Is Sacubitril/Valsartan a Safe and Effective Option in Real World Patients with Mild to Severe Chronic Kidney Disease?

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Abstract: Aims: Sacubitril/valsartan has shifted the landscape of heart failure (HF) treatment. As renal function (RF) is often compromised in HF patients, this study aimed to assess the evolution of RF in patients with HF with a reduced ejection fraction (HFrEF) and initiating treatment with sacubitril/valsartan. Methods and results: We present a secondary data analysis of a prospective cohort of HFrEF patients. Inclusion criteria: patients who started sacubitril/valsartan between November 2017 and August 2019, after previous optimal medical therapy, had a New York Heart Association classification of II or III, at least 6 months of follow-up, and an estimated glomerular filtration rate (eGFR) below 90 mL/min/1.73 m². Main endpoint: annualized change in eGFR. A total of 52 patients met the inclusion criteria. The average eGFR reduced from 54.2 to 52.5 mL/min/1.73 m², at baseline and last follow-up, respectively. The average eGFR annualized change from baseline decreased 3.1 mL/min/1.73 m²/year without statistical significance (95% confidence interval: −8.7 to 2.5). No subgroup analysis presented a statistically significant annualized change in eGFR. Mean left ventricular ejection fraction increased from 30.4% to 37.9% at last follow-up. Conclusion: This real-world study demonstrated sacubitril/valsartan promoted no major harm in renal function, while maintaining effectiveness in a population of HFrEF patients with mild to severe renal disease.

Keywords: heart failure; chronic kidney disease; renal failure; sacubitril/valsartan; angiotensin receptor-neprilysin inhibitor; real world evidence

1. Introduction

Heart failure (HF) and chronic kidney disease (CKD) often coexist, sharing common risk factors, such as hypertension, diabetes, or atherosclerosis, and pathogenic mechanisms, which include haemodynamic abnormalities, sympathetic hyperactivity, renin–angiotensin–aldosterone system activation, inflammation, and oxidative stress [1,2]. In fact, both acute or chronic dysfunction of the heart or kidneys can induce the same dysfunction in the other organ. In addition, both heart and kidney function can be impaired by an acute or chronic systemic disorder. The term “cardiorenal syndrome” has been applied to these interactions [3].

The prevalence of patients with at least moderate CKD was found to be 51% in a population-based study of HF patients [4].

Moreover, a recent meta-analysis demonstrated a significant risk of all-cause mortality in patients presenting both HF and CKD, showing a 2.3-fold higher risk of death, compared to patients without CKD [5]. Other consequences of CKD in HF patients include a decrease in treatment options, as frequently recommended drugs for HF may aggravate kidney function [6,7]. A study in a cohort of Swedish patients demonstrated that patients with...
more severe kidney dysfunction were less likely to receive angiotensin-converting enzyme inhibitors (ACEi), beta-blockers, and aldosterone blockade, or, if under treatment, they were less likely to receive the target dose. Still, independent of treatment, CKD was also strongly associated with mortality in HF patients [4].

In 2014, the pharmacological treatment landscape of HF with a reduced ejection fraction (HFrEF) changed with the publication of PARADIGM-HF trial results, which showed the benefits of the first-in-class angiotensin receptor-neprilysin inhibitor—sacubitril/valsartan—over the standard of care—enalapril (a long-acting ACEi). Neprilysin degrades vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling. Combined inhibition of the renin–angiotensin system and neprilysin had effects that were superior to those of either approach alone [8]. Patients treated with sacubitril/valsartan showed a 20% reduction in the risk of cardiovascular death and hospitalization over patients treated with enalapril, in a population of HFrEF [8]. Although this trial excluded patients with severe CKD (eGFR < 30 mL/min/1.73 m²), in a secondary analysis, sacubitril/valsartan was shown to aid in the preservation of kidney function. In this regard, the rate of decline in eGFR was slower with sacubitril/valsartan than with enalapril, over a period of 44 months: −1.3 vs. −1.8 mL/min per 1.73 m² per year; p < 0.0001 [9]. More recently, a trial was conducted to compare sacubitril/valsartan with irbesartan (an angiotensin receptor blocker) in a population of HF patients with moderate to severe CKD. After 12 months of treatment, sacubitril/valsartan did not significantly affect kidney function compared to irbesartan [10].

Considering the limited experience of sacubitril/valsartan in HF patients with CKD, it is important to demonstrate cardiac and renal outcomes in a real-world setting, bearing in mind potential dose-adjustment restrictions. Therefore, our study aimed to assess the mean annual eGFR change in HFrEF patients with mild to severe CKD treated with sacubitril/valsartan, as a safety indicator, and the left ventricular ejection fraction (LVEF) variation, as a surrogate for effectiveness.

2. Methods

A secondary data analysis was conducted in a cohort of prospectively followed patients at the HF Clinic (HFC) of Cascais Hospital, Portugal.

The HFC currently follows 171 heart failure patients. Patients are usually referred to the HFC by the attending physician within the hospital or following an emergency room visit or hospitalization due to acute heart failure. Other referral criteria include LVEF less than 40%, specific diagnosis of hypertrophic or restrictive cardiomyopathy, and having a cardiac device implanted for primary or secondary prevention of sudden cardiac death.

For the purpose of this study, the patient inclusion criteria comprised previous diagnosis of HFrEF, a New York Heart Association (NYHA) functional class II–III, and mild to severe CKD, excluding terminal disease (eGFR < 90 mL/min/1.73 m² and >15 mL/min/1.73 m²) at the time of sacubitril/valsartan initiation. Patients eligible also have started sacubitril/valsartan between November 2017 and August 2019, after optimal medical therapy (OMT) and had at least 6 months of follow-up.

The standard follow-up care consisted of a multidisciplinary approach, including an evaluation by a HF-trained nurse, appointments with a cardiologist specialized in HF, and support from other medical specialties whenever needed, including internal medicine, pulmonology, psychiatry, nephrology, gastroenterology, and nutrition.

The clinical and prognostic impact of the HFC management has been previously published [11].

Follow-up appointments were scheduled after a maximum of six weeks with a minimum of at least three appointments during a one-year period.

Moreover, it is important to point out that all echocardiograms were performed by the hospital’s echocardiography laboratory staff.
The main endpoint of the current study was the annualized change in eGFR defined as the difference between eGFR at last follow-up date and at baseline, divided by the follow-up time. Several predefined subgroup analyses of the endpoint according to sex, age, aetiology of HF, NYHA functional class, CKD status, diabetes diagnosis, sacubitril/valsartan dose, serum potassium level, creatinine level, and LVEF at baseline were also performed. CKD status was defined as an eGFR $\leq 60$ mL/min/1.73 m$^2$, according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12]. Considering the baseline sacubitril/valsartan dose, two subgroups were created: one with a low dose, which included all patients that were on the 24/26 mg twice daily dose, and another with an intermediate/maximum dose, including all patients on the 49/51 mg or 97/103 mg twice daily doses. Baseline was defined as the date of sacubitril/valsartan initiation.

Baseline characteristics are presented in terms of descriptive statistics, with the mean and standard deviation (SD) or median and interquartile range (IQR) given for continuous variables, and percentages given for categorical variables.

Annualized changes in eGFR were estimated by linear regression models. Residual analysis was conducted to guarantee that the model assumptions were not violated.

Statistical analysis was performed using R software version 3.6 [13]. A significance level of 5% was adopted for all the statistical analysis. $p$-values $< 0.05$ were considered to indicate statistical significance.

Finally, all patients included in this study freely signed an informed consent form (that has been approved by the institutional ethics committee), authorizing prospective data collection for research purposes.

3. Results

A total of 52 patients met the inclusion criteria and had a median follow-up of 1.1 (IQR: 0.7) years. The baseline patients’ characteristics are summarized in Table 1.

Table 1. Baseline characteristics of the overall study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients ($n = 52$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>74.3 (9.0)</td>
</tr>
<tr>
<td>Male sex, $n$ (%)</td>
<td>39 (75.0)</td>
</tr>
<tr>
<td>Weight (Kg), mean (SD)</td>
<td>76.3 (15.4)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.7 (5.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), mean (SD)</td>
<td>128.9 (21.3)</td>
</tr>
<tr>
<td>Heart rate (bpm), mean (SD)</td>
<td>71.4 (16.3)</td>
</tr>
<tr>
<td>Ischemic heart disease, $n$ (%)</td>
<td>34 (64.4)</td>
</tr>
<tr>
<td>NYHA functional class, $n$ (%)</td>
<td>III 30 (57.7)</td>
</tr>
<tr>
<td></td>
<td>II 22 (42.3)</td>
</tr>
<tr>
<td>CKD stage, $n$ (%)</td>
<td>Mild ($\geq 60$ and $&lt;90$ mL/min/1.73 m$^2$) 22 (42.3)</td>
</tr>
<tr>
<td></td>
<td>Moderate ($\geq 30$ and $&lt;60$ mL/min/1.73 m$^2$) 25 (48.1)</td>
</tr>
<tr>
<td></td>
<td>Severe ($&lt;30$ mL/min/1.73 m$^2$) 5 (9.6)</td>
</tr>
<tr>
<td>Valvular prosthesis, $n$ (%)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Comorbidities, $n$ (%)</td>
<td>Atrial fibrillation 27 (51.9)</td>
</tr>
<tr>
<td></td>
<td>Anaemia 11 (21.1)</td>
</tr>
<tr>
<td></td>
<td>COPD 4 (7.7)</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus 19 (36.5)</td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia 25 (48.1)</td>
</tr>
<tr>
<td></td>
<td>Hypertension 36 (69.2)</td>
</tr>
<tr>
<td>Treatment at baseline, $n$ (%)</td>
<td>ACEi 41 (78.8)</td>
</tr>
<tr>
<td></td>
<td>ARB 5 (9.6)</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers 49 (94.2)</td>
</tr>
<tr>
<td></td>
<td>Digitalis glycosides 1 (1.9)</td>
</tr>
<tr>
<td></td>
<td>If-channel blockers 7 (13.5)</td>
</tr>
<tr>
<td></td>
<td>Loop diuretics 43 (82.6)</td>
</tr>
<tr>
<td></td>
<td>MRA 27 (51.9)</td>
</tr>
<tr>
<td></td>
<td>Thiazides 1 (1.9)</td>
</tr>
</tbody>
</table>

ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate value calculated using the CKD-EPI equation; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonists; NYHA: New York Heart Association; SD: standard deviation.
The mean age of the study population was 74.3 (SD: 9.0) years and 75.0% of the patients were male. The mean body mass index was in the range of excess weight (mean: 26.7; SD: 5.0 Kg/m²) and the mean systolic blood pressure was in the range of 128.9 ± 21.3 mm Hg. The majority of patients had HF due to ischemic heart disease (64.4%) and were in NYHA functional class II (57.7%). All the patients had impaired renal function, according to the inclusion criteria defined, mostly moderate (48.1%), followed by mild (42.3%) and severe (9.6%) CKD. Regarding comorbidities, hypertension was the most prevalent (69.2%), followed by atrial fibrillation (51.9%), dyslipidaemia (48.1%), and diabetes mellitus (36.5%). A high percentage of patients was on beta-blocker (94.2%) and more than 70% of patients took a loop diuretic (82.6%) or an ACEi (78.8%).

The mean eGFR changed from 54.2 (SD: 19.8) mL/min/1.73 m² at baseline to 52.5 (SD: 22.0) mL/min/1.73 m², at last follow-up. The mean eGFR annualized change from baseline estimated at −3.1 (95% confidence interval (95% CI): −8.7 to 2.5) mL/min/1.73 m²/year did not present statistical significance (Figure 1).

For almost all subgroups, the analysis suggested a consistent statistically non-significant trend towards decreasing eGFR after starting sacubitril/valsartan. Notwithstanding, patients with diabetes showed a trend towards estimated annualized eGFR increase (1.5 [95% CI: −7.1 to 10.1] mL/min/1.73 m²/year), as well as patients with a baseline creatinine level above 2.1 mg/dL, which presented an estimated annualized eGFR increase of 5.0 (95% CI: −8.7 to 18.2) mL/min/1.73 m²/year.

Figure 1. Mean eGFR annualized change, overall and by subgroups. M: male gender; F: female gender; NYHA: New York Heart Association; CKD: Chronic Kidney Disease; SAC/VAL: Sacubitril/Valsartan; int/max: intermediate/maximum dose; LVEF: left ventricular ejection fraction; N: No; Y: Yes.
CI: −1.0 to 11.0) mL/min/1.73 m²/year. Regardless of the dose of sacubitril/valsartan administered at baseline, no statistically significant annualized change of eGFR was found (mean: 0.9; 95% CI: −8.9 to 9.0 and mean: 5.6; 95% CI: −13.2 to 1.9 mL/min/1.73 m²/year for low dose and intermediate to maximum dose, respectively). Additionally, patients with and without CKD at baseline also presented a statistically non-significant decrease in eGFR over time.

Clinically, it should be noted that an inferior number of patients had congestion signs (mainly peripheral oedema) at last follow-up comparing to the baseline (Table 2).

### Table 2. Evolution of renal and cardiac parameters, from baseline to last follow-up.

<table>
<thead>
<tr>
<th>Parameters *</th>
<th>Baseline (n = 52)</th>
<th>End of Follow-Up (n = 52)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema, n (%)</td>
<td>9 (18.8)</td>
<td>5 (10.4)</td>
<td>0.289</td>
</tr>
<tr>
<td>Serum Sodium (mmol/L)</td>
<td>139.7 (3.9)</td>
<td>140.3 (2.7)</td>
<td>0.543</td>
</tr>
<tr>
<td>Serum Potassium (mmol/L)</td>
<td>4.6 (0.5)</td>
<td>4.8 (0.5)</td>
<td>0.251</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.4 (0.5)</td>
<td>1.4 (0.5)</td>
<td>0.229</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>30.4 (7.1)</td>
<td>37.9 (10.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*All data are presented as mean (standard deviation); LVEF: left ventricular ejection fraction. p-value < 0.05 indicates statistical significance.

Regarding serum ions, both sodium and potassium levels showed a slight increase over the study period, whereas the mean level of creatinine remained stable (Table 2).

Irrespective of renal impairment, it was possible to observe improvements in cardiac function (Table 2). The mean LVEF changed from 30.4% at baseline to 37.9% at last follow-up (p-value < 0.001).

### 4. Discussion

In this real-world study, after initiating sacubitril/valsartan, patients showed a mean annual eGFR change of −3.1 (95% CI: −8.7 to 2.5) mL/min/1.73 m², but which did not reach statistical significance. The mean annual change was assessed in prespecified subgroups and there was also a non-significant statistical trend towards decrease that was consistent in almost all subgroups.

Recognizing the close relationship between cardiac and renal functions, several published studies have addressed the influence of sacubitril/valsartan in renal outcomes, while also focusing on efficacy or effectiveness data [10,14–17].

Previous published clinical trials included patients with an eGFR level between 20 and 40 mL/min/1.73 m², while the current study included patients with an eGFR between 90 and 15 mL/min/1.73 m² [10,17]. The study conducted by Damman et al., for instance, showed an annual decrease of 1.6 (95% CI: −1.8 to −1.4) mL/min/1.73 m² [17]. In the clinical trial conducted by Haynes et al., the mean baseline eGFR was 34.0 (±0.8) mL/min/1.73 m² and changed to 29.8 (±0.5) mL/min/1.73 m² at last follow-up, with both values being lower than those in the current study [10].

On the contrary, some real-world studies demonstrated improvement in the eGFR after initiating sacubitril/valsartan and over the study period [15,16]. In the study conducted by Quiroga, et al., improvement in the eGFR was demonstrated over the first three months, but mean eGFR declined in the sixth month after initiating sacubitril/valsartan [16]. In the study conducted by Spannella, et al., mean eGFR increased from 59.4 mL/min/1.73 m² at baseline to 65.6 mL/min/1.73 m² after one year of follow-up [15]. Nevertheless, both serum potassium and sodium had slight increases over the study period, consistent with the current study. Greater improvements in eGFR were observed in younger patients (<65 years) and patients with CKD, which was not the case for the current study [15].

Apart from renal outcomes, all studies, regardless of the observational or interventional nature, unequivocally demonstrated the benefits on LVEF over the study period,
without major compromises in renal outcomes [10,14–18]. Additionally, a published case report in a patient with HFrEF, undergoing haemodialysis, suggested the beneficial effect of sacubitril/valsartan even on terminal CKD [19].

Therefore, the current study demonstrated results consistent with previous published studies. Renal outcomes were in line with clinical trial data, which demonstrated slight decreases in renal function [10,17].

The results of the current study should be analysed in the light of some limitations. First, the study had a small sample size, which might have affected the results for the subgroup analysis. In fact, in this study, only patients with, at least, mild renal impairment were included, which limits the potential dimension of the study population. Nonetheless, previous observational studies have been published with smaller or similar sample sizes [14–16].

Eligibility criteria precluded the inclusion of patients with the length of follow-up below 6 months; nevertheless, renal function might have a slower development and studies should aim for longer follow-up periods. For instance, clinical trials observed the renal outcomes over a minimum period of 12 months [10,17]. Notwithstanding, the current study had a longer follow-up period than other published observational studies and was able to demonstrate renal outcomes consistent with clinical trials.

Although the absence of a comparator group prevented the comparison of the study results with standard of care, one should be aware that sacubitril/valsartan was a first in class drug that changed the paradigm of HF treatment, demonstrating a reduced mortality and hospitalization over the standard of care.

Moreover, the value of real-world data should be highlighted outside the clinical trial environment that has the disadvantage of limited generalizability of results. This is particularly relevant in the cardiovascular domain, as real-world patients are usually older, suffer from more comorbidities, and often present worse baseline clinical status than in randomized trials [20]. Therefore, this study adds to the body of evidence, since it studies the renal outcomes in a real-world HFrEF population.

Additionally, Cascais Hospital, where the HFC is based, has a Joint Commission International accreditation and has a Stage 7 certificate from the Electronic Medical Record Adoption Model by the Healthcare Information and Management Systems Society Analytics, which emphasizes a paperless environment, with more focus on patient care and enhanced medical records. This makes the information reported in the current study highly reliable, increasing confidence in the results presented.

5. Conclusions

The results of this real-world study complement the results from clinical trials, demonstrating no major harm on patients’ renal function, while maintaining effectiveness in a population of HFrEF patients with mild to severe CKD, with the exception of terminal disease.

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Informed Consent Statement: Written Informed Consent was obtained from all subjects involved in the study to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.
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