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Original article

Short-Term Echocardiographic Evaluation by Global Longitudinal Strain in Patients with Heart Failure Treated with Sacubitril/Valsartan

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Abstract

Background: Heart failure (HF) is a clinical syndrome characterized by dyspnea, easy fatigability, and fluid retention. **This study aimed to** assess the effects of ARNI on GLS and myocardial mechanics in patients with HFrEF. **Methods:** This prospective observational study that included 50 Patients diagnosed with heart failure. All studied cases were subjected to the following: 12-Lead ECG, laboratory investigations [Baseline Serum creatinine (with eGFR calculation using Cockcroft- Gault equation), serum electrolytes, complete blood count, liver function tests and NT-proBNP, Serum creatinine, eGFR calculation and serum electrolytes.], conventional Echo Doppler Study, 2D Speckle tracking Global Longitudinal Strain and medication management. **Results**: LVEF and peak GLS were significantly improved at 6 months compared to the baseline measurement (P<0.001 and <0.001 respectively), while LVEDV and LVESV were significantly reduced after 6 months compared to the baseline measurement (P=0.019 and <0.001 respectively). LAV, sPAP, TAPSE, and MRV were insignificantly different between baseline and 6 months measurements. DD grade was insignificantly different between baseline and 6 months measurements. **Conclusion:** treatment with sacubitril/valsartan significantly improved key echocardiographic parameters, notably left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), in patients with heart failure with reduced ejection fraction (HFrEF). Notably, these improvements were accompanied by a marked reduction in NT-proBNP levels and enhancements in NYHA functional class, highlighting the efficacy of ARNI in improving both myocardial mechanics and clinical symptoms over a six-month period.

Keywords: Short-Term Echocardiographic; Global Longitudinal Strain; Heart Failure; Sacubitril/Valsartan.

Abbreviations:

HF: Heart Failure
ARNI: Angiotensin Receptor-Neprilysin Inhibitor
GLS: Global Longitudinal Strain
HFrEF: Heart Failure with Reduced Ejection Fraction

ECG: Electrocardiogram
eGFR: Estimated Glomerular Filtration Rate
LVEF: Left Ventricular Ejection Fraction
LVEDV: Left Ventricular End-Diastolic Volume
LVESV: Left Ventricular End-Systolic Volume
LAV: Left Atrial Volume
sPAP: Systolic Pulmonary Artery Pressure
TAPSE: Tricuspid Annular Plane Systolic Excursion
MRV: Mitral Regurgitant Volume
DD: Diastolic Dysfunction
NT-proBNP: N-terminal pro-B-type Natriuretic Peptide
NYHA: New York Heart Association

Introduction

Heart failure (HF) is a clinical syndrome characterized by dyspnea, easy fatigability, and fluid retention. It results from an imbalance in the homeostasis between structural, functional, and neurohumoral factors which result in the impairment of ventricular filling or ejection of blood after a pathological insult (1).

HF is an increasing, global epidemic that results in significant health care expenditure, disability, and mortality (2). In developed countries, the prevalence of HF is approximately 1% - 2% of the adult population, with the prevalence rising to ≥10% among persons 70 years of age or older. HF exacerbations in the USA result in an estimated one million hospitalizations yearly (3).

According to current European Society of Cardiology (ESC) Guidelines, HF is classified into three left ventricular ejection fraction (LVEF) categories: (i) HF with reduced ejection fraction (EF< 40%, HFrEF), (ii) HF with mid-range EF (40–49%, HFmrEF) and (iii) HF with preserved EF (≥50%, HFpEF) (4). Approximately up to half of patients with HF have HFpEF, and the proportion of HFpEF in the overall HF population is increasing. While there

are pharmacological therapies with mortality benefit in HFrEF, no therapy has yet shown to convincingly reduce morbidity and mortality in patients with a LVEF of 40% or higher (5).

The initial response to any pathological insult to the cardiac tissue is the activation of the vasoconstrictor and anti-natriuretic systems (the sympathetic nervous system, the renin–angiotensin–aldosterone system, the arginine vasopressin system, and endothelin) which leads to increasing afterload on an already damaged heart as a result of increased sympathetic tone and cardiac remodeling and hypertrophy as a result of fluid retention and fibrotic changes in the myocardium. This is physiologically counterbalanced by vasodilator and natriuretic systems (the prostaglandin system, the nitric oxide system, the dopaminergic system, and the natriuretic peptide system (6).

The complex pathophysiological interactions between the above-noted systems have recently therefore been the mainstay of development of targeted medical therapy. The

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conventional therapies for heart failure with reduced ejection fraction (HFrEF) include beta-blockers targeting the SNS, while angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonist (MRA) target the over activated RAS on pathologic ventricular remodeling (7).

Sacubitril/valsartan, the first-in-class angiotensin receptor neprilysin inhibitor (ARNI) combines an angiotensin receptor blocker with a neprilysin inhibitor. This treatment has changed the management of heart failure with reduced ejection fraction, demonstrating to be more effective than enalapril in reducing cardiovascular mortality and hospital admission when started in a stable phase in outpatients (8).

Recent studies have shown that ARNI led to a greater reduction in N-terminal pro B-type natriuretic peptide (NT-proBNP) than enalapril among patients admitted with acute decompensated heart failure (17). The reduction in NT-proBNP achieved with ARNI was also correlated with signs of reverse cardiac remodeling at 1 year, in terms of an increase in left ventricular ejection fraction (LVEF) and a decrease in indexed left ventricular end-diastolic and systolic volumes (9). ARNI also significantly improved cardiac volumes and ejection fraction, with standard transthoracic echocardiography (TTE), and improvements in mitral regurgitation and diastolic function parameters were also observed, with a medium term dose dependent effect (10).

However, it is known that evaluation by standard TTE is limited by intra-observer variability. Global longitudinal strain (GLS) assessment, on the other hand, through a semi-automatic procedure that identifies the endocardial border and its movement over time, appears to have more sensitivity and specificity in the detection of left ventricular systolic dysfunction, thus improving the detection of early changes of contractile function, in contrast with standard biplane ejection fraction evaluation (11)

The purpose of this study was to assess the effects of ARNI on GLS and myocardial mechanics in patients with HFrEF.

Patients and methods

This multi-center prospective observational study included 50 patients diagnosed with heart failure with reduced ejection fraction (HFrEF), defined as an ejection fraction (EF) of less than 40%. Patients visited either Benha University Hospital, Qaliobia, Egypt, and Al-Zaitoun Specialized Hospital, Cairo, Egypt, as outpatients or inpatients.

Signed written informed consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine,

Benha University (**Approval code: MD 5- 12 – 2020).**

Enrollment started on the 1st of March 2022 with follow-up of the last enrolled patient ended on 28th of April 2023.

Inclusion criteria were symptomatic patients with NYHA class I-III despite being on conventional guideline directed medical therapy, LVEF of < 40 % evaluated by standard transthoracic echocardiography and 2D speckle tracking GLS at baseline time at enrollment or a previous echocardiographic assessment done within 6 months before enrollment. with elevated natriuretic peptides (NT-proBNP > 125 pg/ml), systolic blood pressure ≥ 90 mmHg, age ≥ 18 years.

Exclusion criteria were patients already started on sacubitril/valsartan before enrollment in the study, history of hypersensitivity or intolerance (unmodifiable) to Sacubitril/valsartan, an ACEI or ARB as well as known or suspected contraindications (including hereditary angioedema) to the study drugs, estimated glomerular filtration rate by Cockroft-Gault equation (Cockcroft & Gault, 1976) (eGFR) < 30 mL/min/1.73 m2 at baseline, serum potassium > 5.5 mmol/L, severe liver dysfunction (Childs-Pugh Class C), active infection, primary hypertrophic or infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis, or tamponade, known pregnancy or anticipated pregnancy within the next 24 weeks after enrollment or breastfeeding mothers, atrial, ventricular septal defects and complex congenital heart diseases, cardiac resynchronization therapy, co-morbid conditions that may interfere with completing the study protocol or cause death within 1 year, significant aortic regurgitation and any significant stenosis of semilunar valves at valvular, pre-valvular or post-valvular levels, and discontinuation of medication due to non-compliance, death or precluding conditions.

All studied cases were subjected to the following: History taking & clinical examination, including [Age, sex, presence of hypertension, diabetes mellitus, ischemic heart disease, presence of atrial fibrillation, smoking status, NYHA class and cardiac examination.]. **12-Lead ECG. Laboratory investigations [**Baseline Serum creatinine (with eGFR calculation using Cockcroft- Gault equation), serum electrolytes, complete blood count, liver function tests and NT-proBNP**,** Serum creatinine, eGFR calculation and serum electrolytes**. Conventional Echo Doppler Study**. **2D Speckle tracking Global Longitudinal Strain**. **Medication management.**

Conventional Echo Doppler Study: Done as baseline and again at 24 weeks using PHILIPS EPIQ Elite Ultrasound System with focusing on the following parameters: Left ventricular ejection fraction using both M-mode (Teichholz method) and 2D Simpson's method (summation-of-disks approach)

Left atrial volume in 2D by measuring the LA planimetry area (both in apical

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4-chamber and apical 2-chamber views "Biplane method") and LA long axis at end-ventricular systole. The machine then automatically calculates the left atrial volume. Left ventricular end diastolic and end systolic volume using real-time 2D echocardiography probe with automatic machine processing. Pulmonary artery systolic pressure that is equivalent to the right ventricular systolic pressure (in case of no significant stenosis at the right ventricular outflow tract or the pulmonary valve) and can be estimated by measuring the TR jet maximum velocity by continuous wave (CW) spectral Doppler and the RA pressure (RAP) estimated by the size and respiratory collapsibility of the inferior vena cava. Diastolic dysfunction assessment according to the 2016 update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging (12).

Mitral regurgitation quantitative assessment by measuring the mitral regurgitant volume using stroke volume method with MR considered to be significant if ≥ 30 ml/beat (more than mild MR).

2D Speckle tracking Global Longitudinal Strain (GLS) Longitudinal global strain measured after obtaining good quality apical views, four-chamber view, long-axis view, and two-chamber view imaged with a good frame rate and completed in the following steps (13).

Reduce the depth of the image and the width of the sector to get a good quality image without any dropouts and increase the frame rate to more than 60 fps. Breath was held in expiration and minimized the motion artifacts. Apical long-axis, four-chamber, and two-chamber images were gained for three cardiac cycles. Aortic closure was marked at the peak of the electrocardiographic T-wave. At this stage, software was chosen for strain analysis depending on the vendor. With

PHILIPS EPIQ Elite Ultrasound System formed the measurement protocol. The region of interest was marked by placing the points at the base of the left ventricle near the atrioventricular posterior and anterior annulus and finally the apex. The left ventricular walls have been highlighted in colors depicting the basal, mid, and apical segments. This process was interrogated to all selected views (Apical long- axis (three-chamber) view, Four-chamber view and Two-chamber view). Thus, all the 17 segments were be interrogated. On completion of the analysis, the machine used various types of color coding, one for the segments analyzed and the others for the strain parameters of interest and finally generate the quad screen and bull's eye images. At this phase, each of the three imaging planes generated four pictures in the quad format, to identify the myocardial segments each in unique colors, the color-coded sector image. Normally, all segments move in parallel, with the basal segments showing lesser excursion than the apical segments. The color coding is such that good peak systolic strain is depicted as red,

suboptimal strain as various shades of pink, and positive strain as blue, meaning that segment is dyskinetic.

This sequence of image analysis was done for six segments of the apical long-axis view, apical four-chamber view, and apical two- chamber view. Once all the three apical images have been interrogated and saved, the AFI software displayed the bull's eye picture of 17 segments of the left ventricle with measured peak systolic longitudinal strain values.

Medication management: patients received: Conventional heart failure treatment as indicated (e.g., Beta Blockers, RAAS inhibitors and Mineralocorticoid receptor antagonist). Sacubitril/valsartan started as follows: 36 hours after stopping ACE inhibitors and at the next dose time in patients receiving ARBs.

Sacubitril/valsartan maximum dose (97/ 103 mg) twice daily was given to patients receiving total daily dose of ≥ 10 mg Perindopril or therapeutically equivalent doses of other ACE inhibitors and in patients receiving total daily dose of > 160 mg Valsartan or therapeutically equivalent doses of other ARBs. Sacubitril/valsartan intermediate dose (49/ 51 mg) twice daily was given to patients receiving total daily dose of ≤ 10 mg Perindopril or therapeutically equivalent doses of other ACE inhibitors and in patients receiving total daily dose of ≤ 160 mg Valsartan or therapeutically equivalent doses of other ARBs. Sacubitril/valsartan low dose (24/26 mg) twice daily was given to patients receiving total daily dose of ≤ 5 mg Perindopril or therapeutically equivalent doses of other ACE inhibitors and in patients receiving total daily dose of ≤ 80 mg Valsartan or therapeutically equivalent doses of other ARBs. Dose of sacubitril/valsartan was doubled every 2 - 4 weeks as tolerated by the patient to reach the higher dose in patients with allowed haemodynamic.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the three measurements utilizing ANOVA (F) test with post hoc test (Tukey). Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi- square test or Fisher's exact test when appropriate. A two-tailed P value ≤ 0.05 was considered statistically significant.

Results

Table 1 shows demographic data, history of comorbidities, etiology of heart failure and history of medications of the studied patients.

There was a significant difference in the prevalence of different ARNI dosage at baseline, at 3 months and at 6 months from starting ARNI (P<0.001). SBP, DBP, and mean BP were significantly lower at 3 months and at 6 months compared to baseline measurement (P1 and P2 <0.001), and at 6 months compared to 3 months measurement (P3<0.001). NHYA

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classification was significantly different between baseline and 6 months measurements (P<0.001). **Table 2**

Hemoglobin (Hb) levels showed no significant change between baseline and 6 months (12.7 ± 1.54 g/dL vs. 12.8 ± 1.3 g/dL, P=0.701), indicating that anemia status remained stable throughout the study period. While Hb levels did not significantly affect the outcomes, monitoring it was crucial, as anemia is often associated with worse prognosis in heart failure patients. On the other hand, NT-proBNP levels showed a significant reduction from baseline (2498.9 ± 1060.3 pg/mL) to 6 months (1909.1 ± 931.7 pg/mL), with a P-value of 0.004, indicating a marked improvement in heart failure status. Creatinine, potassium, sodium, magnesium, and eGFR were also measured, but none showed significant changes over time. **Table 3**

LVEF and peak GLS were significantly improved at 6 months compared to the baseline measurement (P<0.001 and <0.001 respectively), while LVEDV and LVESV were significantly reduced after 6 months compared to the baseline measurement (P=0.019 and <0.001 respectively). LAV, sPAP, TAPSE, and MRV were insignificantly different between baseline and 6 months measurements. DD grade was insignificantly different between baseline and 6 months measurements **Table 4.**

Significant mitral regurgitation (MR) was reported in 33 (66%) patients at baseline. However, there was no significant improvement in MR at the 6-month follow-up, as the mitral regurgitant volume (MRV) remained insignificantly different between baseline and 6 months (42.4 ± 17.32 mL vs. 41.7 ± 17.5 mL, P=0.846). Regarding complications of the studied patients, 8 (16%) patients had systolic hypotension, and 8 (16%) patients had renal deterioration. No angioedema was recorded in any patients during the period of study. Regarding hospitalization, 7 (14%) patients were hospitalized. Finally, a substantial stability of the NYHA functional class was documented, and no change in the heart rate trend was calculated during the outpatient visit **Table 5.**

Case Presentation

A 62-year-old woman with a past medical history of hypertension (HTN), diabetes mellitus (DM), and ischemic cardiomyopathy (ICM) presented with exertional shortness of breath, classified as NYHA class III. **Figure 1 and Figure 2**

Before Treatment:

- **LVEF:** 28.6% (measured by Simpson method)
- **Peak GLS:** 7.4%
- **NT-proBNP:** 3200 pg/mL

After 6 Months of Treatment with Sacubitril/Valsartan:

- **LVEF:** Improved to 35.2%
- **Peak GLS:** Improved to 10.1%
- **NT-proBNP:** Reduced to 1600 pg/mL
- **Symptomatic Improvement:** NYHA class improved to II.

Table 1: Demographic data, history of comorbidities, etiology of heart failure and history of medications of the studied patients

		n=50
Age (years)		56.6 ± 10.73
Sex	**Male**	27 (54%)
	Female	23 (46%)
Weight (kg)		81.1 ± 15.71
Height (m)		1.7 ± 0.08
BSA (m^2)		1.9 ± 0.21
BMI (kg/m^2)		29.4 ± 4.56
History of comorbidities		
HTN		23 (46%)
DM		26 (52%)
CKD		9 (18%)
Anemia		16 (32%)
Smoking		16 (32%)
Atrial fibrillation		12 (24%)
Etiology of heart failure		
Idiopathic		17 (34%)
Valvular		8 (16%)
IHD		25 (50%)
History of medications		
ACEI		28 (56%)
ARBS		22 (44%)
BB		47 (94%)
MRA		41 (82%)
SGLT2i		33 (66%)
Loop diuretics		50 (100%)

Data represented as Mean ± SD or frequency (%). HTN: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease. BSA: Body surface area, BMI: Body mass index. IHD: Ischemic heart disease. ACEI: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin receptor blocker, BB: Beta blockers, MRA: Mineralocorticoid receptor antagonist, SGLT2i: Sodium glucose co transporter 2 inhibitor.

Table 2: Prevalence of ARNI dosages and Blood pressure in the studied patients at baseline, at 3 months and at 6 months from starting ARNI, NHYA classification of the studied patients at baseline and after 6 months from starting ARNI

		Baseline	3 Months	6 Months	P-value
ARNI (mg)	**97/103** mg	7 (14%)	17 (34%)	25 (50%)	**<0.001***
	49/51 mg	22 (44%)	24 (48%)	13 (26%)	
	24/26 mg	21 (42%)	9 (18%)	12 (24%)	
SBP (mmHg)		129 ±14.37	119.8 ± 12.02	115.9 ± 9.79	<0.001* P1<0.001* P2<0.001* P3<0.001*
DBP (mmHg)		75.1 ± 10.96	68.7 ± 9.39	65.5 ± 7.09	<0.001* P1<0.001* P2<0.001* P3<0.001*
Mean BP (mmHg)		93 ± 11.8	85.7 ±9.75	82.3 ± .68	<0.001* P1<0.001* P2<0.001* P3<0.001*
		Baseline		**6 Months**	
NHYA classification	**Class 1** (%)	0 (0%)		9 (18%)	**<0.001***
	Class 2 (%)	30 (60%)		34 (68%)	
	Class 3 (%)	20 (40%)		7 (14%)	

ARNI: Angiotensin receptor neprilysin inhibitor. NHYA: New York Heart Association. * Significant as P-value ≤ 0.05.

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Table 3: Hemoglobin and NT ProBNP of the studied patients at baseline, and after 6 months from starting ARNI and Laboratory investigation of the studied patients at baseline, at 4 weeks, and at 6 months from starting ARNI

	Baseline		6 months	P-value
Hb (g/dL)	12.7 ± 1.54		12.8 ± 1.3	0.701
NT ProBNP (pg/mL)	2498.9 ± 1060.3		1909.1 ± 931.7	**0.004***
Laboratory investigation	**Baseline**	**4 weeks**	**6 months**	**P-value**
Creatinine (mg/dl)	0.9 ± 0.26	1 ± 0.37	1 ± 0.39	0.13
Potassium (mEq/L)	4.2 ± 0.48	4.1 ± 0.49	4.4 ± 0.48	0.184
Sodium (mEq/L)	136.9 ± 5.34	137.7 ± 3.78	136.7 ± 3.81	0.492
Magnesium (mmol/L)	0.8 ± 0.13	0.8 ± 0.09	0.8 ± 0.1	0.072
eGFR (mL/min/1.73m^2)	88.4 ± 26.9	79.7 ± 26.29	78.7 ± 26.81	0.137

Hb: Hemoglobin, NT ProBNP: N-terminal pro b-type natriuretic peptide. eGFR: Estimated Glomerular Filtration Rate. * significant as P-value ≤ 0.05

Table 4: Echocardiographic data, DD grade of the studied patients at baseline, and at 6 months from starting ARNI

		Baseline	6 Months	P-value
LVEF (%)		28.6 ± 6.58	33.8 ± 7.91	**<0.001***
LAV (mL/m^2)		93.6 ± 14.7	92.9 ± 14.8	0.797
LVEDV (ml)		180.7 ± 20.45	170.8 ± 21.02	**0.019***
LVESV (ml)		129.3 ± 21.88	113.7 ± 23.38	**<0.001***
Peak GLS (%)		7.4 ± 1.83	9.7 ± 2.75	**<0.001***
sPAP (mmHg)		36.8 ± 10.16	35.8 ± 10.41	0.628
TAPSE (mm)		15.9 ± 3.14	16.1 ± 3.46	0.763
MRV (ml)		42.4 ± 17.32	41.7 ± 17.5	0.846
DD grade	**1**	16 (32%)	18 (36%)	0.716
	2	24 (48%)	25 (50%)	
	3	10 (20%)	7 (14%)	

LVEF: Left ventricular ejection fraction, LAV: Left atrial volume, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end systolic volume, GLS: Global longitudinal strain, sPAP: Systolic pulmonary artery pressure, TAPSE: Tricuspid annular plane systolic excursion, MRV: mitral regurgitation volume. * significant as P-value ≤ 0.05.

Table 5: Significant MR, complications and hospitalization in the studied patients

	n=50
Significant MR	33 (66%)
Complications	
S.hypotension	8 (16%)
Hyperkalemia	11 (22%)
Renal deterioration	8 (16%)
Angioedema	0 (0%)
Hospitalization	7 (14%)

MR: Mitral regurgitation

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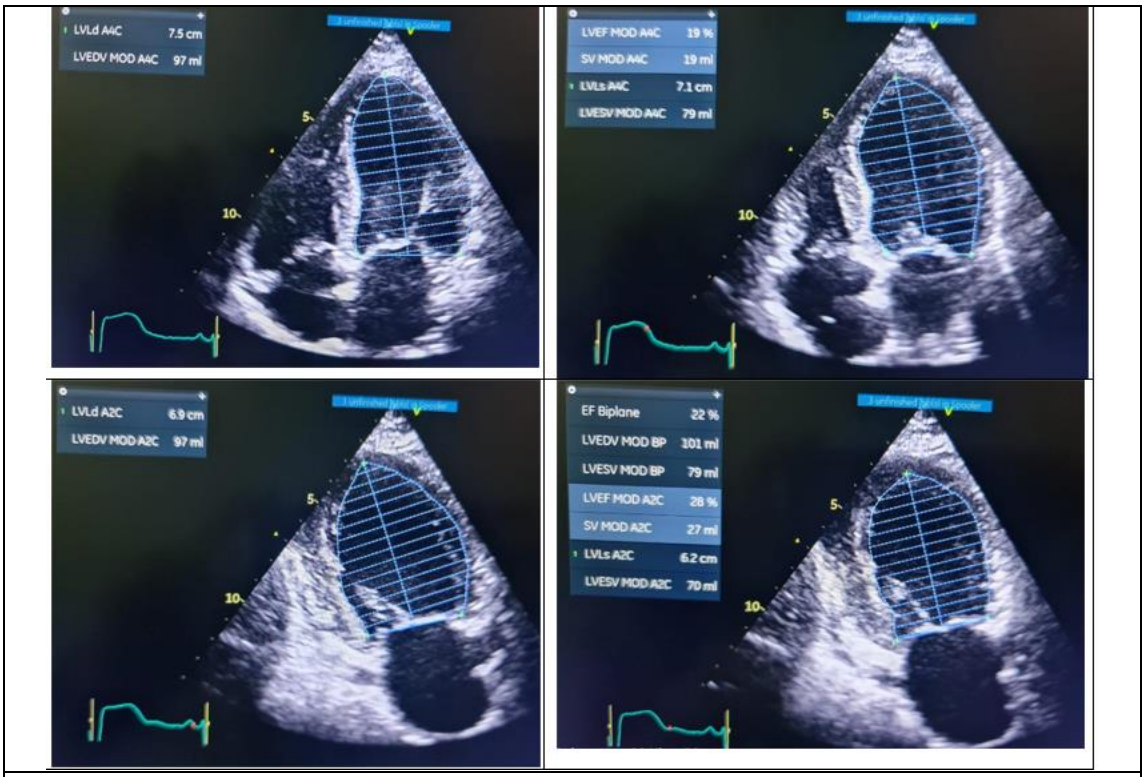

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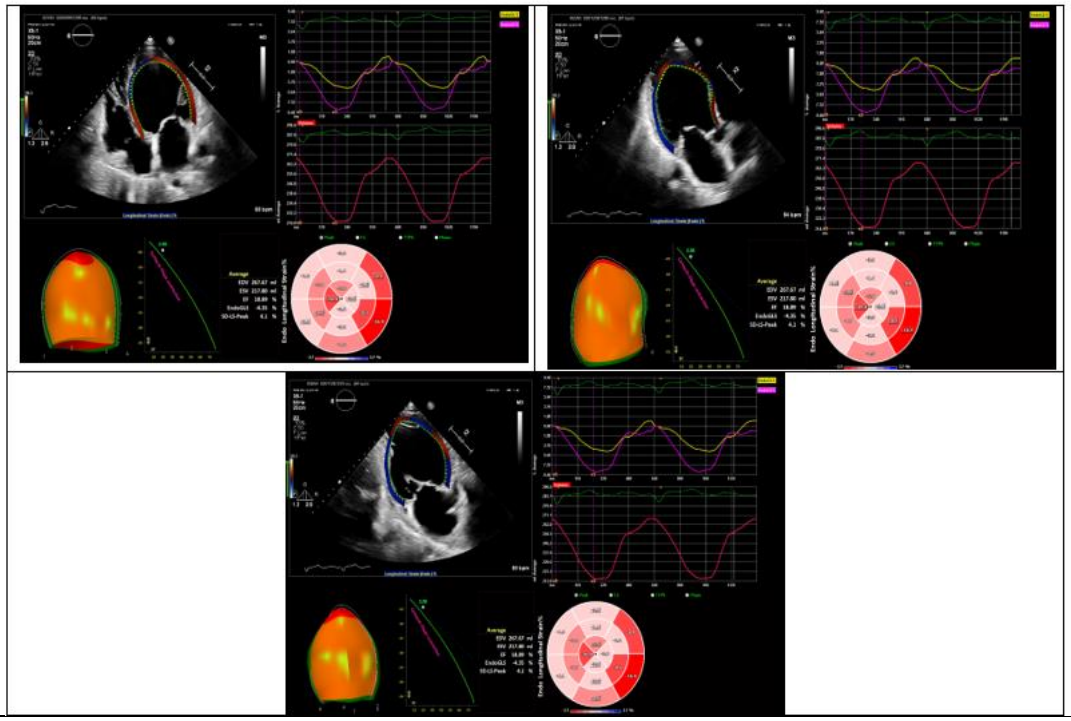
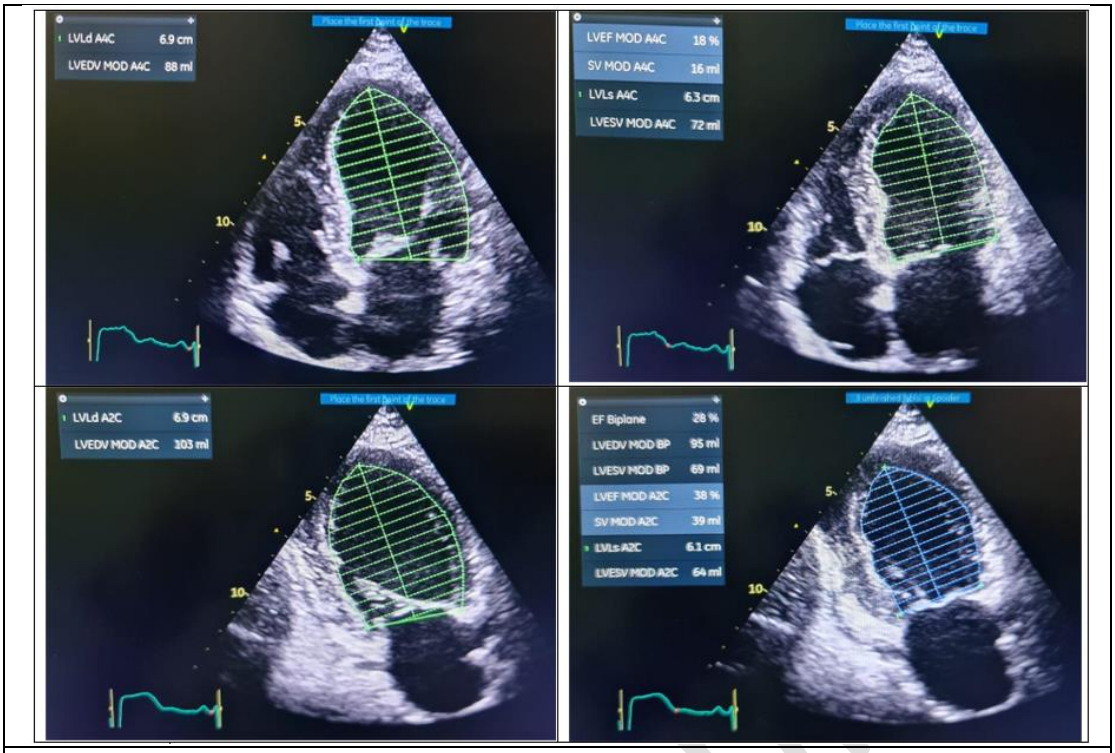
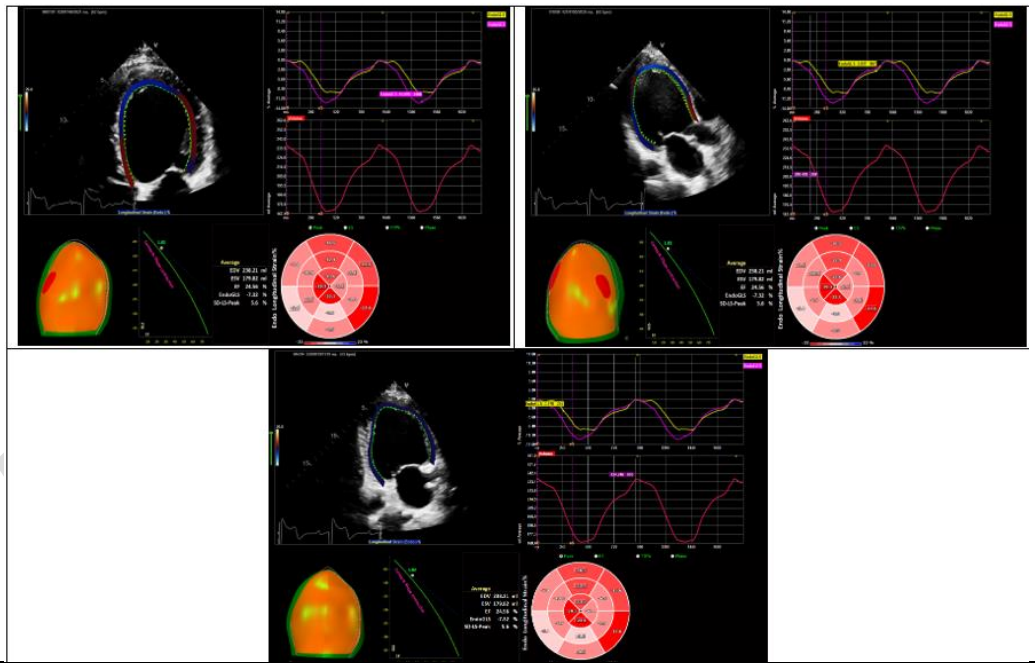


(B)

Figure 1: (A) EF Estimation by Simpson method and (B) Global Longitudinal Strain (GLS) Estimation pre administration of Sacubitril/valsartan



(A)



(B)

Figure 2: (A) EF Estimation by Simpson method and (B) Global Longitudinal Strain (GLS) Estimation posted administration of Sacubitril/valsartan

Discussion

There was a significant difference in the prevalence of different ARNI dosage at baseline, at 3 months and at 6 months from starting ARNI ($P<0.001$).

This cautious approach to dosing and titration is supported by several studies. For instance, (14) reported similar challenges in the PARADIGM-HF trial, where dose adjustments were frequently needed to manage blood pressure and renal effects, affirming that patient-specific dosing strategies are crucial for maximizing benefits while mitigating risks in heart failure management with ARNI. In PARADIGM-HF, dosing was similarly initiated and adjusted based on blood pressure and prior ACEI/ARB therapy, underscoring the importance of individualizing treatment based on a patient's clinical status (14).

The significant changes in the prevalence of ARNI dosage at different time points in our study provide a real-world insight into the practical challenges of managing complex therapies in heart failure. Literature such as the study by Vardeny et al. similarly highlights variable dosing in community settings, where patient-specific factors often necessitate deviations from ideal dosing regimens (14).

NHYA classification was significantly different between baseline and 6 months measurements with significant improvement at 6 months ($P<0.001$).

Our findings align with those from the PARADIGM-HF trial. This pivotal trial compared the effects of sacubitril/valsartan (ARNI) against enalapril in patients with heart failure with reduced ejection fraction (HFrEF). The study found that ARNI was superior to enalapril in reducing the risks of death and hospitalization for heart failure. Specifically, one of the secondary outcomes was improvement in the NYHA classification, which more patients in the ARNI group experienced compared to those on enalapril. This trial is critical because it not only demonstrated the overall efficacy of ARNI in reducing mortality but also its impact on improving patients' functional status and quality of life (14).

The significant reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (mean BP) observed at 3 months and 6 months post-initiation of sacubitril/valsartan (ARNI) treatment in our study highlight the potent vasodilatory effects of this medication. These findings are attributable to ARNI's mechanism of action, where the inhibition of neprilysin increases levels of natriuretic peptides, leading to enhanced vasodilation, natriuresis, and diuresis. Additionally, the blockade of angiotensin receptors contributes to the reduction in vasoconstriction, further lowering blood pressure.

This dual action on the renin-angiotensin-aldosterone system

(RAAS) and the natriuretic peptide system by ARNI is well-documented in the literature for its effectiveness in managing blood pressure in heart failure patients (15).

For instance: PARADIGM-HF Trial, a landmark study reported significant reductions in blood pressure with sacubitril/valsartan compared to enalapril. The reductions were noted as a beneficial side effect that contributed to the decreased cardiovascular mortality and morbidity observed in the ARNI group (14).

Research indicates that the hemodynamic changes induced by ARNI, including reduced blood pressure, are associated with improved cardiac output, and reduced cardiac preload and afterload. These effects are beneficial for heart failure patients, as they decrease the work required by the heart to pump blood, potentially slowing the progression of heart failure, and improving clinical outcomes.

In the PARADIGM-HF trial, patients treated with sacubitril/valsartan experienced lower rates of severe hyperkalemia compared to those treated with enalapril, suggesting that

sacubitril/valsartan not only reduces blood pressure more effectively but also may be safer in terms of electrolyte management when used in conjunction with mineralocorticoid receptor antagonists (MRAs). This supports our observations of the beneficial hemodynamic effects of ARNI, demonstrating its ability to lower blood pressure without compromising potassium levels significantly (16).

Regarding echocardiographic parameters, LVEF and peak GLS were significantly improved at 6 months compared to the baseline measurement ($P<0.001$ and <0.001 respectively), while LVEDV and LVESV were significantly reduced after 6 months compared to the baseline measurement ($P=0.019$ and <0.001 respectively). LAV, sPAP, TAPSE, and MRV were insignificantly different between baseline and 6 months measurements.

Sacubitril/valsartan enhances cardiac function by reducing preload and afterload, leading to improved myocardial efficiency. The increase in LVEF and GLS reflects this enhanced contractility and overall cardiac function. The decrease in LVEDV and LVESV suggests a reduction in cardiac dimensions, typically associated with reduced myocardial stress and an improved heart failure state.

Similarly, other researchers in their study reported that alongside reductions in NT-proBNP levels, there were notable correlations with improvements in LVEF and decreases in LVEDV and LVESV. This suggests that the biomarker reductions reflect underlying beneficial changes in cardiac structure and function, a finding that aligns with our observations of significant improvements in LVEF and peak GLS, alongside reductions in LVEDV and LVESV at 6 months post-treatment initiation. These results are significant as they reinforce the mechanistic

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impact of sacubitril/valsartan in promoting cardiac recovery and reverse remodeling in heart failure with reduced ejection fraction (HFrEF) (17).

In line with our results, Mazzetti et al. conducted a study to assess global longitudinal strain in patients with heart failure treated with sacubitril/valsartan. A significant increase in LVEF and a decrease in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were observed after 6 months of sacubitril/valsartan treatment. These changes highlight the potent impact of sacubitril/valsartan in improving cardiac function, which is consistent with the well- documented benefits of this therapy in promoting cardiac recovery (11).

Conclusion

The study demonstrated that treatment with sacubitril/valsartan significantly improved key echocardiographic parameters, notably left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), in patients with heart failure with reduced ejection fraction (HFrEF). Notably, these improvements were accompanied by a marked reduction in NT-proBNP levels and enhancements in NYHA functional class, highlighting the efficacy of ARNI in improving both myocardial mechanics and clinical symptoms over a six-month period. Despite challenges in medication titration due to side effects like hypotension and renal function deterioration, most patients showed positive outcomes.

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