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# Effect of Sacubitril/Valsartan on Echocardiographic Parameters and Functional Class in Patients of Heart Failure with Reduced Ejection Fraction

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** This study sought to determine, in retrospect, the effect of Sacubitril/Valsartan on the echocardiographic and functional class of ambulatory HFrEF patients taking conventional heart failure therapy.
**Methods:** We conducted a retrospective observational single-center cohort of ninety HFrEF patients with NYHA Class II-III attending as an outpatient at a tertiary cardiac care facility between November 2018 and January 2020. Standardized two-dimensional transthoracic echocardiography and functional class evaluation were conducted at baseline and after 03-month of SV treatment.
**Results:** At 03-month follow-up evaluation, SV treatment was found to contribute substantially in reversing the cardiac remodeling of HFrEF patients as evidenced by improvement in LVEF (28.51±5.06 to 36.01±10.63; p < 0.001), LVEDD (57.29±7.99 to 53.14±8.22; p <0.001), and LVESD (46.07±9.49 to 43.20±9.22; p <0.001). Additionally, an improvement in sPAP (34.13±9.49 to 32.46±8.14; p <0.001) was observed along with a significant NYHA functional class recovery (2.76

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to 1.89, p < 0.001). Upon gender-based stratification, the data suggested no gender-based differences in reverse remodeling effects of SV; though statistically insignificant, LA (38.51±8.23 to 37.3±5.92 mm) and RV (27.10±5.74 to 26.42±2.81 mm) diameters were observed to reduce only in men.

**Conclusion:** Our study maintained that earlier commencement of SV in parallel with conventional heart failure therapy results in a significant amount of improvement in LVEF, LVEDD, LVESD, and sPAP in HFrEF patients irrespective of their gender. Simultaneously, SV alleviates the heart failure-related morbidity through rapid functional status (NYHA Class) recovery.

*Keywords: Sacubitril/Valsartan; heart failure; 2-D echocardiography; NYHA functional class; sex differences.*

## 1. INTRODUCTION

Heart failure has become a global health burden influencing at least 26 million people worldwide and is continued to increase in prevalence [1]. According to WHO, cardiovascular diseases are taking the lead in increasing annual mortality rates across the globe with a reported estimate of 31% of all deaths as per 2016 statistics [2]. A Swedish study regarding the epidemiology of heart failure stated that the annual incidence of heart failure has been observed to be declining, whereas the prevalence appears to be increasing [3]. Heart failure with reduced ejection fraction (HFrEF), defined as an ejection fraction of less than or equal to 40%, is found to be prevalent in nearly 46% of patients hospitalized with heart failure [4].

Considering its huge impact on global health, there is a need for an effective treatment strategy. In this regard, FDA, in 2015, approved a novel oral combination of Sacubitril plus Valsartan to reduce cardiovascular morbidity and mortality in patients with chronic heart failure (NYHA Class II-IV) [5]. Sacubitril/Valsartan (SV), being first-in-class angiotensin receptor neprilysin inhibitor (ARNi), demonstrated a very meaningful survival advantage in patients of HFrEF in the PARADIGM-HF trial, which compared the mortality reducing the effect of Sacubitril/Valsartan and Enalapril [6-7]. Concerning safety and efficacy, a meta-analysis has shown the superiority of Sacubitril/Valsartan over placebo and ACEi/ARB [8].

Several speculators have indicated with consistent results, that HFrEF patients who were treated with Sacubitril/Valsartan exhibited a remarkable improvement in their left ventricular function as well as in functional class [9-11].

Due to the paucity of local data, we sought to determine, in retrospect, the effects of Sacubitril/Valsartan (SV) on Left Ventricular echocardiographic parameters and functional class of the HFrEF patient after 3 months follow-up in an outpatient setting of Cardiology Department, Dr. Ruth KM Pfau Civil Hospital Karachi, Karachi, Pakistan.

## 2. METHODS

This is a retrospective observational single-centre cohort study involving diagnosed ambulatory chronic heart failure patients with reduced ejection fraction (stabilized on standard heart failure therapy) who attended as an outpatient at the Department of Cardiology of Dr. Ruth KM Pfau Civil Hospital Karachi, Pakistan in the period between November 2018 and January 2020. Patients, after providing written informed consent, were registered for the study and commenced on Sacubitril/Valsartan (50, 100, or 200 mg twice daily), and after a 3-month duration, were followed up in an OPD setting. Echocardiographic and functional parameters were noted on a data collection proforma through non-probability purposive sampling technique at baseline registration and 03-month follow-up visit. Importantly, before prescribing Sacubitril/ Valsartan, a complete history, physical examination, and renal function were evaluated. A wash-out period of 36 hours was allowed before initiating Sacubitril/Valsartan for those patients who were already taking an ACE inhibitor. The starting dose for the majority of patients was 24/26mg.

The inclusion criteria for study participants as per the PARADIGM-HF [7] clinical and safety criteria are enlisted as under:

1. Ambulatory chronic HF patients aged 18 and/or above, either gender.
2. Patients with Left Ventricular Ejection Fraction (LVEF) of 40% and below as estimated by standard 2D echocardiography

3. Symptomatic ambulatory chronic heart failure patients as defined by NYHA Functional Class [12] II-III.
4. Patient on a stable dose of beta-blocker, ACE inhibitors, or ARBs for at least 04 weeks.
5. Serum potassium level of <5.2 mEq/L

Whereas, the exclusion criteria comprised:

1. Patient with any previous history of angioedema.
2. Patients with any evidence of congenital heart disease.
3. Patients who had undergone cardiac resynchronization therapy.
4. Patients with a Blood pressure of ≤100 mmHg.
5. Patients with Glomerular filtration rate (eGFR) <30 ml/min/1.73m2
6. Patients who were hypersensitive to Sacubitril/Valsartan or any of its excipients.
7. Pregnant and lactating women.

Echocardiographic measures were measured by standard transthoracic echocardiography (TTE) as per the guidelines of the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) [13], using commercially available echocardiographic system (Vivid S5; GE-Vingmed Ultrasound, NY, USA) and with a 3.5 MHz transducer. Each study participant was placed in a left lateral decubitus position while taking the echocardiographic images performed by the sonographer blinded to the patient's clinical status. Baseline and follow-up echocardiographic measures were captured by the same echocardiographic system and sonographer. The recorded parameters include: LVEF; Left ventricle end-diastolic dimension (LVEDD); Left ventricle end-systolic dimension (LVESD); systolic pulmonary artery pressure (sPAP); Left atrial (LA) diameter; Right ventricle (RV) diameter; Left ventricle posterior wall diameter (LVPWd) and Inter-ventricular septum diastolic diameter (IVSTD). LVEF was calculated using visual assessment as well as the Simpson biplane method. LA and RV diameters along with other linear measurements were estimated using two-dimensional measurements. sPAP was calculated by combining continuous wave Doppler regurgitate tricuspid jet signal and inferior vena cava diameter.

The recorded data was entered and analysed using SPSS version 23.0 (IBM Corp., NY, USA). Continuous variables were expressed as mean ± Standard Deviation (SD), whereas categorical variables were presented as frequencies and percentages. Means of Echocardiographic and Functional parameters were compared at baseline and after 3 months by applying paired sample t-test and a 2-tailed p-value of <0.05 was considered statistically significant.

## 3. RESULTS

The study retrospectively enrolled 115 diagnosed ambulatory chronic heart failure patients with a reduced ejection fraction between November 2018 and January 2020, who were on a guideline-directed heart failure regime. Among 115 patients, eight patients were lost to follow-up, three died of unreported aetiology and five discontinued the treatment before follow-up for an undocumented reason. Consequently, the final study population comprised 90 patients including 55.6% (50) males and 44.4% (40) females. The mean age was 53±13, the majority were non-smokers (51.1%), hypertensive (84.4%) and with a non-ischemic (60%) heart failure aetiology. All the baseline characteristics have been elucidated in Table 1. Left Ventricular ejection fraction (LVEF) of subjects at baseline was noted as less than or equal to 40%. Before initiation of Sacubitril/Valsartan (SV), baseline medications of study participants include ACE-I/ARB, beta-blockers, loop diuretics, and Mineralocorticoid Receptor Antagonist (MRA) at the prescription rates of 28.9%, 82.2%, 85.6%, and 84.4% respectively. At baseline, 64.4% (58) patients were on 24/26mg, 33.3% (30) on 49/51mg, and the remaining 2.3% (2) were placed on 97/103mg from the start. During the course of the study, the up-titration, down-titration, and maintenance were tailored to the hemodynamic status of the patient at intermittent follow-up visits to meet the need for dosage adjustment. Eventually, the follow-up prescription rates of SV were observed as: 97/103mg in 28.8% (26) patients; 49/51mg in 52.2% (47) patients and 24/26mg in 18.8% (17) patients.

The comparison of TTE related parameters of the study population at baseline and follow-up is summarized in Table 2. With the commencement of SV in parallel with standard treatment, the 03-month follow-up has exhibited convincing results in terms of clinically significant recovery in LVEF (28.51±5.06 to 36.01±10.63; $p < 0.001$), LVEDD (57.29±7.99 to 53.14±8.22; $p <0.001$), LVESD (46.07±9.49 to 43.20±9.22; $p <0.001$) and sPAP (34.13±9.49 to 32.46±8.14; $p <0.001$). The

gender-based evaluation of echocardiographic parameters, as summarized in Table 3, has revealed that the improvement effect of SV on LVEF, LVEDD, LVESD, and sPAP is essentially gender-independent. In addition, it is noteworthy that, despite not reaching statistical significance, LA (38.51±8.23 to 37.3±5.92 mm) and RV (27.10±5.74 to 26.42±2.81 mm) diameters are observed to reduce in men compared to women.

**Table 1. Baseline population characteristics**

| Variables | Total Population (N=90) |
|---|---|
| **Demographics** | |
| Age (years) | 53±13 |
| **Gender (%)** | |
| Male, n (%) | 50 (55.6) |
| Female, n (%) | 40 (44.4) |
| **Smoking Status (%)** | |
| Current smoker, n (%) | 13 (14.4) |
| Ex-smoker <12 months, n (%) | 10 (11.1) |
| Ex-smoker >12 months, n (%) | 21 (23.3) |
| Never smoked, n (%) | 46 (51.1) |
| **Heart Failure Etiology** | |
| Ischemic, n (%) | 36 (40) |
| Non-ischemic, n (%) | 54 (60) |
| **Co-morbidities** | |
| Diabetes mellitus, n (%) | 30 (33.3) |
| Hypertension, n (%) | 76 (84.4) |
| Hyperlipidemia, n (%) | 29 (32.3) |
| **NYHA Class** | |
| I, n (%) | 0 (0) |
| II, n (%) | 33 (36.7) |
| III, n (%) | 57 (63.3) |
| IV, n (%) | 0 (0) |
| **Guideline directed Heart Failure therapy** | |
| ACE-I or ARB, n (%) | 26 (28.9) |
| Beta blockers, n (%) | 74 (82.2) |
| Aldosterone antagonist, n (%) | 76 (84.4) |
| Loop diuretic, n (%) | 77 (85.6) |

*Abbreviations: NYHA: New York Heart Association; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker*

**Table 2. Echocardiographic and Functional parameters at baseline and 03-month follow-up***

| Parameters | Baseline | 3 months | P-value |
|---|---|---|---|
| LVEDD (mm) | 57.29±7.99 | 53.14±8.22 | **<0.001** |
| LVESD (mm) | 46.07±9.49 | 43.20±9.22 | **<0.001** |
| LVEF (%) | 28.51±5.06 | 36.01±10.63 | **<0.001** |
| IVSTD (mm) | 9.01±1.49 | 9.02±1.43 | 0.691 |
| LVPWd (mm) | 9.24±1.46 | 9.16±1.46 | 0.262 |
| sPAP (mm Hg) | 34.13±9.49 | 32.46±8.14 | **<0.001** |
| LA (mm) | 37.51±7.92 | 37.43±5.80 | 0.896 |
| RV (mm) | 26.50±5.35 | 26.08±2.51 | 0.486 |
| NYHA Class | 2.76±1.04 | 1.89±0.64 | **<0.001** |

*Abbreviations: LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; IVSTD, inter-ventricular septum thickness in diastole; LVPWd, left ventricular posterior wall diameter; sPAP, systolic pulmonary artery pressure; LA, left atrium diameter; RV, right ventricle diameter; NYHA, New York Heart Association.*

**Values are expressed as Mean ± standard deviation and a p-value of <0.05 was considered significant*

**Table 3. Men vs. Women Echocardiographic parameters at follow-up***

| Parameters | Men (n=50) | P-value | Women (n=40) | P-value |
|---|---|---|---|---|
| LVEDD | 58.73±8.05 | | 55.49±7.63 | |
| LVEDD 3 months | 54.40±7.88 | **<0.001** | 51.57±8.45 | **0.014** |
| LVESD | 46.69±10.43 | | 45.31±8.22 | |
| LVESD 3 months | 43.86±9.49 | **0.002** | 42.37±8.93 | **0.047** |
| LVEF | 28.14±4.53 | | 28.97±5.68 | |
| LVEF 3 months | 33.58±9.15 | **<0.001** | 39.06±11.64 | **<0.001** |
| IVSTD | 9.21±1.53 | | 8.77±1.43 | |
| IVSTD 3 months | 9.06±1.36 | 0.072 | 8.97±1.54 | 0.285 |
| LVPWd | 9.30±1.42 | | 9.18±1.53 | |
| LVPWd 3 months | 9.24±1.34 | 0.533 | 9.07±1.60 | 0.35 |
| sPAP | 37.60±11.08 | | 34.20±9.25 | |
| sPAP 3 months | 31.34±6.52 | **<0.001** | 29.87±5.24 | **<0.001** |
| LA | 38.51±8.23 | | 36.27±7.42 | |
| LA 3 months | 37.3±5.92 | 0.334 | 37.60±5.72 | 0.339 |
| RV | 27.10±5.74 | | 25.75±4.80 | |
| RV 3 months | 26.42±2.81 | 0.481 | 25.67±2.03 | 0.788 |

*Abbreviations: LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; IVSTD, inter-ventricular septum thickness in diastole; LVPWd, left ventricular posterior wall diameter; sPAP, systolic pulmonary artery pressure; LA, left atrium diameter; RV, right ventricle diameter.*

**Values are expressed as Mean ± standard deviation and a p-value of <0.05 was considered*

The Functional improvement of patients, as assessed by changes in NYHA Class from baseline to follow-up, is demonstrated. At baseline enrolment, 36.7% of patients were found to be in NYHA Class II while a majority (63.3%) belonged to NYHA Class III. Following initiation of SV, a remarkable functional class recovery has been observed as at the 03-month follow-up majority (57.7%) of patients improved their functional status to NYHA Class II with a substantial strength of patient population (24, 26.7%) managed to reach NYHA Class I. With respect to statistical analysis, NYHA Class improved from 2.76 to 1.89 ($p < 0.001$).

## 4. DISCUSSION

HFrEF carries a substantial risk of morbidity and mortality compared to other heart failure population [14-15]. Therefore, management of these patients demands a systematic step-wise medical approach parallel with diligent risk stratification and therapeutic adjustments, where needed [16]. The latest heart failure management guidelines recommend the provision of SV in place of renin-angiotensin-aldosterone-system (RAAS) blockers, in ambulatory HFrEF patients who failed to show any improvement despite being on guideline-directed heart failure therapy [17]. Following the approval, to date, several studies have been conducted probing and stating the promising clinical implications of SV in improving various aspects of failing heart such as reverse remodelling, cardiac function, and symptomatic recovery but with a small study population and sometimes differing findings. In this study, we analysed the impact of commencing SV in parallel with conventional heart failure therapy on echocardiographic and functional parameters of HFrEF patients. Our study findings have maintained that SV served the purpose in terms of substantial progressive improvement in cardiac remodelling and subsequent systo-diastolic functioning of the heart within a short period. From baseline to follow-up, LVEF, sPAP, and linear dimensions, including LVEDD and LVESD, are observed to improve incrementally.

The PARADIGM-HF trial has demonstrated that, compared with Enalapril, SV substantially recovers the health-related quality of life outcomes in HFrEF patients in which physical and social activity limitations are much more prevalent [18]. In our study, shifting to SV has shown a significant amount of NYHA functional class recovery as a majority of the study population improved to functional Class II with a noteworthy count of 24 patients reaching an asymptomatic state (NYHA Class I). The reported improvement was observed independent of dosage frequency and potency. Likewise, several other speculators have evidenced the functional class improvement

effect of this novel therapeutic agent in real-life cohorts and routine clinical practices [19-21].

In prior studies, data are scarce on the gender-based differential impact of SV on echocardiographic parameters. In a recent study, Landolfo et al indicated that most of the echocardiographic parameters improved significantly in men compared to women; however, LA diameter and sPAP improved only in women [22]. In our study, after sex-stratification, it has been found that LVEF, LVEDD, LVESD, and sPAP improved indiscriminately in both men and women throughout the follow-up; however, in contrast to Landolfo et al study, though statistically non-significant, LA and RV diameters improved only in men.

Left ventricular reverse remodelling (LVRR) characterizes the attenuation of LV dimensions and volumes which is translated as improvement in systo-diastolic cardiac functioning at follow-up in HFrEF patients [23]. This reverse remodelling effect of SV has long been proven in various HFrEF experimental models as it poses a clinically significant ameliorating impact on the pathophysiological mechanisms of cardiac remodelling [24-25]. This compelling benefit is duly reflected in real-life cohorts as well [26-27]. A recent retrospective cohort of 48 HFrEF patients has shown an improvement in LVEF (reflected as a dose-dependent relationship with SV) and other remodelling measures at a 3-month follow-up [28]. Similarly, a prospective observational cohort of the Taiwanese population has demonstrated the efficacy of SV in improving LVEF with a simultaneous reduction in linear dimensions including LVEDD and LVESD [29], which is confirmed in our study findings along with a reduction in sPAP. Moreover, D'Auria and colleagues suggested in their study that LVRR is greater in patients with lower baseline ejection fraction and non-ischemic heart failure aetiology, which is also consistent with our study findings [30].

## 5. CONCLUSION

Our study provided evidence regarding the earlier commencement of SV in patients with heart failure with reduced ejection fraction improves several echocardiographic parameters including LVEF, LVEDD, LVESD and sPAP irrespective of the sex of the patients. Hence slowing down the process of remodeling and at the same time SV alleviates the heart failure-related morbidity through rapid functional status (NYHA Class) recovery.

## CONSENT

Patients, after providing written informed consent, were registered for the study and commenced on Sacubitril/Valsartan (50, 100, or 200 mg twice daily), and after a 3-month duration, were followed up in an OPD setting.

## ETHICAL APPROVAL

The study was approved by the local ethics committee of Dow University of Health Sciences and Dr. Ruth KM Pfau Civil Hospital Karachi and performed in accordance with the Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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