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Effect of Sacubitril/Valsartan on Echocardiographic Parameters in HFrEF Patients

[1]Mahnoor Laghari, [2]Fazeela Rizwan, [3]Dr Shoaib Sarwar Hashmi, [4]Muzna Hameed Dar, [5]Munira Khursheed, [6]Mashkoor Ansari

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[1]Lecturer in department of pharmacology Bilawal medical college Jamshoro
[2]Lecturer in department of pharmacology Bilawal medical college Jamshoro
[3]SR Cardiology CPEIC Wazirabad
[4]Assistant professor in department of pharmacology Bilawal medical college Jamshoro
[5]Mphil trainee in department of pharmacology Liaquat university of medical health sciences Jamshoro
[6]Associate Professor in department of pharmacology Liaquat university of medical health sciences Jamshoro

ABSTRACT:
BACKGROUND: Heart failure with reduced ejection fraction (HFrEF) continues to be one of the leading causes of cardiovascular illness and death. An angiotensin receptor neprilysin inhibitor, Sacubitril/Valsartan, seems to enhance cardiac function via reverse remodeling. This study seeks to evaluate the change in echocardiographic parameters after administering the drug for three months.
METHODS: This study was a prospective observational study conducted with a sample of 76 patients diagnosed with HFrEF (LVEF < 40%). Along with Echocardiographic measures, a patient's age and gender, associated illnesses, socioeconomic status, and in some cases lab results were registered. During the study, LVEF, LVEDd, and SWT were measured three months' post therapy to evaluate the impact of Sacubitril/Valsartan. Results were analyzed using paired t-test.
RESULTS: Between baseline and three months, there was a marked LVEF improvement from 31.5% ± 3.3 to 46.3% ± 4.2 ($p < 0.001$). Also, LVEDd was noted to decrease to 51.3 ± 4.3 mm from 57.8 ± 4.3 mm ($p < 0.001$) and SWT was noted to reduce from 10.1 ± 0.8 mm to 8.7 ± 0.6 mm ($p < 0.001$). All patients exhibited these changes.
CONCLUSION: There is a significant improvement of echocardiographic parameters in HFrEF patients after taking Sacubitril/Valsartan, demonstrating its efficacy.

INTRODUCTION:
Heart failure (HF) is defined as a clinical syndrome with signs and symptoms stemming from a cardiac abnormality, more precisely a structural and/or functional defect, supported by elevated levels of natriuretic hormone peptides or objective evidence of pulmonary or systemic

congestion [1]. Regardless of the differing definitions, HF is commonly understood as the heart's inability to pump or fill with blood efficiently, and left ventricular ejection fraction (LVEF) is a critical parameter in diagnosing, prognosing, and managing HF [2]. The frequency of heart failure (HF) is about more than 30% of the population over 45 years of age, which is one of the primary concerns in healthcare in Pakistan and in the industrialized world. The direct financial burden of HF in Western countries is between 1%-3% of the total health expenditure. In addition, HF is the leading cause of hospital admissions among older individuals [3]. Approximately half of patients with HF have a reduced ejection fraction, predominantly due to ischemic cardiomyopathy which is the most common cause of systolic dysfunction [4].

The most common diseases that affect people worldwide are cardiovascular diseases. It is estimated that they make up about 31% of deaths [5]. As of 2016, more than 64 million individuals suffered from heart failure, and this number is expected to increase as the population ages [6]. Heart failure's pathogenesis involves the sympathetic neural system adaptive overactivity which impairs neuroendocrine function as well as cardiovascular and renal function [7]. Within this type of heart failure, ejection fraction HFrEF (heart failure with reduced ejection fraction) is the most common with some data suggesting almost 46% of hospital admissions are due to this type of heart failure [8].

Given the substantial burden of HF on global health, there remains an urgent gap in more efficacious therapeutic approaches. Responding to this gap, in 2015 the food and drug administration sanctioned an oral chronic heart failure therapy called Sacubitril/Valsartan targeted to reduce cardiovascular morbidity and mortality in patients of NYHA class II-IV [9]. As the first agent in the angiotensin receptor neprilysin inhibitor (ARNI) class, Sacubitril/Valsartan has shown significant clinical benefits in patients with HFrEF [10]. The pivotal PARADIGM-HF trial highlighted its superiority over enalapril in reducing mortality. Sacubitril/Valsarta exhibited a remarkable improvement in their left ventricular function as well as in functional class [11].

Despite these promising results, there remains limited evidence on the drug's effects on echocardiographic parameters, particularly in real world settings. Left ventricular remodeling is an essential determinant of prognosis in HFrEF. It has not been comprehensively evaluated with Sacubitril/Valsartan. The universal definition of HF proposed in 2021 further emphasizes LVEF categorization, identifying HFrEF, (≤40%), HFmrEF (41–49%), HFpEF (≥50%), and HF with improved EF (HFimpEF), where a patient's LVEF increases ≥10% points from baseline.

Given this evolving classification and the dynamic nature of HF pathophysiology, the present study aims to evaluate the hypothesis that Sacubitril/Valsartan, by reducing neurohormonal activation and lowering myocardial afterload, improves echocardiographic outcomes in patients with HFrEF. The study specifically seeks to assess its effect on Ejection Fraction (EF), left ventricular end-diastolic diameter (LVEDD), and septal wall thickness (SWT). By investigating these parameters, this research aims to contribute valuable evidence to optimize management strategies for HFrEF and improve clinical outcomes.

MATEREIALS AND METHODS:

This prospective study was conducted over a six-month period by the Department of Pharmacology and Therapeutics, LUMHS Jamshoro, in collaboration with the Cardiology Department of LUH Jamshoro and Taluka Hospital Qasimabad, Hyderabad. The sample size was calculated to be 76 based on a heart failure prevalence of 6.2% in Pakistan, [12] using a 95% confidence interval, 5% margin of error. Patients included in this study were aged above 18 years, had a LVEF of 40% or less, had been hospitalized for HF within the previous 12 months, and were not receiving ACE inhibitors or ARBs at baseline 100mmHg, an estimated glomerular filtration rate (eGFR) less than 30ml/min/1.73m^2, serum Potassium levels above 5.2 mmol/L, a history of angioedema, or adverse reactions to ACEi/ARB therapy. All patients underwent baseline clinical evaluation, ECG and Transthoracic echocardiography (TTE), including Doppler imaging to measure LVEDD and septal wall thickness (SWT). These echocardiographic parameters were re-evaluated after three months of sacubitril/valsartan therapy. Clinical data were recorded using a structured questionnaire. Statistical analysis was performed using SPSS, with continuous variables expressed as mean ± standard deviation (SD), and comparison made using the unpaired student's t-test. A p-value <0.05 was considered statistically significant.

RESULTS:

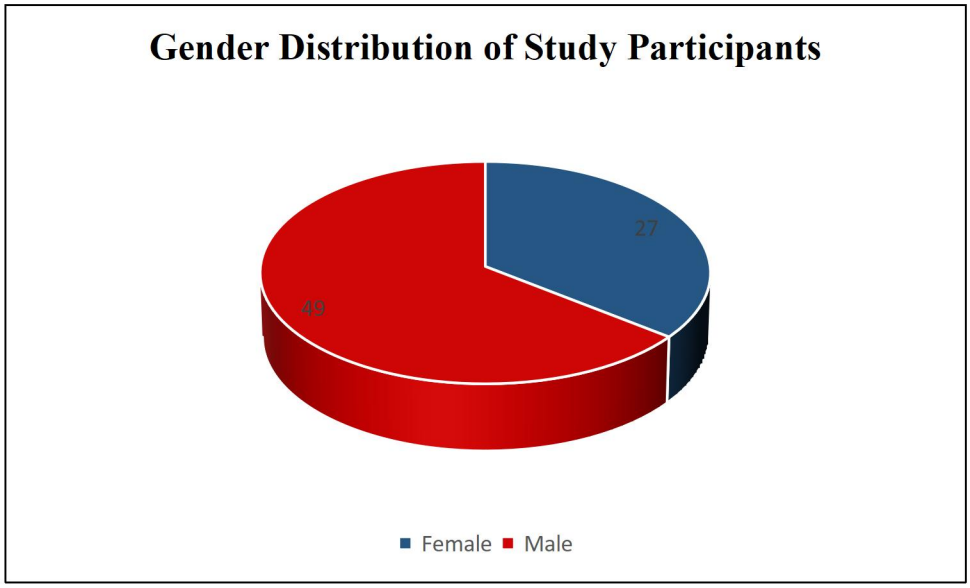
A total 76 patients with HFrEF were enrolled in this study. The mean age of the study population was 52.2 ± 6.6 years. A majority of patients (61.8%) were older than 50 years. The cohort consisted of 49 (64.5%) males and 27 (35.5%) females as shown in Graph 1. The mean BMI was 24.3 ± 2.4 kg/m², and the mean heart rate was 73.3 ± 4.2 beats per minute. Baseline renal function showed a mean serum creatinine of 92.37 ± 25.3 mmol/L and an average eGFR of 81.3 ± 24.5 mL/min/1.73 m², as shown in Table 1.

Comorbid conditions were common: 63 patients (82.9%) were hypertensive, 41 (53.9%) had diabetes mellitus, 18 (23.7%) had atrial fibrillation, and 33 (43.4%) were smokers. A total of 29 patients (38.2%) were classified as overweight or obese. Most patients belonged to NYHA functional class II (61.8%), while 38.2% were in class III as shown in Table 1 and Graph 2. Regarding etiology. Ischemic cardiomyopathy was the most frequent cause of HF, seen in 48 patients (63.2%), followed by dilated and valvular cardiomyopathy, each in 14 patients (18.4%). Socioeconomic status distribution showed 43.4% of patients from a low-income group, 39.5% from a middle-income group, 17.1% from a high-income group as shown in Table 1.

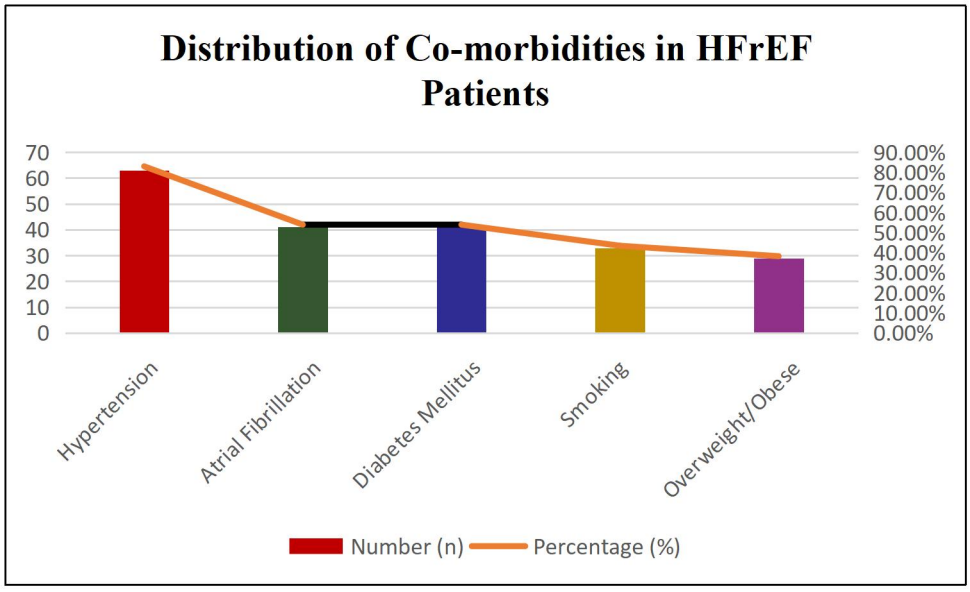
Echocardiographic parameters showed statistically significant improvement following three months of Sacubtril/Valsartan therapy. The mean LVEF increased 31.45 ± 3.28% at baseline to 46.33 ± 4.24% post-treatment ($p < 0.001$). similarly, a significant reduction in LVEDd was observed from 57.79 ± 4.27 mm to 51.27 ± 4.31 mm ($p < 0.001$). Septal wall thickness (SWT) also decreased significantly from 10.06 ± 0.82 mm to 8.7 ± 0.63 mm ($p < 0.001$), as shown in Table 2 and Graph 3.

Table 1. Baseline Clinical and Demographic Characteristics of Study Participants

Study Variable	Mean ± SD or n (%)
Age (years)	52.2 ± 6.6
BMI (kg/m²)	24.3 ± 2.4
Heart Rate (bpm)	73.3 ± 4.2
Creatinine (mmol/L)	92.37 ± 25.3
eGFR (ml/min/1.73m²)	81.3 ± 24.5
Age Category	
≤ 50 years	29 (38.2%)
> 50 years	47 (61.8%)
Gender	
Female	27 (35.5%)
Male	49 (64.5%)
Hypertension	
No	13 (17.1%)
Yes	63 (82.9%)
Atrial Fibrillation	
No	58 (76.3%)
Yes	18 (23.7%)
Diabetes Mellitus	
No	35 (46.1%)
Yes	41 (53.9%)
Smoking	
No	43 (56.6%)
Yes	33 (43.4%)
Overweight/Obese	
No	47 (61.8%)
Yes	29 (38.2%)
NYHA Class	
Class II	47 (61.8%)
Class III	29 (38.2%)
Etiology of HF	
Dilated	14 (18.4%)
Ischemic	48 (63.2%)
Valvular	14 (18.4%)
Socioeconomic Status	
Low	33 (43.4%)
Middle	30 (39.5%)
High	13 (17.1%)



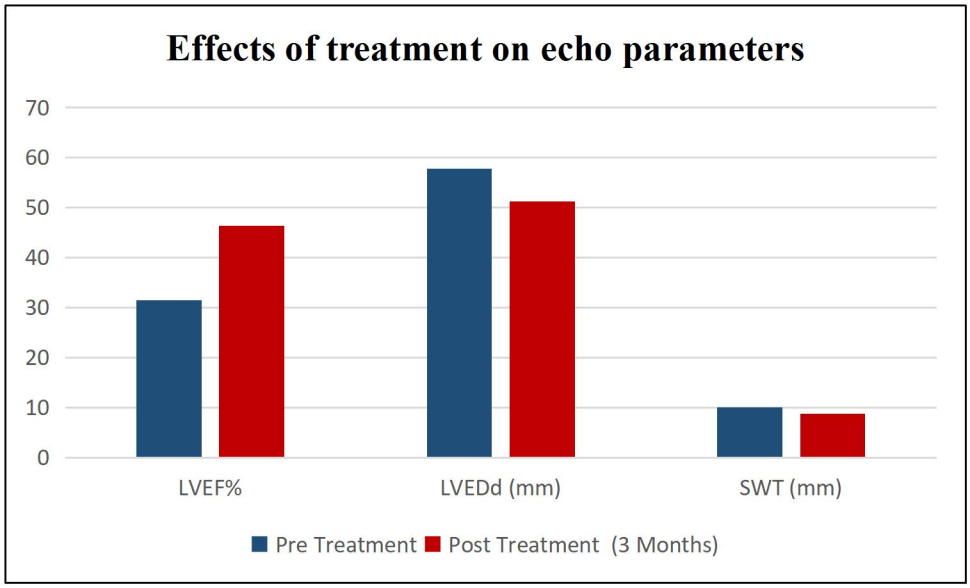
Graph 1. Gender distribution of the study participants.



Graph 2. Co-morbidities Distribution of the study participants.

Table 2. Effect of Sacubitril/Valsartan on Echocardiographic Parameters in HFrEF Patients.

Echo Parameters	Pre Treatment	Post Treatment after 3 Months	P-value
LVEF%	31.45 ± 3.28	46.33 ± 4.24	<0.001
LVEDd (mm)	57.79 ± 4.27	51.27 ± 4.31	<0.001
SWT (mm)	10.06 ± 0.82	8.7 ± 0.63	<0.001



Graph 3. Effect of Sacubitril/Valsartan on Echocardiographic Parameters in HFrEF Patients.

DISCUSSION:

HF significantly impairs patients' quality of life (QoL) across all domains, with physical role and functioning being more severely affected compared to other chronic illnesses. Evidence suggests that optimizing treatment to improve NYHA class positively influences patient's perception of QoL especially through the use of medications like beta blockers and ACE inhibitors [13].
Several studies have highlighted the therapeutic benefit of Sacubtril/Valsartan in patient with HFrEF, Halle et al, demonstrated improved exercise capacity with Sacubtril/Valsartan, comparable to enalapril [14]. Our study aligns with this evidence by showing significant improvement in LVEF. Similarly significant improvement in Sacubitril/Valsartan over Enalapril in reducing cardiovascular outcomes in HFrEF patients [15], which is consistent with our finding. Piepoli et al, assessed its impact on physical activity and 6MWT distance, supporting overall clinical improvement with Sacubitril/Valsartan [16]. while our study did not evaluate exercise capacity directly, we observed a significant enhancement in ejection fraction, aligning with Liu et al's prospective study from Taiwan, which reported similar LVEF improvements with this therapy [14]. Tsutsui et al found a trend towards better NYHA class deterioration compared to those on Enalapril [17]. Over 12 week follow up also showed favorable results in functional status. Additionally, Florea et al observed enhanced LVEF with Sacubitril/Valsartan, which corroborates our findings [18].
Sacubitril/Valsartan has also been linked to improved performance in routine activities, including sexual and other bodily functions, while reducing hospitalizations and mortality in HFrEF patients [19-20]. It is important to note, however, that smoking may blunt the full benefits of therapy, as highlighted by observations of reduced exercise response in heavy smokers [21].

CONCLUSION:

Sacubitril/Valsartan significantly improved echocardiographic parameters in HFrEF patients over 3 months, with consistent benefits. Notably there was a marked increase in LVEF along with significant reductions in LVEDd, SWT. These findings support its role in reversing cardiac remodeling and improving heart function.

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