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Effect of Sacubitril/Valsartan on Kidney Function in Heart Failure Patients with Reduced Ejection Fraction

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Abstract

***Background*: Patients with heart failure (HF) & other cardiovascular diseases frequently experience a decline in their renal function. When compared to renin-angiotensin system inhibitors alone, sacubitril/valsartan appears to protect heart failure patients against the deterioration of renal function. *Aim:* This study aimed to assess effect of sacubitril/valsartan on kidney function among patients with heart failure. *Material and Methods:* Fifty-one adult patients with HFrEF were evaluated before, after three-month & six-month treatment with sacubitril/valsartan (S/V) therapy by kidney function test. *Results:* This study included 45 patients. The patients' ages varied from 35 to 74 years old, with a mean age of 55.6±9.3. Prior to S/V, 73.3% of patients were on ACE-I or ARBs. The majority of patients (73.3%) began their S/V therapy on dosage 24/26 mg, whereas 26.7% began on dose 49/51 mg. At three & six months of follow-up, patients' blood levels of urea, creatinine, sodium, & potassium increased statistically significantly ($p<0.05$), but these values remain within normal range with no significant deterioration in kidney function in the study population. *Conclusion:* Our results corroborate that Sacubitril/valsartan therapy had no significant detrimental effect on kidney function.**

***Keywords*:** HFrEF, Sacubitril/valsartan, Serum Urea, creatinine, sodium and potassium.

Introduction

Heart failure (HF) constitutes a major socioeconomic and clinical burden all over the world. For decreasing morbidity and mortality, multiple therapeutic options are available nowadays. On the top of the list, are angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists (MRA). Recently, a new class f Angiotensin Receptor Neprilysin Inhibitors (ARNIs) proved to markedly decrease morbidity and mortality, in addition to improving clinical aspects and overall prognosis. Sacubitril/valsartan (SV) is a good example of this class[1]. At least 32% of patients with heart failure have deteriorating renal function, & there is a strong correlation between renal impairment & the presence of HF. Renal hemodynamic alterations result from a decreased renal blood flow caused by compromised cardiac function with lower cardiac output [2,3]. In spite of

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the significantly decreased renal blood flow, glomerular capillary hydrostatic pressure rises as a result of angiotensin II-mediated vasoconstriction of the efferent arteriole & compensatory renin-angiotensin system activation. The development of glomerulosclerosis & glomerular injury as a result of this compensatory mechanism are expensive [4,5]. The effect of sacubitril/valsartan on kidney function in heart failure patients with reduced ejection fraction is still not clear till now, however, in comparison with renin-angiotensin system (RAS) inhibitors, Sacubitril/Valsartan seems to prevent the deterioration of kidney function and the progression of chronic kidney disease (CKD) in heart failure patients[2,3].

Patients and Methods

Study population

This study prospectively included 51 patients with symptomatic HFrEF who were eligible for sacubitril/valsartan (S/V) treatment between February 2022 & April 2023. Other requirements for participation were not having used S/V treatment in the past & being in NYHA functional class II or III. The American College of Cardiology/American Heart Association (2017) & the European Society of Cardiology (2016) both suggest optimum heart failure treatment for all patient. Severe decompensated heart failure patients using cardiac inotropes, LV assisted devices, or CRT; patients who were pregnant or nursing; patients who had previously experienced hypersentivity to SV therapy or intolerance to ACEI/ARB; patients who displayed symptomatic hypotension; patients with a history of angioedema; estimated glomerular filtration rate (eGFR) less than 30 mL/min/m2; potassium concentration greater than 5.5 mmol/L; & poor quality transthoracic echocardiogram images were among the exclusion criteria. The study protocol & the informed consent were in accordance were approved by the Bioethics Committee of Suez Canal University of Medical Sciences. Following the enrollment process, the following factors were evaluated for each patient: Age, sex, BMI, & risk factors (smoking, diabetes, hypertension, dyslipidemia, & chronic kidney disease) are the baseline variables. cause of heart failure (ischemic or non-ischemic); prior usage of ACE inhibitors or ARBs prior to sacubitril/valsartan administration. Following three & six months, the patients' SV dosage, & kidney function tests (sodium, potassium, urea, & serum sodium levels) were monitored.

Statistical Analysis

A Microsoft Excel sheet containing the patient's data was used for data entry, & version 25.0 of the Statistical Package for Social Sciences software was used for analysis. P values of less than (0.05) were deemed statistically significant (At 95% level of confidence) when statistical significance tests were employed. For quantitative variables, descriptive statistics were shown as (Means ± Standard Deviation), & for qualitative variables, as (Percent). For quantitative variables, the significance of the difference was tested using the Student t test. The Chi square test was applied to examine relationships between qualitative variables. After gathering information on patients, physicians, & imaging studies, as well as researching the relationships between various aspects, the management outcomes were displayed in tables & graphs.

Results

This study included 51 patients with HFrEF who started Sacubitril/valsartan. From 51

patients included, 6 patients were dropped out, with percent of drop:11.7 % due to the following causes: one patient died, 2 patients had severe hyperkalemia K > 5.5 mg/dl, 2 patients had severe hypotension & one patient had acute kidney injury, the net number was 45 patients (figure 1).

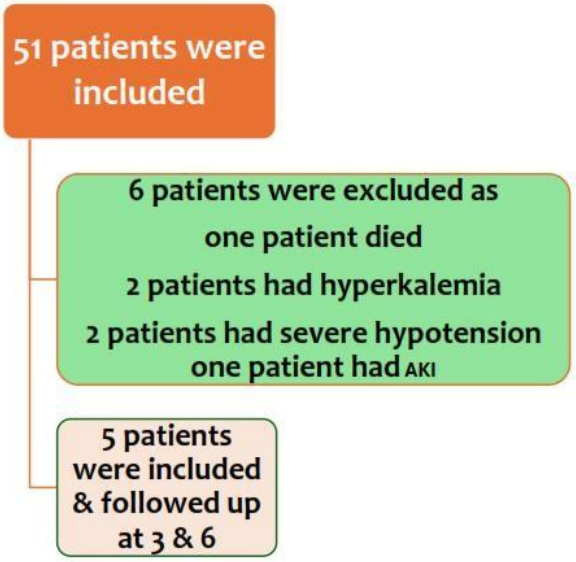

Table 1: Baseline characteristics of the study patients (n=45).			
Age (years)	Mean ±SD	55.6±9.3	
	Range	35-74	
Gender	Male	34	75.6%
	Female	11	24.4%
Smoking status	Ex-smoker	16	35.6%
	Smoker	15	33.3%
	Non smoker	14	31.1%
BSA (m^2)	Mean ±SD	1.92±0.2	
	Range	1.6-2.2	
ACE-I or ARBs before S/V	Yes	33	73.3%
	No	12	26.7%
Dose of Sacubtril/Valsartan (mg)	24 /26	33	73.3%
	49 /51	12	26.7%

Quantitative variables were expressed as mean±SD, while qualitative variables were expressed as numbers & percentages. Abbreviations: BSA; body surface area, ACE-I; angiotensin-converting enzyme inhibitor, ARBs; Angiotensin receptor blockers, SV; Sacubtril/Valsartan.

According to Table 1, the patients' ages varied from 35 to 74 years old, with a mean age of 55.6±9.3. Of these, men made up over half (75.6%), while women made up 24.4%. Their BSA was 1.92±0.2 on average. Of them, 31.1% were non-smokers, 33.3% were smokers now, & 35.6% were ex-smokers. Prior to S/V, 73.3% of patients were on ACE-I or ARBs. The majority of patients (73.3%) began their S/V therapy on dosage 24/26 mg, whereas 26.7% began on dose 49/51 mg. In figure 2, 30 patients (66.7%) had hypertension, 20 patients (44.4%) had diabetes mellitus, 18 (40%) patients had dyslipidemia and 14 patients (31.1%) had CKD.

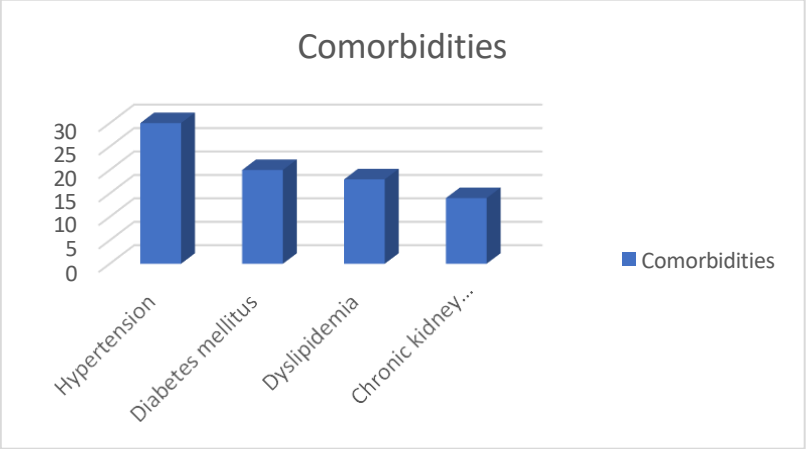

Figure 2: Comorbidities distribution among the study patients (n=45).

Table 2 Baseline laboratory data the study patients (n=45).

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Urea (mg/dL)	**Mean ±SD**	**39.4±11.7**
	Range	**20-59**
Serum creatinine (mg/dL)	**Mean ±SD**	**1.16±0.43**
	Range	**0.6-2.0**
Serum sodium (mmol/L)	**Mean ±SD**	**137.6±4**
	Range	**130-145**
Serum Potassium (mmol/L)	**Mean ±SD**	**4.03±0.43**
	Range	**3.1-5.0**

According to Table 2, most of the patients included in our study at the start had normal renal profiles. Mean serum urea was 39.4±11.7 mg\dl, mean serum creatinine was 1.16±0.43 mg\dl, mean serum sodium level was 137.6±4 mmol\l, and mean serum potassium level of 4.03±0.43 mmol\l. In figure 3, at three months, many patients received higher doses of SV as 7 patients (15.5%) were taking 97/103 mg twice daily, 17 patients (37.8%) were taking 24/26 mg twice daily, and 21 patients (46.7%) were taking 49/51 mg twice daily. At six months, most of the patients reached successfully higher doses of SV, as 14 patients (31.1%) were taking 97/103 mg twice daily, 19 patients (42.2%) were taking 49/51 mg twice daily, and only 12 patients (26.7%) were taking 24/26 mg twice daily. According to Table 3, patients had statistically significant increases in serum levels of urea, creatinine, sodium, and potassium level at 3 and 6 months of follow-up, but these values remained within the normal range with no significant deterioration in kidney function in the study population.

Discussion

Research on sacubitril/valsartan's effects on the kidneys is now concentrated on heart failure patients, indicating that the drug's cardiac benefits remain crucial for nephroprotection. Studies on hypertensive individuals have also shown that this novel medication consistently lowers blood pressure more than olmesartan does[6,7]. However, these studies solely considered renal function as a negative consequence, raising doubts about the validity & consistency of the results. Therefore, the purpose of this study was to assess effect of sacubitril/valsartan on kidney function among patients with heart failure.

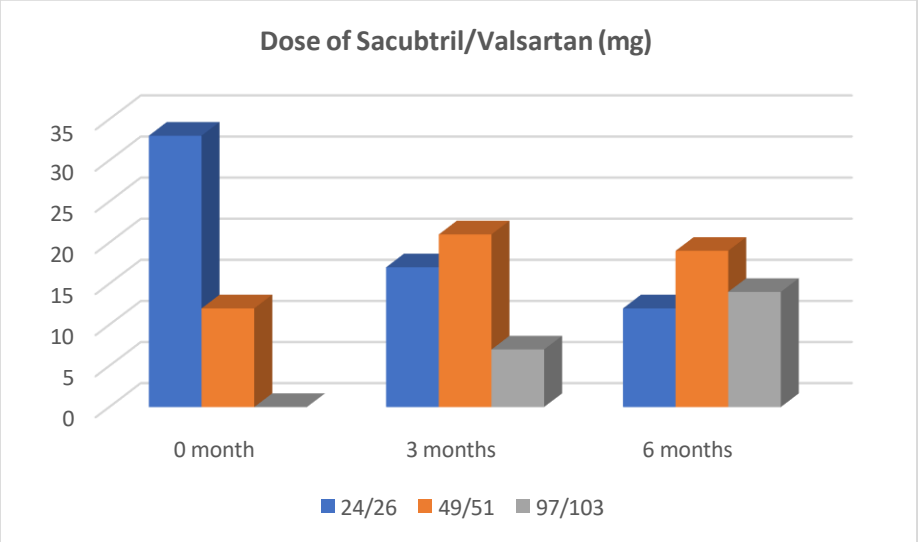

Figure 3: Dose of Sacubtril/Valsartan at 0, 3 and 6 months among the study patients (n=45).

Table 3: Laboratory data at 0, 3 & 6 months among the study patients (n=45).				
	Baseline	3 months	6 months	P-value
Urea (mg/dL)	39.4±11.7	42.3±10.2	44.6±10.1	**<0.001***
Serum creatinine (mg/dL)	1.16±0.43	1.21±0.39	1.32±0.45	**<0.001***
Serum sodium (mmol/L)	137.6±4	135.9±3.8	138.4±4.6	**0.012***
Serum Potassium (mmol/L)	4.03±0.43	4.16±0.57	4.42±0.53	**<0.001***

Quantitative variables were expressed as mean±SD, while qualitative variables were expressed as numbers & percentages. Repeated measure ANOVA test used.
**statistically significant as p<0.05.*

This study involved 45 HFrEF patients who had SV Cardiology. For 33 patients (73.3%), the first dosage of sacubitril/valsartan therapy was 24/26 mg twice day, whereas for 12 patients (26.7%), it was 49/51 mg twice day. At the 3-month point, 7 patients (15.5%) were taking 97/103 mg twice day, 17 patients (378.8%) were taking 24/26 mg, & 21 patients (467.7%) were taking 49/51 mg. By the time the six months had passed, 14 patients (31.1%) were taking 97/103 mg twice day, 12 patients (26.7%) were taking 24/26 mg, & 19 patients (42.2%) were taking 49/51 mg. We found that at three & six months of follow-up, patients' blood levels of urea, creatinine, sodium, & potassium increased statistically significantly ($p<0.05$). One RCT looked at how

sacubitril/valsartan affected individuals with kidney disease's ability to function outside of heart failure. Patients with advanced chronic kidney disease were included in the UK HARP-III trial if their eGFR was between 20 & 45 mL/min/1.73 m2 or between 45 & 60 mL/min/1.73 m2 & their urine albumin/creatinine ratio was more than 20 mg/mmol. Patients on sacubitril/valsartan & patients on irbesartan do not vary in terms of eGFR progression or albuminuria at 12 months[8]. In spite of this, sacubitril/valsartan also reduced blood pressure & cardiac biomarkers, which may have contributed to a decrease in cardiovascular risk even in individuals with severe chronic kidney disease. This RCT, however, was underpowered to detect changes in eGFR over long-term & had a number of drawbacks[9]. Furthermore, half of the individuals developed CKD due to conditions other than tubulointerstitial nephritis & hereditary nephritis, where glomerulosclerosis was not the primary aetiology of disease development. Ultimately, the study's length was too short, & many data were missing by the conclusion. There are too many restrictions to make reliable findings. Consequently, even if the medication is probably safe, the impact of sacubitril on renal outcomes in patients with severe CKD—especially if they have an eGFR < 30 mL/min/1.73 m2—remains a pertinent unsolved concern[10]. The favourable renal outcomes of the two biggest trials of sacubitril in HF patients conducted to date are the primary driving force behind the results of our results[11,12]. Despite a higher BP drop & irrespective of both CKD & albuminuria, patients utilising sacubitril/valsartan saw a smaller eGFR decline throughout the follow-up patients on enalapril, according to Damman et al.'s secondary analysis of PARADIGM-HF. Patients with type 2 diabetes mellitus had a higher decrease in eGFR decline in the sacubitril group than patients without T2DM, according to a different sub-analysis of PARADIGM-HF[13]. It's interesting to note that a cyclic guanosine monophosphate deficiency & an excess of sodium-hydrogen exchanger activity in the proximal renal tubule may be responsible for some of the accelerated nephropathy & glomerular hyperfiltration commonly associated with type 2 diabetes. These effects may be mitigated by neprilysin inhibition[11]. Compared to patients receiving valsartan alone, individuals using sacubitril/valsartan in the PARAGON-HF had a reduced risk of deteriorating renal function (1.4% vs. 2.7%, HR 0.50; 95% CI 0.33–0.77). Furthermore, cardiovascular death & HF hospitalisation reached statistical significance in the sub-analysis on patients with baseline eGFR < 60 mL/min/1.73 m2, favouring the sacubitril/valsartan group[14].

Conclusion

Our results corroborate the impact of Sacubitril/Valsartan on renal function preservation, although it causes a statistically significant rise in kidney function parameters. Research on the renal effects of sacubitril/valsartan treatment is desperately needed outside of the heart failure context, such as in advanced chronic kidney disease and type 2 diabetes, where the available data is still scant.

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