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*Original Article*

# Retrospective real-world study on effectiveness and safety of sacubitril/valsartan in Indian patients with heart failure

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**Abstract:** Objective: This study aimed to evaluate the clinical, biochemical, and functional outcomes of sacubitril/valsartan therapy in Indian patients with heart Failure (HF) with reduced ejection fraction (HFrEF) in routine practice. Methods: We conducted a retrospective, single-centre, observational study at The Heart Clinic, New Delhi, India. Adult patients (≥18 years) with the New York Heart Association (NYHA) class II-IV HF who were newly initiated on sacubitril/valsartan and had ≥12 months of follow-up were included in the study. Clinical, echocardiographic, and biochemical data were extracted from the electronic medical records. The primary outcomes at 12 months were changes in left ventricular ejection fraction (LVEF), NYHA classification, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, estimated glomerular filtration rate (eGFR), and the number of patients receiving the maximum dose of sacubitril/valsartan. The secondary outcomes were cardiovascular and all-cause mortality. Results: A total of 300 patients were analyzed (mean age, 61.3 years; 69.7% male). Hypertension (266 patients, 88.7%), diabetes (163 patients, 54.3%), and chronic kidney disease (153 patients, 51%) were the most frequent comorbidities. At 12 months, the mean LVEF increased significantly from 29.57% to 34.66% (absolute gain of 5.09%, $P<0.0001$). A significant improvement in functional ability was observed, with 282 patients (94%) classified as NYHA class II at 12 months compared with 22 patients (7.3%) at baseline ($P<0.0001$), and the NT-proBNP levels decreased from 2344.5 ± 1951.8 pg/mL to 564 ± 410.3 pg/mL ($P<0.0001$). Renal function remained stable (mean change in eGFR +2.01 mL/min/1.73 $m^2$, $P=0.088$). Over half of the cohort (52.3%) achieved a target dose of 200 mg twice daily. No cardiovascular or all-cause deaths were observed. Conclusion: In this real-world Indian cohort, sacubitril/valsartan was associated with significant improvements in systolic function, functional class, and NT-proBNP levels, with preserved renal function and good tolerability. These findings support the use of sacubitril/valsartan as a cornerstone therapy for HFrEF management in routine clinical practice.

**Keywords:** Heart failure with reduced ejection fraction (HFrEF), real-world practice, sacubitril/valsartan

## Introduction

Heart failure (HF) affects an estimated 64 million individuals globally and is classified as a global epidemic. HF exerts a major burden on patient morbidity and mortality, resulting in reduced functional capabilities and quality of life, as well as high societal and healthcare costs [1]. HF affects approximately 1% of the Indian population and around 2% of the world population, rising to 10% in individuals over the age of 70 [2-4].

According to the National Heart Failure Registry of India, the most prevalent cases were heart failure with reduced ejection fraction (HFrEF) (65%), followed by HF with slightly reduced ejection fraction (HFmrEF) (22%) and HF with preserved ejection fraction (HFpEF) (13%) [5, 6]. The pharmacological treatment of Indian patients with HFrEF has been structured through Guideline-Directed Medical Therapy (GDMT). In India, HFrEF has a poor prognosis, as shown by the Trivandrum Heart Failure Registry, which reported an in-hospital death

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rate of 8.4%, exceeding similar rates in the United States [3]. Furthermore, the International Congestive Heart Failure study found a 37% higher death rate among Indians with HFrEF [7, 8].

Pharmacological management of HFrEF is structured around GDMT, comprising four foundational pillars that target neurohormonal activation: (1) Angiotensin receptor-neprilysin inhibitors (ARNIs) such as sacubitril/valsartan (preferred over angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blockers (ARB)); (2) Evidence-based beta-blockers (carvedilol, bisoprolol, metoprolol succinate); (3) Mineral corticoid receptor antagonists (MRAs) (spironolactone, eplerenone); and (4) Sodium-glucose cotransporter-2 inhibitors (SGLT2i) (dapagliflozin, empagliflozin). Comprehensive GDMT implementation reduces all-cause mortality by 60-73%, cardiovascular mortality by 38-73%, and first heart failure hospitalization by 41-60% compared with no therapy, while improving the New York Heart Association (NYHA) functional class, exercise capacity, and quality of life. The sequential addition of these agents yielded additive benefits, with quadruple therapy conferring the greatest absolute risk reduction. However, Indian registries reveal persistent underutilization of GDMT, contributing to excess mortality and readmissions [9].

According to the most recent European Society of Cardiology (ESC) guidelines for the management of HFrEF, sacubitril/valsartan is one of the four foundational pillars of GDMT. It is recommended as the preferred first-line therapy in place of ACEi/ARB for patients with HFrEF owing to its superior efficacy in reducing morbidity and mortality [9]. In addition, the use of ARNI reduces the risk of mortality and hospitalization in patients with NYHA functional class II to III HF [10]. Recent real-world studies in India have begun to explore the effectiveness of sacubitril/valsartan in routine clinical practices. A multicenter retrospective cohort study protocol was designed to assess the incidence of hypotension and dosing strategies specifically in Indian patients with HFrEF, addressing concerns about optimal dosing without treatment discontinuation. This study enrolled approximately 1,039 patients from approximately 150 healthcare institutions, reflecting the interest in generating Indian-specific, real-world evidence [11]. The advent of sacubitril/valsartan, an ARNI, has transformed the management of heart failure [9]. Its mechanism entails dual action: inhibition of the renin-angiotensin system while concurrently diminishing the degradation of natriuretic peptides, thereby offering enhanced neurohumoral modulation rather than simple inhibition. The Indian sub-analysis of the PARADIGM-HF trial provided initial evidence for the efficacy of sacubitril/valsartan in the Indian population, demonstrating treatment benefits similar to those in the global cohort, despite the distinct patient characteristics [12]. Compared with already established drugs (e.g., enalapril), ARNI use has lowered cardiovascular deaths by 20% and all-cause mortality by 16% [13]. In patients with HFrEF who were hospitalized for acute decompensated HF, the initiation of sacubitril/valsartan treatment led to a greater reduction in the N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels than enalapril therapy [14].

Although sacubitril/valsartan has emerged as an established cornerstone therapy for HFrEF management, supported by robust evidence from pivotal clinical trials, real-world data regarding its utilization, patient characteristics, and resource implications in routine Indian clinical practice remain substantially limited, as do comprehensive assessments of its impact on treatment outcomes in this population [15]. This retrospective real-world study addressing the clinical profile analysis and comprehensive impact assessment of sacubitril/valsartan on functional, biochemical, echocardiographic, and safety parameters represents a critical research priority to bridge existing evidence gaps, optimize treatment strategies, and ultimately improve patient outcomes in Indian heart failure management.

## Methodology

This retrospective, single-centre, observational study was conducted at The Heart Clinic, New Delhi, India. This study evaluated patients with HF who were prescribed sacubitril/valsartan as part of standard clinical practice. Data were extracted from electronic medical records for all eligible patients.

### *Study population*

Inclusion criteria: (1) All adult patients (≥18 years) with HF in NYHA class II-IV who had been

newly initiated on sacubitril/valsartan and followed up for ≥12 months; (2) Patients who have been newly prescribed (sacubitril/valsartan) and followed up at least for a period of one year or death during follow-up; (3) In all cases previous treatment with ARBs and ACEI is to be suspended prior to starting sacubitril/valsartan.

Exclusion criteria: (1) Patients who are/were enrolled in any other trial; (2) Patients who have discontinued ARNI during follow-up; (3) Patients who had incomplete records.

*Data collection*

Eligible patients were retrospectively identified by the investigators and study personnel using hospital medical records. All available clinical data were systematically extracted, including demographic characteristics (age, sex, and comorbidities), clinical parameters (NYHA functional class, vital signs, and symptoms), laboratory biomarkers (NT-proBNP, BNP, serum creatinine, electrolytes, and liver function tests), echocardiographic measurements (LVEF, LV end-diastolic volume, LV end-systolic volume, left atrial volume, and E/e' ratio), medication details (sacubitril/valsartan dose, concomitant GDMT, diuretics), and safety events (hypotension, hyperkalemia, renal dysfunction, and angioedema). Data were entered into a secure web-based electronic case report form (eCRF) database. The index date was defined as the date of the first prescription of sacubitril/valsartan (baseline visit).

(1) First visit (3 months or first available contact): If 3-month data were unavailable, the first measurement of each variable after sacubitril/valsartan initiation, regardless of clinical setting or time from prescription, was recorded. (2) Second visit (4-8 months): All available data for this interval were captured. (3) Study end (9-12 months): The last measurement of each variable before study completion was recorded, regardless of clinical setting or time from initiation.

*Study outcomes*

The primary outcomes at 12 months were as follows: (1) Change in LVEF; (2) Change in NYHA functional class; (3) Change in NT-proBNP; (4) Change in eGFR; (5) Proportion of patients (%) achieving maximum recommended sacubitril/valsartan dose.

Secondary outcomes included: (1) Cardiovascular mortality; (2) All-cause mortality.

*Ethical considerations*

This study was conducted in accordance with the Declaration of Helsinki (2013) and the Indian Council of Medical Research guidelines. This study was approved by the Institutional Ethics Committee of the Heart Clinic, New Delhi (2023). Owing to the retrospective nature of the study, informed consent was obtained from the patients during the baseline data collection stage.

*Statistical analysis*

Continuous variables are presented as mean ± standard deviation (SD) or median interquartile range (IQR), based on distribution normality (assessed via the Shapiro-Wilk test), and categorical variables as frequencies with percentages. Paired comparisons from baseline to follow-up were performed using the paired t-test (normally distributed continuous data), Wilcoxon signed-rank test (non-normally distributed continuous data), or McNemar's test (categorical data). Baseline characteristics are presented as mean ± SD, with 95% confidence interval (CI) calculated where appropriate. The primary endpoint (NT-proBNP) was analyzed using the Wilcoxon signed-rank test. The secondary endpoints included LVEF (paired t-test) and NYHA class improvements (McNemar's test). Statistical significance was set at $P<0.05$. Analyses were conducted using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

## Results

*Baseline and clinical characteristics*

A total of 300 patients with heart failure were included in this study. The majority of patients (65%) were aged >60 years, followed by 32.33% in the 40-60-year age group and only 2.67% in the 18-40-year age group. The mean age of the cohort was 61.3 years. Males constituted a larger proportion of the population (69.67%). The mean height was 166.26 ± 8.13 cm (95% CI: 165.34-167.18), mean weight was 71.65 ± 13.79 kg (95% CI: 70.09-73.21), and mean body mass index (BMI) was 25.92 ± 4.56 kg/m$^2$ (95% CI: 25.4-26.43). The mean resting heart rate was 74.62 ± 11.28 beats/min (95% CI: 73.34-75.9). The average systolic and dia-

stolic blood pressures were 110.39 ± 10.08 mmHg (95% CI: 109.25-111.53 mmHg) and 66.46 ± 8.12 mmHg (95% CI: 65.54-67.38), respectively. The mean duration of heart failure was 17.28 ± 4.1 months (95% CI: 16.81-17.74).

Concomitant medical conditions were common in the study population. Hypertension (HTN) was the most prevalent comorbidity reported in 88.67% of the patients, followed by coronary artery disease (CAD) (72%), diabetes mellitus (DM) (54.33%), and chronic kidney disease (CKD) (51%). Dyslipidemia was present in 5% of patients and other conditions (asthma and hypothyroidism etc.) were reported in 10.67% of total population. Other multidrug class combinations accounted for 42% of the prescriptions. Endocrine and metabolic drugs were used in 80% of patients, with 31.33% receiving one drug, 13.66% receiving a combination of two, and 35% of patients received ≥3 drugs. Gastrointestinal medications were prescribed to 53.65% of patients, most commonly as two-drug regimens (35.66%). Respiratory drugs were used by 34.67% of patients, nutritional and supplementary agents by 28.67%, hematologic and rheumatologic drugs by 24%, and central nervous system drugs by 15.67%. Pain and anti-inflammatory drugs were prescribed in a smaller proportion (3.67%), as shown in **Table 1**.

A total of 68 patients (22.67%) received a single GDMT agent, while 134 patients (44.67%) were prescribed a combination of two GDMT agents. Triple GDMT therapy was administered to 88 patients (29.33%), whereas 10 patients (3.33%) did not receive any GDMT. The distribution of GDMT therapy among the study population is shown in **Figure 1**.

At baseline, the distribution of CKD stages according to eGFR revealed that 28.33% patients were categorized as stage 3a (eGFR 45-59 mL/min/1.73 $m^2$), while 21.67% were in stage 3b (eGFR 30-44 mL/min/1.73 $m^2$), and only 1% were categorized as stage 4 (eGFR 15-29 mL/min/1.73 $m^2$) as shown in **Figure 2**.

*The primary study outcomes were reported at 12 months*

Among 300 patients with paired measurements, the mean LVEF at baseline was 29.66 ± 5.53% (95% CI: 29.03-30.29). The mean LVEF significantly increased to 34.58 ± 5.36% (95% CI: 33.97-35.18) at the 12-month follow-up visit. The mean absolute improvement in LVEF compared with baseline was 4.92 ± 4.16% (95% CI: 4.45-5.39), which was statistically significant (P<0.0001) (**Table 2**).

A significant improvement in functional ability was observed at the 12-month follow-up. At baseline, the majority of patients were classified as NYHA Class III (278 patients; 92.67%), while only 22 patients (7.33%) were categorized as Class II. At the end of the follow-up (Visit 4) at 12 months, 282 patients (94%) had progressed to NYHA Class II, whereas only 18 patients (6%) remained in Class III. The transition in functional status from baseline to 12 months was statistically significant (*P*<0.0001) (**Table 3**).

NT-proBNP levels significantly declined over the study period. At baseline, the mean NT-proBNP concentration was 2344.5 ± 1951.85 pg/mL (95% CI: 326.65-6009.85). After 12 months of follow-up (Visit 4), the levels decreased to 564 ± 410.32 pg/mL (95% CI: 130.43-1686.55). The mean absolute reduction from baseline was -1534 ± 1886.43 pg/mL (95% CI: -5194.5 to 442.02), which was statistically significant (*P*<0.0001, Wilcoxon signed-rank test) (**Table 4**).

Renal function, as evaluated by eGFR, was consistent during the 12-month follow-up period. At baseline, the average eGFR was 66.13 ± 26.2 mL/min/1.73 $m^2$ (95% CI: 63.17-69.1). At 12 months, the average eGFR was 68.14 ± 28.6 mL/min/1.73 $m^2$ (95% CI: 64.91-71.38). The average absolute change from baseline was +2.01 ± 20.33 mL/min/1.73 $m^2$ (95% CI: -0.29 to 4.31), which was not statistically significant (P=0.0884). The results indicated that sacubitril/valsartan did not negatively impact renal function over the follow-up period. At the final follow-up (Visit 4), 157 of the 300 patients (52.33%) successfully attained the target maximum dose of sacubitril/valsartan (200 mg twice daily) (**Table 5**).

*Secondary outcomes reported at 12 months*

No deaths due to cardiovascular or any other causes were reported during the study period.

**Table 1.** Baseline levels and clinical characteristics of the enrolled patients

| Parameters | | | Total (N=300) |
|---|---|---|---|
| Age (years)# | 18-40 | | 8 (2.67%) |
| | 40-60 | | 97 (32.33%) |
| | >60 | | 195 (65%) |
| Gender# | Male | | 209 (69.67%) |
| | Female | | 91 (30.33%) |
| Height (cm)* | | | 166.26 ± 8.13 (165.34 to 167.18) |
| Weight (kg)* | | | 71.65 ± 13.79 (70.09 to 73.21) |
| Body Mass Index (kg/m$^2$)* | | | 25.92 ± 4.56 (25.4 to 26.43) |
| Heart Rate (beats/min)* | | | 74.62 ± 11.28 (73.34 to 75.9) |
| Blood Pressure (mmHg)* | Systolic BP | | 110.39 ± 10.08 (109.25 to 111.53) |
| | Diastolic BP | | 66.46 ± 8.12 (65.54 to 67.38) |
| Heart Failure Duration (months)* | | | 17.28 ± 4.1 (16.81 to 17.74) |
| Previous hospitalization for Heart Failure before starting the therapy (in last 1 year)# (n=300) | Yes | 2 times | 11 (3.67 %) |
| | | 3 times | 24 (8 %) |
| | | 4 times | 8 (2.67 %) |
| | No | | 257 (86%) |
| Concomitant medical history and medications# (n=300) | HTN | | 266 (88.67%) |
| | CAD | | 216 (72.00%) |
| | DM | | 163 (54.33%) |
| | CKD | | 153 (51.00%) |
| | Dyslipidemia | | 15 (5%) |
| | Other conditions (Asthma, Hypothyroidism, etc.) | | 32 (10.67%) |
| | GDMT Distribution | No GDMT | 10 (3.33%) |
| | | Single GDMT | 68 (22.67%) |
| | | Double GDMT | 134 (44.67%) |
| | | Triple GDMT | 88 (29.33%) |
| | Endocrine and Metabolic Drugs | 1 drug | 94 (31.33%) |
| | | 2 drugs | 41 (13.66%) |
| | | ≥3 drugs | 105 (35%) |
| | Gastrointestinal Drugs | 1 drug | 40 (13.33%) |
| | | 2 drugs | 107 (35.66%) |
| | | ≥3 drugs | 14 (4.66%) |
| | Respiratory Drugs | | 104 (34.67%) |
| | Nutritional and Supplementary Agents | | 86 (28.67%) |
| | Hematologic and Rheumatologic Drugs | | 72 (24%) |
| | CNS Drugs | | 47 (15.67%) |
| | Pain and Inflammatory Drugs | | 11 (3.67%) |

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CNS, central nervous system; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; HTN, hypertension; MRA, mineral corticoid receptor antagonist; n, number of patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SD, standard deviation. *Data presented as mean ± SD (95% CI); #Data presented as n (%).

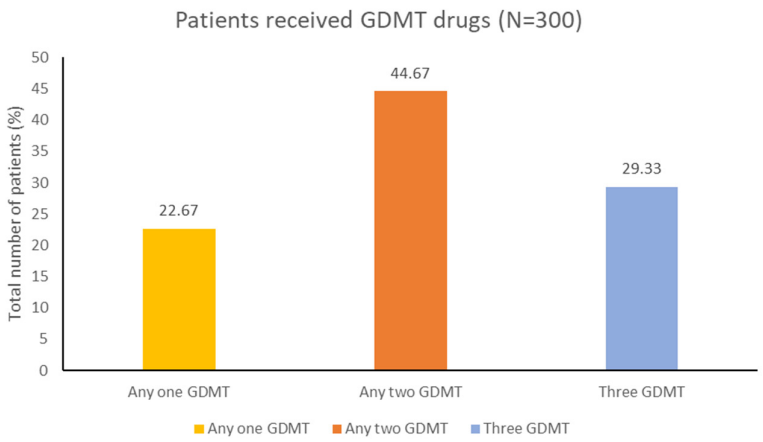


**Figure 1.** Distribution of GDMT therapy in patients with HF. GDMT, Guideline-directed medical therapy; HF, heart failure.

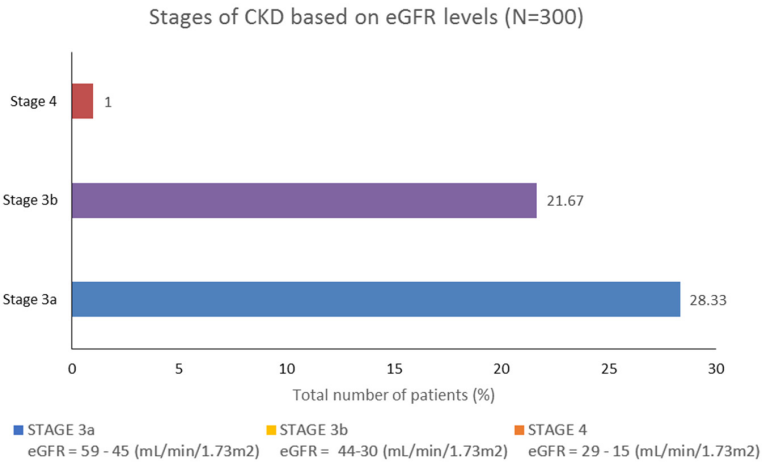


**Figure 2.** Distribution of CKD stages based on eGFR levels. CKD, chronic kidney disease; eGFR, glomerular filtration rate.

## Discussion

In this single-center, retrospective real-world cohort study of 300 Indian patients with HFrEF, treatment with sacubitril/valsartan was associated with consistent improvements in objective and patient-centered measures of disease severity over 12 months. The mean age and male predominance were comparable to those of landmark trials, such as PARADIGM-HF (median age 63 years; 78% male). Notably, our patients had a very high burden of cardiometabolic comorbidities: Hypertension (266 patients, 88.7%), diabetes (163 patients, 54.3%), and chronic kidney disease (153 patients, 51%). These prevalences exceed those often seen in Western trials (PARADIGM-HF reported 40% HTN, 30% DM, and 23% with significant renal impairment) [12]. Our study findings were also consistent with the SAVE study, which was conducted in Indian patients with HF, where out of 60 patients, 57% were males, and 60% of the total study population reported with type 2 diabetes and hypertension [15]. A cross-sectional study conducted in an Indian clinical setting reported comparable findings, with 163 clinical experts sharing their perspectives on heart failure patients; among them, 41% identified DM as the most prevalent comorbidity [16]. Compared with Western trials, the greater multimorbidity observed in our cohort likely reflects the epidemiological transition, delayed presentation, and higher baseline cardiovascular risk in the Indian population. This high-risk substrate is critical for interpreting both therapeutic responses and dose tolerance.

Among 300 patients, 68 patients (22.67%) received single GDMT therapy, 134 patients (44.67%) received double GDMT therapy, 88 patients (29.33%) received triple GDMT therapy, and 10 patients (3.33%) did not receive GDMT. This pattern mirrors other registries noting the underuse of all GDMT components, despite guideline recommendations. Real-world registries, such as CHAMP-HF, have similarly documented incomplete uptake and sub-target dosing of GDMT in routine practice, highlighting the gap between guideline recommendations and everyday prescriptions [17]. Even within a specialized heart failure clinic, many eligible patients were unable to achieve maximal ARNI dosing because of hypotension or financial constraints [18]. Therefore, our cohort represented a higher-risk, multimorbid Indian HF population, which is an important context when interpreting outcomes such as dose tolerance.

The use of sacubitril/valsartan was associated with improved systolic function, where the

**Table 2.** Positive change in LVEF from baseline to 12-month follow-up including analysis of 300 patients

| Parameter | Data | Change as compared to Baseline | *P* value# |
|---|---|---|---|
| LVEF (%)* (Visit 1) (N=300) | 29.66 ± 5.53 (29.03 to 30.29) | NA | <0.0001 |
| LVEF (%)* (Visit 4) (N=300) | 34.58 ± 5.36 (33.97 to 35.18) | 4.92 ± 4.16 (4.45 to 5.39) | |

Abbreviations: CI, confidence interval; LVEF, left-ventricular ejection fraction; N, number of patients; SD, standard deviation. *Data presented as mean ± SD (95% CI); #P - as compared to baseline (Paired t-test).

**Table 3.** Change in NYHA functional class from baseline to 12-month follow-up (Per Protocol)

| NYHA class | Visit 1* (N=300) | Visit 4* (N=300) | *P*-value# |
|---|---|---|---|
| 2 | 22 (7.33%) | 282 (94.00%) | <0.0001 |
| 3 | 278 (92.67%) | 18 (6.00%) | |

Abbreviations: N, number of patients; NYHA, New York Heart Association. *Data presented as n (%); % calculated from No. of patients analyzed; #P - as compared to baseline (McNemar's Chi-squared test).

mean LVEF increased from 29.57 ± 5.47% (95% CI: 28.95-30.19) to 34.66 ± 5.27% (95% CI: 34.06-35.27), with a significant difference of 5.09 ± 3.95% (95% CI: 4.64-5.55) at 12-month (*P*<0.0001).

This magnitude of reverse remodeling is consistent with other reports of ARNI therapy in similar patients. The SAVE study demonstrated a 23% increase in LVEF (from a mean of 34% to 42%; *P*<.0001) along with a marked reduction in NT-proBNP levels (from a mean of 1220.5 pg/mL to 118.1 pg/mL; P<.0001) following three months of treatment with sacubitril/valsartan [15]. A real-world study conducted by Cabral *et al.* reported consistent findings, where each year of ARNI therapy was associated with a 6.6% absolute LVEF improvement [18]. The PROVE-HF study demonstrated improvements in cardiac structure and function over 12 months with sacubitril/valsartan and reported larger absolute LVEF increases in some subgroups (LVEF increased from 28.2% to 37.8% (difference, 9.4% [95% CI, 8.8% to 9.9%]; *P*<.001)) [19]. Real-world studies have reported variable LVEF responses depending on baseline characteristics, follow-up duration, and dosing; single-center switch cohorts and registry analyses documented LVEF improvements of 5-10% after ARNI initiation, especially when therapy was up-titrated [20, 21]. Collectively, these findings confirm that sacubitril/valsartan facilitates reverse remodeling in HFrEF, although the extent of the benefit may differ depending on baseline characteristics and the intensity of dose titration.

We observed a marked improvement in functional status: nearly all patients shifted to NYHA class II by 12 months (94% vs. 7.3% at baseline). This magnitude of clinical improvement is consistent with the randomized and observational evidence. In the Indian population, three months of sacubitril/valsartan therapy resulted in significant improvement in functional status, as assessed by NYHA class, with patients classified as NYHA IV at baseline shifting to class II (50%) and class III (50%) post-treatment [15]. PROVE-HF and multiple real-world reports have documented improvements in functional capacity and QoL metrics following ARNI initiation [19-21]. Therefore, our results corroborate that the symptomatic benefit of ARNI therapy is in consistent with the routine clinical care, including in a high-comorbidity Indian population.

The mean NT-proBNP level decreased sharply from a very high baseline. This large relative and absolute decline reflected improved hemodynamics and was statistically significant (*P*<0.0001). Similarly, PROVE-HF found median NT-proBNP falling from 816 pg/mL (interquartile range [IQR], 332-1822) to 455 pg/mL (IQR, 153-1090) at 12 months (*P*<0.001) [19]. Our cohort had higher baseline NT-proBNP levels than many trial populations, which may explain the large absolute decline observed in our study. Greater absolute reductions are anticipated when the initial values are high. Decreased NT-proBNP levels serve as a significant proxy for an enhanced hemodynamic state and have been linked to improved outcomes in several studies [14]. Therefore, the correlation between LVEF enhancement and NT-proBNP

**Table 4.** Change in NT-proBNP levels from baseline to 12-month follow-up (Per Protocol)

| Parameter | Data | Change as compared to Baseline | *P* value# |
|---|---|---|---|
| NT-proBNP (pg/mL)* (Visit 1) (N=300) | 2344.5 ± 1951.85 (326.65 to 6009.85) | NA | <0.0001 |
| NT-proBNP (pg/mL)* (Visit 4) (N=300) | 564 ± 410.32 (130.43 to 1686.55) | -1534 ± 1886.43 (-5194.5 to 442.02) | |

Abbreviations: CI, confidence interval; N, number of patients; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide. *Data presented as median ± SD (95% CI); #P - as compared to baseline (Wilcoxon Signed-Rank Test).

**Table 5.** Change in eGFR levels from baseline to 12-month follow-up

| Parameter | Data | Change as compared to Baseline | *P* value# |
|---|---|---|---|
| eGFR (mL/min/1.73 $m^2$)* (Visit 1) (N=300) | 66.13 ± 26.2 (63.17 to 69.1) | NA | 0.0884 |
| eGFR (mL/min/1.73 $m^2$)* (Visit 4) (N=300) | 68.14 ± 28.6 (64.91 to 71.38) | 2.01 ± 20.33 (-0.29 to 4.31) | |

Abbreviation: CI, confidence interval; eGFR, glomerular filtration rate; N, number of patients; NA, not available. *Data presented as mean ± SD (95% CI); #P - as compared to baseline (Paired t-test).

reduction in our study is physiologically feasible and consistent with the mechanistic findings of previous studies.

Renal function remained steady during the 12-month follow-up (mean eGFR +2.0 mL/min/1.73 $m^2$, P=0.0884), even though 50% of the population presented with stage 3 CKD at baseline. This finding aligns with trial data showing that sacubitril/valsartan is renal-safe and, in some analyses, is associated with a lower risk of progressive renal dysfunction than ACEi/ARB [12, 22]. TRANSITION and PIONEER-HF also demonstrated acceptable renal safety in patients who started ARNI after hospitalization for acute HF [14, 23]. The stability of renal function in our cohort supports the renal tolerability of ARNI, even in patients with pre-existing CKD, although careful monitoring remains essential in clinical practice.

More than half (52.3%) of the patients achieved the maximal recommended dose (200 mg twice daily) by Visit 4. This rate is higher than that of some observational studies but lower than that of target attainment in trials with stricter titration protocols and selection criteria [19, 23]. Obstacles to up-titration, hypotension, alterations in renal function, hyperkalemia, and local practice patterns, including drug costs, are well documented in registries such as CHAMP-HF and in real-world analyses [17, 20]. Elevated goal attainment may indicate proactive titration by physicians at a specialized center; however, over half of the patients failed to achieve the target dosage, highlighting the ongoing difficulty in optimizing GDMT in routine practice.

No cardiovascular or all-cause deaths were recorded during the 12-month observation period. While reassuring, the absence of deaths should be interpreted cautiously, given the single-center design and limited sample size; pivotal trials with larger populations and longer follow-up (PARADIGM-HF) demonstrated a significant reduction in CV and all-cause mortality with sacubitril/valsartan compared to enalapril [12]. Recent pooled analyses (PIONEER-HF + PARAGLIDE and contemporary analyses) indicate that ARNI reduces the combined endpoints of CV death compared with ACEi/ARB in higher-risk post-discharge populations; however, the magnitude varies with baseline risk and timing of initiation [14, 24].

Our data therefore indicate that while sacubitril/valsartan produces clear physiological and symptomatic benefits, reducing recurrent disease progression in a real-world high-risk Indian population will likely require a multipronged approach (early initiation, aggressive GDMT up-titration, comorbidity management, heart-failure disease management programs). Results from the REAL.IT (Italy) cohort, among other European and Asian real-world trials and single-center switch cohorts, indicate generally analogous directional effects of ARNI on LVEF, NT-proBNP, and symptoms, although the magnitudes differ according to the initial patient demographics and follow-up time [21, 25].

*Limitations*

This single-center design limits the generalizability of our findings beyond specialized HF clinics. Retrospective data collection risks mi-

ssing unscheduled events or incomplete biomarker/echocardiographic assessments. Selection bias favored adherent patients who could afford/tolerate ARNI. The short 12-month follow-up period precluded hard endpoints, such as mortality and hospitalization rates. No control group prevented causal attribution versus natural history or GDMT intensification. The small sample size (n=300) reduced the power of the subgroup analyses.

*Future prospects*

This study provides important real-world evidence supporting the effectiveness and safety of sacubitril/valsartan in Indian patients with HFrEF. However, future research should focus on multicenter prospective studies to validate these findings across diverse populations, longer follow-ups to assess hard outcomes such as mortality and recurrent hospitalizations, and comparative effectiveness analyses against conventional ACE inhibitors, as demonstrated in the PARADIGM-HF trial. Further work is also needed to optimize titration strategies, evaluate cost-effectiveness in resource-limited settings, identify predictors of response through biomarker and phenotypic profiling, and integrate therapy within structured heart failure programs aligned with recommendations from the ESC. Additionally, national registries and expanded research into HFmrEF and HFpEF populations, building on evidence from PARAGON-HF, would help strengthen the evidence base and guide personalized, sustainable heart failure management in India.

## Conclusion

In this single-center real-world Indian cohort, sacubitril/valsartan therapy demonstrated statistically and clinically significant enhancements in LVEF, NT-proBNP, and NYHA functional class over 12 months, without any decline in renal function; approximately half of the patients attained the recommended target dosage.

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## Disclosure of conflict of interest

Kapil Dev Mehta and Komal Mangaonkar are employees of JB Chemicals and Pharmaceuticals Ltd. Dr. Ashwani Mehta declares no personal conflicts of interest.

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