Original Article

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Benefits of Angiotensin Receptor-Neprilysin Inhibitor in Heart Failure with Reduced Ejection Fraction: A Longitudinal Study

Internal Medicine Section

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ABSTRACT

Introduction: Combination of Angiotensin Receptor and Neprilysin Inhibitors (ARNI) has become the mainstay drug in treatment of Heart Failure (HF) with reduced Ejection Fraction (HFrEF). However, there are very few studies to evaluate the extent and spectrum of benefit of ARNI therapy in Indian HFrEF patients.

Aim: To observe the benefits of sacubitril/valsartan (ARNI) therapy on left ventricle function, parameters of cardiac remodelling, N terminal pro Brain-natriuretic peptide (NT-proBNP), rate of rehospitalisation for HF and detailed subgroup analysis in symptomatic HFrEF patients who are already receiving optimal medical therapy.

Materials and Methods: This longitudinal study was conducted at Cardiology Department of Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India, from September 2018 to August 2020. Total 200 patients of HFrEF with previous echocardiographic records of past six months, who did not show any further improvement in left ventricle dysfunction or cardiac dimensions were included in the study out of these 200 patients, 174 (87%) completed the one year follow-up. Patients were started on ARNI initially from 100 mg/day and up titrated to 400 mg/day. At each follow-up (6 weeks, 4 months, 6 months, 9 months and 1 year) clinical examination, New York Heart Association (NYHA) functional class, 2D Echocardiography and NT-ProBNP were done. Echocardiographic parameters of Cardiac Reverse Remodelling (CRR) i.e., Left Ventricular Ejection Fraction (LVEF), Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricle End-Systolic Diameter (LVESD) were recorded at each follow-up. All categorical variables were shown in the form of frequency, mean with standard deviation and percentage. Intergroup comparison between different time periods was done by one-way Analysis of Variance (ANOVA) and paired t-test. A p-value <0.05 was considered statistically significant.

Results: Mean age of study population was 58.61±11.95 years, of whom 104 (59.77%) were males, and 70 (40.22%) were females. Mean LVEF increased from 30.42% at baseline to 45.98%, after 1 year (p-value <0.05). There was reduction in mean LVEDD of 4.5 mm (p<0.05) and LVESD of 3.86 mm (p-value <0.05) at 1 year. These benefits of CRR were observed in all the subgroups of study population (including diabetics, hypertensive, tobacco users, age, gender). Reduction in NT-ProBNP from 1097.65±769.7 pg/mL at baseline to 127.28 pg/mL after 1 year with mean reduction of 970.37±731.33 pg/mL (p-value <0.05). Rate of rehospitalisation for HF was 13.2% (N=23). A positive although weak correlation was seen between change in NT-ProBNP level and change in LVEF, LVEDD, LVESD as per Spearman's rank correlation coefficient.

Conclusion: The ARNI was well tolerated in this Indian population as 72% achieved maximum dose of 400 mg. There was significant improvement in LV systolic function and cardiac dimensions and benefits extended to different subgroups of HFrEF patients along with positive although weak correlation between fall in NT-ProBNP level and improvement in LV function and cardiac dimensions over and above optimal medical therapy.

Keywords: Cardiac remodelling, Left ventricular dysfunction, N-terminal pro brain naturetic peptide, Sacubitril/valsartan

INTRODUCTION

In this era of non communicable diseases, Heart Failure (HF) has emerged as a leading cause of mortality and morbidity. Chronic HF is a complex and progressive clinical syndrome resulting from any abnormality of cardiac structure or function. The prevalence of HF as well as rehospitalisation for HF are increasing, and the prognosis is poor with mortality within 5-years which is worse than many cancers [1,2]. Multiple recent advancement has been done in the arena of therapeutic management of HF. Combination of ARNI has established itself as a cornerstone evidence based drug in management of HF as per some recent landmark trials [3,4]. Neprilysin is a neutral endopeptidase, which degrades several endogenous vasoactive peptides including natriuretic peptides, bradykinin, and adrenomedullin [5-7]. Due to inhibition of neprilysin, the level of these substances increases, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling [8,9]. Inhibition of both the renin-angiotensin system and neprilysin has effects that are superior to those of either approach alone in experimental studies [10,11].

The PARADIGM-HF trial showed in comparison to enalapril, sacubitril/valsartan reduced the primary composite endpoint of cardiovascular death or HF hospitalisation by 20% [3]. Although the physiological mechanisms of action of ARNI (sacubitril/valsartan) are well known, its effects on Left Ventricular Ejection Fraction (LVEF) and left ventricular dimensions have not been well studied in Indian population. In patients with Heart Failure with Reduced Ejection Fraction (HFrEF) left ventricular remodelling is a major mechanism underlying disease progression [12].

The primary aim of this study was to see the benefits of Angiotensin Receptor and Neprilysin Inhibitors (ARNI) over and above background optimum medical therapy on LV function and parameters of cardiac remodelling in Indian patients of HFrEF. The variables observed in each follow-up were echocardiographic parameters of Cardiac Reverse Remodelling (CRR) i.e., Left Ventricular Ejection Fraction (LVEF), Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricle End-Systolic Diameter (LVESD) along with NT-pro BNP and rate of rehospitalisation for HF. Detailed subgroup analysis according to risk factors, age and gender in Indian patients of HFrEF was also done.

MATERIALS AND METHODS

This longitudinal study was done in Cardiology Department at Institute of Medical Sciences, Banaras Hindu University, Varanasi,

Uttar Pradesh, (tertiary care centre of north India) from September 2018 to August 2019 and patients were further followed-up for next one year (till August 2020). Ethical clearance was taken from the Institutional Ethics Committee (vide letter number EC/1419).

Sample size calculation: Estimated sample size was 158, assuming mean LVEF at baseline 25% and 34% at 3 months [13], keeping standard deviation of 0.4, α=0.05 and power=0.80.

Inclusion criteria: Patients of HFrEF with New York Heart Association (NYHA) class II-IV, age ≥18 years and LVEF of ≤40% who were symptomatic despite optimal medical therapy of HF {like ACE-I/ARB, beta blockers, Mineralocorticoid Receptor Antagonist (MRS), diuretics} and were required to have previous echocardiographic records of past 6 months who did not show any further improvement in LV dysfunction or cardiac dimensions were included in the study. Patients were required to have report of plasma NT pro BNP level >450 pg/mL along with stabilised Acute Decompensated Heart Failure (ADHF) patients admitted in Cardiac Care Unit (CCU). Patients suspected to have ischaemic aetiology have already undergone coronary angiography and revascularisation accordingly 3 months back before starting ARNI.

Exclusion criteria: Patients with symptomatic hypotension, a systolic blood pressure of less than 100 mmHg, estimated Glomerular Filtration Rate (e-GFR) below 30 mL/minute/1.73 m^2 of body-surface area at screening or baseline serum creatinine ≥2 mg/dL, serum potassium >5.4 mmol/L or history of angioedema or unacceptable side-effect, hypersensitivity to sacubitril, valsartan, any ARBs, neprilysin inhibitors, or any of the sacubitril/valsartan excipients, presence of haemodynamically significant mitral and/or aortic valve disease except mitral regurgitation secondary to left ventricular dilatation, diagnosis of chemotherapy induced cardiomyopathy within the 12 months prior to admission were excluded.

Study Procedure

In case of prior history of Angiotensin Converting Enzyme inhibitor (ACE-I) intake, ACE-I was discontinued for a 36-hour washout period before starting sacubitril/valsartan. Although for ARB no such washout period was required and sacubitril/valsartan was given on the same day. Dose escalation (doubling of dose) was done to maximum permissible dose of 200 mg twice daily over a period of 4 weeks. Sacubitril/valsartan uptitration was done with the goal of achieving and maintaining sacubitril/valsartan 200 mg twice daily.

Patients with primary diagnosis of ADHF were stabilised before starting sacubitril/valsartan during hospitalisation. In these patients, haemodynamic stability was defined by maintenance of a systolic blood pressure of at least 100 mm Hg for the preceding 6 hours, with no increase in the dose of intravenous diuretics and no use of intravenous vasodilators during the preceding 6 hours and no use of intravenous inotropes during the preceding 24 hours.

These patients were followed for one year. The first visit was scheduled at two weeks after starting treatment with follow-up visits at 6 weeks, 4 months, 6 months, 9 months and 1 year. At each visit assessment of tolerability of sacubitril/valsartan was done. Transthoracic echocardiography was performed on Esaote 2D Echocardiography system with 3.5 MHz transducer. The Echocardiography analysis included the evaluation of LVEF, Left Ventricular End Systolic Dimension (LVESD) and Left Ventricular End Diastolic Dimension (LVEDD). NT-proBNP measurements was done at each visit. Primary outcome was improvement in LVEF and LV dimensions (systolic and diastolic) at the end of 1 year. Secondary outcome was improvement in NT-ProBNP level. Subgroup analysis was also done according to risk factors

STATISTICAL ANALYSIS

Statistical analysis was done using STATA software version 17.0. All continuous variables were shown in the form of mean with standard deviation and categorical variables in the form of frequency with percentage. The difference of NT-proBNP values from baseline to after one year of therapy was calculated and log transformation of square of this difference was done to make the normality of data. Data was analysed by using proper statistical test (parametric and non parametric). Intergroup comparison between different time periods was done by one-way Analysis of Variance (ANOVA) and paired t-test. A p-value <0.05 was considered statistically significant. Panel/longitudinal analysis was done with mean change in LVEF and log of square of NT-proBNP as panel data to assess changes in continuous echocardiography parameters between baseline and one year follow-up. Same statistical analysis was done for each subgroup of interest.

RESULTS

Total of 200 patients were enrolled.Total 84 patients were enrolled from Inpatient Department (IPD) or CCU with diagnosis of acute decompensated HF, while rest of the patients (n=116) were enrolled from OPD with diagnosis of chronic compensated HF. Out of these 200 patients, 174 (87%) completed the one year follow-up. Data analysis was done for 174 patients as 14 patients died due to fatal arrhythmias and sudden cardiac death, eight patients were lost to follow-up and ARNI was discontinued in four patients due to adverse effects of drug (symptomatic hypotension in three, and worsening of renal function in one).

Mean age of study subjects were 58.61±11.95 years, of whom 104 (59.77%) were male and 70 (40.22%) were female. At the onset of study, majority of the patients were in NYHA class III 98 (56.32%). Ischaemic aetiology of HF was reported in 153 (87.93%), and others were of unknown aetiology (designated as idiopathic dilated cardiomyopathy). Total 59.7% (N=104) of study subjects had history of coronary revascularisation. Distribution of risk factor as shown in [Table/Fig-1] with 19 (10.9%) patients without any risk factor. At baseline mean±SD for LVEF was 30.42±5.12, for LVEDD was 60.57±3.12 mm and for LVESD was 46.56±4.03 mm. Atrial fibrillation was seen in 11 (6.32%) patients. Maximum dose of ARNI 400 mg/day was achieved by 125 (71.8%), 200 mg/day in 44 (25.3%) and 100 mg/day in 5 (2.3%) patients.

Parameters	Mean±SD/n (%)
Age (years)	58.61±11.95
Age quantile	
Age quantile 1 (Range: 19-53)	43.68±9.90
Age quantile 2 (Range: 54-58)	55.90±1.32
Age quantile 3 (Range: 59-65)	62.95±2.25
Age quantile 4 (Range: 66-86)	73.30±4.35
Gender	
Male	104 (59.77%)
Female	70 (40.22%)
Blood pressure	
Systolic blood pressure (mmHg)	127.47±15.74
Diastolic blood pressure (mm of Hg)	79.87±10.72
Creatinine (mg/dL)	1.25±0.40
Haemoglobin (gm/dL)	12.05±1.7
LVEF (%)	30.42±5.12
LVEDD (mm)	60.57±3.12
LVESD (mm)	46.56±4.03
NT-pro BNP (pg/mL)	1097.65±769.7
Atrial fibrillation	11 (6.32%)
NYHA II	30 (17.24%)
NYHA III	98 (56.32%)
NYHA IV	46 (26.4%)
No risk factor	19 (10.91%)

Hypertension	29 (16.67%)
Diabetes mellitus	24 (13.8%)
Tobacco	55 (31.60%)
Tobacco and Diabetes mellitus	8 (4.6%)
Diabetes mellitus and hypertension	23 (13.22%)
Tobacco and Hypertension	16 (19.19%)
Beta blockers	136 (78.1%)
ACE-I/ARB	140 (80.4%)
Mineralocorticoid receptor antagonists	121 (69.5%)
Diuretic	148 (85%)
Past coronary revascularisation	104 (59.7%)

[Table/Fig-1]: Baseline characteristics of the study population (N=174).
SD: Standard deviation; LVEF: Left ventricular ejection fraction; NT-proBNP: N terminal pro Brain-natriuretic peptide; NYHA: New York heart association; ACE-I/ARB: Angiotensin converting enzyme-inhibitors/Angiotensin-receptor blockers; LVEDD: Left ventricular end-diastolic dimension; LVESD: Left ventricular end-systolic dimension

Background medical treatment consisted of beta-blocker, ACE-I/ARB, mineralocorticoid receptor antagonist and diuretics [Table/Fig-1], along with optimal medical therapy for coronary artery disease in ischaemic aetiology

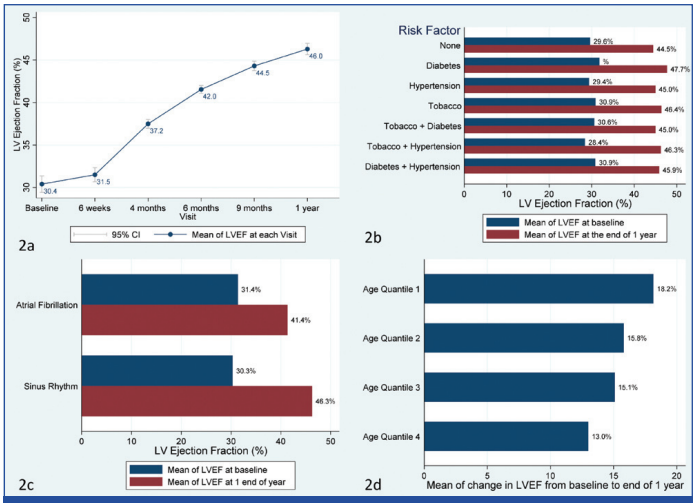
Benefits in LV systolic function: There was significant improvement in mean difference of ejection fraction from baseline to one year 15.56±6.82 (95% CI 14.55-16.59, p-value <0.05). Mean of LVEF increased sequentially from baseline value of 30.42±5.12 to 31.52±5.78 (p-value <0.05) at six weeks, with major difference in absolute mean value from baseline was found at 4 months (30.42±5.10 vs. 37.17±7.16, p-value <0.05) and further at 6 months 41.97±7.18 (p-value <0.05), at 9 months 44.48±7.1 (p-value <0.05) and in one year 45.98±6.96 (p-value <0.05). Panel/longitudinal data analysis shows improvement in LVEF at each visit with maximum benefits started to appear after four months of therapy [Table/Fig-2a].

There was significant improvement in mean LVEF from baseline to one year across all the spectrum of risk factors [Table/Fig-2b] the mean increase in LVEF across all the risk factor ranges from 14.37-17.81%, maximum absolute increase in mean LVEF was seen with tobacco+Hypertension subgroup but on applying one way ANOVA test between the mean increase in LVEF among all risk factors, no statistical significance was found, thereby implying that benefits of ARNI are independent of risk factors. Gender based analysis showed similar benifit among male and female with mean increase in LVEF of 15.54% in males and 15.61% in females.

Age was divided into quantile subgroups and analysis was done which showed maximum improvement in LVEF in 1st quantile of 18.16±6.9% and minimum benefits of 13±7.0% in 4th quantile [Table/Fig-2c]. On applying one-way ANOVA test between 1st and 4th quantile it was found to be statistically significant with p-value <0.05 which implies that maximum beneifit of ARNI therapy was seen with 1st quantile which corresponds to younger age group. Comparison of improvement in LVEF in atrial fibrillation versus sinus rhythm group was also done. Change in ejection fraction from baseline to one year was significant in both atrial fibrillation and sinus rhythm group, however, the mean change was only 10% (95% CI: 5.5-14.5, p-value <0.05) in atrial fibrillation subgroup, while it was 15.95% (95% CI: 14.9-16.99, p-value <0.05) in sinus rhythm group [Table/Fig-2d].

Subgroup analysis of improvement in LVEF with ARNI therapy was done according to diffrent risk factors, age quantiles and gender which showed that benefits with ARNI therapy was across all the subgroups [Table/Fig-3].

Benefits in cardiac dimensions: The mean LVEDD at baseline was 60.57±3.12 mm and 56.03±3.16 mm at the end of one year. There was significant decrease in mean LVEDD of 4.5±1.1 mm (95% CI: 5.1-3.8, p-value <0.05) after one year of therapy. Subgroup analysis showed benefit across all subgroups as shown in [Table/Fig-4].



[Table/Fig-2]: a) Line chart with 95% CI showing improvement in EF at each visit, maximum benefits started to appear after 4 months of therapy. Panel/longitudinal data analysis; b) There was significant improvement in mean ejection fraction from base line to 1 year across all the spectrum of risk factors; c) One way ANOVA test showed significant improvement in EF from base line to 1 year in among 1st and 4th quantile of age group reflecting that maximum benefit of ARNI was seen in younger patients compared to elderly; d) Change in ejection fraction from baseline to 1 year was significant in both Atrial Fibrillation (AF) and sinus rhythm (SR) subgroup, however the mean change was only 10% (95% CI 5.5 to 14.5, p-value <0.05) in AF subgroup, while it was 15.95% (95% CI 14.9-16.99, p-value <0.05).

Parameters	Mean±SD (change in EF from baseline to 1 year)	95% CI	p-value (paired t test)
Male	15.5±7.2	14.2-16.95	<0.05
Female	15.6±6.2	14.1-17.1	<0.05
Diabetic	15.3±5.9	13.7-16.9	<0.05
Non diabetic	15.7±7.2	14.4-17.0	<0.05
Age quantile 1	18.2±6.9	16.1-20.3	<0.05
Age quantile 2	15.8±6.1	13.9-17.7	<0.05
Age quantile 3	15.1±6.5	13.2-16.98	<0.05
Age quantile 4	13.00±7.1	10.7-15.3	<0.05
Hypertension	15.6±6.96	12.9-18.2	<0.05
Tobacco	15.4±6.8	13.6-17.3	<0.05
Diabetes+Tobacco	14.4±7.8	7.9-20.9	0.0006
Hypertension+Tobacco	17.8±8.4	13.3-22.3	<0.05
Diabetes+Hypertension	15±5.2	12.7-17.2	<0.05
No risk factor	14.8±7.9	10.99-18.7	<0.05

[Table/Fig-3]: Change in mean Ejection Fraction (EF) from baseline to one year in each subgroup.

Parameters	Mean±SD (change LVEDD from baseline to 1 year)	95% CI	p-value (paired t test)
Male	4.4±1.03	4.2-4.6	<0.05
Female	4.7±1.2	4.3-4.9	<0.05
Diabetic	4.4±1.3	4.1-4.7	<0.05
Non diabetic	4.6±1.04	4.4-4.8	<0.05
Age quantile 1	4.4±0.8	4.1-4.6	<0.05
Age quantile 2	4.6±1.1	4.3-4.9	<0.05
Age quantile 3	4.4±1.6	3.9-4.9	<0.05
Age quantile 4	4.6±0.8	4.4-4.9	<0.05
Hypertension	4.9±1.1	4.5-5.3	<0.05
Tobacco	4.41±1.1	4.1-4.7	<0.05
Diabetes+Tobacco	4.4±0.9	3.6-5.1	<0.05
Hypertension+Tobacco	4.4±0.6	4.1-4.8	<0.05
Diabetes+Hypertension	4.4±0.9	3.9-4.8	<0.05
No risk factor	4.6±1.01	4.1-5.1	<0.05

[Table/Fig-4]: Change in mean Left Ventricular End Diastolic Diameter (LVEDD) from baseline to one year in each subgroup.

The mean LVESD at baseline was 46.56±4.03 mm versus 42.90±4.1 mm at 12 months. There was statistically significant reduction in mean of LVESD of 3.66±1.1 mm (95% CI: 3.82-3.49, p-value <0.05) after one year of therapy. Sub group analysis shows statistically significant improvement in cardiac dimensions in all the subgroups as shown in [Table/Fig-5].

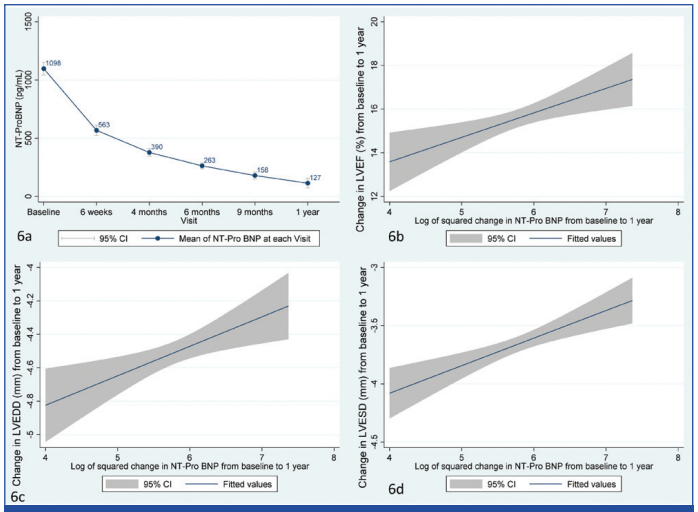
Parameters	Mean±SD (change in LVESD)	95% CI	p-value (paired t test)
Male	3.7±0.9	3.5-3.9	<0.05
Female	3.6±1.4	3.3-3.9	<0.05
Diabetic	3.7±0.9	3.4-3.9	<0.05
Non diabetic	3.7±1.2	3.4-3.9	<0.05
Age quantile 1	3.4±1.6	2.9-3.9	<0.05
Age quantile 2	3.7±0.7	3.5-3.9	<0.05
Age quantile 3	3.7±0.9	3.4-3.9	<0.05
Age quantile 4	3.8±0.9	3.5-4.1	<0.05
Hypertension	3.9±0.80	3.6-4.2	<0.05
Tobacco	3.5±1.7	3.1-3.9	<0.05
Diabetes+Tobacco	3.9±0.8	3.2-4.6	<0.05
Hypertension+Tobacco	3.8±0.7	3.4-4.2	<0.05
Diabetes+Hypertension	3.7±0.8	3.3-4.0	<0.05
No risk factor	3.6±0.8	3.2-3.9	<0.05

[Table/Fig-5]: Change in mean Left Ventricle End-Systolic Diameter (LVESD) from baseline to one year in each subgroup.

Rehospitalisation: Total of 23 patient required rehospitalisation for HF. Rate of rehospitalisation for HF was 13.2%.

Reduction in NT-proBNP levels: Mean NT proBNP level at base line was 1097.65 pg/mL and after 12 months of ARNI therapy was 127.28 pg/mL. There was significant reduction in mean of NT-proBNP 970.37±731.33 pg/mL (95% CI: 1086.13-854.60, p-value <0.05). Panel/longitudnal analysis [Table/Fig-6a] shows decrease in NT-proBNP level with each visit with maximum absolute reduction occuring after 6 weeks of therapy 535.03±61.49 pg/mL (95% CI: 655.98-404.08, p-value <0.05)

NT-proBNP data was transformed for the purpose of normalisation by taking log of square of NT-proBNP and compared with change in mean LVEF, LVEDD and LVESD. Spearman's rank correlation coefficient was calculated to find any association between reduction in NT-proBNP level with change in LVEF, LVEDD, LVESD. Positive although weak correlation was found between mean change in NT-proBNP and change in LVEF, LVEDD, LVESD as shown in [Table/Fig-6b-d].



[Table/Fig-6]: a) Line chart with 95% CI showing reduction in mean of NT proBNP at each visit, with maximum absolute reduction occurring at 6 weeks. Panel/longitudinal data analysis; b) Linear fit plot between difference of mean EF at 1 year and baseline and log of square of change in NT proBNP shows weak positive correlation, spearman's rank correlation coefficient ρ (rho)=0.1,; c) Linear fit plot between difference of mean LVEDD at 1 year and baseline and log of square of change in NT proBNP shows weak positive correlation, spearman's rank correlation coefficient ρ (rho)=0.13; d) Linear fit plot between difference of mean LVESD at 1 year and baseline and log of square of change in NT proBNP shows weak positive correlation, spearman's rank correlation coefficient ρ (rho)=0.14.

DISCUSSION

Patients with HF have an estimated 5 year mortality of 59% as per Trivandrum HF registry [14]. For the past 25 years, an add-on therapy approach to chronic HF has been used, beginning with diuretics, then adding ACE inhibitors (or ARBs) and beta blockers, followed by mineralocorticoid receptor antagonists [15-17]. Ivabradine, which reduces heart rate, is also approved as an add-on therapy in HF [18]. Nevertheless, morbidity and mortality remain high, therefore there was an unmet need for new therapeutic targets in HF. Following the disappointing outcomes of combined ACE-I/neprilysin inhibition, the combination of an ARB and neprilysin inhibitor was investigated.

In the present study, the major aetiology of HFrEF was ischaemic heart disease, which was found in 153 (87.93%) subjects. In the study done by Balmforth C et al., an analysis of PARADIGM-HF outcomes and effect of treatment according to aetiology in HFrEF demonstrated that among the 8,399 patients randomised, 5,036 (60.0%) had an ischaemic aetiology [19]. Gheorghiade M et al.,in a review of 24 trials published between 1986 and 2005, reported that 62% of patients had an investigator-reported ischaemic aetiology and in more recent trials the proportion has varied between 65%-70% in studies with a high proportion of European patients (especially from Central/Eastern Europe) to 56% in another large global trial with significant numbers of patients from Asia and Latin America [3,18,20-22].

In the present study, ARNI lead to significant improvement in LVEF of about 15% along with significant reduction in LVESD of 3.6 mm and LVEDD of 4.5 mm after one year of therapy. Almufleh A et al., demonstrated Sacubitril/Valsartan use was associated with an average 5% (±1.2) increase in EF, from a mean baseline of 25.33% to 30.14% (p-value <0.001) with a median duration of treatment 3 months [13]. They concluded sacubitril/valsartan was found to improve EF and multiple measures of reverse cardiac remodelling beyond the effects of concomitant optimal medical therapy. Gonzalez-Torres L et al.,observed that after 3 months of therapy with ACEI/ARB, there was an initial increase of LVEF, maintaining constant values along time from 3-9 months after that when ARNI was started, further significant increase of LVEF was observed [23]. Therapy with ARNI increased LVEF from 31±6-36.5±8%, (p-value <0.002) and decreased LVEDD from 62±6-60±6 mm, (p-value <0.02) and significantly decreased Left Ventricular End-Diastolic Volume (LVEDV) from 141±17 mm to 119±15 mm (p-value <0.01). The major finding of this study is that sacubitril/valsartan was able to reverse the cardiac remodelling, in the form of increasing LVEF by 5-6% and decreasing LV size. Additionally, treatment with sacubitril/valsartan was correlated to a significant improvement of NYHA functional class.

Martens P et al.,conducted a prospective study which included 125 HFrEF patients (66±10 years) with a median (IQR) follow-up of 118 (77-160) days after initiation of sacubitril/valsartan has shown significant LVEF improvement (29.6±6% vs 34.8±6%; p-value <0.001) and reduction in Left Ventricular End Systolic (LVESV) and LVEDV which was statistically significant [24]. A dose-dependent effect was noted for changes in LVEF (p-value <0.001) and LVESV (p-value=0.031), with higher doses of sacubitril/valsartan leading to more reverse remodelling. They concluded switching therapy in eligible HFrEF patients from a RAS-blocker to sacubitril/valsartan induces beneficial reverse remodelling of both metrics of systolic as well as diastolic function. Wang Y et al.,conducted a meta-analysis to compare the effects of ARNI versus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on CRR indices [25]. They searched databases for studies published between 2010 and 2019 that reported CRR indices following ARNI administration. Twenty studies enrolling 10175 patients were included. Angiotensin

receptor and neprilysin inhibitors outperformed angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in terms of CRR indices, with striking changes in left ventricular EF, diameter, and volume. Improvements in CRR indices were observed at 3 months and became more significant with longer follow-up to 12 months. They concluded ARNI distinctly improved left ventricular size and hypertrophy compared with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in HF with reduced EF patients, even after short-term follow-up. Patients appeared to benefit more in terms of CRR treated with ARNI as early as after 3 months of therapy. The benefits of ARNI were manifest at 3 months and lasted for 12 months.

In the present study, the significant benefit of ARNI started at 6 weeks and continued for 1 year but major change in absolute mean value of LVEF seen at 4 months of ARNI therapy, more importantly different subgroup analysis done in present study showed that benefit of ARNI therapy extends across all the risk factors, age groups and gender. The rate of rehospitalisation for HF in present study was 13.2% which is comparable to first rehospitalisation due to HF seen in paradigm HF trial (12.8%) [10]. In PROVE HF trial, reduction in NT-proBNP level correlation with improvement in marker of cardiac volume and LVEF was studied [4]. At 12 months, the change in log2-NT-proBNP concentration was correlated with changes in LVEF. At 12 months, LVEF increased from 28.2-37.8%, while LVEDVI decreased from 86.93-74.15 mL/m^2. In the present study also, a positive although weak correlation was seen in change in NT-proBNP level and improvement in LV function and cardiac dimensions.

The benefits, in terms of improvement in LVEF and cardiac dimension, in the present study are attributed to ARNI therapy as it was prescribed in HFrEF patients symptomatic despite on optimal medical therapy and the pervious echocardiographic records of past 6 months didn't showed any further improvement in LV function or cardiac dimensions. It is known from the earlier studies that beta blockers improve LVEF by 4-12% [26], ACEI/ARB improve LVEF between 1-4% [27-29], and MRA by another 4% [28]. In the present study, additional benefit in LVEF of approximately 15% and reduction in cardiac dimensions, a marker of CRR were seen only after switching therapy from ACEI/ARB to ARNI over and above other standard drug therapy for HFrEF.

Limitation(s)

An observational study was performed and the sample size of the studied group was limited. The single-centre study design may affect the generalisability of results. Large randomised controlled trials are needed in Indian subset with special emphasis on multicentre clinical experience and strong follow-up data.

CONCLUSION(S)

Angiotensin receptor and neprilysin inhibitors (sacubitril/valsartan) was found to improve LVEF and left ventricular dimensions (LVESD, LVEDD) in symptomatic HFrEF patients over and above optimal medical therapy used in management. A favourable response to ARNI starts at 6 weeks with maximum benefit being manifested at 4 months and consistent up to one year. Benefits extend to all subgroups of HF patients and there was also reduction in rate of rehospitalisation for HF. Admitted patients with ADHF after stabilisation and chronic HFrEF were benefited with early initiation of ARNI.

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