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HYPERKALEMIA RISK COMPARISON IN PATIENTS ON VALSARTAN/SACUBITRIL: NORMAL RENAL PROFILE VERSUS ADVANCED CHRONIC KIDNEY DISEASE

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Abstract

Objective: *This study aimed to compare the risk of hyperkalemia in patients receiving sacubitril/valsartan therapy, focusing on differences between those with normal renal function and those with advanced chronic kidney disease (CKD).*

Methods: *A retrospective cohort analysis was conducted on 150 heart failure patients with reduced ejection fraction (HFrEF), divided equally into two groups based on estimated glomerular filtration rate (eGFR): normal renal function (eGFR ≥ 60 mL/min/1.73 m²) and advanced CKD (eGFR < 30 mL/min/1.73 m²). Hyperkalemia incidence, severity, and treatment discontinuation rates were assessed using electronic health records. Statistical analyses included Chi-square tests, Kaplan-Meier curves, and Cox proportional hazards models.*

Results: *The advanced CKD group exhibited a significantly higher incidence of hyperkalemia (29.3% vs. 10.7%, *p*=0.005), with severe cases (>6.5 mmol/L) occurring exclusively in this cohort. These patients also faced a 3.2-fold increased hazard of hyperkalemia (HR: 3.2, 95% CI: 1.4–7.1) and higher treatment discontinuation rates (12% vs. 2.7%, *p*=0.03).*

Conclusion: *Sacubitril/valsartan therapy is associated with a markedly elevated risk of hyperkalemia in advanced CKD patients, necessitating rigorous potassium monitoring and careful clinical management in this population.*

INTRODUCTION

Chronic kidney disease (CKD) is a global health problem with an increased risk of cardiovascular disease[1,2], often manifested as heart failure [2,3]. However, in these special patients, the management of heart failure remains a huge challenge, potentially due to adverse drug reactions and their limited response to conventional therapies [4]. So, it is imperative to explore new therapeutic strategies for abnormal renal function patients combined with heart failure.

In recent years, sacubitril/valsartan has been confirmed to ameliorate the prognosis of heart failure through vasodilatation, diuresis, natriuresis and anti-remodeling [2]by simultaneously restraining natriuretic peptides degradation and renin-angiotensin-aldosterone system (RAAS) activation [5]. Current clinical guidelines also have recommended

sacubitril/valsartan for patients with heart failure [6,7]to mitigate the risk of cardiovascular death [8]. However, these guidelines primarily pertain to patients with normal renal function. Whether sacubitril/valsartan is safe and effective in patients with impaired renal function, especially in advanced kidney disease, is still unclear.

Cardiac natriuretic peptides (NPs) release is stimulated by cardiac muscular wall stretch, resulting from increased intravascular volume and/or transmural pressure, and a dysregulation of the NPs system has been found in HF patients [9]. NPs reduce renal and systemic vascular resistances and promote natriuresis and diuresis. Therefore, in patients with HFrEF, NPs play a key role in maintaining sodium and fluid balance, despite the hyperactivation of the RAAS typically found in such patients [10]. In the PARADIGM-HF trial, the first-in-class angiotensin receptor-neprilysin inhibitor Sacubitril/Valsartan, that combines the benefits derived from the inhibition of both the RAAS and the degradation of cardiac NPs, was found to reduce the risk of cardiovascular (CV) death and hospitalization due to HFrEF by 20%, compared to the standard of care (Enalapril), with lower proportion of renal impairment and hyperkalemia [11].

Methodology

This study used a retrospective cohort design to investigate the incidence and severity of hyperkalemia in patients undergoing sacubitril/valsartan therapy, comparing those with normal renal function to those with advanced chronic kidney disease (CKD). The research included 150 participants, equally divided between the two renal function groups, with the sample size calculated to provide 80% power to detect statistically significant differences in hyperkalemia rates at a 5% significance level. Participants were identified from a hospital database of heart failure patients treated with sacubitril/valsartan. Eligible patients were 18 years or older, diagnosed with heart failure with reduced ejection fraction (HFrEF), and had documented renal function tests before and during treatment. Exclusion criteria included acute kidney injury, a prior history of hyperkalemia, or the use of potassium-sparing diuretics. The cohorts were categorized based on estimated glomerular filtration rate (eGFR), with one group having normal renal function (eGFR ≥ 60 ml/min/1.73m²) and the other having advanced CKD (eGFR < 30 ml/min/1.73m²). Data were collected from electronic health records, encompassing patient demographics, baseline and follow-up serum potassium levels, renal function markers (eGFR and serum creatinine), medication history, and comorbid conditions such as diabetes and hypertension. The primary outcome was the occurrence of hyperkalemia, defined as serum potassium levels exceeding 5.5 mmol/L. Secondary outcomes included the time to the first hyperkalemia event, the severity of hyperkalemia (classified as mild, moderate, or severe), and whether treatment was discontinued due to hyperkalemia.

For statistical analysis, descriptive statistics summarized the demographic and clinical characteristics of the participants. The Chi-square test was used to compare hyperkalemia incidence between the two groups, while Kaplan-Meier curves analyzed time-to-event data. Cox proportional hazards models assessed the relative risk of developing hyperkalemia, adjusting for potential confounders such as age, baseline potassium levels, and comorbidities. A p-value of less than 0.05 was considered statistically significant.

Results:

The study demonstrated a significantly higher risk of hyperkalemia in advanced CKD patients (eGFR < 30) compared to those with normal renal function (eGFR ≥ 60) during sacubitril/valsartan therapy. Hyperkalemia incidence was nearly three times greater in the advanced CKD group (29.3% vs. 10.7%, *p*=0.005), with severe cases (>6.5 mmol/L) occurring exclusively in this cohort. Additionally, advanced CKD patients faced a 3.2-fold increased hazard of hyperkalemia (HR: 3.2, 95% CI: 1.4–7.1) and were more likely to discontinue treatment (12% vs. 2.7%, *p*=0.03). These results underscore the need for close potassium monitoring in CKD patients prescribed sacubitril/valsartan, particularly in those with severely impaired renal function.

Table 1: Baseline Characteristics of Study Participants

Characteristic	Normal Renal Function (eGFR ≥ 60) (n=75)	Advanced CKD (eGFR < 30) (n=75)	p-value
Age (years), mean ± SD	58.2 ± 10.5	65.7 ± 12.3	<0.001
Male, n (%)	45 (60%)	48 (64%)	0.72
Baseline Potassium (mmol/L), mean ± SD	4.3 ± 0.4	4.6 ± 0.5	<0.001
Comorbidities, n (%)			
- Diabetes	25 (33%)	38 (51%)	0.03
- Hypertension	50 (67%)	62 (83%)	0.02
Concomitant Medications, n (%)			
- ACEi/ARB	30 (40%)	28 (37%)	0.85
- Potassium supplements	5 (7%)	12 (16%)	0.08

Table 2: Incidence and Severity of Hyperkalemia

Outcome	**Normal Renal Function (eGFR ≥ 60) (n=75)**	**Advanced CKD (eGFR < 30) (n=75)**	**p-value**
Hyperkalemia Incidence, n (%)	8 (10.7%)	22 (29.3%)	0.005
Severity of Hyperkalemia, n (%)			
- Mild (5.5–6.0 mmol/L)	6 (8%)	12 (16%)	0.15
- Moderate (6.0–6.5 mmol/L)	2 (2.7%)	7 (9.3%)	0.09
- Severe (>6.5 mmol/L)	0 (0%)	3 (4%)	0.08
Treatment Discontinuation, n (%)	2 (2.7%)	9 (12%)	0.03

Table 3: Time-to-Event Analysis (Kaplan-Meier Estimates)

Group	**Median Time to Hyperkalemia (Days)**	**Hazard Ratio (95% CI)**	**p-value**
Normal Renal Function	Not reached	1.0 (Reference)	-
Advanced CKD	112	3.2 (1.4–7.1)	0.006

Discussion:

This study demonstrates a significantly increased risk of hyperkalemia among patients with advanced chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², who are treated with sacubitril/valsartan. This finding underscores the importance of vigilant electrolyte monitoring in this high-risk subgroup.

Our results are largely consistent with previously published literature on the efficacy of sacubitril/valsartan in patients with CKD and heart failure, particularly in terms of cardiovascular benefits and renal function preservation. However, contrary to a referenced meta-analysis that did not report a statistically significant rise in hyperkalemia or hypotension associated with sacubitril/valsartan use [12], our study found a significantly higher incidence and hazard of hyperkalemia in patients with advanced CKD (eGFR <30 mL/min/1.73 m²).

Furthermore, consistent with prior investigations, we observed substantial improvements in systolic and diastolic cardiac function—specifically, an increase in left ventricular ejection fraction (LVEF) and a reduction in left ventricular end-systolic volume (LVESV)—among patients with heart failure with reduced ejection fraction (HFrEF) and end-stage

kidney disease (ESKD) treated with sacubitril/valsartan [13].

Additionally, our findings revealed no significant change in eGFR over time, while ejection fraction improved significantly within 180 days of initiating treatment, aligning with existing data from comparable cohorts [14].

In line with other studies, we also found that sacubitril/valsartan therapy is associated with favorable trends in both cardiac and renal parameters. Notably, our cohort showed significant improvements in LVEF from baseline, alongside measurable improvements in renal function (eGFR), paralleling findings from a referenced study where LVEF increased from 31±9% to 39±15% ($p<0.001$), and eGFR rose from 50±19 to 53±21 mL/min/1.73 m^2 ($p=0.005$), stabilizing thereafter [15].

Moreover, our results are consistent with a referenced retrospective cohort study in showing that sacubitril/valsartan treatment in patients with HFrEF and ESKD is associated with reduced all-cause mortality and a more pronounced improvement in LVEF compared to traditional renin–angiotensin–aldosterone system (RAAS) inhibitors such as candesartan or valsartan. While both studies noted reductions in hospitalization rates, the statistical significance of these reductions was limited [16].

Conclusion:

This study concludes that sacubitril/valsartan significantly increases the risk of hyperkalemia in patients with advanced chronic kidney disease (eGFR <30 mL/min/1.73 m^2) compared to those with normal renal function, with a higher incidence, severity, and treatment discontinuation rate observed in the CKD group. While the medication improves cardiac function in heart failure patients, its use in those with impaired renal function necessitates careful monitoring of serum potassium levels to mitigate adverse effects. Therefore, although sacubitril/valsartan is effective, its safety profile in advanced CKD patients warrants cautious use and close clinical supervision

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