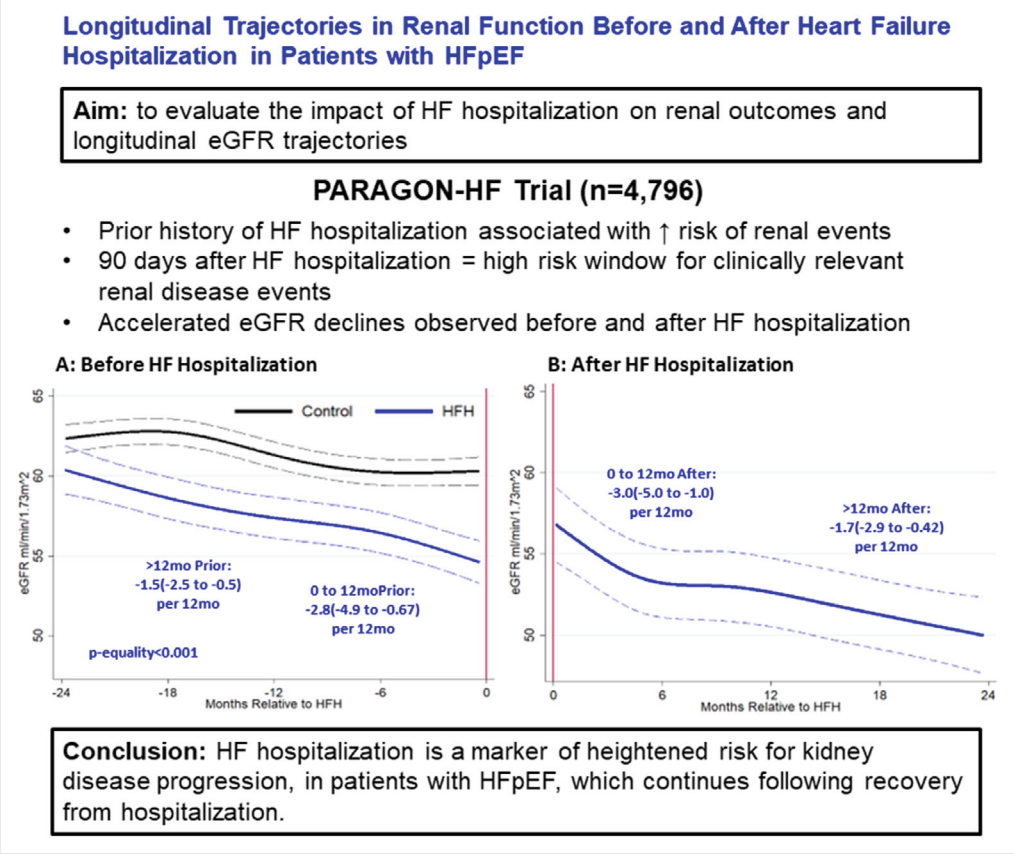
Conclusions Heart failure hospitalization denotes increased risk for kidney disease progression which continues following recovery from HF decompensation in patients with HF with preserved ejection fraction.
Clinical Trial Registration: PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction), ClinicalTrials.gov NCT01920711.

Graphical Abstract



Longitudinal trajectories in renal function before and after heart failure hospitalization (HFH) in Patients with heart failure with preserved ejection fraction (HFpEF). eGFR, estimated glomerular filtration rate; HF, heart failure.

Keywords Heart failure with preserved ejection fraction • Hospitalization • Kidney function • Sacubitril/valsartan

Introduction

Hospitalization for heart failure (HF) represents a destabilizing event in the clinical trajectory of patients with chronic HF.[1] The time period around hospitalization is characterized by particular vulnerability to recurrent clinical events, irrespective of left ventricular ejection fraction (LVEF).[2,3] Hospitalized patients with HF carry a high prevalence of comorbid kidney disease across the LVEF spectrum.[4] Renal function during and immediately following acute HF admissions is often changing dynamically with a substantial proportion of such admissions resulting in worsening kidney function.[5] How the long-term trajectory of renal function is altered in relation to a HF hospitalization (both prior to and immediately following) is not well described.

Although HF therapies including sacubitril/valsartan have been shown to reduce renal events and attenuate estimated glomerular filtration rate (eGFR) decline,[6] renal dysfunction remains one of the most common reasons for suboptimal use of guideline-directed

medical therapy.[7] Prior work has highlighted proximity to HF hospitalization as a risk marker for clinical disease progression with the greatest absolute benefits of sacubitril/valsartan observed early after hospitalization.[8] Whether this extends to renal outcomes in patients with HF with preserved ejection fraction (HFpEF) remains to be determined.

As such, understanding how HF hospitalization may modify the course of renal function decline and risk of kidney disease progression, especially given the availability of potential risk lowering therapies, is increasingly important. In this *post hoc* analysis of the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial, we aimed: (i) to evaluate renal outcomes and treatment effects of sacubitril/valsartan according to recency of prior HF hospitalization (occurring pre-randomization), and (ii) to describe the longitudinal trajectory of eGFR before and after HF hospitalization (occurring during the study period).

Methods

Study design

The design and results of the PARAGON-HF trial have been previously reported.[9,10] In brief, PARAGON-HF was a double-blind, randomized, controlled trial comparing sacubitril/valsartan versus valsartan in patients ≥50 years of age with symptomatic HF (New York Heart Association [NYHA] class II–IV), preserved ejection fraction (LVEF ≥45%), evidence of structural heart disease, elevated natriuretic peptides, and necessity for diuretics for at least 30 days. Key exclusion criteria were acute decompensated HF at screening, symptomatic hypotension or systolic blood pressure <100 mmHg at screening, eGFR <30 ml/min/1.73 m^2, or serum potassium >5.2 mmol/L at screening. The study protocol was approved by the ethics committee at each study site and the study participants provided written informed consent.

Clinical endpoints

The composite renal outcome was a pre-specified secondary endpoint defined as follows: (i) time to ≥50% decline in eGFR relative to baseline; (ii) development of end-stage renal disease; or (iii) death attributable to renal causes.

Heart failure hospitalization status

Analyses were performed according to: (i) history and timing of HF hospitalization prior to randomization, and (ii) the occurrence of a HF hospitalization during the study period. Timing of prior HF hospitalizations was based on patient history and medical record corroboration when available and was categorized based on a prior PARAGON-HF publication[8]: ≤30 days, 31–90 days, 91–180 days, >180 days, or never previously hospitalized. Where only the month of the prior hospitalization was known, the date was assigned as the 1st of the month and in cases where only the year of hospitalization was known, the date was assigned as the 1st of January. HF hospitalizations during the study were blindly adjudicated according to pre-specified criteria.[10]

Statistical analysis

Baseline characteristics of patients with and without a prior history of HF hospitalization were compared with Student's *t*-tests and Pearson chi-square tests where appropriate. Baseline characteristics according to recency of prior HF hospitalization have been previously published.[8] Data were reported as mean ± standard deviation when distributed normally, frequency (percentage) for categorical variables and median (interquartile range) for skewed distributions. All analyses were carried out in the intention-to-treat population.

We first examined the association between history of prior HF hospitalization (occurring pre-randomization) and eGFR slope. eGFR was calculated according to the Modification of Diet in Renal Disease formula. Changes in eGFR over a period of 192 weeks were assessed using repeated measures mixed-effect models with available data from randomization and at 4, 16, 32 and 48 weeks as well as every 24 weeks thereafter. Treatment, time, and the interaction between assigned treatment and time were included as fixed effects. Annual decline in eGFR from baseline was analysed according to a history of prior HF hospitalization and treatment. Interaction testing was performed to assess for differences in treatment effects of sacubitril/valsartan versus valsartan on eGFR decline in patients with and without a prior history of HF hospitalization.

Next, we evaluated the renal composite outcome according to timing from prior hospitalization (occurring pre-randomization) using Cox proportional hazard models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) stratified according to geographic region. Kaplan–Meier curves were used to depict time to first event of the renal composite outcome based on recency of HF hospitalization. The association between timing of prior HF hospitalization and the renal composite outcome was evaluated in models that were both unadjusted and adjusted for age, sex, LVEF, NYHA class, and log transformed N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), baseline eGFR, albumin, sodium, haemoglobin and systolic blood pressure, which were all selected *a priori*. Treatment effect of sacubitril/valsartan on the incidence of the renal composite outcome was assessed within each category.

Lastly, the temporal trajectory of eGFR before and after HF hospitalization occurring during the study period was characterized using repeated measures regression models with restricted cubic splines. eGFR was plotted relative to time defined as the number of months prior to or immediately following the HF hospitalization event or end of follow-up. An estimate of the average trajectory of eGFR that would have been observed if patients were continuously monitored prior to and following hospitalization for HF was derived from pre-specified trial visits. Estimates of the average decline or recovery in eGFR during each time frame before and after hospitalization were determined using linear piecewise models. For this analysis, patients who experienced HF hospitalization during the study period were compared to a control population who remained free of all-cause hospitalization during the follow-up period. In addition, patients who survived hospitalization for HF were followed up for potential recovery in eGFR in the post-discharge period. A p-value < 0.05 was considered statistically significant and all analyses were conducted using STATA version 16.0 (StataCorp., College Station, TX, USA).

Results

Patient characteristics

From July 2014 to December 2016, 4796 patients were randomized in PARAGON-HF. Of the randomized patients, 2306 (48.1%) had a prior history of hospitalization for HF before randomization. Patients with prior history of HF hospitalization were

Table 1 Baseline characteristics by prior heart failure hospitalization before randomization

	No prior HF hospitalization ($n = 2490$)	Prior HF hospitalization ($n = 2306$)	p-value
Randomization to sacubitril/valsartan	1272 (51.1%)	1135 (49.2%)	0.20
Age, years	74 ± 8	72 ± 9	<0.001
Women	1366 (54.9%)	1113 (48.3%)	<0.001
Race			0.22
Caucasian	292 (11.7%)	315 (13.7%)	
Black	48 (1.9%)	54 (2.3%)	
Asian	108 (4.3%)	72 (3.1%)	
Other	2042 (82.0%)	1865 (80.9%)	
Geographic region			<0.001
Asia/Pacific and other	349 (14.0%)	413 (17.9%)	
Central Europe	853 (34.3%)	862 (37.4%)	
Latin America	221 (8.9%)	149 (6.5%)	
North America	284 (11.4%)	275 (11.9%)	
Western Europe	783 (31.4%)	607 (26.3%)	
Serum creatinine, mmol/L	95.3 ± 26.8	97.6 ± 27.8	0.003
eGFR, ml/min/1.73 m^2	62.4 ± 18.5	62.7 ± 19.7	0.56
Body mass index, kg/m^2	30.0 ± 4.9	30.5 ± 5.1	0.001
Systolic blood pressure, mmHg	130 ± 15.3	131 ± 15.6	0.50
Heart rate, bpm	70 ± 12.0	71 ± 12.5	0.003
EF, %	58 ± 7.9	57 ± 7.8	<0.001
NYHA class			0.018
I	51 (2.0%)	86 (3.7%)	
II	1995 (80.2%)	1711 (74.2%)	
III	440 (17.7%)	492 (21.3%)	
IV	3 (0.1%)	16 (0.7%)	
Stroke	16 (0.7%)	263 (11.4%)	0.07
Myocardial infarction	544 (21.8%)	539 (23.4%)	0.21
Atrial fibrillation	753 (30.4%)	799 (34.7%)	0.001
Diuretics	2346 (94.2%)	2239 (97.1%)	<0.001
Furosemide dose equivalent (mg)	40 (20–40)	40 (25–60)	<0.001
MRA	509 (20.4%)	730 (31.7%)	<0.001
ACEi/ARB	2165 (86.9%)	1974 (85.6%)	0.18
Beta-blocker	1957 (78.6%)	1864 (80.8%)	0.05

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

slightly younger (72 vs. 74 years, $p < 0.001$), less often women (48.3% vs. 54.9%, $p < 0.001$), had similar baseline eGFR (62.7 vs. 62.4 ml/min/1.73 m^2, $p = 0.56$), more severe HF symptoms, higher baseline diuretic use and more often had history of atrial fibrillation than those without a prior history of HF hospitalization (*Table 1*).

Change in estimated glomerular filtration rate over time in patients with and without a prior history of hospitalization for heart failure occurring pre-randomization

Patients with a prior history of HF hospitalization appear to experience a similar degree of eGFR decline compared to those without prior history of HF hospitalization (−2.2 vs. −2.0 ml/min/1.73 m^2, $p = 0.08$) (*Figure 1*). Treatment with sacubitril/valsartan versus valsartan resulted in attenuation of eGFR decline, irrespective of prior history of HF hospitalization. Patients with (mean between-arm difference of 0.4 ml/min/1.73 m^2; 95% CI 0.1–0.8, $p = 0.01$) and without (mean between-arm difference of 0.6 ml/min/1.73 m^2; 95% CI 0.2–0.9, $p < 0.0001$) a prior history of HF hospitalization, experienced a similar degree of attenuation in eGFR decline with sacubitril/valsartan ($p_{interaction} = 0.36$).

Composite renal outcome according to history of prior hospitalization for heart failure occurring pre-randomization

Overall, the incidence of the pre-specified renal composite outcome occurred in 57 (2.5%) patients with a prior history of

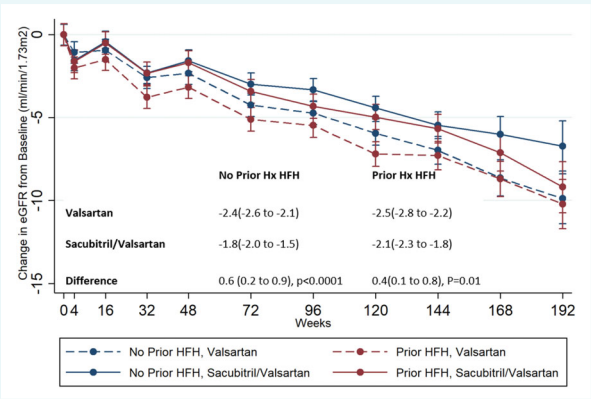


Figure 1 Change in estimated glomerular filtration rate (eGFR) over time in patients with and without prior history (Hx) of heart failure hospitalization (HFH) according to treatment assignment. Annual decline in eGFR (ml/min/1.73 m^2) calculated according to the Modification of Diet in Renal Disease with error bars denoting 95% confidence intervals. *P*-values are reported for differences in annual eGFR decline between treatment groups (valsartan vs. sacubitril/valsartan).

HF hospitalization and in 40 (1.6%) patients without such history, yielding a significantly increased risk for the development of the renal composite outcome (HR 1.60; 95% CI 1.06–2.40, $p = 0.02$) in patients with a prior history of HF hospitalization. Treatment effect on the renal composite outcome of sacubitril/valsartan compared with valsartan was similar between patients with (HR 0.43; 95% CI 0.24–0.76) and without (HR 0.63; 95% CI 0.33–1.18; $p_{interaction} = 0.39$) a history of prior HF hospitalization (*Figure 2*).

Incidence of the renal composite outcome and treatment effect according to recency of heart failure hospitalization occurring pre-randomization

Incident rates of the renal composite outcome were highest in those most recently hospitalized and decreased with longer time from last hospitalization: ≤30 days (1.1 [0.7–1.7] per 100 patient-years), 31–90 days (0.8 [0.5–1.4] per 100 patient-years), 91–180 days (0.7 [0.4–1.4] per 100 patient-years), >180 days (0.8 [0.5–1.3] per 100 patient-years), and never hospitalized (0.6 [0.4–0.8] per 100 patient-years) (*Table 2*). Those screened within the first 30 days of prior hospitalization for HF experienced the highest risk of the renal composite outcome (HR 2.19; 95% CI 1.26–3.81) compared to those never hospitalized. This remained significant after adjustment for age, sex, ejection fraction, NYHA class, NT-proBNP level, baseline eGFR, albumin, sodium, haemoglobin, and systolic blood pressure.

The treatment effect on the renal composite outcome of sacubitril/valsartan compared with valsartan alone appeared consistent regardless of timing of prior hospitalization for HF ($p_{interaction} = 0.39$). As such, the greatest absolute benefits were observed in those hospitalized within 90 days (*Figure 3*). In those patients treated with sacubitril/valsartan, the absolute risk reductions were: 0.8% (≤30 days), 0.9% (31–90 days), 0.4% (91–180 days) and 0.5% (>180 days) compared to 0.3% in those never hospitalized.

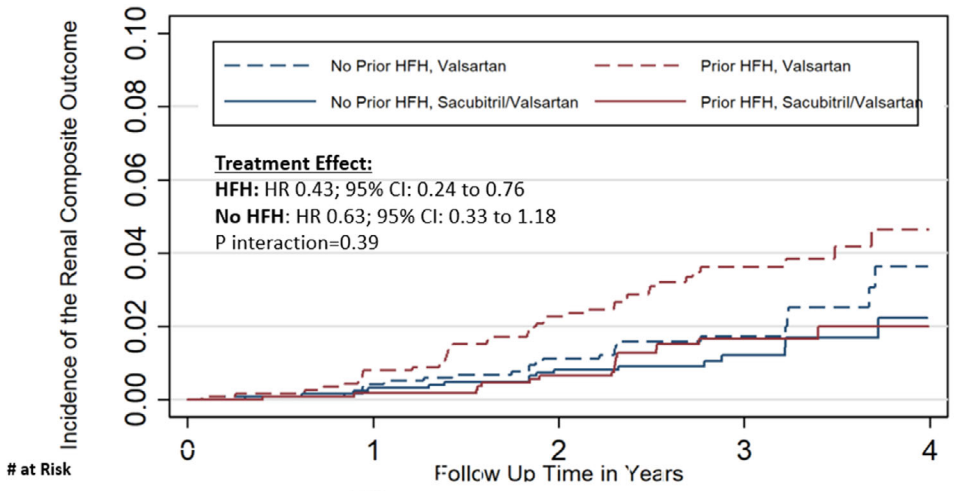


Figure 2 Kaplan–Meier analysis for time to first occurrence of the renal composite outcome according to prior history of heart failure hospitalization (HFH). CI, confidence interval; HR, hazard ratio; Sac/Val, sacubitril/valsartan; Val, valsartan.

Table 2 Renal outcomes and treatment response to sacubitril/valsartan versus valsartan by timing from prior hospitalization

Time from prior hospitalization to screening	*N*	First events	Incident rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Treatment effect (Sac/Val vs. Val)
≤30 days	622	19	1.1 (0.7–1.7)	2.19 (1.26–3.81)	1.81 (1.03–3.17)	0.39 (0.14–1.03)
31–90 days	555	13	0.8 (0.5–1.4)	1.48 (0.79–2.78)	1.14 (0.60–2.18)	0.27 (0.07–0.98)
91–180 days	435	9	0.7 (0.4–1.4)	1.28 (0.62–2.65)	1.01 (0.49–2.11)	0.54 (0.13–2.18)
>180 days	694	16	0.8 (0.5–1.3)	1.45 (0.81–2.59)	1.40 (0.78–2.53)	0.49 (0.17–1.42)
Never hospitalized	2490	40	0.6 (0.4–0.8)	Ref.	Ref.	0.63 (0.33–1.18)

CI, confidence interval; HR, hazard ratio; Sac/Val, sacubitril/valsartan; Val, valsartan.

$p_{interaction} = 0.39$.

[a]Adjusted for age, sex, ejection fraction, New York Heart Association class, log transformed N-terminal prohormone of B-type natriuretic peptide, baseline estimated glomerular filtration rate, albumin, sodium, haemoglobin and systolic blood pressure and stratified by geographic region.

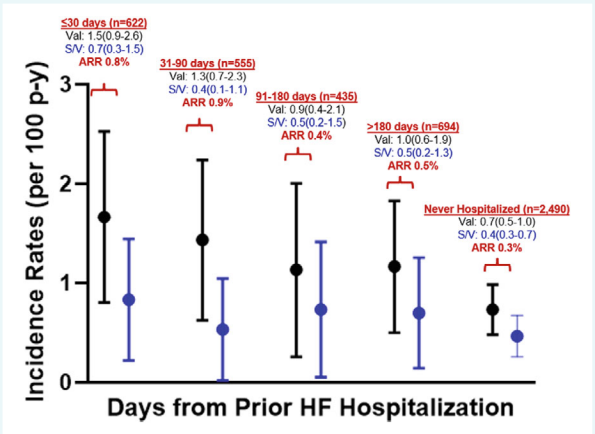


Figure 3 Incidence rates of the renal composite outcome in sacubitril/valsartan (S/V) and valsartan (Val) alone treatment arms by group categorized by time from prior heart failure (HF) hospitalization. All incidence rates are expressed per 100 patient-years (p-y). ARR, absolute risk reduction.

Temporal trajectory of estimated glomerular filtration rate before and after heart failure hospitalization occurring during the study period

In PARAGON-HF, 838 patients experienced a first post-randomization HF hospitalization. Differences in baseline characteristics are outlined in online supplementary *Table S1*. Compared to the control population ($n = 2009$), patients who experienced a HF hospitalization during the study were slightly older (74 ± 9 vs. 71 ± 9 years, $p < 0.001$), with an overall greater burden of comorbidities including atrial fibrillation (36.3% vs. 30.8%, $p = 0.005$), stroke (12.6% vs. 9.4%, $p = 0.01$) and history of myocardial infarction (25.2% vs. 21.5%, $p = 0.03$). Patients with a post-randomization HF hospitalization had a lower baseline eGFR (59 ± 19 vs. 65 ± 19 ml/min/1.73 m^2), more severe NYHA class ($p < 0.001$), more frequent use of a diuretic (96.9% vs. 95.1%, $p = 0.03$), with higher baseline mineralocorticoid receptor antagonist use (30.4% vs. 24.3%, $p < 0.001$) but lower angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use (82.7% vs. 88.9%, $p < 0.001$). eGFR declined substantially prior to a post-randomization HF hospitalization in comparison to a relative stable trajectory observed in patients without a HF hospitalization occurring during the course of the study ($p < 0.001$) (*Figure 4A*). A change in the rate of kidney function decline was observed at 12 months preceding hospitalization for HF (average eGFR decline of −2.8 ml/min/1.73 m^2). eGFR decline continued at a similarly steep rate in the 12 months after hospitalization (average eGFR decline of −3.0 ml/min/1.73 m^2) (*Figure 4B*). Among patients who remained free of all-cause hospitalization after 12 months, eGFR decline resumed at a similar rate to that occurring pre-hospitalization (−1.7 vs. −1.5 ml/min/1.73 m^2).

Discussion

In this *post hoc* analysis of the PARAGON-HF trial we observed that: (i) a prior history of HF hospitalization (occurring pre-randomization) was associated with an increased risk for renal events and the benefit of sacubitril/valsartan on renal outcomes was consistent irrespective of hospitalization history; (ii) the period early post-hospitalization was associated with the highest risk for renal disease progression with similar relative benefits (and thus higher absolute benefits) of treatment with sacubitril/valsartan observed in this high-risk window; and (iii) accelerated declines in eGFR were observed in the 12-month period immediately preceding and following HF hospitalization (occurring during the study period) (*Graphical Abstract*). Taken together, these data suggest that HFpEF patients experiencing HF hospitalization represent a distinct cohort at elevated risk for accelerated kidney disease progression which continues after recovery from hospitalization. These patients may benefit from risk lowering therapies early after hospitalization.

Previous work has demonstrated that the treatment effect of sacubitril/valsartan on the primary endpoint of PARAGON-HF

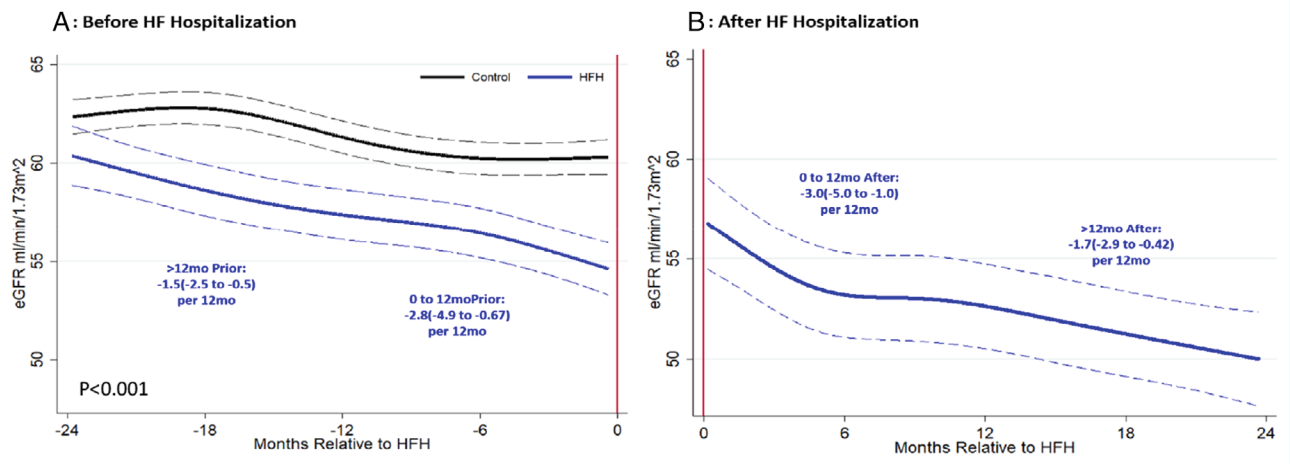


Figure 4 Trajectory of estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) before (*A*) and after (*B*) heart failure (HF) hospitalization (HFH) occurring during the study period. Decline in eGFR (ml/min/1.73 m^2) is presented for patients who experienced a post-randomization HFH (blue line) and patients who did not experience a post-randomization HFH (black line). The red line denotes timing of the HFH event.

(total HF hospitalizations and cardiovascular death) may be influenced by proximity to prior HF hospitalization, with patients more recently hospitalized deriving greater benefit.[8] The current analyses are consistent with this observation and suggest similar relative benefits (and thus greater absolute benefits) with respect to the renal composite outcome among those recently hospitalized. A number of mechanistic factors contribute differentially to the increased risk of renal disease progression that is observed in patients who experience HF hospitalization: reduced cardiac output, increased filling pressures, right ventricular dysfunction, intravascular volume depletion resulting from aggressive decongestion therapies, and acquired hospital comorbidities such as infection or blood loss.[5] Moreover, the period preceding hospitalization for acutely decompensated HF is often characterized by initiation or increase of diuretic therapies, which also influences renal function.

Additionally, activation of neurohormonal pathways contribute to the development of kidney dysfunction which often complicates admissions for acute HF.[5] A more marked dysregulation of such pathways, activation of pro-inflammatory states and ongoing congestion in the peri-hospitalization period may explain the increased renal risk and resulting greater absolute renal benefits observed early after hospitalization with sacubitril/valsartan. How risk and treatment effect are influenced across the spectrum of eGFR and in patients with severe kidney disease would be important to characterize in future studies.

Chronic kidney disease represents a significant comorbidity among patients with chronic HF regardless of ejection fraction. Recent large scale registry data show that greater than 60% of hospitalized patients with HF had an eGFR of <60 ml/min/1.73 m^2.[4] Another study demonstrated similarly high rates of renal dysfunction at 60–70% among patients with decompensated HF.[11] Specifically in HFpEF, both short-term and long-term deterioration in kidney function are markers of adverse outcomes.[12,13] Importantly, our data suggest that the increased renal risk observed in proximity to hospitalization for HF may potentially be modifiable through early initiation of risk lowering therapies. While other therapies such as mineralocorticoid receptor antagonists[14] and sodium–glucose cotransporter 2 inhibitors[15] have been shown to reduce HF events in HFpEF, these therapies have not definitively been shown to attenuate risk of clinically important kidney disease events in patients with HFpEF. In our analysis, sacubitril/valsartan demonstrated risk reductions of the key secondary endpoint of composite renal events and slowed eGFR decline consistently irrespective of prior history and timing from prior HF hospitalization. As such, there may be greater absolute risk reductions when sacubitril/valsartan is initiated in the post-discharge setting, which this analysis highlights as a high-risk period for renal disease progression. This hypothesis requires prospective validation and represents an important secondary outcome of the randomized controlled trial PARAGLIDE-HF (NCT03988634) which is evaluating sacubitril/valsartan in acute HFpEF.

Suboptimal implementation of guideline-directed HF medical therapy is frequent[16] and may be linked to worsening HF.[17] Variation in kidney function is a common reason for premature drug discontinuation and often contributes to clinical inertia limiting new initiation or up-titration of evidence-based HF therapies. However, these therapies may actually prevent further renal decline and may also improve renal function over time. Worsening renal failure post-discharge is adversely prognostic[18] and our data demonstrating consistent efficacy of sacubitril/valsartan on renal outcomes in proximity to HF hospitalization further emphasize the importance of capitalizing on this opportunity to optimize medical therapy.

Multiple prior studies have established HF hospitalization as a marker of increased risk of cardiovascular outcomes; however, less is known about how HF hospitalization precisely influences the long-term trajectory of renal function. Similarly steep rates of

decline are seen within 12 months pre and post HF hospitalization occurring during the study period. Interestingly, recovery from decompensation is not mirrored by similar recovery in renal function following hospitalization. This suggests that patients with HFpEF who experience HF hospitalization represent a distinct high-risk group of patients that are on a steeper trajectory for progression of kidney disease which continues after recovery from the HF hospitalization. Notably, the rate of kidney function decline appears somewhat recoverable after 1 year, resuming a similar rate of decline observed 12 months prior to hospitalization (−1.7 vs. −1.5 ml/min/1.73 m^2).

As mentioned previously, this analysis highlights the post-discharge period as a high-risk period for renal disease progression. Prior studies have characterized the occurrence of worsening renal function that occurs following hospital discharge.[13] The novel methods outlined in this study not only allow a more granular analysis of the changes that occur in relation to hospitalization, but importantly enable a description of kidney function trajectory prior to the destabilizing event. We found that while starting from a slightly lower baseline, eGFR decline begins well before the actual HF hospitalization event. To our knowledge this is the first such characterization of eGFR trajectory prior to HF hospitalization and underscores the pre-admission period as a similarly high-risk period. Thus, the pre-admission period may also represent an important opportunity for up-titration of risk lowering HFpEF therapies in suitably stable patients on a declining trajectory. Emerging continuous monitoring strategies that could incorporate serial biomarker evaluation such as eGFR measurements, may aid in identifying patients at high risk for renal events and/or clinical deterioration. Indeed, greater variability in indicators of renal function is independently associated with risk for adverse clinical outcomes.[12]

Several limitations of this analysis are worth noting. First, the analyses assessing eGFR trajectory, development of the renal composite outcome, and treatment response to sacubitril/valsartan according to history and timing of prior HF hospitalization were not pre-specified and thus should be considered hypothesis-generating. Second, the observed number of renal events was quite small limiting conclusions especially in subgroups related to timing of HF hospitalization. Third, patients with severe chronic kidney disease (eGFR<30 ml/min/1.73 m^2) were excluded from PARAGON-HF and as such the findings from this study may not extend to this population. Lastly, the lack of granular data for specific variables at each eGFR measurement included in the analysis of eGFR trajectory, especially at the time of hospitalization or soon after, limits the ability to adjust for covariates that may have impacted kidney function.

In summary, hospitalization for HF represents a pivotal moment in the trajectory of kidney function and signals patients who are at increased risk for kidney disease progression. Kidney function decline occurs well in advance of decompensation and continues following recovery from hospitalization. The increased risk observed in proximity to hospitalization for HF may be potentially modifiable through initiation of risk lowering HFpEF therapies in the peri-hospitalization window.

Supplementary Information

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

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