



## Research Brief

# A clinical experience of Indian patients with heart failure with reduced left ventricular ejection fraction using an angiotensin receptor-neprilysin inhibitor [ARNI] on an outpatient basis

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## ABSTRACT

The goal of this study is to portray an initial experience with the efficacy, safety, and, acceptance of ARNI in ambulatory cardiology practices in India. The research is a retrospective review of single-centre data who began therapy with ARNI in HFrEF between 2019 and 2020. The analysis included data for 454 symptomatic patients, aged  $57 \pm 20.8$  years in NYHA class II-III. During follow-up, patients experienced significant improvement in HF symptoms determined by using Kansas City Cardiomyopathy Questionnaire (KCCQ) and a considerable reduction in NT-proBNP levels. ARNI is associated with substantial clinical benefit in an outpatient setting in HFrEF.

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## 1. Introduction

Sacubitril/valsartan is the first agent in a unique class of drugs called ARNI. The PARADIGM-HF analysis, included patients of HFrEF, showed superiority in the primary endpoint of sacubitril/valsartan over enalapril. The study demonstrated a 20% reduction in risk of cardiovascular death, a 21% reduction in the risk of HF hospitalization, and a 16% reduction in the risk of all-cause mortality.<sup>1</sup>

Sacubitril/valsartan was included in the HFrEF recommendations of the European Society of Cardiology and American College of Cardiology/American Heart Association in 2016 (Class IB) and approved as a substitute for ACEI in ambulatory care patients who

remain symptomatic following optimal therapy and who meet PARADIGM-HF requirements to further minimize the risk of hospitalization or death.<sup>1</sup> As experience using the ARNI in ambulatory clinical practice is limited, we evaluated the initial experience regarding the efficacy, tolerance, and safety of sacubitril/valsartan on the OPD basis in India.

## 2. Materials and methods

The study group included patients with HFrEF who sought treatment with sacubitril/valsartan between February 2019 and February 2020 and who were followed up for 6-months. The research is a retrospective review of the clinical and laboratory data collected who have prescribed the drug within the stated time and agreed to take part in this study. We collected their data, which included their demography, symptoms using NYHA functional class and Kansas City Cardiomyopathy Questionnaire (KCCQ), past medical history, clinical presentations, vital parameters, clinical examinations, baseline investigations, and coronary angiography. The initial starting dose was 24/26 mg twice daily along with other anti-failure drugs. Patients who had the blood pressure of  $\geq 110/70$  mm Hg were given ARNI. Patients having unstable

*Abbreviations:* ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; ARNI, Angiotensin receptor blockers-neprilysin inhibitors; HFrEF, Heart failure with reduced ejection fraction; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; OPD, Outpatient basis; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

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hemodynamic conditions, elevated serum creatinine, h/o hyperkalaemia and, angioedema was excluded. They were asked for 1st follow-up after 1 week for the OPD visit to see the result of the medical therapy. Those who showed symptomatic improvement advised for 2nd and 3rd follow-up visits after 1-month each and subsequently every 3-months.

### 3. Statistical analysis

The statistical analysis was performed using Windows SPSS software. The data were presented as absolute numbers with percentages in the case of nominal data and means with standard deviation in the case of continuous data. For the comparison of changes within the study group during subsequent visits, the Wilcoxon test for paired samples was used. A p-value < 0.05 was considered statistically significant.

### 4. Results

The analysis included data on 454 patients aged 57 ± 20.8 years, of whom 70.2% were males. The baseline characteristics are presented in Table 1. In 98.2% of patients, sacubitril/valsartan was started at the lowest dose (24/26 mg BID). At consecutive visits after 4–6 weeks, the dose was increased to 49/51 mg BID in patients. Finally, in the follow-up period, the dose was increased to the target dose of 97/103 mg BID only in 26.7% of patients. Detailed

**Table 1**  
Demographics and clinical features of patients prescribed on angiotensin receptor neprilysin inhibitors.

Clinical Parameters	Mean ± SD/percentage
Age (years)	57 ± 20.8
Sex (female)	29.8%
Weight	66 ± 34.6 kg
BMI	31 ± 12.4 kg/m <sup>2</sup>
NYHA class:	
II	53%
III	48%
LVEF	13–43% (28 ± 4)
<b>Symptoms</b>	
Breathlessness	98%
Paroxysmal Nocturnal dyspnea	68%
Orthopnea	32%
Easy fatigability	12%
Chest pain	10%
<b>Types of heart failure</b>	
Left heart failure	75%
Combined left and right heart failure	25%
Recurrent Heart failure	56%
New onset heart Failure	44%
<b>HF etiology</b>	
Ischemic	18%
Non-ischemic	27%
Unknown	55%
<b>Cardiac rhythm</b>	
Sinus rhythm	95%
Atrial fibrillation	3%
Atrial Flutter	2%
<b>Device based therapy</b>	
ICD	11%
CRT-P	5%
CRT-D	2%
No-device	82%

The body-mass index is the weight in kilograms divided by the square of the height in meters. Patient status at the time of randomization is expressed in the data for the New York Heart Association (NYHA) class.  
Body mass index = BMI; New York Heart Association = NYHA; Left ventricular ejection fraction = LVEF; Implantable cardioverter defibrillator = ICD; Cardiac resynchronization therapy pacemaker = CRT-P; Cardiac resynchronization therapy with defibrillator = CRT- D.

data on pharmacological treatment before the initiation of the sacubitril/valsartan presented in Table 2.

During the six-month follow-up, the first follow-up visit was held after a mean of 8 days (7–10 days). 98% of patients came to two follow-up visits and 88% came to three follow-up visits. The second visit was held after a mean of 33 days from treatment initiation (28–38 days), while the third visit was held after a mean of 65 days (58–89 days).

In 97.6% of patients who qualified for the administration of ARNI showed improvement of symptoms on 6 ± 4 days of follow-up. All treated patients had a significant reduction in HF symptoms assessed using the NYHA functional class, with a drop from 2.6 ± 0.5 to 1.1 ± 0.3 [95% Confidence interval (CI), 1.446 to 1.554; p < 0.001], and a significant decrease in the mean NT-proBNP levels from 9813 ± 1850 to 1867 ± 1432 pg/mL [95% CI, 7730.28 to 8161.72; p < 0.001]. We could complete 6-month follow-up in 97.8% of patient and could record echocardiographic data in 78.3% of patients during 6-month follow-up.

### 5. Safety and adverse events

Although symptomatic hypotension was not observed there were insignificant decreases in mean SBP (from 132 ± 24 to 130 ± 10 mmHg; 95% CI, -0.40 to 4.40; p = 0.1016), mean DBP (from 80 ± 10 to 79.7 ± 7 mmHg; 95% CI, -0.826 to 1.426; p = 0.6006), but significant reduction in heart rate (from 114 ± 28.7 to 72 ± 7 bpm; 95% CI, 39.276 to 44.724; p < 0.001) were observed. 11.9% showed insignificant rise in mean creatinine levels (from 0.87 ± 0.21 to 0.9 ± 0.43 mg/dL; 95% CI, -0.0741 to 0.0141; p = 0.18). (Table 3).

In the follow-up, 98.7% of patients with HFrEF, sacubitril/valsartan continued. 1.5% of those who did not show an improvement in their symptoms after 4 weeks had a non-compliance with a drug that was related to the cost of treatment. 0.8% of patients had angioedema and there were no reported incidence of cough as a side effect. No substantial changes in HF therapy were noticed during the follow-up period, except for a half reduction in the dose of furosemide. No patient has been hospitalized or died.

### 6. Discussion

Our experience with sacubitril/valsartan in Indian patients with HFrEF offers useful details on the effective therapy of HF when the medication is started and continued in an outpatient setting. Starting sacubitril/valsartan in the outpatient setting should be associated with necessary patient monitoring during frequent follow-up visits. The patient should be informed about the risk of hypotension and the need for daily BP measurements in the home setting.<sup>2,3,4</sup>

ARNI reduced cardiovascular mortality, heart failure– associated hospitalization, 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, as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ).<sup>5</sup> According to the sacubitril/valsartan Summary of Product Characteristics, treatment should be initiated with the dose of 49/51 mg BID in patients who well-tolerated high doses of ACEI/ARB, with normal renal and hepatic function and SBP > 110 mmHg. Such an approach in the initial period was also suggested by experts from the “Working Group on HF of the Cardiological Society of India”.<sup>6,7</sup> A low dose of sacubitril/valsartan is especially useful for initiation in patients that have not received ACEI/ARB or administered low doses of these drugs, as well as individuals with renal or hepatic dysfunction or low SBP ranging from 100 to 110 mmHg. The decision on further dose management should be followed by an evaluation of renal function and potassium levels.<sup>8–10</sup>

**Table 2**

Baseline treatment using angiotensin converting enzyme inhibitors/angiotensin receptor blockers and other Concomitant pharmacological treatment before the starting on angiotensin receptor neprilysin inhibitors.

Drugs prior to the use of ARNI	No. of Patients (proportion/percentage)
ACEI	68.9%
ARB	31.1%
Loop diuretics	100%
Beta-blockers	93%
Mineralocorticoid receptor antagonist	78%
Ivabradine	64%
Digoxin	49%
Amiodarone	8%

Angiotensin converting enzyme inhibitor = ACEI; Angiotensin receptor blocker = ARB.

**Table 3**

Comparison of vital parameters and laboratory values before starting therapy with angiotensin receptor neprilysin inhibitors and at 1st and 6-month follow-up.

Clinical and laboratory parameters	Baseline value	First follow-up visit value	Confidence Interval (95% Confidence Interval)	p-Value
Systolic BP [mmHg]	132 ± 24	130 ± 10	−0.40 to 4.40	0.1016
Diastolic BP [mmHg]	80 ± 10	79.7 ± 7	−0.826 to 1.426	0.6006
Heart rate [bpm]	114 ± 28.7	72 ± 7	−39.276 to 44.724	<0.001
NT- proBNP [pg/mL]	9813 ± 1850	1867 ± 1432	−7730.28 to 8161.72	<0.001
Creatinine [mg/dL]	0.87 ± 0.21	0.9 ± 0.43	0.0741 to 0.0141	0.18
Potassium [mEq/L]	4.50 ± 0.4	4.55 ± 0.5	−0.1090 to 0.0090	0.0965
		<b>At 6-month follow-up</b>		
NYHA Class	2.6 ± 0.5	1.1 ± 0.3	−1.446 to 1.554	<0.001
KCCQ overall summery score	26.7 ± 12.3	78.7 ± 15.6	−53.832 to −50.168	<0.001
Ejection fraction [%]	13.4–38.9% (32.8 ± 5)	19.1–47.6% (42.9 ± 4)	+10.690 to −9.510	<0.001

Plus–minus values are means ± SD.

mmHg = millimetre of mercury; pg/ml = picogram per millilitre; mg/ml = milligram per millilitre; mg/dl = milligram per decilitre; mEq/L = milliequivalent per litre; NT-proBNP = N-terminal Prohormone Brain natriuretic peptide; BPM = Beats per minute; BP = Blood Pressure; NYHA = New York Heart Association; KCCQ = Kansas City cardiomyopathy questionnaire.

The analysis showed that not all patients had their NT-proBNP levels tested when new treatment eligibility was assessed. In India, it is practically not available in the outpatient setting; therefore, using the BNP level as an eligibility criterion is very difficult.<sup>11,12</sup>

Even though in most patients only the initial sacubitril/valsartan dose of 24/26 mg was used, a significant improvement in the patient's well-being was achieved. Unquestionably, the existing cost of the drug with sacubitril/valsartan in India is high and may preclude a deterrent to its commencement.<sup>13,14</sup>

### 7. Limitations of the study

A retrospective study was performed, and the sample size of the studied group was limited, and patients were not treated according to the defined protocol. Using larger randomized controlled trials in the Indian subset, we emphasize on multicentreclinical experience and stronger follow-up data.

### 8. Conclusions

The use of sacubitril/valsartan in outpatients with HFReF is safe and is associated with a significant clinical improvement, as reflected by improvement in NYHA class, KCCQ score and a significant reduction in the NT-proBNP level. A noticeable clinical improvement in the form of exercise tolerance was achieved soon after treatment initiation.

### Declaration of competing interest

There no competing or conflict of interest.

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