



Original Article

1 year follow Up results of “ARTIM HF TRIAL” (angiotensin receptor neprilysin inhibitor effect on TEI index & left ventricular mass in heart failure)



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ABSTRACT

Background: Sacubitril/Valsartan (ARNI) has now class 1 recommendation for treatment of heart failure with reduced ejection fraction (HFrEF). It has been shown to reduce cardiovascular morbidity & mortality in Heart failure with reduced ejection fraction (HFrEF) and significant improvement in all echocardiographic parameters besides TEI index. Tei index is a marker of inflammation, myocardial cell metabolism and its contractile function has not been evaluated as a distinctive entity so we took up this study to evaluate the effects of ARNI on the LV functions using two dimensional (2D)ECHO parameters in Indian population and to assess TEI index for myocardial function.

Methods: 256 patients with class II, III or IV HF and EF<40% were enrolled. 171(66.8%) were males and 85(33.2%) were females. Patients were evaluated at baseline, 6 and 12 months for LVEF, LV mass &,LVMPI. Drug was discontinued in 2 patients due to angioedema, in 5 patients due to acute kidney injury and in 2 patients due to hypotension. LV mass measurement done by linear echocardiographic method and Flow Doppler method used for TEI index calculation.

Results: Baseline parameters in 247 patients were mean EF = $26.33 \pm 6.28\%$, mean LV mass = 270.84 ± 68.94 gm, mean Tei Index = 0.852 ± 0.22 . ARNI use was associated with an average gradual increase in EF, from a mean baseline of $26.33 \pm 6.28\%$ to $33.88 \pm 7.73\%$ ($p = 0.000001$) after 1 year of treatment. There was a significant progressive reduction of 57.97 g/m² in mean LV mass index after 1 year of treatment ($p = 0.000001$). TEI index showed significant reduction from baseline mean 0.85 ± 0.22 to 0.70 ± 0.12 ($p = 0.000001$) after 1 year of treatment.

Conclusion: Use of ARNI as additive adjunct to standard care of treatment resulted in significant progressive decline in LV mass and increase in TEI index.

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1. Introduction

Heart failure has emerged as a major global health issue, with an estimated worldwide prevalence of >37.7 million¹ and current Indian estimates from 1.3 to 23 million.² In heart failure, myocardial dysfunction causes an increase in neurohormonal activity, which functions as an adaptive and compensatory mechanism in response

to the reduction in cardiac output initially but persistent increased neurohormonal activation leads to myocardial damage. Ventricular remodelling can be defined by molecular, cellular, and interstitial changes in the myocardium, resulting in alterations in the size, mass, geometry, and function of the heart as a result of a myocardial injury. Various clinical and experimental evidences suggest that the renin–angiotensin–aldosterone system and sympathetic nervous system contribute to cardiac remodelling.

The mainstay of medical treatment for patients with heart failure with reduced ejection fraction (HFrEF) are diuretics, beta blockers (BB), angiotensin converting enzyme inhibitors (ACEi)/ angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA).

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Cardiac reverse remodelling indices that directly reflected changes in cardiac structure includes 2D echocardiographic indices of hypertrophy (LV mass index [LVMI]), and indices of atrial remodelling (left atrial volume [LAV]), LV ejection fraction and LV volume and dimension (end-systolic volume, end-diastolic volume, end-systolic diameter, end-diastolic diameter).

ACE inhibitors, as demonstrated in the SOLVD studies, reduced the rate of cardiac dilation and promoted regression in cardiac dilation.³ Studies on angiotensin II receptor blockers demonstrated their beneficial effect on ventricular remodelling. In the ELITE study, both patients receiving ACE inhibitors and those receiving angiotensin II AT1 receptor-antagonists (ARB) showed similar results regarding ventricular reverse remodelling.⁴ In MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment) trial, carvedilol produced a dose-related improvement in LV function as assessed by radionuclide-determined EF.⁵

The Val-HeFT study demonstrated that patients with the highest ventricular volumes and lowest baseline left ventricular ejection fractions presented higher mortality.⁶

Sacubitril/Valsartan is a first-in-class FDA approved angiotensin receptor-neprilysin inhibitor (ARNI) for the treatment of HF. It promotes effects of natriuretic peptides by inhibiting neprilysin with Sacubitril and blocking angiotensin II type 1 receptors with Valsartan.

Although the physiological mechanisms of action of Sacubitril/Valsartan are well described and PROVE-HF and EVAPORATE-HF have shown that treatment with Sacubitril/Valsartan is associated with a statistically significant increase in LVEF and a trend towards improved reverse remodelling.^{7,8} Both studies together strongly suggest that ARNI therapy can promote cardiac reverse remodelling in patients with HFrEF but neither of the two assessed this question as its primary end point. Study done by Subodh Verma et al. showed a significantly greater improvement in LVEF in patients with dilated CM as, compared to patients with ischemic Cardiomyopathy after 1 year of ARNI therapy.⁹

The goal of our study was to evaluate the effect of Sacubitril/Valsartan on LV mass and TEI index (LV myocardial performance index) among patients with HFrEF in Indian population.

2. Methods

It is a one year single centre, prospective, observational single arm trial to study patients of heart failure with reduced ejection fraction initiated on sacubitril/valsartan after written informed consent, at the post graduate department of cardiology, J.L.N Medical College, Ajmer, Rajasthan between Jan 1, 2018 and June 30, 2019. Our institute ethical committee approved for the study protocol. During screening, eligibility requirements were assessed and confirmed (Table 1). Blood and urine samples were also collected during screening for the safety assessment. In patients receiving ARB/ACEI therapy, ARNI was started in patients after 36 h wash out period to reduce the risk of angioedema.

Table 1

| Inclusion criteria | Exclusion criteria |
|---|---|
| <ul style="list-style-type: none"> • Aged ≥ 18 y • NYHA functional class II, III, or IV • LVEF $\leq 40\%$ within the preceding 6 months, and no subsequent documentation of EF $> 40\%$ • Stable dose of loop diuretic for the 2 weeks prior to study | <ul style="list-style-type: none"> • History of hypersensitivity/allergy/angioedema to study- drug component or to drugs of similar chemical classes, including ACEIs, ARBs, or neprilysin inhibitors • Concomitant use of ACEI therapy, nesiritide, aliskiren, or drugs that may affect absorption of the study medication • Current or previous treatment with sacubitril/valsartan • Inadequate washout of ACEI/ARB before study initiation • Potassium > 5.2 mEq/L at screening • Pregnancy • Systolic B.P < 90 mm of hg |

Clinical data collected included demographics, comorbidities, New York Heart Association functional class, duration of heart failure diagnosis, medications and laboratory parameters. Sacubitril/valsartan was started in dose of 24/26 mg twice a day in addition to guideline directed therapy and was kept same throughout the study. Patients undergo treatment for 1 year with visits occurring after 1 month, 6 months until study completion at 12 months. This schedule allows for evaluation of two dimensional echocardiography parameters. LV mass was calculated with the formula recommended by the American Society of Echocardiography (ASE) and was indexed to the body surface area as follows: $LV\ mass = 0.8 \times 1.04 [(LVDD + LVPWd + IVSTd)^3 - (LVDD)^3] + 0.6$, where LVDD was the LV diastolic diameter, IVSTd was the diastolic interventricular septal wall thickness and LVPWd was the diastolic LV posterior wall thickness.¹⁰ The LV ejection fraction (LVEF) was measured using the Teicholz method. TEI index (LVMPI) = $(IVCT + IVRT)/LVET$, calculated by 2D echo by Flow Doppler method in apical 5 chamber view, where IVCT was isovolumic contraction time, LVET was left ventricle ejection time (ET), and IVRT was isovolumic relaxation time. Imaging data were analyzed for LVEF and measures of reverse remodelling including left ventricular mass and LV mass index and TEI index. These changes were evaluated from baseline to 12 months, as well as from baseline to 6 months. Laboratory parameters (serum potassium and creatinine levels) measured at every visit. If any of adverse effects including worsening renal function (defined as an increase in serum creatinine ≥ 0.5 mg/dL, symptomatic hypotension, hyperkalemia (defined as potassium levels > 5.5 mEq/L) observed, drug was temporarily withdrawn for 1–4 weeks. The patient was then reassessed and drug restarted if the patient is stable. Drug was stopped if adverse effects recurred. In case of angioedema drug was stopped and not restarted. If the patient discontinues the drug, the patient was advised for an end-of-study visit.

The primary outcome was change in LVEF, LV mass and TEI index over the three studied time points: baseline, 6 and 12 months post Sacubitril/Valsartan. The secondary outcomes were the death due to any cause, frequency and duration of hospitalisation.

3. Statistical analysis

All data analysis was completed using SPSS software (V 22.0). Continuous variables are presented as mean and standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for nonnormally distributed variables. Descriptive statistics like minimum, maximum mean and standard deviation was calculated on baseline parameters. *T*-test for proportion was used for readmitted patients. Paired *T* test were used to observe the drug effect on cases. Association between drug effect and time was checked, after that we set the regression equations and observed the significance at 5% level of significance.

4. Results

A total of 256 patients with HFrEF were initiated with Sacubitril/Valsartan. The baseline characteristics of this patient population are shown in Table 2.

The majority of our patients were on all guideline directed optimal heart failure therapy with 44.1% on beta blockers(BB), 31.3% on Angiotensin receptor blockers (ARB)/ACEI, 35.5% on loop diuretics, 22.3% on digoxin and 37.9% on MRAs. After 12 month follow up, 158 patients were found adhered with the drug, 68 patients discontinued the study drug and 30 patients were lost to follow up.

The primary outcome revealed as a significant decrease in mean LV mass (Fig. 1) following treatment with Sacubitril/Valsartan from 270.84 ± 68.94 gm at baseline to 247.06 ± 57.41 gm at 6 months follow-up ($p < 0.000001$), and further significant reduction after 1 year of treatment to 232.79 ± 57.64 gm ($p = 0.000001$). Reduction in mean LV mass was progressive from 23.75 gm at end of 6 months–38.74 at the end of 1 year of treatment. LV mass index was also significantly reduced from baseline by 43.35 gm/ m^2 ($p = 0.000001$) and 57.97 gm/ m^2 ($p = 0.000001$) at 6 months and 12 months with ARNI therapy (Tables 3 and 4) (see Tables 4–8).

ARNI use was associated with an average gradual increase in EF (Fig. 2), from a mean baseline of $26.33 \pm 6.28\%$ to $31.29 \pm 7.52\%$ ($p = 0.000001$) after 6 months and to $33.88 \pm 7.73\%$ ($p = 0.000001$) after 1 year of treatment, TEI index (Fig. 3) showed significant reduction from baseline mean 0.85 ± 0.22 to 0.74 ± 0.10 ($p = 0.000001$) after 6 months and to 0.70 ± 0.12 ($p = 0.000001$) after 1 year of treatment.

Out of 256 patients, 68 patients showed non adherence to drug and stopped the drug completely. Drug was discontinued in 2 patients due to angioedema, in 5 patients due to acute kidney injury and in 2 patients due to hypotension. They were continued on optimal medical management and were advised for follow up at 6 and 12 months. In defaulter case, total 22 deaths occurred in one year, out of which 9 occurred within initial 6 months and 13 deaths in next 6 months (Table 3).

Insignificant reduction in mean LV Mass of 16.99 gms ($p = 0.052$) and in TEI index of 0.01 ($p = 0.496$) occurred in defaulter patients at 6 months follow up. However reduction in LV mass of 28.4 gms at 1 year of optimal medical therapy was found significant ($p = 0.0091$). Out of 158 patients who on sacubitril/valsartan total 10 (6%) deaths occurred out of hospital in 12 months. Whereas among defaulters, 22 deaths (32%) occurred in one year. In our study, 9% patients

required hospitalisation in 1 year period, out of which 9% were hospitalised once, 6% twice and 1% thrice in a year, thus suggestive of decreased cases of worsening heart failure. Whereas, among patients who discontinued sacubitril valsartan, 45% patients required hospitalisation in one year period. This difference in hospitalisation rates was found significant ($p = 0.00001$).

5. Discussion

Based on results from PARADIGM-HF trial,¹¹ which demonstrated mortality benefits of sacubitril-valsartan over enalapril therapy, ARNI therapy now has a class 1 indication for the treatment of patients with HFrEF. However, neither the PARADIGM-HF trial nor the PIONEER-HF trial,¹² assessed the effect of ARNI on cardiac structure and function.

Following these trials, several studies have been conducted to fill this evidence gap but none of them in rural Indian population. EVALUATE-HF¹³ trial showed improvement in left ventricular ejection fraction or global longitudinal strain at 12 weeks, but there was evidence of reverse remodelling via other measures, including significant reductions in LVESVI, LVED VI, left atrial volume index, and E/e' ratio, mirroring those findings in PROVE-HF¹⁴ that were observed in the absence of a control group.

Sacubitril, neprilysin inhibitor increases the levels of these multiple vasoactive peptides (VAP) including natriuretic peptides, angiotensin, endothelin 1, adrenomedullin, opioids and amyloid- β peptide ($A\beta$). promoting natriuresis, vasodilation and reduction of extracellular fluid volume via sodium excretion; eventually reducing preload and ventricular remodeling.¹⁵ Valsartan by blockade of AT1 receptor reduces vasoconstriction, sodium and water retention and myocardial hypertrophy. In experimental studies, ARNI have shown to decrease angiotensin-II-mediated cardio-renal fibrosis and cardiac remodeling and dysfunction; attributed to superior inhibition by sacubitril/valsartan on cardiac fibrosis and cardiac hypertrophy than either neprilysin inhibitor or ARB alone.^{16,17} Similar to BB, ACEi, ARB and MRA therapies, our results demonstrate the ability of Sacubitril/Valsartan to significantly improve LVEF, and reduce LV mass.

However, Sacubitril/Valsartan is only prescribed in our centre in patients with HFrEF who have symptomatic heart failure despite optimal ACEi, BB, and MRA treatment. We therefore believe that the observed effects on LV mass and TEI Index in this study are attributable to Sacubitril/Valsartan. This is further supported by previous LVEF records of the patients which did not demonstrate any change LVEF over 6 months on stable ACEi/ARB, BB and MRA treatments prior to Sacubitril/Valsartan initiation which is later followed by a significant improvement in LVEF and LV MPI after its initiation.

Our findings support the previous animal work by Suematsu and colleagues, which showed that Sacubitril/Valsartan was associated with statistically significant improvement in LVEF.^{18,19}

Increase in mean LVEF of 4.9% at 6 months and 7.5% at 12 months of ARNI therapy in our study showed similar results as in post hoc analyses of PROVE-HF trial.

Indeed, ACE-I and ARBs improve LVEF between 1% and 4%,^{20–22} beta-blockers improve LVEF between 4% and 12%¹⁹ and MRAs generally improve LVEF by another 4%.²⁰ Importantly, in our study an incremental improvement of 7.5% in LVEF after 12 months was noticed after switching therapy from ACE-I or ARB to sacubitril/valsartan.

A meta-analysis of over 69,000 patients by Kramer et al demonstrated that improvement in LVEF and left ventricular remodelling parameters was associated with lower mortality rates among patients with HFrEF.²³

A prospective study conducted by PIETER et al showed that switching therapy in e HFrEF patients from a ACEi/ARB blocker to

Table 2
Baseline Characteristics of patients on Sacubitril/Valsartan.

| Baseline Characteristics | Mean | Mean \pm SD |
|------------------------------------|-------------------|------------------------------|
| Mean Age (Year) | 60 | 60 \pm 11.7 |
| Median NYHA (IQR) | 3 | 2 - 4 (Inter-quartile range) |
| Mean Systolic BP (mg) | 123.41 | 123.41 \pm 24.69 |
| Mean Baseline S. Creatine (mg/dl) | 1.142 | 1.142 \pm 0.663 |
| Mean Body Surface Area | 1.6 | 1.6 \pm 5.1 |
| Mean Baseline Ejection Fraction | 26.4 | 26.4 \pm 6.29 |
| Male (%) | 171 (66.8%) | |
| Female (%) | 85 (33.2%) | |
| Non Ischaemic Etiology (HF) | Percentage | |
| Hypertension (%) | 59 (23%) | |
| Diabetes (%) | 61 (23.83%) | |
| AF | 25 (9.77%) | |
| Others | 111 (43%) | |
| Medications at Baseline | Percentage | |
| Beta Blocker (%) | 113 (44.1%) | |
| ARB/ACEI | 80 (31.3%) | |
| Furosemide | 91 (35.5%) | |
| Digitalis | 57 (22.3%) | |
| MRA | 97 (37.9%) | |

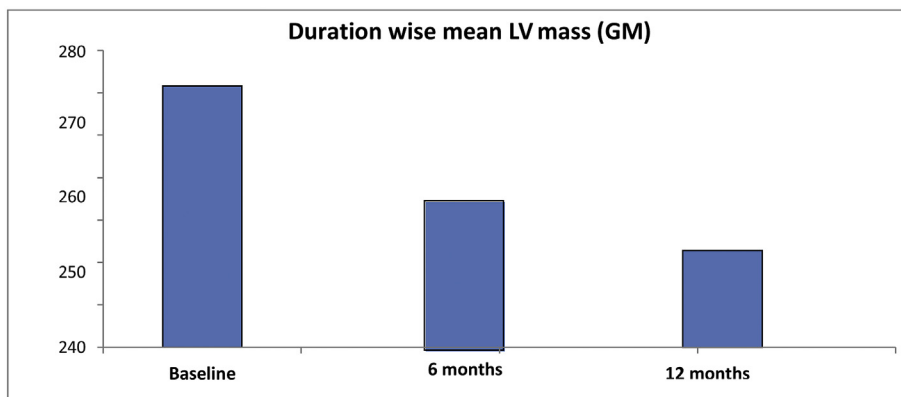


Fig. 1. Change in LVmass with time on ARNI.

Table 3
Comparison of parameters after 6 and 12 months between defaulters and patients on drug.

| Variables | | Non adherent (n = 68) | On Drug (n = 158) | P – Value | Significance |
|-------------------------|-----------------|-----------------------|-------------------|-----------|----------------------------|
| Change in LV mass | After 6 Months | –16.99 | –23.75 | 0.000001 | All are highly significant |
| | After 12 Months | –28.4 | –38.74 | 0.000001 | |
| Change in LVMPI | After 6 Months | –0.0131 | –0.106 | 0.000042 | |
| | After 12 Months | 0.0134 | –0.147 | 0.000113 | |
| Change in LV mass index | After 6 Months | –24.527 | –43.35 | 0.000014 | |
| | After 12 Months | –32.18 | –57.97 | 0.000012 | |
| Change in EF % | After 6 Months | 1.896 | 4.96 | 0.000027 | |
| | After 12 Months | 3.31 | 7.33 | 0.000031 | |
| Death | After 6 Months | 09(13%) | 06(3%) | – | – |
| | After 12 Months | 13(19%) | 04(2%) | – | – |
| Hospital Readmission | After 6 Months | 11(16%) | 6(3%) | – | – |
| | After 12 Months | 20(29%) | 9(5%) | – | – |

Table 4
Compare the effect of treatment after the 1 year on 2D Echo parameters (N = 158).

| 2D Echo Parameters | Baseline | After 1 Year Treatment | Change in Mean | P - Value | Significance |
|---------------------------|----------------|------------------------|----------------|-----------|--------------------|
| | Mean ± S.D. | Mean ± S.D. | | | |
| LVEF (gm) | 26.55 ± 6.44 | 33.88 ± 7.73 | 7.33 | 0.00000 | Highly Significant |
| Lv mass mean (gm) | 271.53 ± 70.95 | 232.79 ± 57.64 | –38.74 | 0.00000 | Highly Significant |
| Lv mass index mean (g/m2) | 231.87 ± 70.97 | 173.49 ± 37.195 | –57.97 | 0.00000 | Highly Significant |
| LVMPI | 0.852 ± 0.22 | 0.705 ± 0.126 | –0.147 | 0.00000 | Highly Significant |

Table 5
Assessment of change in EDV (mL) over time.

| Comparison of EDV (mL) at Various Timepoints vs Baseline | Mean (SD) of Difference | Median (IQR) of Difference | Range of Difference | p value |
|--|-------------------------|----------------------------|---------------------|---------|
| 6 Months - Baseline | –17.14 (62.10) | –23.00 (41.50) | –180.00–224.60 | 0.875 |
| 1 Year - Baseline | –40.48 (69.83) | –52.50 (76.50) | –213.00–239.00 | 0.038 |

As a significant change was observed in EDV (mL) over time using the Friedman Test, post-hoc pairwise analysis was performed to explore at which timepoints the EDV (mL) differed significantly from the Baseline timepoint.

Table 6
Assessment of change in EDV (mL) over time.

| Comparison of ESV (mL) at Various Timepoints vs Baseline | Mean (SD) of Difference | Median (IQR) of Difference | Range of Difference | p value |
|--|-------------------------|----------------------------|---------------------|---------|
| 6 Months - Baseline | –13.55 (58.38) | –18.70 (59.65) | –162.00–179.00 | 0.327 |
| 1 Year - Baseline | –33.04 (61.63) | –38.50 (63.75) | –192.00–178.40 | 0.300 |

sacubitril/valsartan induced beneficial reverse remodeling of both systolic a diastolic function echocardiographic parameters.²⁴

Although an improvement in EF and reverse remodeling may be inferred from the improved mortality shown in the PARADIGM trial, our study provides the human data showing these effects.¹¹

Table 7
Assessment of change in LVEDD (mm) over time.

| Comparison of LVEDD (mm) at Various Timepoints vs Baseline | Mean (SD) of Difference | Median (IQR) of Difference | Range of Difference | p value |
|--|-------------------------|----------------------------|---------------------|---------|
| 6 Months - Baseline | -3.06 (4.45) | -2.00 (3.00) | -20.00–12.50 | <0.001 |
| 1 Year - Baseline | -3.87 (4.92) | -2.70 (6.00) | -24.70 - 0.00 | 0.002 |

As a significant change was observed in LVEDD (mm) over time using the Friedman Test, post-hoc pairwise analysis was performed to explore at which timepoints the LVEDD (mm) differed significantly from the Baseline timepoint.

Table 8
Assessment of change in LVESd (mm) over time.

| Comparison of LVESD (mm) at Various Timepoints vs Baseline | Mean (SD) of Difference | Median (IQR) of Difference | Range of Difference | p value |
|--|-------------------------|----------------------------|---------------------|---------|
| 6 Months - Baseline | -2.69 (4.75) | -2.00 (3.00) | -20.00–17.30 | <0.001 |
| 1 Year - Baseline | -3.25 (5.89) | -2.00 (5.00) | -27.70 - 16.50 | <0.001 |

As a significant change was observed in LVESD (mm) over time using the Friedman Test, post-hoc pairwise analysis was performed to explore at which timepoints the LVESD (mm) differed significantly from the Baseline timepoint.

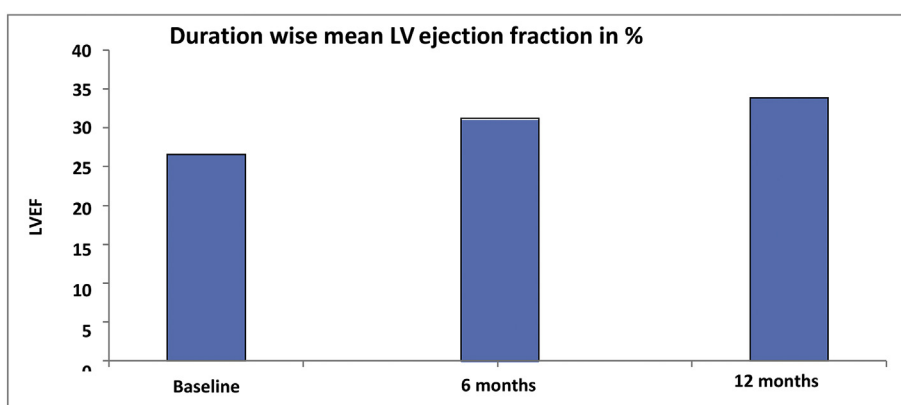


Fig. 2. Change in LVEF with time on ARNI.

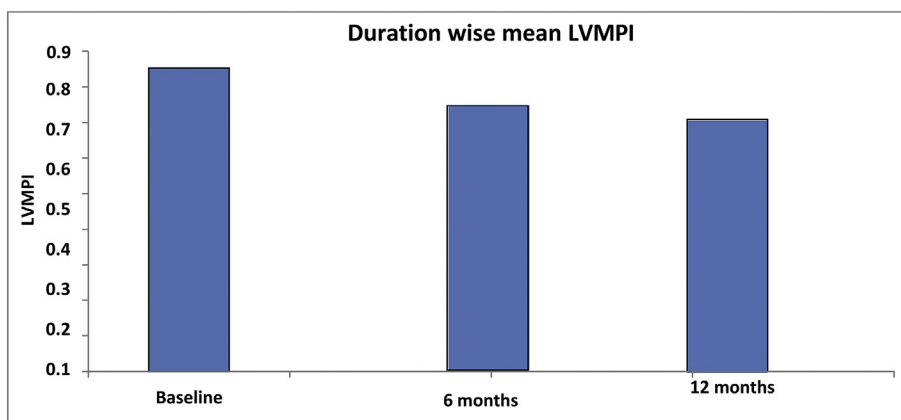


Fig. 3. Change in LVMPI with time on ARNI.

Out of 188 patients on sacubitril/valsartan, 6(3.1%) deaths occurred out of hospital during follow up period, whereas among defaulter 22 deaths(32%) occurred in 1 year.

In Indian scenario cost is an important potential barrier for use of sacubitril/valsartan which lead to increase in defaulter cases. We found that about one fourth of patients initiated on sacubitril/valsartan were non adherent over the next 180 days, which in most cases occurred because of cost. In this study, drug was discontinued

in 2 patients due to angioedema, in 5 patients due to acute kidney injury and in 2 patients due to symptomatic hypotension.

Data analysis from the PROTECT(Pro-BNP out patient tailored Chronic HF Therapy) study found that ambulatory patients with worsening heart failure had a significantly higher rate of HF hospitalization compared with patients without it. Patients with WHF had a significantly higher rate of subsequent HF hospitalization than those without (53% vs. 1%; $p < 0.001$) and a significantly higher

rate of composite outcome of HF hospitalization or cardiovascular death (56% vs. 6%; $p < 0.001$).²⁵

In our study, 9% patients required hospitalisation in 1 year, whereas among patients who discontinued sacubitril valsartan 45% patients required hospitalisation in one year period, thus suggestive of decreased cases of worsening heart failure in patients on ARNI therapy.

6. Study limitations

There are few limitations to our study. It is a single-center prospective observational study to assess LV myocardial function after addition of ARNI in standard care of treatment so did not evaluate all other echocardiographic indices. Despite being a prospective study comparing data at the baseline and after six and 12 months of ARNI therapy, there was no control group under ACEI or ARB therapy. However, Patients included in the study were those who have symptomatic heart failure despite optimal ACEi, BB, and MRA treatment, which suggests that improvements seen in LV function are likely attributable to Sacubitril/Valsartan. As we used low and fixed dose so dose dependent effect of ARNI could not be studied. This may warrant further investigation.

7. Conclusion

Significant reduction in LV mass and improvement in left ventricle myocardial function as evidenced by improvement in TEI index following Sacubitril/Valsartan therapy on long term use could be a final pathway for significant reduction in long term recurrent hospitalization rates, improvement in quality of life and mortality benefits.

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None.

Declaration of competing interest

All authors have none to declare.

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