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Research Article

Comparison of Sacubitril/Valsartan and Dapagliflozin on Functional Status, NT-proBNP Levels, and Hospital Readmissions in Patients with Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF) remains a leading cause of morbidity and mortality globally. Sacubitril/Valsartan and Dapagliflozin have individually demonstrated significant benefits in HFrEF management. However, direct comparative data evaluating their relative efficacy on functional outcomes, biomarker reduction, and hospital readmissions remain limited, particularly in the Indian population.

Objectives: To compare the effects of Sacubitril/Valsartan and Dapagliflozin on functional status (NYHA class, 6-minute walk test), NT-proBNP levels, and hospital readmission rates in patients with HFrEF.

Methods: This prospective, open-label, non-randomized, parallel-group comparative study was conducted at Sri Madhusudan Sai Institute of Medical Sciences, Mudenahalli, from July 2024 to June 2026 (enrolment July 2024–June 2025; 12-month follow-up). A total of 120 patients with HFrEF (LVEF ≤40%) were enrolled and allocated to two groups based on treating physician's decision: Group A received Sacubitril/Valsartan (target dose 97/103 mg twice daily; n = 60) and Group B received Dapagliflozin (10 mg once daily; n = 60), in addition to standard guideline-directed medical therapy. Primary outcomes included changes in NT-proBNP levels, NYHA functional class, 6-minute walk test (6MWT) distance, and hospital readmission rates assessed at 3, 6, and 12 months.

Results: After excluding 6 patients (2 in Group A, 4 in Group B) due to relocation, consent withdrawal, loss to follow-up, or non-cardiac death, 114 patients (58 in Group A, 56 in Group B) completed the study. Both groups demonstrated significant reductions in NT-proBNP from baseline: Group A showed a 50.5% reduction (2968 ± 786 to 1468 ± 428 pg/mL; $p < 0.001$) and Group B showed a 42.1% reduction (3042 ± 818 to 1762 ± 476 pg/mL; $p < 0.001$). The between-group difference at 12 months was statistically significant ($p = 0.001$). The 6MWT distance improved by 78 ± 22 meters in Group A versus 52 ± 18 meters in Group B ($p = 0.004$). NYHA class improvement (≥1 class) was observed in 67.2% of Group A versus 48.2% of Group B patients ($p = 0.040$). Hospital readmission rates at 12 months were 27.6% in Group A and 33.9% in Group B ($p = 0.463$).

Conclusion: Both Sacubitril/Valsartan and Dapagliflozin significantly improved functional status and reduced NT-proBNP levels in HFrEF patients over 12 months. The Sacubitril/Valsartan-based treatment strategy was associated with greater NT-proBNP reduction, greater improvement in 6MWT distance, and a higher proportion of NYHA class improvement compared to the Dapagliflozin-based strategy. Hospital readmission rates were numerically lower with Sacubitril/Valsartan, though the difference was not statistically significant. Both agents represent valuable therapeutic options, and the choice should be individualized based on patient comorbidities and clinical profile.

Keywords: Heart failure with reduced ejection fraction, Sacubitril/Valsartan, Dapagliflozin, NT-proBNP, NYHA functional class, 6-minute walk test, Hospital readmission, SGLT2 inhibitor, neprilysin inhibitor.

1. INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by the inability of the heart to pump sufficient blood to meet the metabolic demands of the body. Among its phenotypic classifications, heart failure with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction (LVEF) ≤40%, constitutes approximately 50% of all HF cases and carries a particularly poor prognosis.[1,20]

The global burden of HF continues to escalate, with an estimated 64 million individuals affected worldwide, imposing substantial morbidity, mortality, and healthcare expenditure.[1]

In India, the prevalence of HF ranges from 1.3 to 4.6 million, with HFrEF being the predominant phenotype, driven by ischemic heart disease, dilated cardiomyopathy, hypertension, and rheumatic heart disease.[28,29] Despite advances in pharmacotherapy, hospital readmission rates remain alarmingly high, with approximately 25-30% of HF patients being readmitted within 30 days of discharge, underscoring the need for optimized therapeutic strategies.[1]

The neurohormonal model of HF has formed the basis for modern pharmacological management.[26,27] Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) have constituted the pillars of guideline-directed medical therapy (GDMT) for decades.[2,5] However, two novel pharmacological classes have fundamentally altered the treatment landscape over the past decade: the angiotensin receptor-neprilysin inhibitor (ARNI), Sacubitril/Valsartan, and the sodium-glucose cotransporter 2 (SGLT2) inhibitor, Dapagliflozin.

Sacubitril/Valsartan combines the neprilysin inhibitor sacubitril with the angiotensin II receptor blocker valsartan. By inhibiting neprilysin, it augments the levels of endogenous natriuretic peptides (ANP, BNP), bradykinin, and adrenomedullin, which promote vasodilation, natriuresis, and inhibition of myocardial fibrosis and hypertrophy.[3,14] The landmark PARADIGM-HF trial demonstrated a 20% relative risk reduction in the composite of cardiovascular death or HF hospitalization with Sacubitril/Valsartan compared to enalapril, establishing its superiority in the management of chronic HFrEF.[3]

Dapagliflozin, an SGLT2 inhibitor initially developed for type 2 diabetes mellitus, has demonstrated remarkable cardioprotective effects independent of glycemic status. The DAPA-HF trial showed that Dapagliflozin reduced the composite of worsening HF events or cardiovascular death by 26% compared to placebo in HFrEF patients, with benefits observed irrespective of the presence or absence of diabetes.[4] Proposed mechanisms include osmotic diuresis, reduction in preload and afterload, improvement in myocardial energetics through enhanced ketone body utilization, and attenuation of cardiac fibrosis and inflammation.[18,19]

While both agents have individually proven their efficacy in landmark trials, direct comparative studies evaluating their relative effects on functional status, cardiac biomarkers, and clinical outcomes remain sparse. The 2022 AHA/ACC/HFSA guidelines recommend both agents as Class I therapies in HFrEF management,[5] yet clinicians often face the pragmatic challenge of choosing between or sequencing these agents, particularly in resource-limited settings where polypharmacy burdens and medication costs influence decision-making.[6]

Furthermore, most existing evidence derives from Western populations, with limited representation of South Asian demographics. Given the distinct clinical profile of Indian HFrEF patients, younger age of onset, higher prevalence of rheumatic etiology, and different comorbidity patterns, region-specific comparative data are essential for informing clinical practice.[28,29]

The present study was therefore designed to compare the effects of Sacubitril/Valsartan and Dapagliflozin on functional status (assessed by NYHA functional class and 6-minute walk test), NT-proBNP levels (as a biomarker of disease severity and treatment response), and hospital readmission rates in patients with HFrEF at a tertiary care center in rural Karnataka, India, over a 12-month follow-up period.

2. MATERIALS AND METHODS

2.1 STUDY DESIGN AND SETTING

This was a prospective, open-label, non-randomized, parallel-group comparative study conducted at the Department of General Medicine, Sri Madhusudan Sai Institute of Medical Sciences, Mudenahalli, Chikkaballapur District, Karnataka, India, over a 12-month period. Patient enrolment was conducted from July 2024 to June 2025, with follow-up completed by June 2026. The study was

conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Sri Madhusudan Sai Institute of Medical Sciences, Mudenahalli. Written informed consent was obtained from all participants before enrollment.

2.2 STUDY POPULATION

INCLUSION CRITERIA: Patients aged 35-75 years with a confirmed diagnosis of HFrEF (LVEF ≤40% on transthoracic echocardiography within the preceding 3 months), NYHA functional class II–IV, serum NT-proBNP ≥400 pg/mL at screening, and stable on optimal guideline-directed medical therapy (beta-blocker, ACE inhibitor or ARB, and MRA) for at least 4 weeks prior to enrollment were included.

EXCLUSION CRITERIA: Patients with symptomatic hypotension (systolic blood pressure <100 mmHg), estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², serum potassium >5.4 mEq/L, history of angioedema, type 1 diabetes mellitus, active malignancy, severe hepatic impairment (Child-Pugh class C), concurrent use of both Sacubitril/Valsartan and Dapagliflozin, pregnancy or lactation, or anticipated cardiac revascularization or transplantation during the study period were excluded.

2.3 GROUP ALLOCATION AND INTERVENTION

Patients were allocated to one of two groups based on treating physician's decision considering individual clinical profiles, comorbidities, and contraindications:

GROUP A (SACUBITRIL/VALSARTAN GROUP, n = 60): Patients received Sacubitril/Valsartan initiated at 24/26 mg twice daily, with dose up-titration every 2-4 weeks as tolerated, targeting a maximum dose of 97/103 mg twice daily, in addition to standard GDMT.

GROUP B (DAPAGLIFLOZIN GROUP, n = 60): Patients received Dapagliflozin 10 mg once daily in addition to standard GDMT. For patients with eGFR 30-45 mL/min/1.73 m², a starting dose of 5 mg was used with subsequent up-titration.

All patients continued their pre-existing GDMT (beta-blocker, ACE inhibitor or ARB [switched to ARNI in Group A], MRA, and diuretics as needed) throughout the study period. In Group A, the pre-existing ACE inhibitor or ARB was discontinued with a mandatory 36-hour washout period before initiating Sacubitril/Valsartan. Accordingly, the comparison reflects two treatment strategies rather than two isolated drugs: in Group A, the pre-existing ACE inhibitor/ARB was replaced by Sacubitril/Valsartan, whereas in Group B, Dapagliflozin was added to the existing background GDMT.

2.4 OUTCOME MEASURES

PRIMARY OUTCOMES

1) Change in serum NT-proBNP levels from baseline to 3, 6, and 12 months;
2) Change in NYHA functional class from baseline to 12 months;
3) Change in 6-minute walk test (6MWT) distance from baseline to 3, 6, and 12 months.

SECONDARY OUTCOMES

1) All-cause hospital readmission rates at 30, 90, 180 days, and 12 months.
2) Heart failure-specific readmission rates.
3) Composite of cardiovascular death or heart failure hospitalization.
4) Adverse events profile.

2.5 DATA COLLECTION AND FOLLOW-UP

Baseline data included demographic characteristics, anthropometric measurements, comorbidity profiles, echocardiographic parameters (LVEF by modified Simpson's biplane method), medication details, serum NT-proBNP (electrochemiluminescence immunoassay, Roche Diagnostics), serum creatinine, eGFR (CKD-EPI 2021 equation), serum electrolytes, and glycated hemoglobin (HbA1c). Follow-up assessments were conducted at 1, 3, 6, 9, and 12 months, with NT-proBNP levels, NYHA class evaluation, and 6MWT performed at 3, 6, and 12 months. Hospital readmissions were ascertained through medical records review and telephonic follow-up.

2.6 STATISTICAL ANALYSIS

Sample size was calculated based on an anticipated 15% difference in NT-proBNP reduction between groups, with 80% power and a two-sided alpha of 0.05, yielding a minimum of 54 patients per group. Accounting for a 10% attrition rate, 60 patients were enrolled per group. Continuous variables were expressed as mean ± standard deviation (SD) and compared using the independent samples t-test or Mann-Whitney U test, as appropriate. Categorical

variables were expressed as frequencies and percentages and compared using the chi-squared test or Fisher's exact test. Within-group comparisons were performed using paired t-tests or Wilcoxon signed-rank tests. Time-to-first-readmission was summarized descriptively; between-group comparisons of readmission and composite-outcome proportions at each time point were performed using the chi-squared or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant. Although the primary analysis relied on between-group comparisons at each prespecified time point, the repeated-measures design would also support mixed-effects modelling; the present analysis reports the prespecified between-group comparisons. All analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.2.

3. RESULTS

3.1 PATIENT ENROLLMENT AND BASELINE CHARACTERISTICS

A total of 148 patients were screened, of whom 120 met the eligibility criteria and were enrolled (60 in each group). During the 12-month study period, 2 patients in Group A (1 relocated, 1 withdrew consent) and 4 patients in Group B (2 lost to follow-up, 1 withdrew consent, 1 died of non-cardiac cause) were excluded, leaving 58 patients in Group A and 56 patients in Group B for the final analysis. The baseline demographic and clinical characteristics are presented in Table 1.

The two groups were well-matched at baseline with no statistically significant differences in age (59.2 ± 7.8 vs. 60.4 ± 7.5 years; p = 0.394), sex distribution (67.2% vs. 62.5% male; p = 0.728), body mass index, mean LVEF (28.6 ± 5.8% vs. 27.9 ± 6.2%; p = 0.524), baseline NT-proBNP levels (2968 ± 786 vs. 3042 ± 818 pg/mL; p = 0.618), baseline 6MWT distance (254 ± 58 vs. 260 ± 62 meters; p = 0.592), and NYHA functional class distribution (p = 0.952). Comorbidity profiles, including diabetes mellitus, hypertension, chronic kidney disease, and atrial fibrillation, were comparable between groups.

Table No. 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Group A: Sacubitril/Valsartan (n=58)	Group B: Dapagliflozin (n=56)	p-value
Age (years), mean ± SD	59.2 ± 7.8	60.4 ± 7.5	0.394
Male sex, n (%)	39 (67.2)	35 (62.5)	0.728
BMI (kg/m²), mean ± SD	26.2 ± 3.6	26.8 ± 3.9	0.396
Systolic BP (mmHg)	122.6 ± 13.8	124.2 ± 14.6	0.536
Heart rate (bpm)	80.8 ± 11.4	82.6 ± 12.8	0.442
LVEF (%), mean ± SD	28.6 ± 5.8	27.9 ± 6.2	0.524
NT-proBNP (pg/mL), mean ± SD	2968 ± 786	3042 ± 818	0.618
6MWT distance (m), mean ± SD	254 ± 58	260 ± 62	0.592
eGFR (mL/min/1.73 m²)	58.6 ± 16.8	56.4 ± 15.6	0.482
HbA1c (%), diabetic patients	7.8 ± 1.3	7.8 ± 1.3	0.468
NYHA Class II, n (%)	16 (27.6)	14 (25.0)	0.952
NYHA Class III, n (%)	36 (62.1)	36 (64.3)	—
NYHA Class IV, n (%)	6 (10.4)	6 (10.7)	—
Ischemic etiology, n (%)	36 (62.1)	33 (58.9)	0.712
Diabetes mellitus, n (%)	26 (44.8)	27 (48.2)	0.717
Hypertension, n (%)	34 (58.6)	32 (57.1)	0.872
CKD (eGFR 30–60), n (%)	16 (27.6)	14 (25.0)	0.754
Atrial fibrillation, n (%)	12 (20.7)	14 (25.0)	0.582
Beta-blocker use, n (%)	56 (96.6)	54 (96.4)	1.000
MRA use, n (%)	50 (86.2)	48 (85.7)	0.942
Loop diuretic use, n (%)	46 (79.3)	44 (78.6)	0.924

SD: Standard Deviation; BMI: Body Mass Index; BP: Blood Pressure; LVEF: Left Ventricular Ejection Fraction; 6MWT: 6-Minute Walk Test; eGFR: estimated Glomerular Filtration Rate; CKD: Chronic Kidney Disease; MRA: Mineralocorticoid Receptor Antagonist.

3.2 CHANGES IN NT-proBNP LEVELS

Both treatment groups demonstrated significant reductions in NT-proBNP levels from baseline throughout the 12-month follow-up period (Table 2, Figures 1 and 1A). In Group A, NT-proBNP decreased from 2968 ± 786 pg/mL at baseline to 2186 ± 618 pg/mL at 3 months (26.4% reduction; $p < 0.001$), 1782 ± 512 pg/mL at 6 months (39.9% reduction; $p < 0.001$), and 1468 ± 428 pg/mL at 12 months (50.5% reduction; $p < 0.001$). In Group B, NT-proBNP decreased from 3042 ± 818 pg/mL to 2426 ± 674 pg/mL at 3 months (20.2% reduction; $p < 0.001$), 2062 ± 568 pg/mL at 6 months (32.2% reduction; $p < 0.001$), and 1762 ± 476 pg/mL at 12 months (42.1% reduction; $p < 0.001$).

The between-group difference in NT-proBNP reduction was statistically significant at 6 months ($p = 0.008$) and 12 months ($p = 0.001$), with Group A demonstrating a greater absolute and percentage reduction. The difference at 3 months was marginally significant ($p = 0.038$).

Table No. 2: NT-proBNP Levels (pg/mL) at Different Time Points

Time Point	Group A (mean±SD)	% Change	Group B (mean±SD)	% Change	p-value[1]
Baseline	2968 ± 786	—	3042 ± 818	—	0.618
3 Months	2186 ± 618	−26.4%	2426 ± 674	−20.2%	0.038*
6 Months	1782 ± 512	−39.9%	2062 ± 568	−32.2%	0.008*
12 Months	1468 ± 428	−50.5%	1762 ± 476	−42.1%	0.001*
Within-group p	**<0.001**	**—**	**<0.001**	**—**	**—**

[1]Between-group p-value (independent samples t-test); *statistically significant ($p<0.05$)

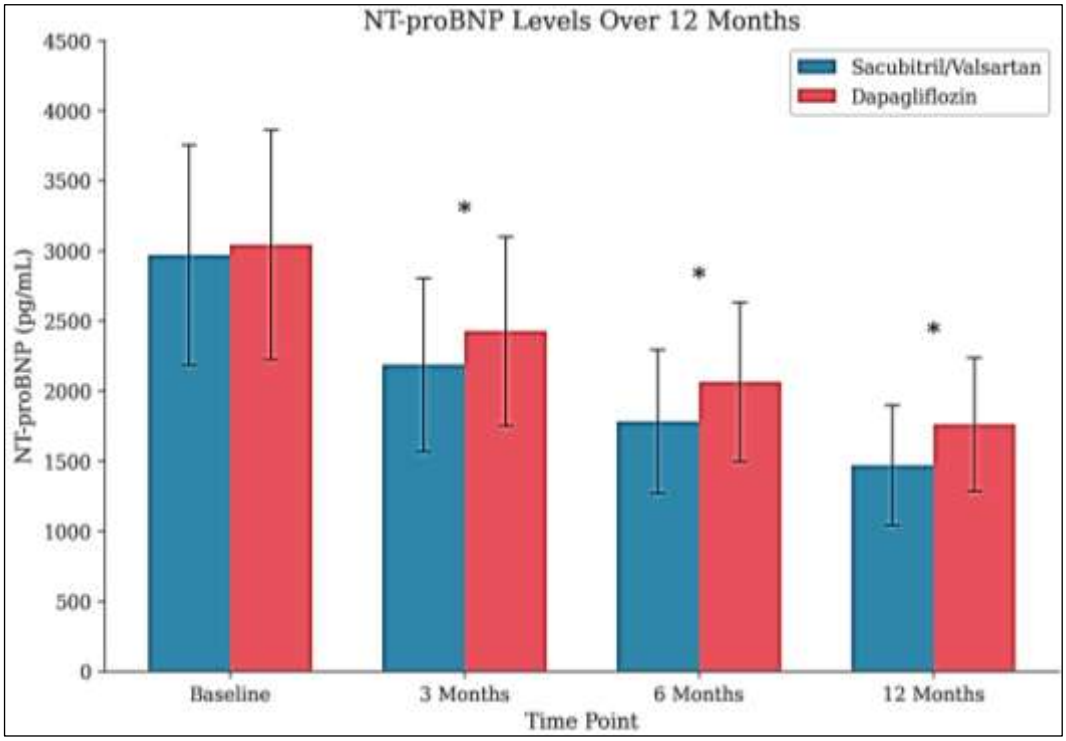

Figure No. 1: NT-proBNP levels (pg/mL) at baseline, 3 months, 6 months, and 12 months in both treatment groups. Error bars represent standard deviation. *$p<0.05$ between groups.

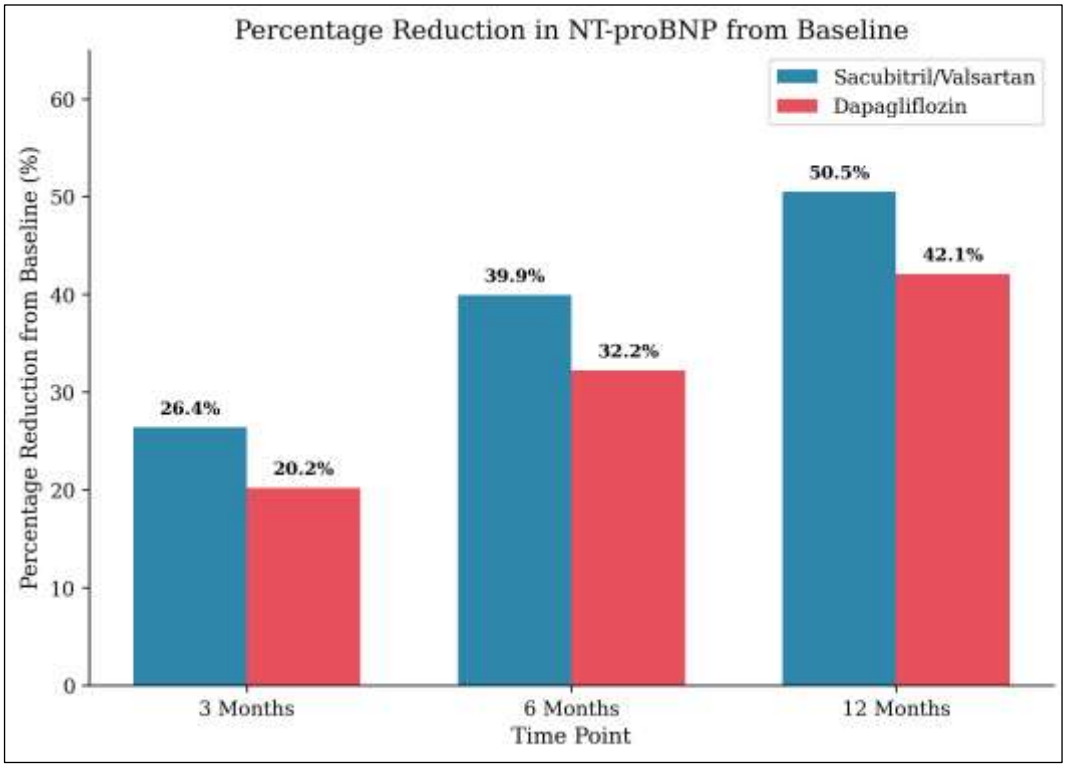

Figure No. 1A: Percentage reduction in NT-proBNP from baseline at 3, 6, and 12 months. Sacubitril/Valsartan demonstrated greater percentage reduction at all-time points.

3.3 CHANGES IN 6-MINUTE WALK TEST DISTANCE

The 6MWT distance improved significantly in both groups from baseline to 12 months (Table 3, Figure 2). In Group A, the mean 6MWT distance increased from 254 ± 58 meters at baseline to 286 ± 54 meters at 3 months (Δ = +32 ± 13 m; $p < 0.001$), 308 ± 50 meters at 6 months (Δ = +54 ± 17 m; $p < 0.001$), and 332 ± 46 meters at 12 months (Δ = +78 ± 22 m; $p < 0.001$). Group B demonstrated increases from 260 ± 62 meters to 282 ± 58 meters at 3 months (Δ = +22 ± 11 m; $p < 0.001$), 296 ± 54 meters at 6 months (Δ = +36 ± 14 m; $p < 0.001$), and 312 ± 50 meters at 12 months (Δ = +52 ± 18 m; $p < 0.001$).

The between-group difference in 6MWT improvement from baseline was significant at 6 months ($p = 0.014$) and 12 months ($p = 0.004$), favoring the Sacubitril/Valsartan group.

Table No. 3: 6-Minute Walk Test Distance (meters) at Different Time Points

Time Point	Group A (mean ± SD)	Δ from BL	Group B (mean ± SD)	Δ from BL	p-value[1]
Baseline	254 ± 58	—	260 ± 62	—	0.592
3 Months	286 ± 54	+32 ± 13	282 ± 58	+22 ± 11	0.072
6 Months	308 ± 50	+54 ± 17	296 ± 54	+36 ± 14	0.014*
12 Months	332 ± 46	+78 ± 22	312 ± 50	+52 ± 18	0.004*

Δ: Change from baseline; BL: Baseline; [1]Between-group p-value; *statistically significant

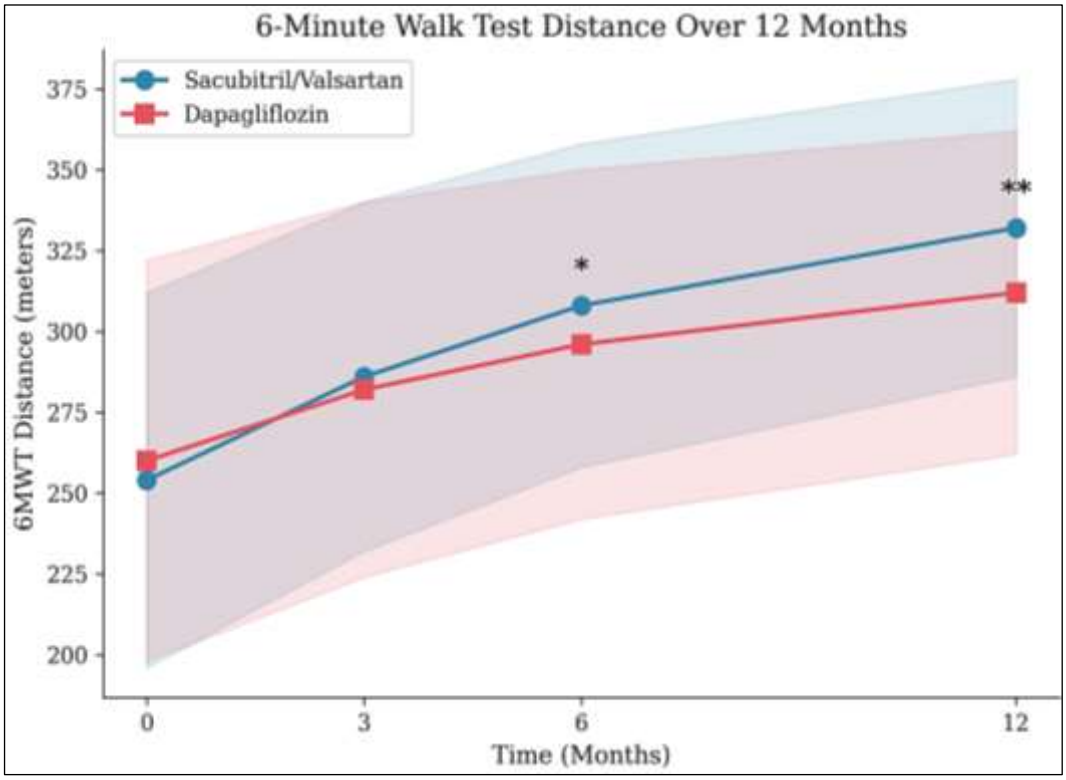

Figure No. 2: Change in 6-minute walk test distance (meters) over 12 months. Shaded bands represent ±1 standard deviation. Both groups showed progressive improvement, with Sacubitril/Valsartan demonstrating greater gains.

3.4 CHANGES IN NYHA FUNCTIONAL CLASS

At 12 months, a significant improvement in NYHA functional class was observed in both groups (Table 4, Figure 3). In Group A, 39 patients (67.2%) demonstrated an improvement of at least one NYHA class, compared to 27 patients (48.2%) in Group B ($p = 0.040$). The proportion of patients in NYHA Class I increased from 0% to 8.6% in Group A and from 0% to 5.4% in Group B. NYHA Class II proportion increased from 27.6% to 58.6% in Group A and from 25.0% to 46.4% in Group B, while NYHA Class III decreased from 62.1% to 27.6% in Group A and from 64.3% to 41.1% in Group B. NYHA Class IV decreased from 10.4% to 5.2% in Group A and from 10.7% to 7.1% in Group B.

Table No. 4: NYHA Functional Class Distribution at Baseline and 12 Months

NYHA Class	Group A Baseline	Group A 12 Months	Group B Baseline	Group B 12 Months
Class I	0 (0)	5 (8.6)	0 (0)	3 (5.4)
Class II	16 (27.6)	34 (58.6)	14 (25.0)	26 (46.4)
Class III	36 (62.1)	16 (27.6)	36 (64.3)	23 (41.1)
Class IV	6 (10.4)	3 (5.2)	6 (10.7)	4 (7.1)
Improved ≥1 class	**—**	**39 (67.2)**	**—**	**27 (48.2)**

Values expressed as n (%). Between-group comparison of ≥1 class improvement: $p = 0.040$ (chi-squared test without continuity correction).

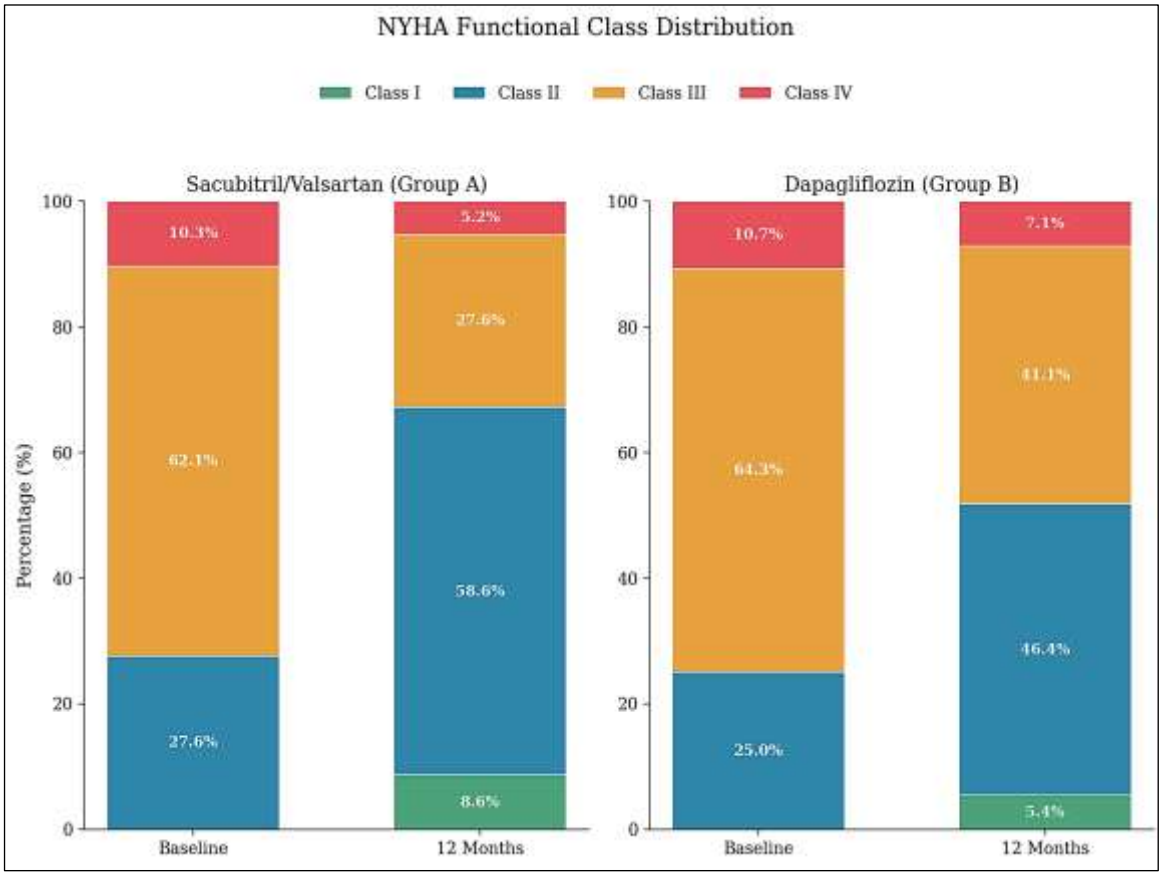

Figure No. 3: NYHA functional class distribution at baseline and 12 months in Sacubitril/Valsartan (left) and Dapagliflozin (right) groups. Both groups showed a shift toward lower (improved) NYHA classes.

3.5 HOSPITAL READMISSION RATES

Hospital readmission rates are summarized in Table 5 and Figure 4. At 30 days, 3 patients (5.2%) in Group A and 7 patients (12.5%) in Group B were readmitted (p = 0.200). At 90 days, the readmission rates were 13.8% (8 patients) in Group A and 17.9% (10 patients) in Group B (p = 0.552). At 180 days, readmission occurred in 12 patients (20.7%) in Group A and 14 patients (25.0%) in Group B (p = 0.583). At 12 months, cumulative all-cause readmission rates were 27.6% (16 patients) in Group A and 33.9% (19 patients) in Group B (p = 0.463). Heart failure-specific readmissions at 12 months were 20.7% (12 patients) in Group A and 25.0% (14 patients) in Group B (p = 0.583). None of these between-group differences reached statistical significance, though a consistent numerical trend favoring Group A was observed at all time points.

The composite endpoint of cardiovascular death or heart failure hospitalization at 12 months occurred in 12 patients (20.7%) in Group A and 14 patients (25.0%) in Group B (p = 0.583); as no cardiovascular deaths occurred in either group among the analyzed patients, this composite is numerically identical to HF-specific readmission alone.

Table No. 5: Hospital Readmission Rates at Different Time Points

Outcome	Group A, n (%)	Group B, n (%)	p-value
30-day all-cause	3 (5.2)	7 (12.5)	0.200
90-day all-cause	8 (13.8)	10 (17.9)	0.552
180-day all-cause	12 (20.7)	14 (25.0)	0.583
12-month all-cause	16 (27.6)	19 (33.9)	0.463
12-month HF-specific	12 (20.7)	14 (25.0)	0.583
CV death or HF hospitalization	12 (20.7)	14 (25.0)	0.583

HF: Heart Failure; CV: Cardiovascular. p-values for all readmission and composite-outcome proportions by chi-squared or Fisher's exact test, as appropriate.

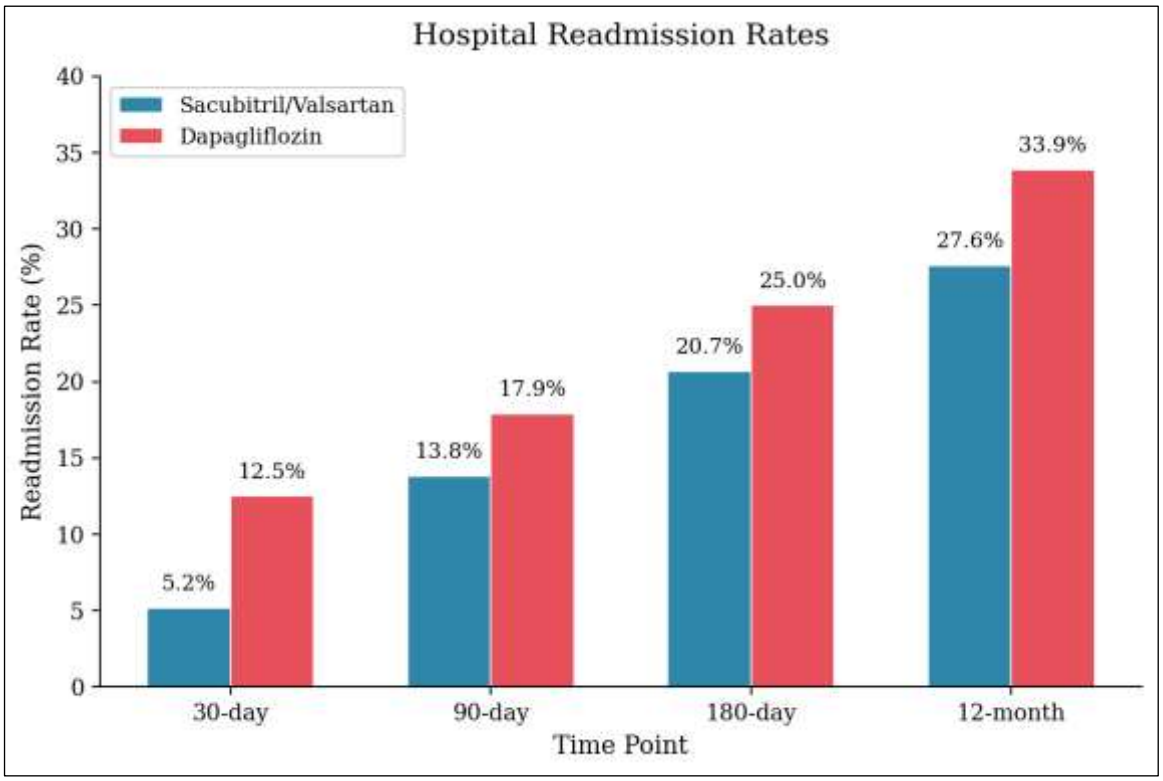

Figure No. 4: Hospital readmission rates (%) at 30 days, 90 days, 180 days, and 12 months. Although numerically lower in the Sacubitril/Valsartan group, between-group differences were not statistically significant

3.6 ADVERSE EVENTS

The adverse events profile is summarized in Table 6. Symptomatic hypotension occurred more frequently in Group A (13.8% vs. 7.1%; p = 0.362), while genital tract infections were exclusively observed in Group B (12.5%; p = 0.006). Hyperkalemia (>5.5 mEq/L) rates were comparable between groups (5.2% vs. 7.1%; p = 1.000). Volume depletion was numerically more common in Group B (12.5% vs. 5.2%; p = 0.198). No cases of diabetic ketoacidosis, Fournier's gangrene, or angioedema were reported. One death occurred in Group B due to a non-cardiac cause (road traffic accident) and was excluded from the efficacy analysis.

Table No. 6: Adverse Events during the Study Period

Adverse Event	Group A, n (%)	Group B, n (%)	p-value
Symptomatic hypotension	8 (13.8)	4 (7.1)	0.362
Hyperkalemia (>5.5 mEq/L)	3 (5.2)	4 (7.1)	0.714
Worsening renal function	3 (5.2)	4 (7.1)	0.714
Genital tract infections	0 (0)	7 (12.5)	0.006*
Urinary tract infections	1 (1.7)	4 (7.1)	0.200
Volume depletion/dehydration	3 (5.2)	7 (12.5)	0.198
Dizziness	6 (10.3)	2 (3.6)	0.272
Cough	2 (3.4)	1 (1.8)	1.000
Nausea	3 (5.2)	2 (3.6)	1.000
Drug discontinuation	2 (3.4)	1 (1.8)	1.000

*Statistically significant (p<0.05). Values expressed as n (%).

4. DISCUSSION

The present study provides a direct comparative evaluation of Sacubitril/Valsartan and Dapagliflozin, two cornerstone therapies in contemporary HFrEF management, on functional status, NT-proBNP levels, and hospital readmission rates in an Indian tertiary care setting over a 12-month follow-up. To our knowledge, this is among the first prospective comparative studies from rural India comparing these two treatment strategies.

Our principal findings demonstrate that both Sacubitril/Valsartan and Dapagliflozin produce clinically meaningful improvements in functional capacity and biomarker reduction in HFrEF patients. However, Sacubitril/Valsartan was associated with a statistically greater reduction in NT-proBNP levels (50.5% vs. 42.1% at 12 months; p = 0.001), greater improvement in 6MWT distance (78 ± 22 vs. 52 ± 18 meters; p = 0.004), and a higher proportion of patients achieving at least one NYHA class improvement (67.2% vs. 48.2%; p = 0.040). Hospital readmission rates were numerically lower in the Sacubitril/Valsartan group at all-time points but did not achieve statistical significance.

The magnitude of NT-proBNP reduction observed in our Sacubitril/Valsartan group (50.5% at 12 months) is consistent with prior evidence. In the PARADIGM-HF trial, Sacubitril/Valsartan achieved a 34% greater reduction in NT-proBNP compared to enalapril at 8 months.[3] The PROVE-HF study, a single-arm prospective study of 794 patients, demonstrated a median NT-proBNP reduction of approximately 38% at 6 months and 45% at 12 months with Sacubitril/Valsartan, which aligns closely with our findings.[7] The greater NT-proBNP reduction likely reflects the dual mechanism of neprilysin inhibition enhancing natriuretic peptide bioactivity while simultaneously blocking the deleterious renin-angiotensin-aldosterone system via valsartan.

The 42.1% NT-proBNP reduction observed in our Dapagliflozin group over 12 months is also congruent with existing evidence. In the DAPA-HF trial, Dapagliflozin reduced NT-proBNP by approximately 300 pg/mL (a relative reduction of approximately 25-35%) over a median follow-up of 18.2 months. The DEFINE-HF trial found that while mean NT-proBNP was not significantly reduced, 36.3% of patients experienced a clinically meaningful (≥20%) reduction with Dapagliflozin at 12 weeks. Our results extend these observations over a full 12-month follow-up and confirm the sustained biomarker-lowering effect of SGLT2 inhibition.[4,31]

The improvement in 6MWT distance observed in both groups reflects enhanced functional capacity and exercise tolerance. The 78-meter improvement in the Sacubitril/Valsartan group well exceeds the established minimal clinically important difference (MCID) of 30-36 meters for the 6MWT in HF populations,[21] indicating a robust and clinically meaningful benefit. Similarly, the 52-meter improvement in the Dapagliflozin group also surpasses this threshold. The 12-month follow-up allowed for the full therapeutic benefit of both agents to manifest, which may explain the slightly larger improvements compared to shorter-duration studies. Our findings are consistent with the EVALUATE-HF trial, which demonstrated improvements in aortic impedance and functional parameters with Sacubitril/Valsartan,[17] and with the PRESERVED-HF trial, which showed a 20-meter improvement in 6MWT distance with Dapagliflozin in HFpEF patients.[8,9]

The differential functional improvement between groups may be attributable to the distinct hemodynamic and neurohormonal profiles of these agents. Sacubitril/Valsartan's augmentation of natriuretic peptides produces more pronounced vasodilation, afterload reduction, and diuresis compared to the primarily volume-modulating effects of SGLT2 inhibition.[18,19] Additionally, Sacubitril/Valsartan has been shown to improve arterial-ventricular coupling and left ventricular reverse remodeling, which may translate into greater exercise capacity.[7,17]

The NYHA class improvement observed in 67.2% of Sacubitril/Valsartan patients and 48.2% of Dapagliflozin patients over 12 months is clinically relevant, as NYHA class is a validated predictor of mortality and hospitalization in HFrEF.[2,20] The TRANSITION trial demonstrated that early in-hospital initiation of Sacubitril/Valsartan led to NYHA class improvement in approximately 55% of patients at 10 weeks, which is directionally consistent with our findings over a longer duration.[10,13] The NYHA improvement rates with Dapagliflozin in our study are comparable to those reported in subgroup analyses of the DAPA-HF trial.[4,25]

While hospital readmission rates were lower in the Sacubitril/Valsartan group at all time points (30-day: 5.2% vs. 12.5%; 90-day: 13.8% vs.

17.9%; 180-day: 20.7% vs. 25.0%; 12-month: 27.6% vs. 33.9%), the differences were not statistically significant, likely reflecting the limited sample size. The PARADIGM-HF trial reported a 21% reduction in HF hospitalizations with Sacubitril/Valsartan,[3] while the DAPA-HF trial demonstrated a 30% reduction in worsening HF events with Dapagliflozin. [4,11,15,24] The 12-month HF-specific readmission rates were numerically lower in the Sacubitril/Valsartan group (20.7% vs. 25.0%; p = 0.583), consistent with the direction of benefit observed in landmark trials, although the difference did not reach statistical significance. The lack of statistical significance in our readmission comparisons should not be interpreted as therapeutic equivalence, as the study was powered for biomarker outcomes rather than clinical events.

The adverse events profile was consistent with known pharmacological effects. Symptomatic hypotension was more frequent with Sacubitril/Valsartan (13.8% vs. 7.1%), which aligns with PARADIGM-HF data showing a 14% incidence of hypotension.[3] Genital tract infections were exclusively observed in the Dapagliflozin group (12.5%), consistent with the established SGLT2 inhibitor class effect attributable to glycosuria-mediated colonization.[4,12,16] Both agents were well tolerated, with low rates of drug discontinuation (3.4% and 1.8%, respectively).

STRENGTHS AND LIMITATIONS

This study has several strengths: prospective design with a full 12-month follow-up period, comprehensive multi-domain outcome assessment (biomarkers, functional capacity, and clinical events), serial follow-up measurements enabling temporal analysis of treatment response, and a geographically underrepresented study population. The 12-month duration is longer than many comparable studies and allows for a more complete assessment of the sustained therapeutic effects of both agents.[30] However, several limitations should be acknowledged. First, the open-label, non-randomized design introduces potential allocation bias, although baseline characteristics were well-matched. Second, the sample size, while adequate for biomarker outcomes, limits the power to detect differences in clinical event rates. Third, the single-center design limits generalizability. Finally, the study compared these agents as alternatives rather than evaluating their additive effects when used in combination, an approach increasingly advocated in contemporary guidelines. Additionally, because Group A involved replacement of pre-existing ACE inhibitor/ARB therapy with Sacubitril/Valsartan whereas Group B received Dapagliflozin on top of continuing background GDMT, differences in background therapy constitute a potential confounding factor that should be considered when interpreting the results.

CLINICAL IMPLICATIONS

Our findings suggest that both Sacubitril/Valsartan and Dapagliflozin are effective in improving functional status and reducing NT-proBNP in Indian patients with HFrEF over a 12-month period. In clinical scenarios where prioritization is necessary, such as resource-limited settings or when sequential initiation is preferred, the Sacubitril/Valsartan-based strategy may be associated with greater biomarker reduction and functional improvement, although confirmation in randomized trials is warranted. However, the favorable metabolic profile of Dapagliflozin (renoprotection, glycemic benefit, weight reduction) makes it particularly attractive in patients with concomitant diabetes mellitus and chronic kidney disease. Ideally, contemporary GDMT should incorporate both agents, as the 2022 AHA/ACC/HFSA guidelines recommend their combined use in eligible patients.[5,22,23]

5. CONCLUSION

In this prospective comparative study of 114 patients with HFrEF, both Sacubitril/Valsartan and Dapagliflozin significantly improved functional status and reduced NT-proBNP levels over a 12-month follow-up period. Within the limitations of this non-randomized comparative design, the Sacubitril/Valsartan-based treatment strategy was associated with greater NT-proBNP reduction (50.5% vs. 42.1%; p = 0.001), greater improvement in 6-minute walk test distance (78 ± 22 vs. 52 ± 18 meters; p = 0.004), and a higher proportion of patients achieving NYHA class improvement (67.2% vs. 48.2%; p = 0.040). Hospital readmission rates at 12 months were numerically lower with Sacubitril/Valsartan (27.6% vs. 33.9%) but did not reach statistical significance. HF-specific readmission rates were numerically lower with Sacubitril/Valsartan (20.7% vs. 25.0%) but did not reach statistical significance. Both agents

were well tolerated with predictable and manageable adverse event profiles. These findings support the use of both agents as essential components of guideline-directed medical therapy in HFrEF, with the choice between them individualized based on patient comorbidities, tolerability, and clinical priorities. Larger, multicenter, randomized controlled trials with longer follow-up are warranted to further elucidate the comparative and synergistic efficacy of these agents.

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