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Original Article

Clinical comparison of ACE inhibitors and ARNI (Sacubitril Valsartan) in heart failure patients with reduced ejection fraction

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Abstract

Objective: To study the effect of valsartan/sacubitril (angiotensin receptor neprilysin inhibitor [ARNI]) on echocardiographic and clinical parameters as compared to angiotensin- converting enzyme inhibitor (ACEI) in patients of heart failure with reduced ejection fraction (HFrEF) at 6 months follow-up.

Methods: In this prospective, single centre, observational study conducted between July 2020 and June 2021, patients with heart failure with reduced ejection fraction (<40%) were included and randomized to ARNI and ACEI group. A total of 240 patients were included in the present study, 120 each in ARNI and ACE group. All patients underwent 2D echocardiography, six minutes walk test and functional class assessment at baseline and after follow up of 6 months. Statistical analysis was done using Chi-square test and Student's independent t-test.

Results: There was significant improvement in LVEF in ARNI group as compared to ACEI group (p value<0.05). Reduction in LVIDD and LVISD was also significant in ARNI group. Significant improvement in six- minute walk test was seen in ARNI group as compared to ACEI.

Conclusion: The ARNI group showed significant improvement in echocardiographic parameters and functional class at the end of 6 months follow-up compared to ACEI group. (Indian J Cardiol 2022;25 (3-4):5-11)

Introduction

There is increasing trend of heart failure cases across the globe as well as in India[1]. It is estimated that by 2030, the number of heart failure (HF) patients would rise by 25%[2]. Heartfailure increases the mortality, morbidity and worsens the patient's quality of life. Mortality rate is estimated as 50% at 5 years from the initial diagnosis of HF. HF is also a leading cause of hospitalization,where 1-5% of total hospital admissions are due to HF cases. The mortality rate of admitted HF patients is about 2-17%.The current incidence of HF in India is estimated to be between from 1.3 to 23 million[3]. It has been observed that the cases with heart failure with reduced ejection fraction (HFrEF) are more common[3].

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) and beta blockers (BBs) are the guideline directed medical therapy available for HFrEF. These therapies have been shown to reduce morbidity and mortality. The new pharmacological class including angiotensin receptor neprilysin inhibitors (ARNI) appears to

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further improve symptoms and prognosis and have been included in latest HF guidelines in recent years[4]. As per PARADIGM-HF trial[5] the Sacubitril-valsartan (ARNI groups)has been studied for its safety and efficacy in chronic HFrEF patients.Though there is a correlation of myocardial remodeling with HF severity and it predicts the prognostic value, still the property of ARNI to cause a reverse remodeling has yet not been extensively studied.It is still unknown that which echocardiographic parameters are more subjected to improve after treatment with ARNIgroup, hence this study aims to observe the effects of ARNI on echocardiographic and clinical parameters in HFrEF patients after follow up of six months.

Material and Methods

This is a prospective case controlled study, conducted at Department of cardiology, RNT Medical College, Udaipur from 1st July, 2020 to 30th June, 2021. Total of 240 patients participated in the study. Patients were defined eligible for ARNI and ACE inhibitors as per PARADIGM-HF trial eligibility criteria. A patient diagnosed with heart failure, New York Heart Association (NYHA) II-IV and a reduced ejection fraction (≤40%) on a Beta-blocker and MRA as recommended by guidelines, with a systolic blood pressure of ≥100 mm Hg, estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2 and serum potassium ≤5.2 mmol/L.

Exclusion criteria included patients with Cardiac Resynchronization therapy (CRT)(as it also affects cardiac remodeling), any change of home medications within 2 weeks before ARNI initiation. Baseline and follow-up included clinical history, physical examination, vital parameters, routine investigations (hemoglobin, creatinine, uric acid, electrolytes) and standard transthoracic echocardiography (TTE) parameters. The initial dose of ARNI was 24/26 mg for most of the participants. A starting dose of 49/ 51 mg was used for subjects on a previous high dose of ACEi/ARB and blood pressure values 140/90 mmHg at the initial visit. Follow-up visits after six months of ARNI initiation were scheduled. Modifications of ARNI doses were done as per blood pressure and biochemical parameters of patient.All the standard TTE exams were performed with a commercially available system (Philips Affinity 70C). The images were taken in preferred left lateral decubitus position. All reported echocardiography measures were averaged from 3 consecutive cycles (or 5 if atrial fibrillation was present) and assessed as recommended by the American Society of Echocardiography[6]. A baseline and follow-up echocardiography was done for all patients and following parameters weremeasured : LVEF, LVEDV, LVESV, LV mass both at end systole and end diastole, EDV and ESV.

Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD). Variables were expressed in number and percentage. Continuous variables with a normal distribution were compared using independent student's t test and chi square test for paired data. Statistical significance of differences between categorical variables was tested using the chi square test. P value <0.05 was statistically significant. All the analyses were conducted in SPSS version 20 (SPSS Inc, Chicago, IL, USA), Microsoft Windows version, and p significant. 0.05 from 2-sided tests was considered statistically significant.

Results

A total of 240 patients were included in the study. Patients were randomized to both ARNI and ACE inhibitors in 1:1 manner respectively. Mean age of population was 61±(12.6) years in ARNI and 60±(10.4) years in ACE inhibitor group. 74.2% in ARNI group while 72.5% in ACE inhibitor group patients were male.Mean BMI was 26.4±3.6 Kg/m2in ARNI group and 25.2±3.9 Kg/m2 in ACE inhibitor group.(Table 1)

As illustrated in table 1, myocardial infarction in 162 patients(67.5%), prior hospitalization for heart failure in 164 patients (68.3%), hypertension in 126 patients (52.5%), diabetes mellitus in 86 patients (35.8%) and Dyslipidemia in 182 patients (75.8%) were the major comorbid conditions. Out of total 240 patients of study population, 43(17.9%) patients were in NYHA class IV, 78(32.5%) in class III, 119(49.6%) in class II, while 0 patient in class I.

All Patients were on optimized treatment for heart failure in form of diuretics in 233(97.1%),beta-blocker in 211(87.9%), MRAs in 205(85.4%). Digoxin was given to 21(8.75%) patients. ICD (Implantable

Table 1 : Basic Characteristics of the study population

Variables	Category	ACE inhibitors % (n-120)	ARNI % (n-120)	Total % (n-240)	P value
Age(Years)	<30	04 (3.3%)	03(2.5%)	07 (2.9%)	0.84
	31-60	52 (43.3%)	49 (40.83%)	101 (42%)	
	>60	64 (53.3%)	68(56.7%)	132 (55.0%)	
Gender	Female	33(27.5%)	31 (25.8%)	64 (26.7%)	0.77
	Male	87(72.5%)	89 (74.2%)	176(73.3%)	
DM2		40 (33.3%)	46(38.3%)	86(35.8%)	0.42
HTN		59 (49.2%)	66 (55.0%)	125(52%)	0.36
Heart Failure		77(64.2%)	87(72.5%)	164(68.3%)	0.16
MI		76(63.3%)	86 (71.7%)	162 (67.5%)	0.17
CVA		7 (5.8%)	5(4.2%)	12 (5%)	0.55
AF		18 (15%)	14 (11.7%)	32 (13.3%)	0.45
PVD		19 (15.8%)	12(10%)	31 (12.9%)	0.18
Smoking		48(40%)	43(35.8%)	91(37.9%)	0.50
Dyslipidemia		92(76.7%)	90(75%)	182(75.8%)	0.76
NYHA CLASS					
BASELINE	I	00	00	00 (00)	0.12
	II	53 (44.2%)	66 (55%)	119 (49.6%)	
	III	40 (33.3%)	38 (31.7%)	78 (32.5%)	
	IV	27 (22.5%)	16 (13.3%)	43(17.9%)	

Table 2 : Prior treatment received in patients with heart failure in both groups

Drugs used	ACE inhibitors (n-120)	ARNI n-(120)	Total (n-240)	P value
Diuretics	115 (96.3%)	118 (98.3%)	233 (97.1%)	0.25
Beta blocker	107 (89.2%)	104(86.7%)	211 (87.9%)	0.55
MRA	110 (91.2%)	95 (79.2%)	205 (85.4%)	0.006
Digoxin	12 (10%)	9 (7.5%)	21 (8.75%)	0.49
Ivabradine	24(20%)	15(12.5%)	39(16.25%)	0.11
ICD	0	0	0 (0%)	-
CRT	0	0	0 (0%)	-

Cardioverter Defibrillator) and CRT(Cardio resynchronization therapy) were not present in any patient.(Table 2).

Echocardiography-2D echocardiography was done as a baseline and at six months follow-up, where both groups were compared. At baseline LVEF, LVIDD, LVISD, LV mass both in systole and diastole was measured which showed a non-significant comparison data between both groups. In post treatment group same data were reassessed after six months showing that significant increase in LVEF was seen in ARNI group as compared to ACE inhibitors group. (LVEF 32.27±8.14% vs 28.15±8.9%;p<0.05). Reduction in LVIDD and LVISD was significant in ARNI group as compared to ACE inhibitors group.(5.7±0.6cm vs 6.02±0.6cm; p<0.05 and 4.9+_0.7cm vs 5.24+-0.7cm;p<0.05 respectively). A statistically non significant association in post treatment LV systolic and diastolic mass was seen in both groups.(Table 3).

Table 3 : Comparison of 2D echo findings at baseline and at 6 month follow-up in both groups

Parameters	Treatment Groups(Mean (SD))				P Value
	ACE inhibitors		ARNI		
	Baseline	At 6 m	Baseline	At 6 m	
LVEF	23.17 (5.5)	28.15 (8.9)	25.55 (5.5)	32.27 (8.14)	<0.001
LVIDD	6.14 (0.6)	6.02 (0.6)	5.9 (0.5)	5.7 (0.6)	<0.001
LVISD	5.3 (0.6)	5.24 (0.7)	5.2 (0.6)	4.9 (0.7)	<0.001
LV Systole mass (gram)	217.5 (46.3)	210.26 (47.8)	209.5 (42.7)	200.88 (42.18)	0.11
LV Diastole mass (gram)	237.13 (48.5)	229.17 (49.9)	230.75 (45)	218.65 (45.4)	0.09

There was no statistically significant difference noted in the baseline 2D echo parameters in both groups.

Six minute walk test-For functional class assessment, a baseline six minute walk test was performed in both ARNI and ACE inhibitor group, which showed (206.8±81.9 meters in ARNI vs 189.5±88.2 meters in ACE inhibitor group) which was statistically non significant. Similarly it was reassessed six months post treatment, which showed a significant improvement in ARNI group as compared to ACE inhibitors group. (303.3±90.2 meters vs 226±87.2metres) (Table 4)

Table 4 : Comparison of 6 minute walk test at baseline and at 6 month follow-up in both groups

Parameters	Treatment Groups(Mean (SD))				P Value
	ACE inhibitors		ARNI		
	Baseline	At 6 m	Baseline	At 6 m	
6 min walk distance (metres)	189.5 (88.2)	226 (87.2)	206.8 (81.9)	303.3 (90.2)	<0.001

Clinical and investigational parameters : In both pre and post treatment groups ofACE and ARNI, similar features were seen regarding baseline blood pressure and its reduction, variation in serum creatinine/urea and potassium were statistically non significant in both groups. (Table 5). Post treatment improvement in NYHA class in ACE inhibitors and ARNI group was statistically significant suggestive that NYHA class was more improved in ARNI group as compared to ACE inhibitors.Bar graph 1 shows the comparative data of change in NYHA Class in pre and post treatment groups in ACE inhibitors compared to ARNI group.

Table 5 : Pre and post treatment comparison of clinical and biochemical parameters in both group

Parameters	Treatment Groups(Mean (SD))				P Value
	ACE inhibitors		ARNI		
	Baseline	At 6 m	Baseline	At 6 m	
SBP	121.7 (13.2)	119.44 (10.3)	126.8 (18.1)	121.29 (11.5)	0.191
DBP	80.19 (8)	78.33 (4.9)	81.1 (8.2)	79.14 (4.6)	0.188
Creatinine	1.09 (0.23)	1.09 (0.22)	1.09 (0.14)	1.09 (0.14)	1.000
Urea	31.17 (6.4)	35.2 (11.45)	30.92 (5.8)	32.8 (7.2)	0.053
Potassium	4.35 (0.3)	4.44 (0.24)	4.36 (0.2)	4.42 (0.21)	0.493

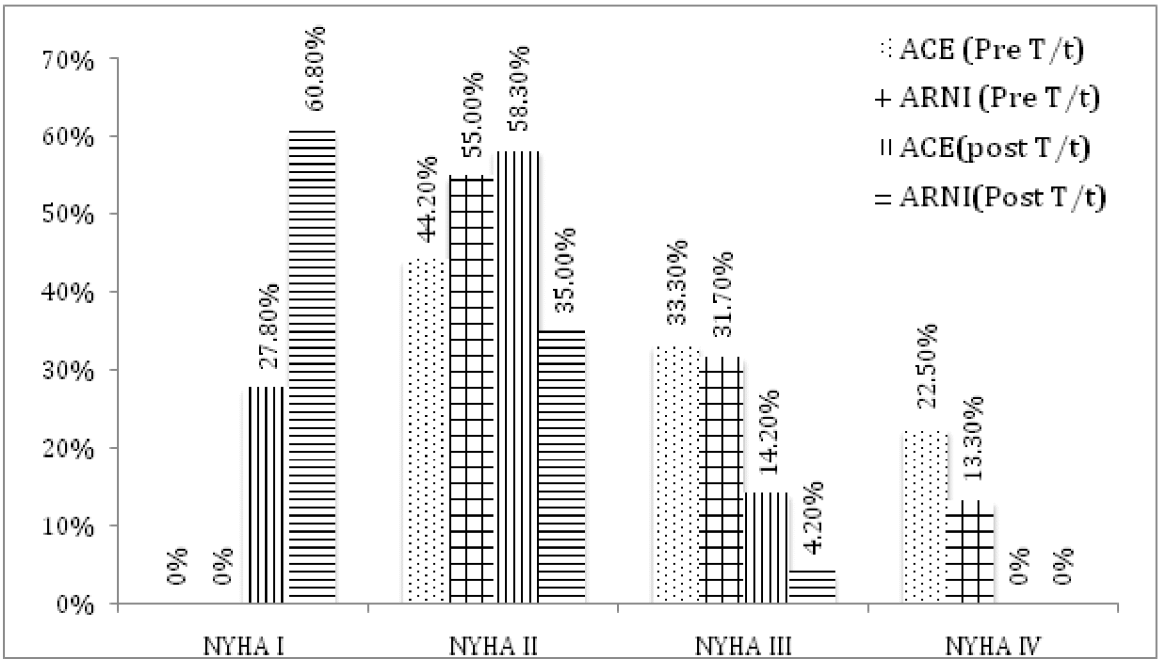

Fig. 1 : Comparative data of change in NYHA Class in pre and post treatment groups in ACE inhibitors compared to ARNI group

Discussion

There have been very few studies assessing the effects of ARNI on cardiac function and myocardial reverse remodeling with echocardiography. The present study analyse the comparative study of ACE inhibitors and ARNI on echocardiographic and clinical parameters of HErEF patients who were previously treated with conventional pharmacological therapy including beta blocker, MRA, diuretics.The mean age in the Trivendrum heart failure registry (THFR), Medanta Registry, INTER-CHF (Indian subset), ADHERE Registry of the USA study was 61.2, 59.1, 56 and 72.4 years respectively[7,8,9,10]. In present study the mean age of heart failure patients was 61±12.6 years.

In present study, 176(73.3%) patients were male and 64 (26.7%) were female.This may suggest that male population seek more health care as compared to female in India. In Trivendrum heart failure registry and Medanta registry male to female ratio was 70:30 and 83:17 respectively.

Ischemic heart disease is the most common etiology of HFrEF both in the USA and India (as per the THFR and Medanta Registry). In our study co-morbidity in the form of prior Myocardial infarction was found in 162(67.5%) patients.

Rodil Fraile et aldemonstrated that ARNIcan relieve symptoms and improve functional NYHA class in HFrEF and advanced HF patients (NYHA III/IV at baseline)[11,12,13]. In present study also a significant improvement in the NYHA class was recorded onsix month follow-up.In this study in comparison to ACE inhibitors, patients treated with ARNIshowed a statistically significant improvement of symptoms at follow-up in terms of lower NYHA class in ARNI group and increased six minute walk distance in ARNI group as compared to ACE inhibitors.

Studies by Geoffrey Bayard et al[14] and Tahir Saleem Bhat et al[15] withHFrEFtreated with ARNI had shown significant improvement in echo parameters. A prospective study by Simone Mazzetti et al showed improving trend in ejection fraction in the patient treated with ARNI[16]. Similarly in the present study a significant increase in LVEF was seen in ARNI group as compared to ACE inhibitors group. (LVEF 32.27±8.14% vs 28.15±8.9%; $p<0.05$). Reduction in LVIDD was significant in ARNI group as compared to ACE inhibitors group (5.9±0.5 to 5.7±0.6cm in ARNI vs 6.14±0.6 to 6.02±0.6cm in ACE inhibitors; $p<0.05$).The non improvement of other echo parameters in six month duration might be due to prolong latency in their reverse modeling.

ARNI has been demonstrated to improved cardiac function by reducing myocardial fibrosis, prevent cardiac rupture after myocardial infarction (MI) by inhibiting the inflammation and the degradation response of macrophages, and improved survival and LV volumes after MI if compared to enalapriland other ACE inhibitors.[17] The ARNI reverse remodeling properties can involve the regulation of proteins expression that contribute to hypertrophy, cardiomyocyte cell death and LV extra- cellular matrix composition, probably causing improvement in LV sizes and ejection fraction. As per Iborra-Egea and colleagues valsartan can reverse the cardiac remodeling by inhibiting guanine nucleotide-binding protein while sacubitril attenuated cardiomyocyte cell death by inhibiting phosphatase and tensin homolog(PTEN)[18]

The Maria Vencenzo Politoet al, supported the safety of ARNI in terms of renal function in HFrEF patients[19]. In the present study, deranged renal function was seen in 4(3.3%) patients in ARNI group while 9 (7.5%) in ACE inhibitors group but overall there was no significant difference was found between pre and post treatment renal function.

Limitation

The small sample size, open label study and the single-center study design may affect the generalizability of our results.Also the follow up period was of 6 month only.

Conclusion

This study showed significant reverse remodeling properties of ARNI with an improvement of LVEF, systolic function, LVIDD, six minute walk, and functional NYHA class as compared to ACEI. Adverse effects and complications associated with ARNI were lower in number as compared to ACE inhibitors. Large Randomized controlled trials are needed to better understand ARNI effects on myocardial function, reverse remodeling and their clinical implications.

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