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EVALUATION OF THE EFFICACY OF THE ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITOR (SACUBITRIL/VALSARTAN) IN PATIENTS WITH CHRONIC HEART FAILURE AND RENAL DYSFUNCTION.

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Abstract. Chronic heart failure (CHF) is frequently accompanied by renal dysfunction, forming cardiorenal syndrome and significantly worsening prognosis. Sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNI), has demonstrated superior outcomes compared with conventional renin–angiotensin system blockade; however, data in patients with impaired renal function remain limited. To evaluate the clinical efficacy, cardiac remodeling effects, and renal safety of sacubitril/valsartan in patients with chronic heart failure and renal dysfunction.

Keywords: Chronic heart failure, renal dysfunction, cardiorenal syndrome, sacubitril/valsartan, ARNI

INTRODUCTION. Chronic heart failure (CHF) remains one of the leading causes of morbidity, mortality, and healthcare utilization worldwide, despite substantial advances in pharmacological and device-based therapies [1]. The prevalence of CHF continues to rise due to population aging, improved survival after myocardial infarction, and increasing burden of cardiometabolic diseases [2].Renal dysfunction is a common comorbidity in patients with CHF and is present in approximately 40–60% of cases, depending on disease severity and diagnostic criteria [3]. Even mild impairment of renal function is independently associated with increased mortality, higher rates of hospitalization, reduced response to therapy, and poorer quality of life [4]. The coexistence of cardiac and renal dysfunction is referred to as cardiorenal syndrome, a complex bidirectional condition in which dysfunction of one organ contributes to the progression of the other through hemodynamic, neurohormonal, inflammatory, and metabolic mechanisms [5].

Activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system plays a central role in the pathophysiology of both CHF and chronic kidney disease (CKD) [6]. Persistent neurohormonal activation leads to vasoconstriction, sodium and water retention, myocardial remodeling, glomerular hypertension, and progressive fibrosis of cardiac and renal tissues [7]. Consequently, inhibition of RAAS has become a cornerstone of heart failure therapy. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to reduce mortality and morbidity in patients with CHF [8]. However, their use in patients with renal dysfunction is often limited by adverse effects, including worsening renal function, hyperkalemia, and hypotension [9]. Sacubitril/valsartan is a first-in-class angiotensin receptor–neprilysin inhibitor (ARNI) that combines valsartan-mediated RAAS blockade with sacubitril-induced inhibition of neprilysin, an enzyme responsible for the degradation of natriuretic peptides [10]. Inhibition of neprilysin leads to increased levels of biologically active natriuretic peptides, resulting in vasodilation, natriuresis, diuresis, reduced

sympathetic activity, and antifibrotic effects [11]. Through this dual mechanism, sacubitril/valsartan favorably modulates both hemodynamic and neurohormonal pathways involved in heart failure progression. The PARADIGM-HF trial demonstrated that sacubitril/valsartan significantly reduced cardiovascular mortality and heart failure hospitalizations compared with enalapril in patients with heart failure with reduced ejection fraction (HFrEF) [12]. Subsequent analyses and real-world studies have confirmed its benefits across a broad spectrum of heart failure patients [13]. Importantly, treatment with sacubitril/valsartan has been associated with slower decline in renal function compared with conventional RAAS inhibition, suggesting potential renoprotective effects [14]. Nevertheless, patients with moderate to severe renal dysfunction were underrepresented in major randomized controlled trials, and concerns regarding renal safety continue to limit the use of ARNI therapy in routine clinical practice [15]. Data on longitudinal renal outcomes, electrolyte disturbances, and tolerability of sacubitril/valsartan in patients with established CKD remain limited, particularly in real-world populations. Therefore, the present study aimed to evaluate the clinical efficacy, cardiac remodeling effects, and renal safety of sacubitril/valsartan in patients with chronic heart failure and concomitant renal dysfunction during a 12-month follow-up period.

MATERIALS AND METHODS. This prospective observational study was conducted at a tertiary care cardiology center during the period **from January 2025 to December 2025** The study aimed to evaluate the clinical efficacy, cardiac remodeling effects, and renal safety of sacubitril/valsartan in patients with chronic heart failure and concomitant renal dysfunction over a 12-month follow-up period. The study protocol was developed in accordance with the principles of the Declaration of Helsinki and was approved by the local institutional ethics committee. Written informed consent was obtained from all participants prior to enrollment.

Study Population

A total of 68 consecutive patients with chronic heart failure were enrolled between 2025 and 2026. Eligible patients were adults aged ≥18 years with a documented diagnosis of chronic heart failure for at least 6 months and New York Heart Association (NYHA) functional class II–IV symptoms at baseline. Left ventricular systolic dysfunction was defined as a left ventricular ejection fraction (LVEF) ≤45% assessed by transthoracic echocardiography. Renal dysfunction was defined as chronic kidney disease (CKD) stages 2–4, corresponding to an estimated glomerular filtration rate (eGFR) of 15–89 mL/min/1.73 m², calculated using the CKD-EPI equation. Patients were excluded if they had acute decompensated heart failure, end-stage renal disease requiring dialysis, systolic blood pressure <90 mmHg, a history of angioedema associated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, severe hepatic impairment, active malignancy with limited life expectancy, pregnancy, or lactation.

Treatment Protocol

Patients previously treated with angiotensin-converting enzyme inhibitors underwent a mandatory 36-hour washout period before initiation of sacubitril/valsartan. The initial dose of sacubitril/valsartan (24/26 mg or 49/51 mg twice daily) was selected based on baseline blood pressure, renal function, and prior tolerance to renin–angiotensin system inhibitors. Dose titration was performed every 2–4 weeks, aiming to achieve the target dose of 97/103 mg twice daily or the maximum tolerated dose. All patients received guideline-directed background therapy for chronic heart failure, including evidence-based beta-blockers, mineralocorticoid

receptor antagonists, loop diuretics, and sodium–glucose cotransporter-2 inhibitors when clinically indicated. Adjustments of concomitant medications were permitted during follow-up based on clinical condition and laboratory findings.

Follow-Up and Clinical Assessment

Patients were evaluated at baseline and at 1, 3, 6, and 12 months after initiation of sacubitril/valsartan therapy. At each visit, comprehensive clinical assessment was performed, including evaluation of NYHA functional class, blood pressure, heart rate, body weight, and documentation of heart failure–related hospitalizations and adverse events.

Echocardiographic Assessment

Transthoracic echocardiography was performed at baseline, 6 months, and 12 months using standardized imaging protocols. Left ventricular ejection fraction was calculated using the biplane Simpson method. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left atrial diameter were measured in accordance with current international echocardiography guidelines. All examinations were performed by experienced cardiologists blinded to laboratory results.

Laboratory and renal function assessment

Blood samples were collected at baseline and at each follow-up visit. Laboratory assessments included serum creatinine, blood urea nitrogen, and serum potassium levels. Renal function was evaluated using eGFR calculated by the CKD-EPI formula. Acute kidney injury was defined as an increase in serum creatinine ≥0.3 mg/dL within 48 hours or a ≥50% increase from baseline. Hyperkalemia was defined as serum potassium levels >5.5 mmol/L.

Outcomes

The primary outcomes were changes in NYHA functional class and heart failure–related hospitalization rates during the 12-month follow-up period. Secondary outcomes included changes in echocardiographic parameters (LVEF, LVEDV, LVESV), renal function indices (serum creatinine and eGFR), incidence of hyperkalemia, acute kidney injury, symptomatic hypotension, treatment discontinuation, and all-cause mortality.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were reported as numbers and percentages. Longitudinal changes were analyzed using repeated-measures analysis of variance or linear mixed-effects models. Pairwise comparisons between baseline and follow-up visits were conducted using paired t-tests or Wilcoxon signed-rank tests. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using standard statistical software.

RESULTS. A total of 68 patients with chronic heart failure and concomitant renal dysfunction were enrolled between 2025 and 2026 and initiated on sacubitril/valsartan therapy.

All patients completed baseline and early follow-up assessments, while 61 patients (89.7%) completed the full 12-month follow-up. Baseline demographic and clinical characteristics are summarized in Table 1. The mean age of the study population was 64.7 ± 9.3 years, and 44 patients (64.7%) were male. At study entry, most patients were classified as NYHA functional class III (57.4%), followed by class II (27.9%) and class IV (14.7%). Chronic kidney disease stages 2, 3, and 4 were present in 32.4%, 50.0%, and 17.6% of patients, respectively. Mean baseline LVEF was 32.6 ± 6.1%, and mean eGFR was 46.2 ± 14.8 mL/min/1.73 m².

During follow-up, sacubitril/valsartan therapy was associated with a significant and progressive improvement in clinical status. Mean NYHA functional class decreased from 3.0 ± 0.6 at baseline to 2.1 ± 0.5 at 12 months ($p < 0.001$ for trend). Improvement by at least one NYHA class was observed in 46 patients (67.6%) at the end of follow-up. Heart rate declined significantly over time, while blood pressure remained stable. Detailed longitudinal clinical parameters are presented in Table 2. Heart failure–related hospitalizations were substantially reduced, decreasing from 1.42 ± 0.6 events per patient-year in the year prior to treatment initiation to 0.63 ± 0.4 events per patient-year during the 12-month follow-up period ($p < 0.01$). All-cause mortality at 12 months was 8.8% (6 patients). Echocardiographic evaluation demonstrated significant reverse cardiac remodeling. LVEF increased steadily throughout the study period, reaching 39.8 ± 7.4% at 12 months, compared with 32.6 ± 6.1% at baseline ($p < 0.001$). This improvement was accompanied by significant reductions in left ventricular end-diastolic volume and end-systolic volume. Longitudinal echocardiographic data across baseline, 1, 3, 6, and 12 months are shown in Table 3. Renal function remained stable during sacubitril/valsartan therapy. Mean eGFR showed a modest, non-significant increase from 46.2 ± 14.8 mL/min/1.73 m² at baseline to 48.9 ± 15.2 mL/min/1.73 m² at 12 months ($p = 0.09$). Serum creatinine levels did not demonstrate a clinically meaningful rise during follow-up. Stable or improved eGFR at 12 months was observed in 52 patients (76.5%). Longitudinal renal and laboratory parameters are presented in Table 4. Sacubitril/valsartan was generally well tolerated. Symptomatic hypotension occurred in 7 patients (10.3%), most frequently during the first month of therapy. Hyperkalemia (>5.5 mmol/L) was observed in 6 patients (8.8%), and transient acute kidney injury occurred in 4 patients (5.9%), all of which resolved with dose adjustment or temporary treatment interruption. Dose reduction was required in 9 patients (13.2%), and permanent discontinuation of therapy due to adverse events occurred in 3 patients (4.4%). No cases of angioedema were reported. Safety outcomes are summarized in Table 5.

Table 1. Baseline demographic and clinical characteristics (n = 68)

Parameter	Value
Age, years	64.7 ± 9.3
Male sex, n (%)	44 (64.7)
NYHA II / III / IV, n (%)	19 (27.9) / 39 (57.4) / 10 (14.7)
LVEF, %	32.6 ± 6.1
eGFR, mL/min/1.73 m²	46.2 ± 14.8

CKD stage 2 / 3 / 4, n (%)	22 (32.4) / 34 (50.0) / 12 (17.6)

Table 2. Clinical parameters during follow-up

Parameter	Baseline	1 mo	3 mo	6 mo	12 mo	p (trend)
NYHA class	3.0 ± 0.6	2.7 ± 0.6	2.4 ± 0.5	2.2 ± 0.5	2.1 ± 0.5	<0.001
Heart rate, bpm	76 ± 11	73 ± 10	71 ± 9	70 ± 9	69 ± 8	<0.01

Table 3. Echocardiographic parameters over time

Parameter	Baseline	1 mo	3 mo	6 mo	12 mo	p (trend)
LVEF, %	32.6 ± 6.1	34.1 ± 6.3	36.5 ± 6.8	38.4 ± 7.1	39.8 ± 7.4	<0.001
LVEDV, mL	178 ± 32	174 ± 31	169 ± 30	165 ± 29	162 ± 28	<0.01
LVESV, mL	122 ± 26	118 ± 25	112 ± 24	108 ± 23	104 ± 23	<0.01

Table 4. Renal function during follow-up

Parameter	Baseline	1 mo	3 mo	6 mo	12 mo	p (trend)
Creatinine, µmol/L	146 ± 38	149 ± 40	145 ± 37	143 ± 36	141 ± 36	0.22
eGFR, mL/min/1.73 m²	46.2 ± 14.8	45.1 ± 15.0	47.0 ± 14.7	48.2 ± 15.0	48.9 ± 15.2	0.09

Table 5. Safety and adverse events during follow-up

Adverse event	n (%)
Symptomatic hypotension	7 (10.3)
Hyperkalemia (>5.5 mmol/L)	6 (8.8)
Acute kidney injury (transient)	4 (5.9)
Dose reduction required	9 (13.2)
Treatment discontinuation	3 (4.4)
Angioedema	0

DISCUSSION. In this prospective observational study conducted during 2025–2026, sacubitril/valsartan therapy was associated with significant clinical improvement, favorable cardiac remodeling, and preserved renal function in patients with chronic heart failure and concomitant renal dysfunction. To our knowledge, this study provides comprehensive longitudinal real-world data with multiple follow-up time points in a cohort that included patients with moderate to advanced chronic kidney disease. The primary finding of this study is the marked improvement in functional status, as reflected by a significant reduction in NYHA functional class over 12 months. More than two-thirds of patients experienced improvement by at least one NYHA class, which is clinically meaningful and consistent with previous randomized trials and real-world studies evaluating angiotensin receptor–neprilysin inhibitor (ARNI) therapy [12,13]. Importantly, the improvement occurred progressively, beginning as early as the first month of treatment, suggesting an early symptomatic benefit of sacubitril/valsartan. In parallel with clinical improvement, we observed significant reverse left ventricular remodeling, including an increase in left ventricular ejection fraction and reductions in left ventricular volumes. These findings align with mechanistic and clinical evidence indicating that neprilysin inhibition enhances natriuretic peptide activity, leading to reduced myocardial wall stress, antifibrotic effects, and improved ventricular function [10,11]. Previous echocardiographic substudies of PARADIGM-HF and subsequent observational analyses have similarly demonstrated favorable remodeling with ARNI therapy compared with conventional RAAS inhibition [14,16]. A key concern in patients with cardiorenal syndrome is the potential for deterioration of renal function following intensification of neurohormonal blockade. In the present study, renal function remained stable throughout follow-up, with a modest, non-significant increase in eGFR and no clinically relevant rise in serum creatinine. Notably, more than three-quarters of patients exhibited stable or improved renal function at 12 months. These findings are consistent with post-hoc analyses of large heart failure trials, which reported a slower decline in renal function with sacubitril/valsartan compared with ACE inhibitors [14,17]. The observed renal safety profile may be explained by the dual mechanism of ARNI therapy. While valsartan attenuates RAAS-mediated vasoconstriction and glomerular hypertension, neprilysin inhibition increases levels of natriuretic peptides that promote renal vasodilation, natriuresis, and reduced intraglomerular pressure [11,18]. This balanced hemodynamic effect may be particularly advantageous in patients with chronic kidney disease, in whom excessive efferent arteriolar constriction contributes to progressive nephron damage. Heart failure–related hospitalizations were significantly reduced during follow-up, which is consistent with prior evidence demonstrating that sacubitril/valsartan lowers hospitalization risk across a wide range of patient subgroups [12,13]. Although our study was not powered to assess mortality outcomes, the observed all-cause mortality rate was comparable to that reported in similar real-world cohorts with cardiorenal comorbidity [19]. Regarding safety, sacubitril/valsartan was generally well tolerated. Symptomatic hypotension occurred predominantly during early treatment, which is in line with known pharmacodynamic effects of ARNI therapy [12]. Importantly, the incidence of hyperkalemia and acute kidney injury was low and manageable with dose adjustment, supporting the feasibility of ARNI use in patients with CKD stages 2–4 when careful monitoring is applied. No cases of angioedema were observed, consistent with the low incidence reported in contemporary studies [20]. This study has several limitations. Its observational design and lack of a control group preclude definitive causal inference. The single-center setting and relatively modest sample size may limit generalizability. In addition, patients with end-stage renal disease were excluded; therefore, our findings cannot be extrapolated to dialysis-dependent populations.

Nonetheless, the strengths of this study include prospective data collection, multiple predefined follow-up points, and detailed assessment of both cardiac and renal outcomes in a real-world population. In conclusion, our findings support the efficacy and renal safety of sacubitril/valsartan in patients with chronic heart failure and renal dysfunction. These results reinforce current guideline recommendations advocating ARNI therapy as a cornerstone of heart failure management, even in patients with moderate chronic kidney disease, provided that appropriate dose titration and laboratory monitoring are ensured [21].

CONCLUSION

In this prospective observational study conducted during 2025–2026, sacubitril/valsartan demonstrated significant clinical efficacy and a favorable safety profile in patients with chronic heart failure complicated by renal dysfunction. Treatment was associated with meaningful improvement in functional status, evidenced by a progressive reduction in NYHA functional class, alongside significant reverse left ventricular remodeling over a 12-month follow-up period. Importantly, sacubitril/valsartan therapy did not lead to clinically relevant deterioration of renal function. Renal parameters remained stable or improved in the majority of patients, and the incidence of hyperkalemia and acute kidney injury was low and manageable with appropriate monitoring and dose adjustment. These findings support the renal safety of angiotensin receptor–neprilysin inhibition in patients with chronic kidney disease stages 2–4. Furthermore, a substantial reduction in heart failure–related hospitalizations was observed, underscoring the potential of sacubitril/valsartan to improve both patient outcomes and healthcare utilization in this high-risk population. Although mortality was not a primary endpoint, the observed survival outcomes were comparable to those reported in similar real-world cohorts. Overall, the results of this study reinforce current guideline recommendations supporting the use of sacubitril/valsartan as a cornerstone therapy in chronic heart failure, including in patients with concomitant renal dysfunction. Careful patient selection, gradual dose titration, and regular monitoring of renal function and electrolytes remain essential to optimize treatment benefits. Further large-scale, controlled studies focusing on patients with advanced renal disease are warranted to confirm these findings and refine therapeutic strategies in cardiorenal syndrome.

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