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Internal Medicine Section

Efficacy and Safety of Angiotensin Receptor Neprilysin Inhibitor versus Angiotensin Converting Enzyme Inhibitor in Heart Failure with Reduced Ejection Fraction- A Prospective Observational Study from a Major Tertiary Care Hospital, Assam, India

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ABSTRACT

Introduction: Angiotensin Receptor Neprilysin Inhibitor (ARNI) has shown to reduce morbidity and mortality in comparison to Angiotensin Converting Enzyme Inhibitors (ACEI) inpatients of Heart Failure with Reduced Ejection Fraction (HFrEF). However, the use of ARNI in real-world practice is limited and has not been studied in North Eastern Indian population

Aim: To compare the efficacy and safety of ARNI with ACEI in the management of symptomatic chronic HFrEF in North Eastern Indian population.

Materials and Methods: The prospective observational study was conducted in the Department of Cardiology at Gauhati Medical College, Guwahati, Assam, India, from April 2019 to October 2020. The study included patients with diagnosis of chronic HFrEF <40%, on ACEI therapy and who had atleast one hospitalisation for Acute Decompensated Heart Failure (ADHF) in the last 6 months. A total of 63 patients were included in this study. Three patients were lost on follow-up. Out of the 60 patients who were included in the final analysis, 30 patients each were included in two groups i.e, ARNI group and ACEI group. As perdiscretion of the treating physician, the patients were started on ARNI 50 mg twice daily which consist of Sacubitril/Valsartan (24/26 mg), along with other anti-heart failure medications, and they were compared with the patients who continued on ACEI. Uptitration was considered with the aim to double the dose till the target dose was achieved at every 2-4 weeks at the treating physician's discretion The endpoints included the rate of repeat HF hospitalisation, mortality, renal outcomes and quality of life. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS, IBM) software version 20.0.

Results: The demographics and clinical characteristics were comparable between the groups. The dose of ARNI was up-titrated to a maximum of 100 mg twice daily in 11 patients. ARNI significantly reduced HF hospitalisation (36.7% vs. 66.7%; p-value=0.039) and mortality (10% vs. 20%, p-value=0.038) compared to patients with ACEI. There was a significant improvement in the KCCQ score in the ARNI group as compared to the ACEI group (p-value=0.001). Treatment with ARNI was also associated with a significant improvement in the New York Heart Association (NYHA) functional class, serum creatinine, and estimated Glomerular Filtration Rate (eGFR) and a significant reduction in N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) level.

Conclusion: In patients with symptomatic HFrEF, shifting to ARNI from background therapy on ACE inhibitors in comparison with continuation of ACE inhibitors appeared to be safe and superior in reducing the risk of death and of hospitalisation, when initiated on outpatient basis. ARNI could not be uptitrated in two-third of patients, yet substantial benefits are evident even at low doses in comparison to ACE inhibitor ramipril.

Keywords: Health related quality of life, Mortality, Ramipril, Risk of death, Sacubitril/valsartan

INTRODUCTION

Heart Failure (HF) has emerged as a global pandemic with 26 million people affected and an estimated health expenditure of United States $31 billion worldwide [1]. Epidemiological data from United States suggest that 5.7 million individuals have HF and estimated prevalence will increase by 25% from current estimates by 2030 [2]. The scarcity of clinical and demographic data on HF is a major limitation in India. The major HF registries from India shows that HF patients in India are younger by 10 years, and the majority of the burden lies below 65 years of age, as compared to the patients from high-income countries [3-5].

The management of Heart Failure with reduced Ejection Fraction (HFrEF) has been revolutionised by the introduction of ARNI consisting of sacubitril-valsartan which has proven to effectively reduce the risk of death from cardiovascular causes or repeat hospitalisations for heart failure. The effect of ARNI was evaluated in Paradigm-HF trial which suggested a 20% relative reduction in primary end point of cardiovascular death or heart HF hospitalisation [6]. These findings provided a strong support for preferential use of Angiotensin Receptor Neprilysin Inhibitor (ARNI) in treatment of chronic HF. The recent American College of Cardiology/American Heart Association classification now include a class I recommendation for replacing Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Blocker (ARB) therapy in patients with chronic symptomatic HFrEF {New York Heart Association (NYHA II or III)} to further reduce morbidity or mortality [7]. In relation to Indian context the improvement observed with of ARNI over and above ACEI in HF with reduced ejection fraction was evident in the sub-study analysis from Paradigm-HF trial among 637 patients of Indian origin. The analysis showed that the primary outcome, Cardiovacular (CV)

death, and the first hospitalisation for HF and all-cause mortality were comparatively lower in the ARNI group than enalapril group and no significant difference was observed between the benefits of treatment in Indian and the total Paradigm-HF cohort [8]. Another study from India showed that ARNI reduces cardiovascular mortality, heart failure associated hospitalisation, and all-cause mortality in patients with heart failure and reduced ejection fraction, also found improvement in overall Health-Related Quality of Life (HRQL) in surviving patients [9].

There is no available registry data on heart failure in North Eastern India. In accordance with the evidence from above-mentioned studies and no such previous studies being conducted in the North Eastern part of the country. This single-centre prospective observational study was undertaken for assessing the clinical efficacy and safety of shifting to ARNI from background therapy on ACE inhibitors, in comparison with continuation of ACEI in the management of symptomatic chronic HFrEF on an outpatient basis.

MATERIALS AND METHODS

The single-centre, open-label, prospective observational study was conducted in the Department of Cardiology at Gauhati Medical College, Guwahati, Assam, India, from April 2019 to October 2020. All patients with diagnosis of chronic heart failure on background ACEI therapy were included after fulfilling study inclusion criteria and after obtaining informed consent. Total enumeration technique was adapted for sampling. Prior ethical clearance was taken from the Institutional Ethics Committee (MC/190/2007/Pt-11/Mar-2019/20).

Inclusion criteria:

- Age of atleast 18 years.
- Patient with history of atleast one hospitalisation with heart failure with reduced ejection fraction (HFrEF) in last six month.
- New York Heart Association (NYHA) class II, III, or IV and an ejection fraction of 40% or less.
- N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) level ≥ 600 pg/mL

Exclusion criteria:

- Symptomatic hypotension, a blood pressure of less than 100 mmHg.
- Chronic kidney disease with eGFR below 30 mL/min/1.73 m^2 of body surface area.
- Patient with confirmed pregnancy.
- History of angioedema or unacceptable side effects during receipt of ACE inhibitors.
- Patients without follow-up data.

A total of 63 patients with heart failure and low ejection fraction were included in this study. Three patients were lost on follow-up before 3 months, two in ARNI group and one in ACEI group and hence, not included in the final analysis. Out of the 60 patients who were included in final analysis, 30 patients each were included in ARNI and ACEI groups.

Study Procedure

As per thetreating physician's discretion, the patients were started on ARNI 50 mg which consisted of sacubitril/valsartan (24/ 26 mg) twice daily, along with other anti-heart failure medications. These patients were compared with those who continued on ACEI. Though uptitration was at the treating physician's discretion however attempt was made to double the dose till the target dose was achieved every 2-4 weeks. The other group continued on ramipril, with aim of dose Uptitration to 10 mg once daily or dose reduction akin to ARNI group. In the ARNI group, patients already on treatment with ACEI, were switched on to ARNI after a wash-out period of 36 hours. Concomitant HF therapies were optimised along with the initiation and uptitration of sacubitril/valsartan. Down-titration or temporary discontinuation of study medication was also done as per the discretion of the physician.

Detailed history, physical examination, and necessary investigations were done in all patients. The data on past medical history, clinical presentations, vital parameters, clinical examinations, baseline investigations, and coronary angiography, NYHA functional class and Kansas City Cardiomyopathy Questionnaire (KCCQ) [10] were collected. Echocardiography was done using Siemens Acuson CV70 to evaluate left ventricular function and regional wall motion abnormality.

Follow-up data were obtained at baseline, 1 month, 3 months and 6 months, for efficacy outcome parameters (Hospitalisation, NYHA functional class, Left Ventricular Ejection Fraction (LVEF), serum NT-proBNP levels, mortality) and key adverse drug effects (blood pressure, serum creatinine, and serum potassium). Those who developed adverse effects (hypotension, raised serum creatinine, or hyperkalaemia) were managed by reducing diuretics dose, stopping Mineralocorticoid Receptor Antagonist (MRA), or reducing ARNI doses.

STATISTICAL ANALYSIS

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS, IBM) software version 20.0. The qualitative data were expressed as number and proportions while the quantitative data were expressed as mean and standard deviation. Categorical and continuous variables were compared with the Chi-square test and Independent sample t-test, respectively. A p-value <0.05 was considered as statistically significant.

RESULTS

The demographics and clinical characteristics were comparable between the groups. The mean age of the patients was 50.4±10.5 years in ARNI group and 49.4±10.5 years in ACEI group. The proportion of male was higher among both the groups. The mean systolic blood pressure was 114.3 mmHg in ARNI group and 113.7 mmHg in ACEI group. The heart rate was slightly higher in ARNI group than ACEI (80.1 vs 78.4; p-value=0.367). The mean left ventricular ejection fraction, serum creatinine levels, NT-proBNP levels were comparable between both the groups. Hypertension (43.3% vs 40%), smoking (36.7% vs. 40%), and dyslipidemia (30% vs 36.7%) were the most common aetiologies observed in both the groups. Majority of patients from both the groups presented with class II NYHA functional class and had a aetiological diagnosis of dilated cardiomyopathy [Table/Fig-1].

Parameters	ARNI (n,%)	ACEI (n,%)	p-value
Age (years), (Mean±SD)	50.4±10.5	49.4±10.2	0.897
Sex			
Male	23 (76.6)	22 (73.3)	0.770
Female	7 (23.3)	8 (26.7)	0.770
Systolic blood pressure (mmHg) (Mean±SD)	114.3±5.6	113.7±4.7	0.656
Heart rate (beats/min), (Mean±SD)	80.1±8.1	78.4±6.5	0.367
Clinical features of heart failure			
Ischaemic cardiomyopathy	6 (20%)	6 (20%)	1
Dilated cardiomyopathy	24 (80%)	24 (80%)	
Left ventricular ejection fraction (Mean±SD)	27.0±0.0	27.0±0.0	0.908
Serum creatinine (mg/dL), (Mean±SD)	1.1±0.2	1.1±0.2	0.803
NT-proBNP Levels (Mean±SD)	1519±661.6	1529±658.7	0.953
Medical history			
Hypertension	13 (43.3%)	12 (40%)	0.798
Smoking	11 (36.7%)	12 (40%)	0.688
Dyslipidemia	9 (30%)	11 (36.7%)	0.702
Diabetes	7 (23.3%)	7 (23.3%)	1
Atrial fibrillation	4 (13.3%)	5 (16.6%)	0.902

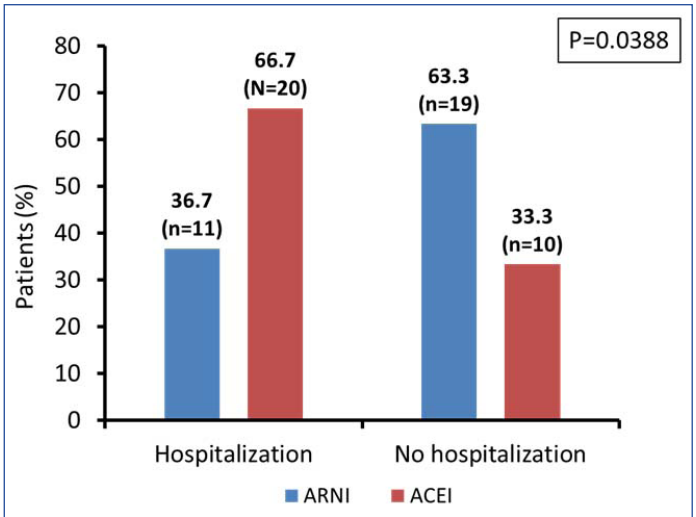
Myocardial infarction	3 (10%)	4 (13.3%)	0.694
Stroke	1 (3.3%)	1 (3.3%)	1
NYHA functional class			
II	20 (66.6%)	22 (73.3%)	0.638
III	9 (30%)	7 (23.3%)	
IV	1 (3.3%)	1 (3.3%)	
Treatments			
Diuretic	30 (100%)	30 (100%)	1
Mineralocorticoid antagonist	27 (90%)	28 (93.3%)	0.647
Beta-blocker	26 (86.7%)	27 (90%)	0.694
Ivabradine	6 (20%)	6 (20%)	1
Digitalis	4 (13.3%)	4 (13.3%)	1

[Table/Fig-1]: Baseline charecteristics in ARNI group (n=30) and ACEI group (n=30). Data shown as n (%), unless otherwise specified; p-value <0.05 was considered as statistically significant

Follow-up: At the end of 6 months, out of 30 patients, 27 patients completed follow-up and three patients died in the ARNI group. The dose of ARNI was up titrated to a maximum of 100 mg (sacubitril 49 mg/valsartan 51 mg) twice daily in 11 patients. Out of the remaining patient uptitration was attempted in 12 patients but because of low blood pressure in 10 patients and hyperkalaemia in two patients, on follow-up were advised to continue on 50 mg (sacubitril 24 mg/valsartan 26 mg) twice daily dosage of ARNI and the remaining 4 patients were continued on sacubitril 24 mg/valsartan 26 mg dosage during the study period. No patients in the ARNI group could be titrated to maximum recommended dose of 200 mg (sacubitril 97 mg/valsartan 103 mg) twice daily.

Similarly, at the end of 6 months, out of a total of 30 patients, 24 patients completed follow-up and six patients died in the group on ACE Inhibitors. The dose of ACE-Inhibitors was uptitrated to a maximum of 10 mg per day in 16 patients and a maximum of 5 mg per day in six patients. The remaining two patients were advised to consume dose of 2.5 mg/day throughout the study period.

Comparison of efficacy outcomes between ARNI and ACEI: The rate of hospitalisation was significantly higher in ACEI compared to ARNI group (66.7% vs 36.7%; p-value=0.039) which indicates that ARNI significantly reduces heart failure hospitalisation over ACEI in patients with heart failure and reduced ejection fraction [Table/Fig-2]. The mortality rate was two-fold increase in ACEI group compared to the ARNI group (20% vs 10%; p-value=0.038).

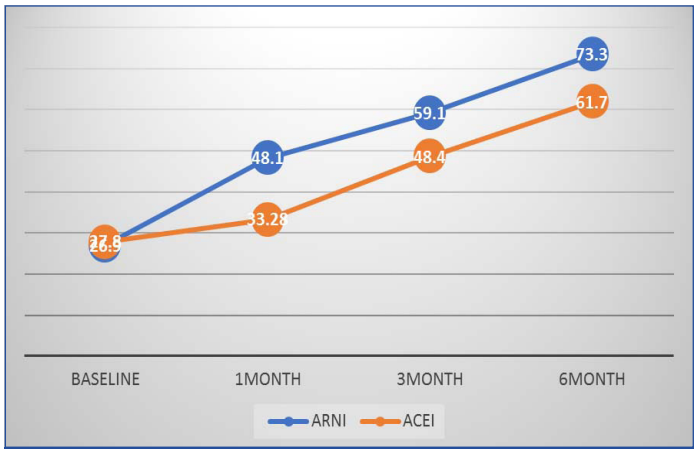


[Table/Fig-2]: Heart failure hospitalisations in ARNI and ACEI groups.

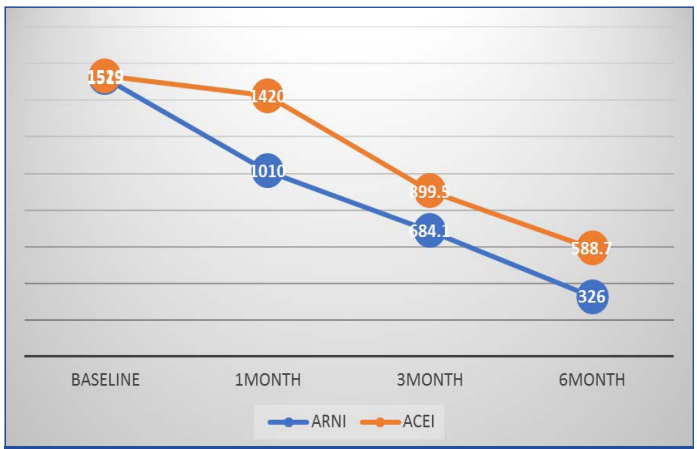
There was a significant improvement in the HRQOL as assessed by KCCQ overall score in the ARNI group as compared to the group treated with ACEI at 6 months. Similarly, mean NYHA class was significantly decreased in ARNI group compared to ACEI group at 6 months follow-up. At baseline, NT-proBNP level was comparable between both the groups. However, ARNI group showed significantly reduced level of NT-proBNP compared to ACEI group at 6 months follow-up. The mean serum creatinine was significantly reduced in ARNI group compared to ACEI. The level of eGFR was comparable between both the groups at baseline, but there was significant improvement in patient on ARNI compared to ACEI at 6 months follow-up [Table/Fig-3]. Significant improvement in health-related quality of life (as assessed using KCCQ score) and significant reduction in NT-proBNP was observed as early as 1 month after switching to ARNI, which was maintained till the end of study [Table/Fig-4,5].

Parameters	At baseline			At 6 months		
	ARNI group (Mean±SD)	ACEI group (Mean±SD)	p-value	ARNI group (Mean±SD)	ACEI group (Mean±SD)	p-value
KCCQ score	26.9±6.1	27.8±5.9)	0.679	73.3 (5.8)	61.7 (4.7)	**0.001**
Ejection fraction (%)	27.0±5.5	27.2±5.0)	0.904	29.1 (5.2)	28.3 (4.2)	0.584
NYHA class	2.3±0.5	2.2±0.5)	0.638	1.4 (0.5)	1.7 (0.4)	**0.048**
NT-proBNP levels (pg/mL)	1519.6± 661.6	1529.6± 658.7	0.953	326.0 (123.2)	588.7 (148.0)	**0.001**
Serum creatinine (mg/dL)	1.0±0.1	1.0±0.1	0.803	0.9 (0.1)	1.0 (0.0)	**0.014**
eGRR (mL/min/1.73 m^2)	77.8±16.0	74.3±18.7	0.438	90.2 (15.0)	80.1 (18.5)	**0.039**

[Table/Fig-3]: Efficacy and safety outcomes at baseline and after 6 months. eGFR: Estimated glomerular filtration rate; KCCQ: Kansas City Cardiomyopathy Questionnaire; NT-proBNP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; p-value<0.05 was considered as statistically significant



[Table/Fig-4]: Temporal trends in change in KCCQ score.



[Table/Fig-5]: Temporal trends in change in NT-proBNP.

Adverse effects: There incidence of symptomatic hypotensionwas 13.3% in ARNI group, compared to 6.6% in ACEI group. However, the incidence of hyperkalemia was higher in the group treated with ACEI (16.6%) compared to ARNI (6.6%). These side-effects rarely required discontinuation of treatment [Table/Fig-6].

Parameters	ARNI group (n,%)	ACEI group (n,%)	p-value
Cough	-	1 (3)	1
Symptomatic hypotension	4 (13.3)	2 (6.6)	0.73
Hyperkalemia	2 (6.6)	5 (16.6)	0.4

[Table/Fig-6]: Adverse effects.

DISCUSSION

The present study represents the first reported real-world experience from North Eastern India on use of ARNI in HFrEF in comparison to ACE inhibitor ramipril when initiated on outpatient basis. The main observation of this study was significant improvement in the various efficacy outcome variables such as decreased rate of hospitalisation for heart failure, improvement in New York Heart Association (NYHA) class and improvement in overall health related quality of life as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) score on treatment with ARNI when compared to therapy with ACE Inhibitors, with non significant improvement in left ventricular ejection fraction. The overall incidence of adverse events was similar in ARNI and ACEI group and none of the adverse events led to withdrawal of any patient from the study. One of the key observations in this study was that, the authors could up titrate ARNI to a maximum of 100 mg twice daily in one-third and none could be up titrated to 200 mg, however substantial benefits are evident even at low doses in comparison to ACE inhibitor ramipril in the study population.

Paradigm-HF trial has shown ARNI to be effective in reducing the risk of death from cardiovascular causes or hospitalisation for heart failure. It also reduced the risk of death from any cause and improved physical functional capacity related to heart failure [6]. In this sub-analysis of Indian patients of Paradigm-HF, treatment with ARNI was superior to enalapril and safe in reducing the risk of cardiovascular death, heart failure hospitalisation and all-cause mortality and the findings are in concordance with the results of the global trial [8]. In another Indian study, the use of ARNI in outpatients with HFrEF was found to be safe and was associated with a significant clinical improvement, as reflected by improvement in NYHA class, KCCQ score and a significant reduction in the NT-proBNP level [9]. Similar to above studies, this study also observed significant improvement in the various efficacy outcome variables such as decreased rate of hospitalisation for heart failure, improvement in NHYA Class on treatment with ARNI when compared to therapy with ACEI, with non significant improvement in left ventricular ejection fraction.

The overall profile of safety events, the present study revealed hypotension was more in the ARNI group and the incidence of hyperkalemia and cough was noticed more in the ACEI group. Paradigm-HF and India sub-analysis had similar observations in the side effect profile with increased of hypotension observed in ARNI group and increased incidence of hyperkalemia and cough in the enalapril group [6,8]. Whereas, the study conducted by Jariwala P et al., treatment was well tolerated without any major side-effects observed during the follow-up after initiation on outpatient basis for a period of 6 months [9]. All the adverse events reported in the present study were mild to moderate in intensity and subsided with treatment. None of the adverse events led to withdrawal of any patient from the study.

Damman K et al., to evaluated the renal effects of ARNI in patients with HFrEF, compared with enalapril. The ARNI led to a slower rate of decrease in the eGFR and improved cardiovascular outcomes, even in patients with chronic kidney disease, despite causing a modest increase in urinary albumin-to-creatinine ratio [11]. The present study also found improved renal parameters in the ARNI group as compared to ACEI and are in contrast to the findings reported by Jariwala P et al., who noted an insignificant rise in mean creatinine levels on follow-up [9].

In the present study, ARNI was uptitrated to a maximum of 100 mg twice daily in one third and none could be up titrated to 200 mg, however substantial benefits are evident even at low doses in comparison to ACE inhibitor ramipril in the study population. Similar to the current study, Vardeny O et al., observed reduced risk of death and HF hospitalisation even by taking lower ARNI doses, compared to ACE inhibitors [12]. Another meta-analysis observed that the dose of 200 mg BID is possible only in 35% of European patients, with a potential of discontinuation in 12.8% of cases [13]. However, this finding is in contrast to another Indian study where uptitration of ARNI was safely achieved in majority of patients [14]. The underdosing of ARNI was necessitated because off fall blood pressure and intolerance to higher dose in the present study group of patients. This was partly contributed by patient population itself as the current study patients had lower blood pressure even at baseline, compared to other Indian studies [9,14]. However, since uptitration was at the discretion of the treating physician, fear of worsening side-effects on part of treating physician, could also contribute to underdosing. Evidence also suggests considerable underdosing and physician underuse of recommended drugs in real-world conditions. Many studies have demonstrated that majority of patients with HFrEF did not receive target doses of medical therapy at any point during follow-up [15,16].

Although, this study was not powered enough to draw conclusions concerning cardiovascular mortality and heart failure-related rehospitalisation rates, yet these indices give us an understanding that shifting to ARNI from background therapy on ACE inhibitors in comparison with continuation of ACE inhibitors appeared to be safe and superior in reducing the risk of death and of hospitalisation, when initiated on outpatient basis.

Limitation(s)

The present study was limited by small sample size and may not be powered enough to detect differences in clinical outcomes. This was a comparative, observational study from a single institution and the results may be confounded by unmeasured confounders. The maximum follow-up duration was for 6 months and hence, some clinical outcome might change on a longer follow-up. Since, in the study centre most of the patients were on ACEI ramipril, benefit of shifting to ARNI from other ACEI were not included. Multicentric, randomised trials with longer follow-up with a larger sample size and longer follow-up are necessary to fully understand and evaluate the efficacy and safety outcomes of ARNI in comparison to ACEI therapy in symptomatic HFrEF in the study population.

CONCLUSION(S)

This study concluded that in patients with symptomatic HFrEF, shifting to ARNI from background therapy on ACE inhibitors in comparison with continuation of ACEI appeared to be safe and superior in reducing the cardiovascular outcome and improving overall health related quality of life, when initiated on outpatient basis. Angiotensin receptor neprilysin inhibitor could not be uptitrated in two-third of patients, yet substantial benefits are evident even at low doses in comparison to ACE inhibitor ramipril.

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