

**Impact of Sacubitril/Valsartan on Myocardial and Hepatic Stiffness in Heart Failure patients with Reduced Ejection Fraction (HFrEF)****Ahmed G. Bakry<sup>a</sup>, Kerollos M. Mounir<sup>b\*</sup> Ahlam M. Sabra<sup>b</sup>**<sup>a</sup>Department of Internal Medicine, Cardiology Division, Qena Faculty of Medicine, South Valley University, Egypt<sup>b</sup>Department of Internal Medicine, Qena Faculty of Medicine, South Valley University, Egypt**Abstract**

**Background:** Sacubitril/valsartan effectively treats HFrEF complications by combining vasodilatory and RAAS inhibitory actions. Its effects on myocardial and hepatic stiffness are possibly due to its anti-inflammatory and anti-fibrotic properties but still under study.

**Objectives:** To assess Sacubitril/valsartan therapy's impact on myocardial and hepatic stiffness in HFrEF patients.

**Patients and methods:** This prospective cohort study at Qena University Hospitals from March 2023 to February 2024 included 50 HFrEF patients. Clinical examinations, echocardiography, and hepatic stiffness assessment were conducted pre and post-sacubitril/valsartan therapy.

**Results:** Mean age of 49.98 years ( $\pm 6.98$ ), comprised 20 males (40%) and 30 females (60%), with a mean BMI of 24.69 kg/m<sup>2</sup> ( $\pm 1.41$ ). None of the participants tested positive for HBsAg or HCV Ab. Pre-management, the ejection fraction (EF) averaged 30.82% ( $\pm 3.19$ ), significantly increasing to 43.24% ( $\pm 3.33$ ) post-management ( $p < 0.0001$ ). LVEDD decreased significantly from 60.8 mm ( $\pm 1.71$ ) to 53.85 mm ( $\pm 4.32$ ) post-management ( $p < 0.0001$ ). Global longitudinal strain (GLS) improved significantly from -6.16% ( $\pm 1.75$ ) to -9.44% ( $\pm 2.62$ ) post-management ( $p < 0.0001$ ). Liver stiffness measurement (LSM) decreased significantly from 7.67 kPa ( $\pm 1.86$ ) to 6 kPa ( $\pm 1.39$ ) post-management ( $p < 0.0001$ ), with a significant decrease in stage F3 fibrosis ( $p = 0.0002$ ). CAP score decreased significantly from 287.2 dB/m ( $\pm 23.21$ ) to 273.82 dB/m ( $\pm 28.18$ ) post-management ( $p < 0.0001$ ), with no significant changes in overall steatosis levels.

**Conclusion:** Our findings demonstrates that Sacubitril/valsartan has significant therapeutic benefits in HFrEF, supporting the evidence based guidelines in recommending that patients with HFrEF should be established on Sacubitril/valsartan as one of the “four pillars” of heart failure treatment.

**Keywords:** Sacubitril/valsartan, myocardial stiffness, hepatic stiffness, Heart failure with reduced ejection fraction.

**\*Correspondence:** [kerollosmalak94@gmail.com](mailto:kerollosmalak94@gmail.com)

**DOI:** 10.21608/SVUIJM.2024.271680.1814

**Received:** 22 February, 2024.

**Revised:** 4 March, 2024.

**Accepted:** 5 March, 2024.

**Published:** 14 May, 2024

**Cite this article as:** Ahmed G. Bakry, Kerollos M. Mounir Ahlam M. Sabra.(2024). Impact of Sacubitril/Valsartan on Myocardial and Hepatic Stiffness in Heart Failure patients with Reduced Ejection Fraction (HFrEF). *SVU-International Journal of Medical Sciences*. Vol.7, Issue 1, pp: 718-734.

## Introduction

Sacubitril/valsartan (Sac/val), known as an angiotensin receptor-neprilysin inhibitor (ARNI), has emerged as a key player in treating heart failure patients with reduced ejection fraction (HFrEF). This medication combines sacubitril's vasodilatory effects with valsartan's inhibition of the renin-angiotensin-aldosterone system (RAAS), providing a two-pronged approach to tackle the complex nature of HFrEF (**Greenberg et al., 2020**). While its effectiveness in reducing mortality and hospitalizations in HFrEF patients is well-established, its impact on myocardial and hepatic stiffness is still under investigation (**Kario et al., 2018**).

Myocardial stiffness is a defining feature of HFrEF, contributing to impaired ventricular filling and reduced cardiac output, worsening heart failure symptoms (**Simmonds et al., 2020; Hieda et al., 2020**). Research on sacubitril/valsartan's effects on myocardial stiffness in HFrEF patients is limited but promising. Initial findings suggest that it may positively influence myocardial mechanics, potentially enhancing ventricular compliance and reducing stiffness, thus improving cardiac function (**Shah et al., 2022; Zile et al., 2019; Cassano et al., 2022**).

Hepatic stiffness is another critical aspect of cardiac dysfunction, reflecting right-sided filling pressure and passive liver congestion in heart failure patients (**Soloveva et al., 2019; Panchani et al., 2022**). While the direct impact of sacubitril/valsartan on hepatic stiffness in HFrEF patients hasn't been extensively studied, its broader effects on circulation and hormonal regulation might indirectly affect hepatic congestion and stiffness. Understanding how sacubitril/valsartan therapy interacts with hepatic stiffness could offer valuable insights into managing HFrEF

comprehensively (**Soloveva et al., 2019; Panchani et al., 2022**).

Additionally, emerging evidence suggests that sacubitril/valsartan may possess anti-inflammatory and anti-fibrotic properties, which could potentially alleviate myocardial and hepatic stiffness in HFrEF patients. By targeting pathways involved in inflammation, oxidative stress, and fibrosis, sacubitril/valsartan may counteract the pathological remodeling processes contributing to stiffness, thereby improving overall cardiac function and reducing the risk of adverse outcomes in HFrEF. (**Litwin et al., 2022; Masarone et al., 2020**).

The main aim of the study was to evaluate the impact of sacubitril/valsartan therapy on myocardial and hepatic stiffness in patients with heart failure and reduced ejection fraction (HFrEF).

## Patients and methods

### Study Population

This prospective cohort study was conducted in the Internal Medicine Department of Qena University Hospitals under ethical code: **SVU/MED/MED018/1/24/2/805** from March 2023 to February 2024, analyzing all clinical, laboratory and echocardiographic parameters of 50 consecutive HFrEF eligible patients, selected from both in-patients and outpatients at Qena University Hospitals, South Valley University and all underwent to sac/val treatment according to the International Guidelines recommendations (**Ponikowski, et al., 2016**).

Thus, only adult patients (age  $\geq 18$  years) with EF  $\leq 40\%$ , in NYHA class II to IV and with fixed doses of angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) for at least 1 month but still symptomatic were considered for the analysis and no contraindications to Sacubitril/Valsartan were screened for enrollment.

Patients with positive chronic hepatitis markers (HBsAg & HCV Ab) or hepatic impairment (Child-Pugh Class C) and those already taking Sacubitril/Valsartan were excluded from the study. No patient had severe renal disease [estimated-glomerular filtration rate (e-GFR) <30 ml/min/1.73 m<sup>2</sup>] or side effects to ACE-I or ARB. None of female patients was pregnant or breastfeeding, none of them had potassium levels >5.4 mmol/L, AF or systolic blood pressure (SBP) <100 mmHg. Patients referred for resynchronization therapy within 1 year before the data collection of and during the study, were excluded from analysis.

Clinical evaluation, laboratory tests, ECG and echocardiograms were evaluated at baseline and after 1 year to estimate the possible benefits and the occurrence of any adverse events.

*All patients were subjected to the following*

#### **I. History and Clinical Examination:**

In the operational design, all patients provided written informed consent after a discussion outlining the risks and benefits of participation. Detailed history-taking which include age, sex, smoking, history of other comorbid conditions such as hypertension, diabetes mellitus type II, cerebrovascular stroke, dyslipidemia, arrhythmia, medications, peripheral artery disease and family history and a comprehensive clinical examination were conducted with the determination of the main anthropometric [weight, height, and body mass index (BMI)] and hemodynamic parameters. This examination included assessing vital signs such as blood pressure, heart rate, and respiratory rate.

#### **II. Laboratory Investigations:**

Laboratory assessments of hepatitis markers (HBsAg & HCV Ab) were performed using ELISA kits on serum samples obtained from patients under aseptic condition. Serum creatinine was assayed by the Roche

Creatinine Plus assay (Homan-La Roche, Basel, Switzerland) on a clinical chemistry analyzer (Roche/Hitachi modular analysis system, module P), renal function was then calculated by e-GFR according to the equation suggested by the Chronic Kidney disease Epidemiology Collaborating Group (CKD-EPI). Serum sodium and potassium levels were measured by indirect potentiometry (Cobas, Roche).

#### **III. Medications:**

Main drug treatments at baseline and during follow-up should be mention as  $\beta$ -blocker, diuretics, statins, antiplatelets, anticoagulants, ACIs or ARBs, antidiabetic drugs, etc.

Patients eligible for sac/val, in addition to their previous therapy, after suspension of ACE-I (at least 36 h before) or ARB, received initial dosage of 24/26 mg or 49/51 mg bid according to clinical parameters; the dosage was increased up to the maximum tolerated dose. Obviously, in addition to sac/val, all the other CV drug classes were also considered and their changes during the follow-up were analyzed.

#### **IV. Twelve-lead electrocardiogram (ECG):**

Standard 12-lead ECG will record at a 25/mm/s paper speed and gain of 10 mm/mV by FUKUDA.

#### **V. Echocardiography:**

Echocardiographic images were obtained using **Affiniti 70 Echo device, Philips**. All patients were examined with conventional two-dimensional echocardiography (using standard two-dimensional, pulse-wave Doppler, color flow Doppler, and M-mode echocardiographic methods) and speckle tracking analysis according to standardized study protocol. Echocardiographic measurements are performed in the left lateral decubitus position according to the recommendations of American society of echocardiography (ASE). All

measurements were achieved by two independent observers to minimize inter observer variability.

### 1-Conventional echocardiography

Conventional echocardiography was performed using (Affiniti 70 Echo device, Philips, Holland, Amsterdam). Left ventricular (LV) diameters were measured from 2D images at the level of the mitral valve tips, ensuring a measurement perpendicular to the long axis of the ventricle. And LV ejection fraction (LVEF) was calculated by two-dimensional echocardiography using the M-mode according to the following formula:  $LVEF = \frac{LVEDV - LVESV}{LVEDV} \times 100 = \%$ . The measurements were obtained according to the international guidelines (Lang, et al., 2015).

Echocardiography was used to assess heart function in individuals with EFs  $\leq$  40%.

**2.Speckle tracking analysis and Global Longitudinal Strain (GLS) measurement** were performed using a Philips Affinity 70 machine with a 2–4 MHz transducer.

Speckle tracking was used to quantify global longitudinal strain (GLS) from LV apical 3-chamber, 4-chamber, and 2-chamber views. Frame rates of 50–90 frames/s were used during breath-holding with stable ECG to reduce foreshortening and highlight endocardial demarcation. GLS was calculated by LV segment strain averages. Briefly, each ventricular wall was analyzed into three segments with a total of 17 segments for the whole myocardium. Longitudinal strain was calculated for each segment, considering the higher value; thus the global longitudinal strain (GLS) was obtained as the mean of all 17 segments (Badano et al., 2018).

### VI. Fibroscan

Transient Elastography using FibroScan 502 (Echosens, France) (by an experienced

observer) to assess fibrosis stages (F0-F4) based on liver stiffness measurement (LSM), expressed in kilopascals (kPa) (Chan et al., 2009) and steatosis grade based on controlled attenuation parameter (CAP) (Myers et al., 2012). Participants were told to fast for 8 hours before the evaluation. The M probe (3.5 MHz) was used to scan the right hepatic lobe of the abdomen following manufacturer instructions. XL probes (2.5 MHz) were used to rescan patients after first examination.

Minimum 10 measurements were collected to estimate the median valid liver stiffness in kilopascals (kPa) and interquartile range. In healthy people, liver stiffness is approximately 5.5 kPa, whereas transient elastography (TE) imaging may measure it from 2.5 to 75.0 kPa. Along with consistent liver stiffness measurements, controlled attenuation parameter (CAP) values in dB/m quantified hepatic steatosis.

Sacubitril/valsartan was given twice daily at 24/26 mg to all patients. The 3-month treatment maintained 97/103 mg twice daily when tolerated with monthly dose adjustments (Amin et al., 2021). All patients had echocardiography and transient elastography done post-therapy to evaluate treatment results.

### Statistical analysis

Data were analyzed using SPSS 20.0. Statistical methods included: Data were expressed as number and percentage for qualitative variables and mean  $\pm$  standard deviation (SD) for quantitative one; using student t-test (t) or Mann-Whitey U test (MWU) for comparing means of two independent groups according to normality of data; Chi-square test (X) or Fisher's exact test (F) for association between qualitative variables. Pearson correlation (r) for correlation between variables. Significance level set at  $p < 0.05$ , where  $p > 0.05$  is non-significant, and  $p < 0.05$  is significant, with smaller p-values indicating greater significance.

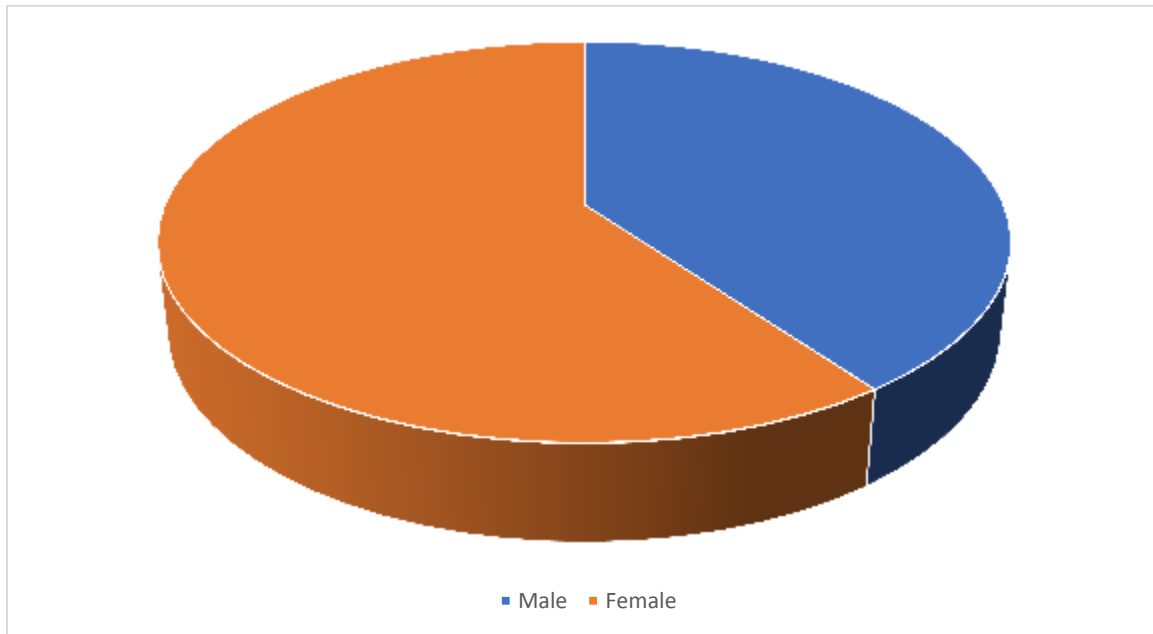
## Results

Basal characteristics of the study cohort demonstrate a mean age of 49.98 years ( $\pm 6.98$ ) with a distribution of 20 males (40%) and 30 females (60%). The mean BMI stands at 24.69 kg/m<sup>2</sup> ( $\pm 1.41$ ). The main etiologies for HF were ischemic heart

disease in 19 (38%) cases and arterial hypertension in 31 (62%) cases. Considering the associated comorbidities, 28% of patients showed chronic obstructive pulmonary disease COPD, 42% had type 2 diabetes mellitus (T2DM), 50% dyslipidemia, (**Table.1, Fig.1**).

**Table 1. Basal characteristics among included subjects**

Variables	Value (N = 50)
Age (Years)	49.98 $\pm$ 6.98
Sex	
• Male	20 (40%)
• Female	30 (60%)
BMI (Kg/m <sup>2</sup> )	24.69 $\pm$ 1.41
Clinical Evaluation	
• Ischemic heart disease	19 (38%)
• Arterial hypertension	31 (62%)
Comorbidities	
• COPD	14 (28%)
• T2DM	21 (42%)
• Dyslipidemia	25 (50%)



**Fig.1. Sex distribution among included subjects**

Prior to management, the ejection fraction (EF) averaged at 30.82% ( $\pm 3.19$ ), which significantly increased to 43.24% ( $\pm 3.33$ ) post-management ( $p < 0.0001$ ). Likewise, the left ventricular end-diastolic diameter (LVEDD) decreased significantly from 60.8 mm ( $\pm 1.71$ ) to 53.85 mm ( $\pm 4.32$ ) post-management ( $p < 0.0001$ ). Also

LVEDD significantly decreased from  $39.3 \pm 2.18$  to  $35.66 \pm 2.8$  mm ( $P < 0.0001$ ). Speckle tracking analysis revealed a significant enhancement in global longitudinal strain (GLS), shifting from -6.16% ( $\pm 1.75$ ) pre-management to -9.44% ( $\pm 2.62$ ) post-management ( $p < 0.0001$ ), (Table.2).

**Table 2. Comparison between pre and post management Doppler data among included subjects**

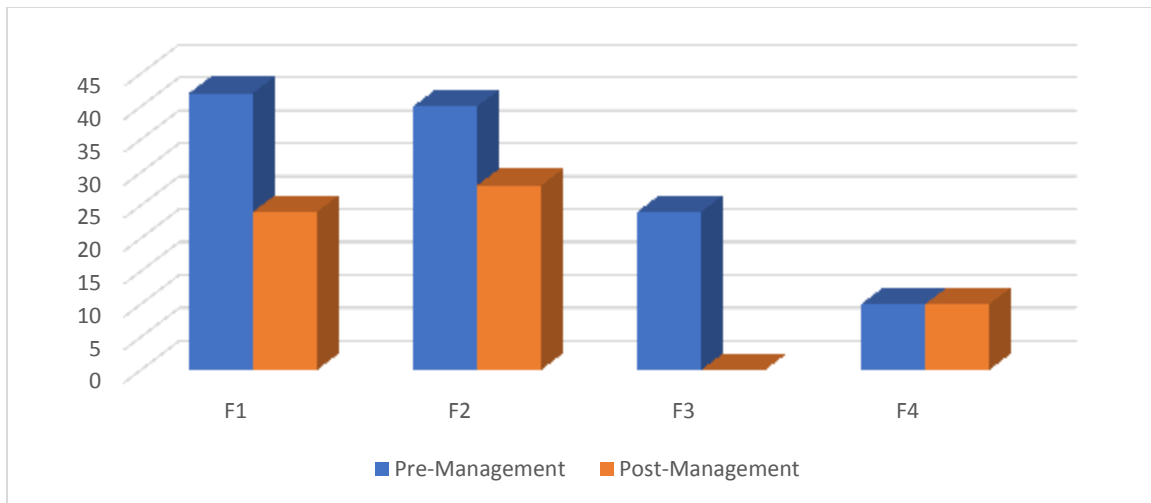
Variables	Pre-Management (N = 50)	Post-Management (N = 50)	P. Value
Ejection Fraction (%)	$30.82 \pm 3.19$	$43.24 \pm 3.33$	$<0.0001^{[MWU]}$
LVEDD (mm)	$60.8 \pm 1.71$	$53.85 \pm 4.32$	$<0.0001^{[MWU]}$
LVEDD (mm)	$39.3 \pm 2.18$	$35.66 \pm 2.8$	$<0.0001^{[MWU]}$
Speckle Tracking Analysis			
Global Longitudinal Strain (GLS) (%)	$-6.16 \pm 1.75$	$-9.44 \pm 2.62$	$<0.0001^{[MWU]}$

Regarding LSM, the average was 7.67 kPa ( $\pm 1.86$ ), decreasing significantly to 6 kPa ( $\pm 1.39$ ) post-management ( $p < 0.0001$ ). However, there were no significant differences in overall fibrosis scores between pre and post management. When assessing individual fibrosis stages, a

significant change in stage F3 fibrosis was noted post-management, decreasing from 24% pre-management to 0% post-management ( $p = 0.0002$ ). Other fibrosis stages (F1, F2, and F4) did not show significant changes post-management (Table. 3, Fig.2).

**Table 3. Comparison between pre and post management Stiffness and fibrosis data among included subjects**

Variables	Pre-Management (N = 50)	Post-Management (N = 50)	P. Value
Liver Stiffness Measurement (kPa)	$7.67 \pm 1.86$	$6 \pm 1.39$	$<0.0001^{[MWU]}$
Fibrosis	$1.62 \pm 1$	$1.92 \pm 1.2$	$0.1408^{[MWU]}$
F1	21 (42%)	12 (24%)	$0.0564^{[X]}$
F2	20 (40%)	14 (28%)	$0.2092^{[X]}$
F3	12 (24%)	0 (0%)	$0.0002^{[F]}$
F4	5 (10%)	5 (10%)	$0.99^{[X]}$



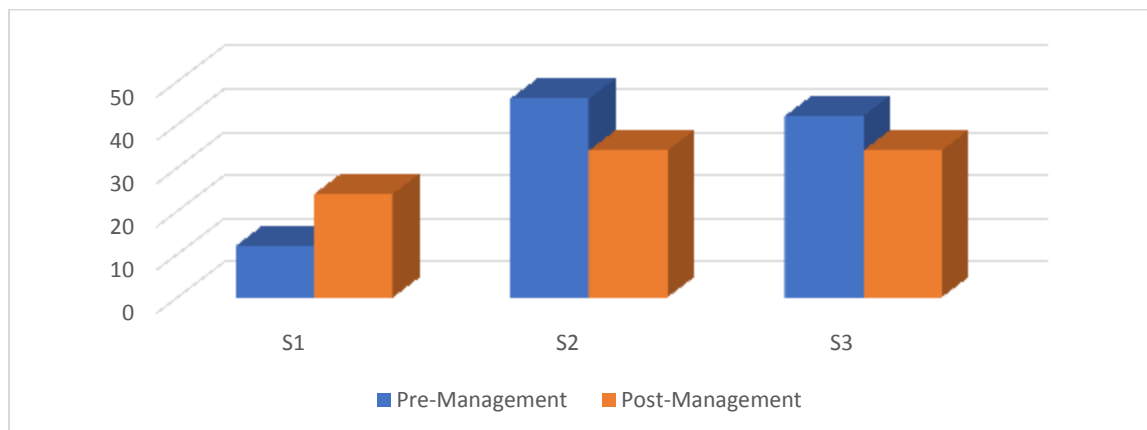
**Fig.2. Comparison between pre and post management fibrosis data among included subjects**

Prior to management, the controlled attenuation parameter (CAP) score averaged at 287.2 dB/m ( $\pm 23.21$ ), showing a significant decrease to 273.82 dB/m ( $\pm 28.18$ ) post-management ( $p < 0.0001$ ). However, no significant differences were

found in steatosis levels overall between pre and post management. When examining individual steatosis grades (S1, S2, and S3), none of the grades showed significant changes post-management (Table. 4, Fig. 3).

**Table 4. Comparison between pre and post management CAP score and steatosis data among included subjects**

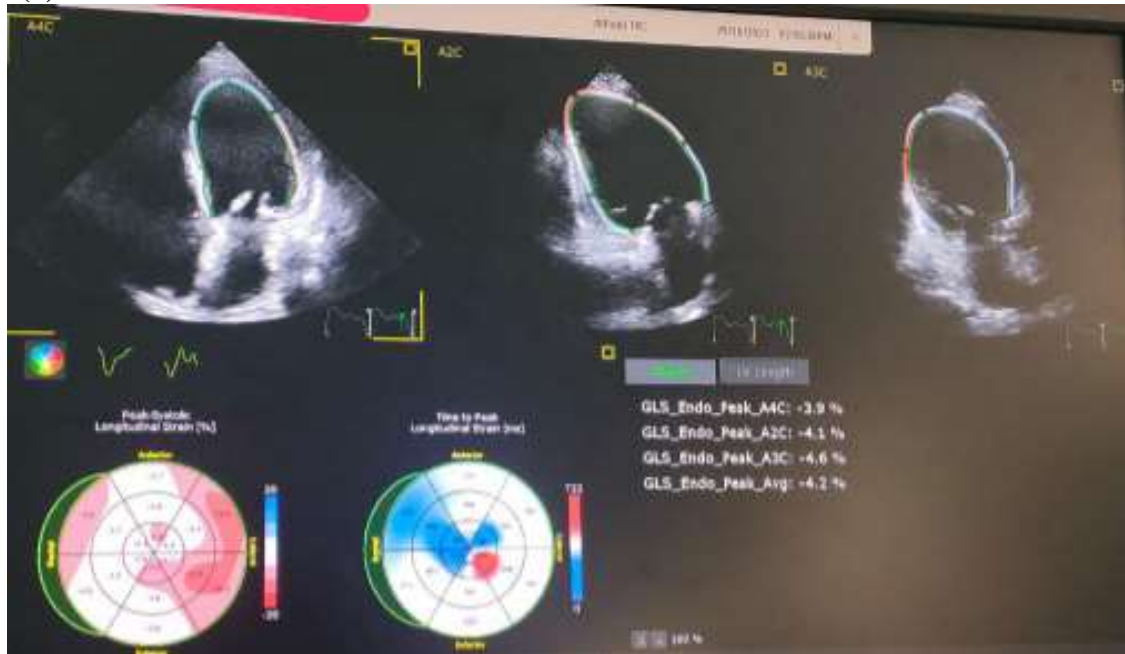
Variables	Pre-Management (N = 50)	Post-Management (N = 50)	P. Value
<b>CAP Score (dB/m)</b>	287.2 $\pm$ 23.21	273.82 $\pm$ 28.18	<0.0001 <sup>[t]</sup>
<b>Steatosis</b>	2.3 $\pm$ 0.67	1.94 $\pm$ 0.95	0.0716 <sup>[MWU]</sup>
<b>S1</b>	6 (12%)	12 (24%)	0.1207 <sup>[X]</sup>
<b>S2</b>	23 (46%)	17 (34%)	0.2248 <sup>[X]</sup>
<b>S3</b>	21 (42%)	17 (34%)	0.415 <sup>[X]</sup>



**Fig.3. Comparison between pre and post management steatosis and fibrosis data among included subjects.**

The following are 2 real cases of the study showing the degree of improvement in the Global Longitudinal Strain (GLS) pre and post management (**Figs. (4, 5)** for case (1) and **Figs. (8, 9)** for case (2) **Case (1):**

respectively). In addition to evaluating the improvement in steatosis and fibrosis data before and after start of treatment (**Figs.(6, 7)** for case (1) and **Figs. (10, 11)** for case (2) respectively).

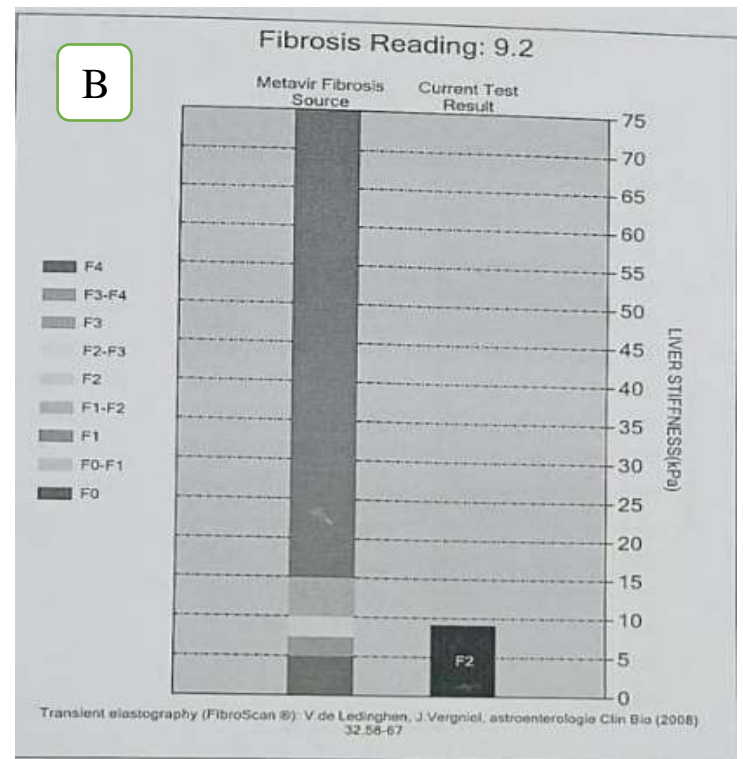
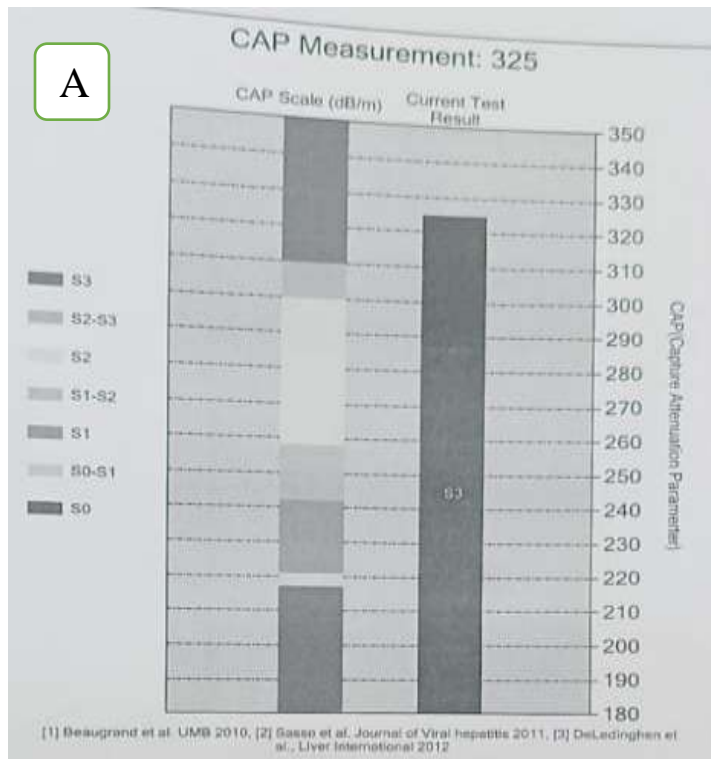


**Fig.4. Pre management Global Longitudinal Strain of 2-dimensional speckle tracking echocardiography.**

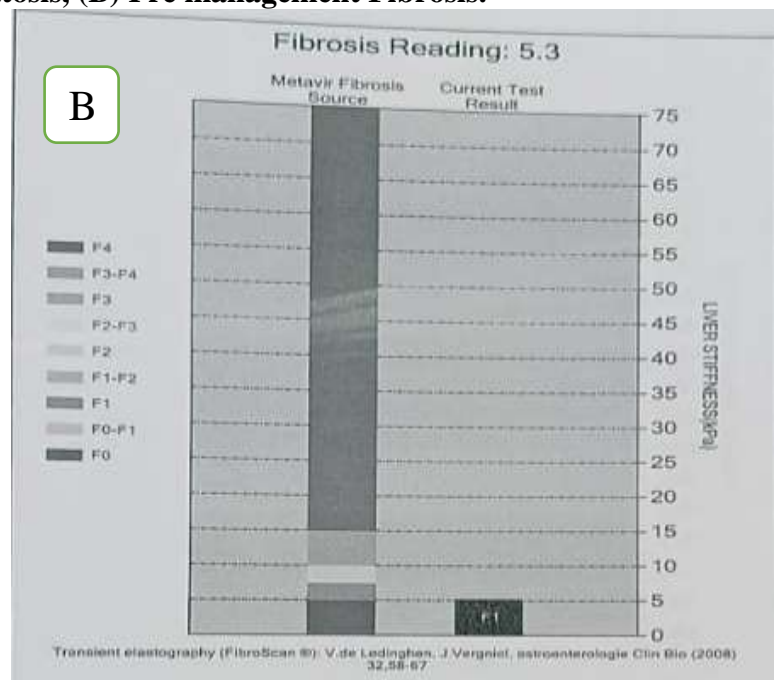
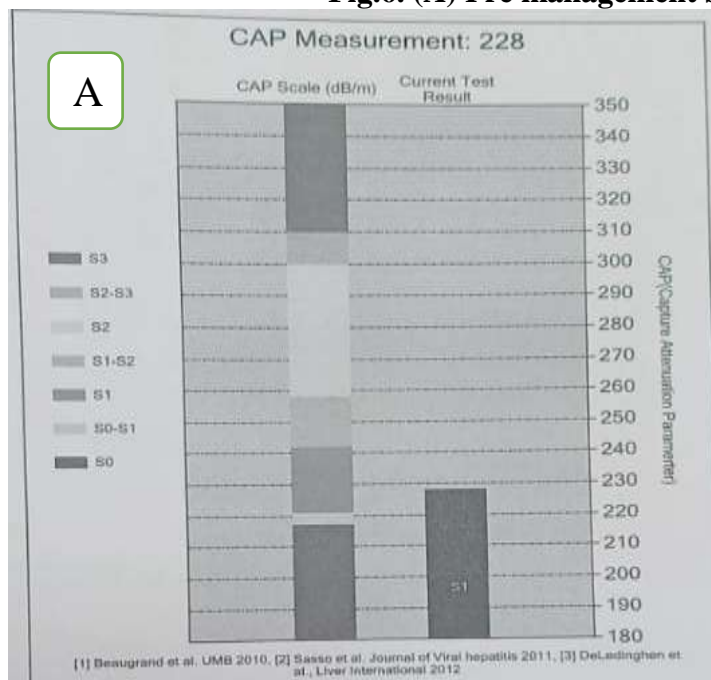


**Fig.5. Post management improvement Global Longitudinal Strain of 2-dimensional speckle tracking echocardiography.**



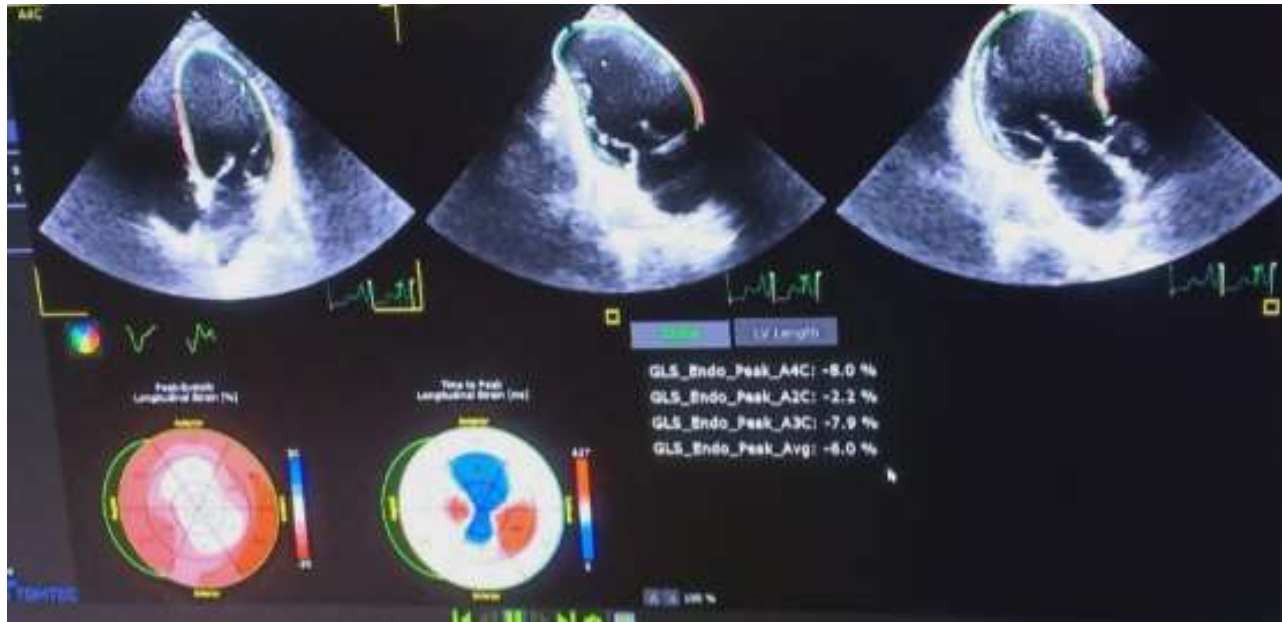


**Fig.6. (A) Pre management Steatosis, (B) Pre management Fibrosis.**

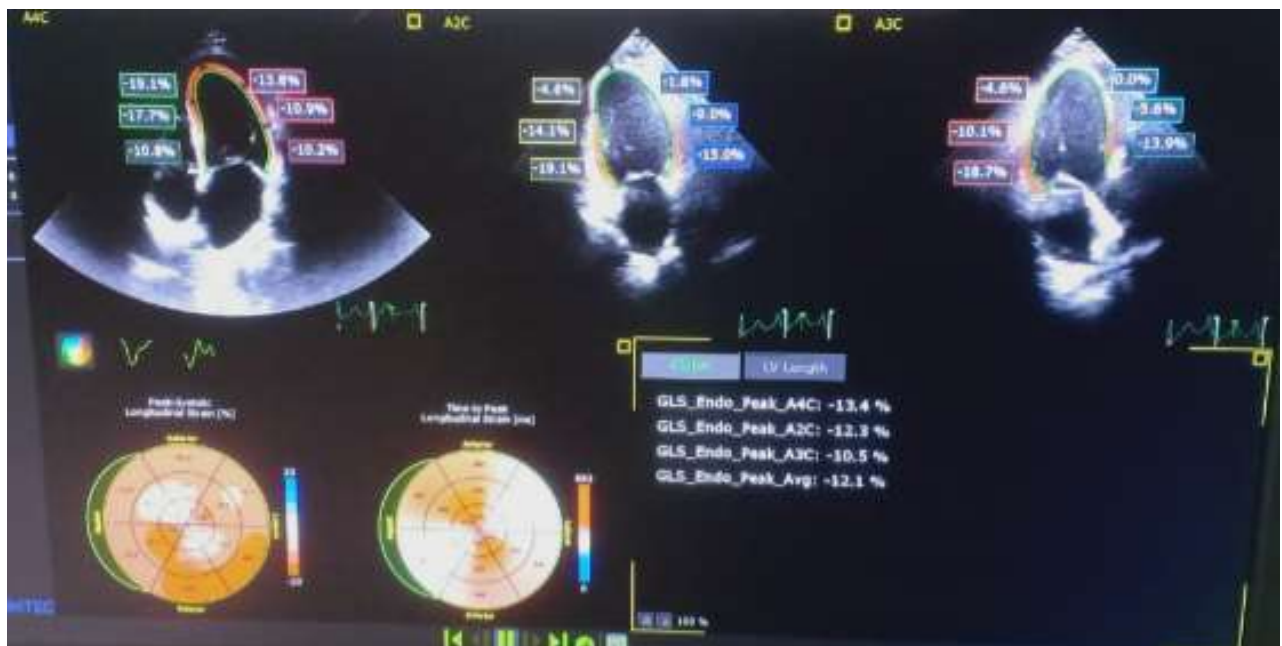


**Fig.7. (A) Post management Steatosis, (B) Post management Fibrosis.**

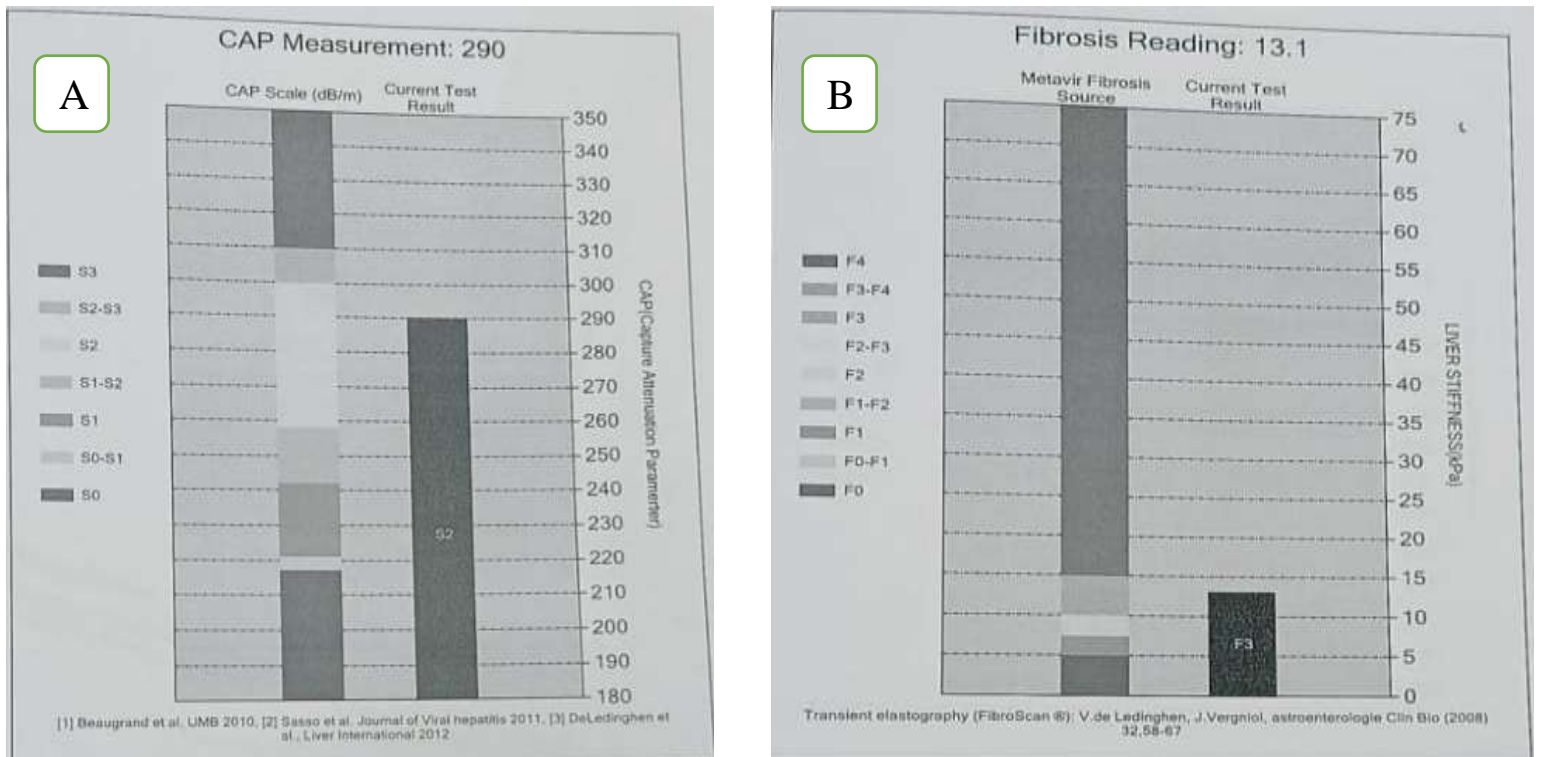
## Case (2):



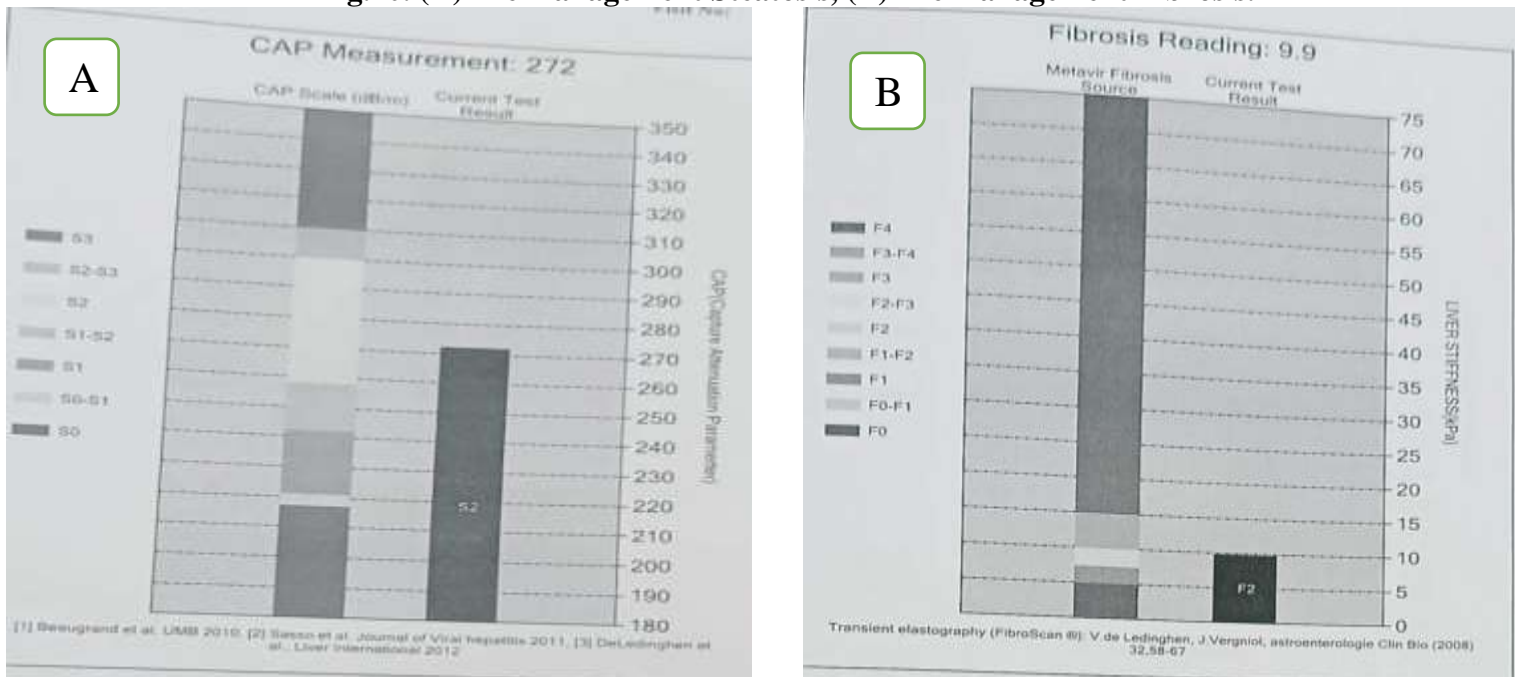
**Fig.8. Pre management Global Longitudinal Strain of 2-dimentional speckle tracking echocardiography.**



**Fig.9. Post management improvement Global Longitudinal Strain of 2-dimentional speckle tracking echocardiography.**



**Fig.10. (A) Pre management Steatosis, (B) Pre management Fibrosis.**



**Fig.11. (A) Post management Steatosis, (B) Post management Fibrosis.**

## Discussion

HF is a complex, vicious circle process based on cardiac remodeling, where there are many variety of neuroendocrine humoral factors that activated and promoted HF (Goldsmith et al., 2018). As such, the mortality and rehospitalization rates for HFrEF remain unacceptably high even when ACEI/ARBs,  $\beta$ -blockers, aldosterone receptor antagonists, diuretics, digoxin and other drugs are used as recommended by current guidelines (Khan et al, 2018, Shah et al., 2017).

The quality-of-life improvement with sac/val treatment is an important topic and, according to that and this finding has been also reported in different real life settings so as Parasail study and Provide-HF (Haddad H, et al., 2020; Mentz RJ, et al., 2020) after a follow-up of 12 weeks and 12 months, respectively.

Our study shows more consistent data because the QoL improvement rises up at shortly by the start of the treatment with sac/val and it persists over 1 year.

On the other hand, the inhibition of angiotensin-2 effects allows exerting antiproliferative effects protecting from hypertrophy and fibrosis at different sites so as myocardium and liver. As previously reported, the great clinical benefit of sac/val has been demonstrated in the PARADIGM-HF trial (McMurray JJ, et al., 2014), however the positive effect of sac/ val treatment in clinical practice is remarked, so as in our study.

In this study, including 50 consecutive HFrEF symptomatic patients despite optimal medical therapy, sac/val treatment showed efficacy and effect durability up to 1 year of follow-up with significant improvement of several clinical, hemodynamic, echocardiographic parameters and fibroscan parameters. According to that, the sac/val treatment was associated with reduction in end-systolic and

end-diastolic LV volumes, together with that, LV contractility also was better, as detected by the significant change in GLS values and LVEF.

Unlike our trial, Desai and Solomon (2019) compared Sacubitril-Valsartan and Enalapril on aortic stiffness in HFrEF patients with a mean age of 67.3 years and 23.5% females. Their research had a greater mean age and lower female representation than ours. The average BMI was 30, greater than in our research..

In contrast, Niu and Yang (2022) examined Sacubitril/Valsartan in end-stage renal disease heart failure patients. Their Sacubitril/Valsartan group had a mean age of 60.96 years, somewhat higher than ours. They also had fewer women in the Sacubitril/Valsartan group (26.92%) than we did. However, BMI results were similar in both groups, suggesting agreement. Our findings match previous studies' tendencies despite these variations.

After sacubitril/valsartan medication, as one of the “four pillars” of heart failure treatment, our study showed higher ejection fraction (EF) and reduced left ventricular end-diastolic diameter (LVEDD), indicating improved cardiac performance and reversal of remodeling. Speckle tracking study showed enhanced global longitudinal strain (GLS), supporting sacubitril/valsartan's myocardial mechanical benefits in HFrEF patients.

These benefits are due to sacubitril/valsartan's dual mechanism of suppressing RAAS and increasing natriuretic peptides. Sacubitril/valsartan decreases myocardial stress, ventricular remodeling, and cardiac contractility by reducing angiotensin II's negative effects and increasing natriuretic peptides' vasodilatory and cardioprotective effects (Pascual-Figal et al., 2021). LVEDD reduction suggests chamber dilation reversal, whereas GLS augmentation

indicates better myocardium deformation with better contractile function. (**Gori et al., 2019**).

Similar to our findings, **Bolla and Fedele (2022)** found enhanced left ventricular ejection fraction (LVEF) with Sacubitril/Valsartan medication, indicating better cardiac function, but no significant changes in LVEDVi. **Landolfo and Piani (2020)** also found that sacubitril valsartan therapy enhanced LVEF and lowered LVIDd, indicating improved cardiac function and structure.

**Desai and Solomon (2019)** examined Sacubitril-Valsartan's impact on HFrEF aortic stiffness. In 12 weeks, mean LVEF rose from 34% to 36% and LVEDVI dropped from 75.1 to 70.3 mL/m<sup>2</sup>, showing better cardiac function and remodeling. Our findings match this study.

**Bouali and Donal (2020)** examined Sacubitril/Valsartan-treated HFrEF patients' myocardial work's prognostic value. LVEF substantially increased (\*p < 0.05 vs. baseline) after 6 and 12 months, reaching 37±11 mm and 40±12 mm, respectively. Indexed LVEDV decreased (\*p < 0.05 vs. baseline) from 105±40 to 94±39 mL/m<sup>2</sup> at 6 months and 93±37 at 12 months, while GLS improved (\*p < 0.05). This supports our study's conclusions.

**Romano and Vitale (2019)** examined Sacubitril/Valsartan's impact on HFrEF cardiac parameters. At follow-up, LVEF rose considerably (p < 0.001) from 27 ± 5.9% at baseline to 30 ± 7.7%, indicating improved cardiac function. There were no significant changes in indexed EDVi from baseline (120.5 ± 31.4 mL/m<sup>2</sup>) to follow-up (120.7 ± 33 mL/m<sup>2</sup>; p = 0.932). The lack of substantial alterations in indexed EDVi contradicts our findings on LVEF.

We found that sacubitril/valsartan treatment improved hepatic stiffness in heart failure patients, suggesting hepatoprotective benefits. Sacubitril/valsartan's vasodilatory,

anti-inflammatory, and anti-fibrotic effects may reduce liver stiffness.

**Wei and Xiao-lan (2023)** investigated the therapeutic effects of Sacubitril/Valsartan on liver function and disease progression in chronic heart failure patients, revealing significant improvements in liver function parameters and a deceleration in disease progression. **Suzuki and Claggett (2020)** demonstrated Sacubitril/Valsartan's superior efficacy in enhancing liver function compared to enalapril, with hepatoprotective effects extending beyond cardiovascular benefits. Although overall fibrosis scores showed no significant alterations, **Suzuki and Claggett's study (2023)** unveiled a significant reduction in stage F3 fibrosis following Sacubitril/Valsartan treatment, suggesting a therapeutic impact on advanced fibrotic stages.

**Kulmatycki and Langenickel (2017)** affirmed the safety profile of sacubitril/valsartan in hepatic impairment patients, supporting its clinical utility in individuals with liver dysfunction. **Hsu and Huang (2020)** elucidated the mechanistic aspects underlying Sacubitril/Valsartan's potential to mitigate hepatic fibrosis, attributing its hepatoprotective properties to its ability to downregulate endothelin-1 expression and suppress oxidative stress and inflammation.

Additionally, our study observed a significant reduction in hepatic fat content, as evidenced by controlled attenuation parameter (CAP) scores, following Sacubitril/Valsartan therapy, corroborating findings by **Barman and Tanyolaç (2022)**, who also noted decrease in hepatic fat content among heart failure patients undergoing Sacubitril/Valsartan treatment.

**Limitations:** There are some limitations need to be noted. First, that study is not a randomized trial and it has not a matched control group. However, as each patient before the enrollment in that study was



treated with the best possible therapy, according to current guidelines, but still symptomatic. Secondly, other limitations are represented by the relatively small population and small sample size, the lack of cardiac magnetic resonance (CMR) parameters for those patients, where CMR represents a well-established method to better characterize the myocardial tissue in particular to detect LV fibrosis.

### Conclusion

In conclusion, our study demonstrates the significant therapeutic impact of sacubitril/valsartan on both cardiac and hepatic parameters in patients with heart failure and reduced ejection fraction (HFrEF). The findings reveal marked improvements in cardiac function, myocardial mechanics, hepatic stiffness, and hepatic fat content following sacubitril/valsartan therapy. These results support the evidence based guidelines in recommending that patients with HFrEF should be established on Sacubitril/valsartan as one of the “four pillars” of heart failure treatment. However, further research is warranted to elucidate the long-term effects of sacubitril/valsartan on liver fibrosis and steatosis in HFrEF patients, ultimately enhancing our understanding and management of this complex cardiovascular condition.

### References:

- **Amin OA, Alaarag AF (2021).** The impact of discontinuation of sacubitril-valsartan and shifting to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with heart failure with reduced ejection fraction. *Anatolian Journal of Cardiology*, 25(3): 163-169.
- **Badano LP, Koliass TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T et al. (2018).** Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European Heart Journal-Cardiovascular Imaging*, 19(6): 591-600.
- **Barman HA, Tanyolaç S, Dogan O, Bal E, Atıcı A, Özyıldırım S et al (2022).** Impact of Sacubitril/Valsartan on Lipid Parameters in Patients with Heart Failure with Reduced Ejection Fraction. *Clinical Drug Investigation*, 42(6): 533-540.
- **Bolla GB, Fedele A, Faggiano A, Sala C, Santangelo G, Carugo S et al (2022).** Effects of Sacubitril/Valsartan on biomarkers of fibrosis and inflammation in patients with heart failure with reduced ejection fraction. *BMC Cardiovascular Disorders*, 22(1): 1-8.
- **Bouali Y, Donal E, Gallard A, Laurin C, Hubert A, Bidaut A et al (2020).** Prognostic usefulness of myocardial work in patients with heart failure and reduced ejection fraction treated by sacubitril/valsartan. *The American journal of cardiology*, 125(12): 1856-1862.
- **Cassano V, Armentaro G, Magurno M, Aiello V, Borrello F, Miceli S et al (2022).** Short-term effect of sacubitril/valsartan on endothelial dysfunction and arterial stiffness in patients with chronic heart failure. *Frontiers in Pharmacology*, 13(1): 1069828-1069842.
- **Chan HY, Wong GH, Choi PL, Chan AH, Chim AL, Yiu KL, et al. (2009).** Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic

- hepatitis B. *Journal of viral hepatitis*, 16(1): 36-44.
- **Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J et al (2019).** Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. *Jama*, 322(11): 1077-1084.
  - **Goldsmith SR, Udelson JE, Gheorghiade M (2018).** Dual vasopressin V1a/V2 antagonism: the next step in neurohormonal modulation in patients with heart failure?. *Journal of Cardiac Failure*, 24(2): 112-114.
  - **Gori M, D'Elia E, Senni M (2019).** Sacubitril/valsartan therapeutic strategy in HFpEF: Clinical insights and perspectives. *International Journal of Cardiology*, 281(1): 158-165.
  - **Greenberg B (2020).** Angiotensin receptor-neprilysin inhibition (ARNI) in heart failure. *International journal of heart failure*, 2(2): 73-90.
  - **Haddad H, Bergeron S, Ignaszewski A, Searles G, Rochdi D, Dhage P et al (2020).** Canadian real-world experience of using sacubitril/valsartan in patients with heart failure with reduced ejection fraction: insight from the PARASAIL study. *CJC open*, 2(5): 344-353.
  - **Hieda M, Sarma S, Hearon Jr CM, Dias KA, Martinez J, Samels M et al (2020).** Increased myocardial stiffness in patients with high-risk left ventricular hypertrophy: the hallmark of stage-B heart failure with preserved ejection fraction. *Circulation*, 141(2): 115-123.
  - **Hsu SJ, Huang HC, Chuang CL, Chang CC, Hou MC, Lee FY et al (2020).** Dual angiotensin receptor and neprilysin inhibitor ameliorates portal hypertension in portal hypertensive rats. *Pharmaceutics*, 12(4): 320-333.
  - **Kario K (2018).** The sacubitril/valsartan, a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI): potential uses in hypertension, heart failure, and beyond. *Current cardiology reports*, 20(1): 1-8.
  - **Khan MS, Siddiqi TJ, Usman MS, Sreenivasan J, Fugar S, Riaz H et al (2018).** Does natriuretic peptide monitoring improve outcomes in heart failure patients? A systematic review and meta-analysis. *International Journal of Cardiology*, 263(1): 80-87.
  - **Kulmatycki KM, Langenickel T, Ng WH, Pal P, Zhou W, Tsu-Han L et al (2017).** Pharmacokinetics and safety of sacubitril/valsartan (LCZ696) in patients with mild and moderate hepatic impairment. *International Journal of Clinical Pharmacology and Therapeutics*, 55(9): 728-735.
  - **Landolfo M, Piani F, Degli Esposti D, Cosentino E, Bacchelli S, Dormi A et al (2020).** Effects of sacubitril valsartan on clinical and echocardiographic parameters of outpatients with heart failure and reduced ejection fraction. *IJC Heart & Vasculture*, 31(1): 100656-100662.
  - **Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. (2015).** Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal-Cardiovascular Imaging*, 16(3): 233-271.
  - **Litwin SE, East CA (2022).** Assessing clinical and biomarker characteristics to optimize the benefits of sacubitril/valsartan in heart failure. *Frontiers in Cardiovascular Medicine*, 9(1): 1058998-1059008.

- **Masarone D, Errigo V, Melillo E, Valente F, Gravino R, Verrengia M et al (2020).** Effects of sacubitril/valsartan on the right ventricular arterial coupling in patients with heart failure with reduced ejection fraction. *Journal of Clinical Medicine*, 9(10): 3159-3169.
- **Mentz RJ, Xu H, O'Brien EC, Thomas L, Alexy T, Gupta B et al (2020).** PROVIDE-HF primary results: patient-reported outcomes investigation following initiation of drug therapy with entresto (sacubitril/valsartan) in heart failure. *American heart journal*, 230(1): 35-43.
- **Myers RP, Pollett A, Kirsch R, Pomier-Layrargues G, Beaton M, Levstik M, et al. (2012).** Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography. *Liver International*, 32(6): 902-910.
- **Niu CY, Yang SF, Ou SM, Wu CH, Huang PH, Hung CL et al (2022).** Sacubitril/Valsartan in Patients With Heart Failure and Concomitant End-Stage Kidney Disease. *Journal of the American Heart Association*, 11(18): e026407-e026428.
- **Panchani N, Schulz P, Van Zyl J, Felius J, Baxter R, Yoon ET et al (2022).** Liver stiffness and prediction of cardiac outcomes in patients with acute decompensated heart failure. *Clinical Transplantation*, 36(3): e14545-e14553.
- **Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, Caravaca-Pérez P, Conde-Martel A, Crespo-Leiro MG et al (2021).** Sacubitril-valsartan, clinical benefits and related mechanisms of action in heart failure with reduced ejection fraction. A review. *Frontiers in Cardiovascular Medicine*, 8(1); 754499-754520.
- **Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al (2016).** 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Polish Heart Journal (Kardiologia Polska)*, 74(10): 1037-1147.
- **Romano G, Vitale G, Ajello L, Agnese V, Bellavia D, Caccamo G et al (2019).** The effects of sacubitril/valsartan on clinical, biochemical and echocardiographic parameters in patients with heart failure with reduced ejection fraction: the “hemodynamic recovery”. *Journal of clinical medicine*, 8(12): 2165-2175.
- **Shah AM, Claggett B, Prasad N, Li G, Volquez M, Jering K et al (2022).** Impact of sacubitril/valsartan compared with Ramipril on cardiac structure and function after acute myocardial infarction: the PARADISE-MI echocardiographic substudy. *Circulation*, 146(14): 1067-1081.
- **Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF et al (2017).** Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *Journal of the American College of Cardiology*, 70(20): 2476-2486.
- **Simmonds SJ, Cuijpers I, Heymans S, Jones EA (2020).** Cellular and molecular differences between HFpEF and HFrEF: a step ahead in an improved pathological understanding. *Cells*, 9(1): 242-264.
- **Suzuki J, Kaji K, Nishimura N, Kubo T, Tomooka F, Shibamoto A et al (2023).** A Combination of an Angiotensin II Receptor and a Neprilysin Inhibitor Attenuates Liver Fibrosis by Preventing Hepatic Stellate



Cell Activation. *Biomedicines*, 11(5): 1295-1309.

- **Suzuki K, Claggett B, Minamisawa M, Packer M, Zile MR, Rouleau J et al (2020).** Liver function and prognosis, and influence of sacubitril/valsartan in patients with heart failure with reduced ejection fraction. *European Journal of Heart Failure*, 22(9): 1662-1671.
- **Wei YAN, Xiao-lan YANG, Hao YANG, Li-ping KANG, Run-mei ZHANG, Wen-juan LI et al (2023).** The Effect of Sacubitril Valsartan on Liver and Kidney Function in Patients with Chronic Heart Failure. *ZHONGHUA YANGSHENG BAOJIAN*, 41(6): 8-11.
- **Zile MR, O'Meara E, Claggett B, Prescott MF, Solomon SD, Swedberg K et al (2019).** Effects of sacubitril/valsartan on biomarkers of extracellular matrix regulation in patients with HFrEF. *Journal of the American College of Cardiology*, 73(7): 795-806.