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Research Article

Efficacy and Tolerability of Very Low-Dose Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction (HFrEF) Patients

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Abstract

Objective: This study aims to evaluate the efficacy and tolerability of Sacubitril/valsartan commenced at a very low dose in patients with Heart Failure and Reduced Ejection Fraction (HFrEF).

Methods: This was a prospective, real-world study conducted in 33 centres in Bangladesh on adult patients with symptomatic Heart failure and reduced ejection fraction (LVEF ≤ 40%) treated with a very low dose of Sacubitril/valsartan (12/13 mg) twice a day along with other standard treatment, with a 12-week follow-up. The primary endpoint was the mean change in NT-proBNP levels from baseline to week 12.

Results: The study included 655 patients with a mean age of 57.98±11.98 years. The mean NT-proBNP level showed a significant decline from 2867.15 pg/mL to 938.41 pg/mL ($p<0.001$). Notably, over 55% of patients achieved a reduction of 50% or more NT-proBNP. Concurrently, LVEF improved significantly from 34.80±6.7% at baseline to 39.20±6.4% at 12 weeks ($p<0.001$). There was also a significant reduction in left ventricular end-diastolic diameter, from 60.26±6.3 mm to 57.34±6.5 mm ($p<0.001$). Furthermore, more than 85% of patients exhibited favourable changes in the New York Heart Association functional class at 12 weeks ($p<0.001$). As there was no up-titration of doses, no patients experienced symptomatic hypotension or any other serious adverse events.

Conclusions: Very Low-dose sacubitril/valsartan demonstrates significant efficacy and tolerability in patients with HFrEF, as evidenced by marked reductions in NT-proBNP levels. The administration of a lower dosage may enhance patient tolerability and adherence to treatment; however, further controlled studies are necessary to confirm these findings.

Keywords: sacubitril/valsartan; heart failure with reduced ejection fraction (hfref); nt-probnp; tolerability; nyha functional class

Abbreviations:

ACEI – Angiotensin-Converting Enzyme Inhibitor AF – Atrial Fibrillation
ARB – Angiotensin Receptor Blocker
ARNI – Angiotensin Receptor–Neprilysin Inhibitor BD – Bis in Die (Twice Daily)
BMI – Body Mass Index
CCR – Creatinine Clearance Rate CVD – cardiovascular disease
eGFR – Estimated Glomerular Filtration Rate ESC – European Society of Cardiology
HF – Heart Failure
HFrEF – Heart Failure with Reduced Ejection Fraction HTN – Hypertension
IQR – Interquartile Range
LVEDD – Left Ventricular End-Diastolic Diameter LVEF – Left Ventricular Ejection Fraction
MI – Myocardial Infarction
MRA – Mineralocorticoid Receptor Antagonist
NT-proBNP – N-terminal pro-B-type Natriuretic Peptide NYHA – New York Heart Association
RCT – Randomized Controlled Trial SD – Standard Deviation
SGLT2 – Sodium-Glucose Cotransporter 2
SPSS – Statistical Package for the Social Sciences SV – Sacubitril/Valsartan
VLD – Very Low Dose

Introduction

Heart failure (HF) represents a serious and life-threatening condition impacting an estimated 37.7 million individuals globally (Shah et al., 2017). It presents a significant public health burden due to its chronic nature, coupled with elevated rates of morbidity and mortality, along with frequent hospital admissions. In Bangladesh, heart failure accounts for approximately 28.5% of all cardiovascular diseases, underscoring a considerable public health challenge within the region (Rahman et al., 2017).

Despite adherence to guideline-directed medical therapy—including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists—patient outcomes remain suboptimal, particularly for those diagnosed with reduced ejection fraction (HFrEF) (Mozaffarian et al., 2015). Mortality rates and the risk of rehospitalization continue to be exceedingly high, thereby highlighting the urgent need for more effective treatment strategies.

Sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNI), has emerged as a promising therapeutic alternative for patients with HFrEF. In the landmark PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, sacubitril/valsartan demonstrated a 20% relative risk reduction in cardiovascular death or heart failure hospitalization compared with enalapril, a standard ACEI (McMurray et al., 2014). These findings led to its incorporation into international clinical practice guidelines, with both the European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) granting it a Class I recommendation for use in patients with chronic symptomatic HFrEF (Ponikowski et al., 2016; Yancy et al., 2017).

Despite strong endorsements for sacubitril/valsartan, its real-world utilization remains limited, with prescription rates falling short of expectations in clinical practice (Du et al., 2019; DeVore et al., 2018; Vicent et al., 2019; Pinto et al., 2019; Greene et al., 2018). Several factors contribute to this gap, many of which originate from treatment protocols used in pivotal trials such as PARADIGM-HF, where patients were required to tolerate a high dose of enalapril before transitioning to sacubitril/valsartan. In real-world settings, many patients are unable to tolerate such doses due to adverse effects like hypotension, renal dysfunction, or hyperkalemia (Oh et al., 2019; Wachter et al., 2019). As a result, clinicians often initiate sacubitril/valsartan at lower doses (50 mg or 100 mg twice daily), and up- titration to the recommended target dose of 200 mg twice daily is frequently not achieved. Observational data suggest that only 27% to 38% of patients reach the target dose in routine practice (Du et al., 2019; Vicent et al., 2019).

Initiating therapy in patients with heart failure with reduced ejection fraction is further complicated by risks such as symptomatic hypotension, renal impairment, and hyperkalemia—particularly in elderly patients or those with low baseline blood pressure or renal dysfunction—leading to delays or underdosing in clinical management (Greene et al., 2018). A low starting dose with a conservative up- titration schedule is recommended. The TITRATION trial shows that gradual dose escalation improves tolerability without affecting long-term efficacy (Desai et al., 2017). Similarly, the PARADIGM-HF trial indicates that patients unable

to reach target doses still benefit clinically (McMurray et al., 2014). Real-world studies confirm that low-dose initiation increases acceptance in high-risk groups while allowing for future titration (Greene et al., 2018). A retrospective analysis by Amitabh et al. (2021) involving 45 of 278 patients revealed significant reductions in NT-proBNP levels across low-dose groups, suggesting that this approach can benefit those who are intolerant to higher doses. Additionally, a study by Hyoeun et al. (2020) showed comparable improvements in NT-proBNP levels and left ventricular ejection fraction for patients starting at a conservative 25 mg BID, with similar adverse event rates. Therefore, a low-dose initiation strategy for sacubitril/valsartan may enhance safety, adherence, and therapeutic outcomes in clinical practice.

Patients with HFrEF in Bangladesh often present with multiple comorbidities, including chronic kidney disease, low body weight, and hypotension, which can heighten the risk of adverse effects from standard doses of sacubitril/valsartan. Additionally, limited access to regular laboratory monitoring and follow-up in resource-constrained settings further complicates the safe initiation and titration of the drug. A low-dose approach may offer improved tolerability and greater feasibility for long-term use in this population. Moreover, economic constraints constitute a significant barrier to the widespread adoption of newer heart failure therapies, and initiating treatment at a very low dose may reduce upfront medication costs, improving accessibility and adherence. While global studies, such as the TITRATION trial and data from Korea and California, support the safety and effectiveness of initiating sacubitril/valsartan at lower-than-recommended doses (Desai et al., 2017; Hyoeun et al., 2020; Amitabh et al., 2021), local data are needed to validate this approach in the Bangladeshi population. Therefore, a region-specific study could provide valuable insights into optimizing heart failure treatment in low-resource settings. This study aims to evaluate the efficacy and tolerability of sacubitril/valsartan commenced at a very low dose in patients with HFrEF.

Methods

Study Design and Setting

This was a prospective, observational cohort study conducted to evaluate the real-world effectiveness and safety of sacubitril/valsartan (SV) in patients with HFrEF. The study was carried out across 33 centers in Bangladesh from November 2023 to October 2024. Adult patients diagnosed with HFrEF and prescribed SV as part of routine clinical care were enrolled and followed over a defined period of 12 weeks. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participants prior to enrollment.

Study Participants & Procedures

A total of 655 patients diagnosed with symptomatic heart failure and reduced ejection fraction (left ventricular ejection fraction ≤ 40%) who received a very low dose of Sacubitril/valsartan (12/13 mg) administered twice daily, in conjunction with other standard treatments, were enrolled in the study. The inclusion criteria specified that subjects must be male or female adults aged 18 years or older, exhibit symptomatic heart failure characterized by New York Heart Association (NYHA) class II–IV, and present with a left ventricular ejection fraction of 40% or less, alongside a systolic blood pressure ranging from 90 to 100 mmHg. Patients with renal dysfunction defined as endogenous creatinine clearance rate (CCR), 30 ml/min/1.73 m2 and estimated glomerular filtration rate (eGFR)5.4 mmol/l, previous intolerance to recommended target doses of ACEI/ARBs, known history of angioedema, current hospitalization for conditions other than decompensated HF and serum potassium level >5.4 mmol/l were excluded.

At baseline, comprehensive sociodemographic data, clinical history, findings from physical examinations, and laboratory investigations—including NT-proBNP levels, serum creatinine, electrolytes, and liver function tests—were systematically collected. NT-proBNP levels were subsequently reassessed at the second follow-up to evaluate biochemical responses. Patients were monitored at 4 weeks and 12 weeks post-enrollment to assess adverse events, including hypotension, renal impairment, and hyperkalemia, as well as any instances of hospitalization or therapy discontinuation.

Study Outcomes

The primary endpoints of the study included the proportional change in NT-proBNP levels and the improvement in NYHA functional class by Week 12. The secondary endpoints encompassed alterations in left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), cardiovascular mortality, hospital re-admission for heart failure, and all-cause mortality, all assessed by Week 12. Additionally, safety endpoints were defined as the percentage of patients withdrawn due to adverse events, as well as the incidence of both adverse events and serious adverse events from baseline to Week 12.

Statistical Analysis

All data were systematically entered and analyzed utilizing SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were employed to summarize the baseline and follow-up characteristics of the participants. Continuous variables were presented as mean ± standard deviation (SD), accompanied by the interquartile range (IQR), with comparisons made using the paired t-test, as appropriate based on the distribution. Categorical variables were reported as frequencies and percentages, with comparisons conducted using the Chi-square test. A p-value of less than 0.05 was deemed statistically significant for all analyses.

Results

Study Population

A total of 914 patients diagnosed with HFrEF and treated with sacubitril/valsartan were initially enrolled in the study. Ultimately, 655 patients had comprehensive data available for both baseline and follow-up measurements of NT-proBNP. These 655 patients were included in the final analysis.

Sociodemographic Characteristics

Out of 655 patients included in the study, the majority were above 60 years (41.6%). The mean age of total patients was 57.98 ± 11.98 years. Males constituted 69.5% of the study population. Most patients had a healthy BMI (53.5%), while 38.9% were overweight and 4.5% were obese. Regarding smoking history, 43.2% were non-smokers, 40.2% were current smokers, and 18.6% were ex-smokers.

Demographic characteristics	Frequency	Percentage
Age		
<50 years	154	23.7%
50-60 years	226	34.7%
>60 years	271	41.6%
Sex		

Male	455	69.50%
Female	200	30.50%
BMI		
Underweight	14	3.10%
Healthy Weight	239	53.50%
Overweight	174	38.9%
Obesity	20	4.50%
Smoking history		
Non-smoker	263	43.2%
Smoker	233	40.2%
Ex-smoker	113	18.6%
Co-morbidity		
Stroke	36	5.5%
Diabetes	342	52.6%
MI	355	54.6%
AF	24	3.7%
Renal failure	67	10.3%
HTN	337	55.7%

Table 1: Demographic characteristics of study populations

Changes in NT-proBNP

Figure 1 and Table 2 provide a summary of the changes observed with sacubitril/valsartan treatment in the primary outcome measure, NT-proBNP, which is an essential biomarker for evaluating the severity of heart failure. At baseline, the mean NT-proBNP level was recorded at 2,867.15 ± 3,817.46 pg/mL. After treatment, this value demonstrated a substantial decrease to 938.41 ± 1,470.22 pg/mL. This reduction was statistically significant ($p < 0.001$), indicating a strong therapeutic effect and suggesting an improvement in cardiac function among the patients included in the final analysis.

Variables	Baseline	After 12 weeks	P-value
NT-proBNP (pg/mL); Mean ± SD	2867.15 ± 3817.46	938.41 ± 1470.22	<0.001
LVEF (%); Mean ± SD	34.80 ± 6.7 (%)	39.20 ± 6.4(%)	<0.001
LVEDD (mm); Mean ± SD	60.26 ± 6.3	57.34 ± 6.5	<0.001
Serum Sodium (mmol/L); Mean ± SD	137.92 ± 5.9	137.63 ± 4.2	0.150
Serum Potassium (mEq/L); Mean ± SD	4.24 ± 0.7	4.25 ± 0.6	0.983
Serum Creatinine (mg/dL); Mean ± SD	1.24 ± 0.4	1.18 ± 0.3	<0.001

Table 2: Changes under treatment with Sacubitril/Valsartan after 12 weeks of follow-up

Figure 2. Changes after 12 weeks treatment with sacubitril/valsartan-mean NT-proBNP (A) level significantly decreased from 2867.15 pg/mL to 938.41 pg/mL ($p<0.001$), LVEF (B) increased significantly from 34.80±6.7% % to 39.20±6.4% ($p<0.001$) and LVEDD (C) reduced significantly from 60.26±6.3 mm to 57.34±6.5 mm ($p<0.001$).

Figure 2 shows the percentage changes across five categories related to the extent of decline or increase. Specifically, 29% of patients exhibited a ≥75% decline in NT-proBNP, while 26.41% experienced a decline between 50% and 74.99%. Additionally, 20.76% of patients had a 25–49.99% decrease, and 19.54% showed a modest reduction of less than 25%. Notably, only 4.27% of patients demonstrated an increase in NT-proBNP levels. These data suggest that the majority of patients experienced a clinically meaningful reduction in NT-proBNP, indicative of improved cardiac status or treatment response.

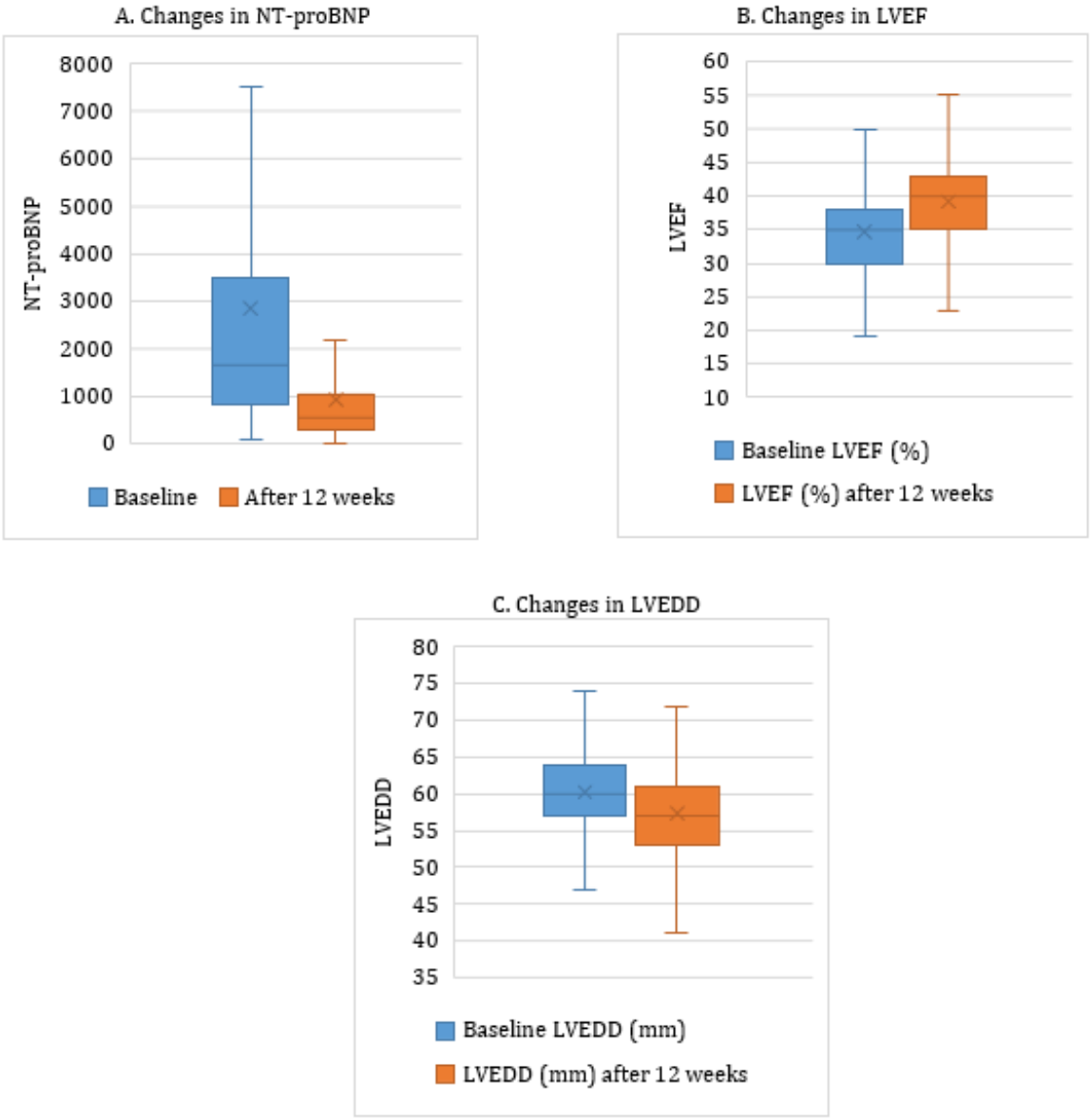

Figure 2: Patient distribution by NT-proBNP change.

Changes in NYHA Classification

In comparison to baseline measurements, the introduction of sacubitril/valsartan was associated with an enhanced clinical function. As illustrated in Figure 3, there was a notable improvement in the NYHA functional class among patients following the 12-week follow-up period. Initially, 0.2% of patients were classified as class I, 14.2% as class II, 71.5% as class III, and 14.2% as class IV. By the end of the 12 weeks, this distribution had improved, with 27.6% in class I, 60.0% in class II, 11.7% in class III, and only 0.6% remaining in class IV.

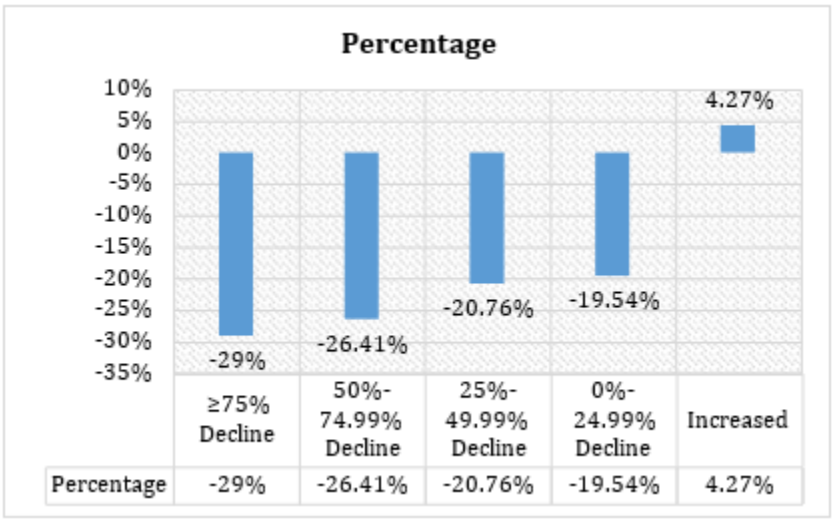

Figure 3. NYHA class before and after treatment with sacubitril/valsartan. Results are expressed as the percentage of patients

Changes in Other Parameters

The changes in LVEF, LVEDD, as well as serum creatinine, sodium, and potassium levels are detailed in Table 2. Notably, the LVEF improved significantly, increasing from 34.80 ± 6.7% to 39.20 ± 6.4% ($p < 0.001$), which indicates enhanced cardiac function. In parallel, the LVEDD showed a decrease from 60.26 ± 6.3 mm to 57.34 ± 6.5 mm ($p < 0.001$), suggesting favorable cardiac remodeling. Serum creatinine levels also exhibited a slight yet statistically significant reduction, from 1.24 ± 0.4 mg/dL to 1.18 ± 0.3 mg/dL ($p < 0.001$), reflecting potential renal stability or improvement. Conversely, the changes observed in serum sodium and potassium levels were not statistically significant, with p- values of 0.150 and 0.983, respectively, indicating electrolyte stability throughout the treatment period.

Adverse Events During Follow-up Periods

The frequency of adverse events generally declined from Follow-up 1 to Follow-up 2, suggesting improved tolerability or resolution of symptoms over time **(Figure 4).** Tolerable cough was the most commonly reported adverse event. Other adverse events observed during the follow-up periods included hypotension, allergic reactions, angioedema, and dizziness.

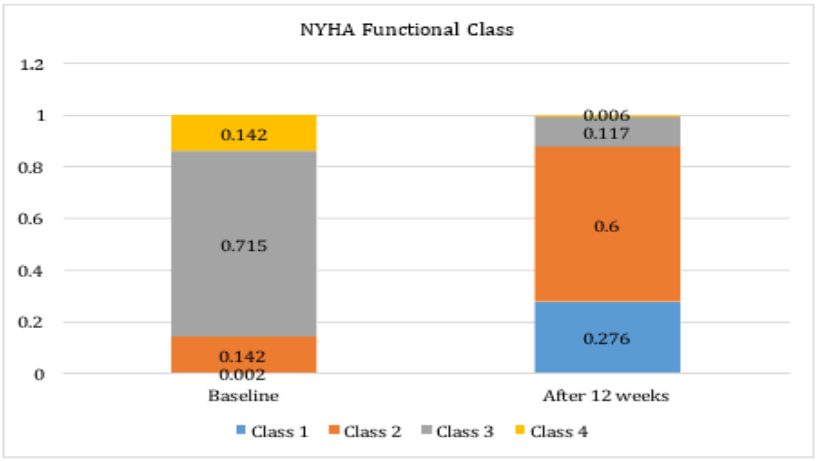

Figure 4: Adverse Events During Follow-up Periods

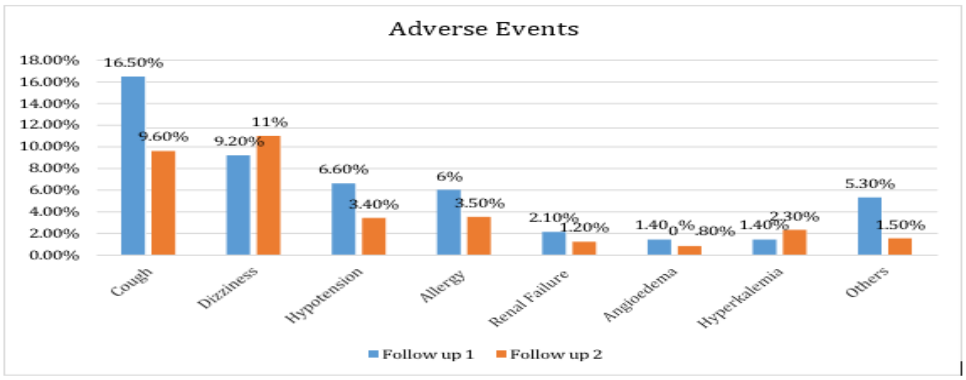

Figure 5: Adverse Events During Follow-up Periods

Discussion

This prospective, multicenter, real-world study in Bangladesh assessed the effectiveness and safety of initiating very low-dose sacubitril/valsartan (12/13 mg twice daily) in patients with heart failure with reduced ejection fraction. The results demonstrate clinically meaningful improvements in NT-proBNP levels, LVEF, LVEDD, and NYHA functional class, while maintaining a favorable safety and tolerability profile. These findings are consistent with those reported in both landmark randomized controlled trials and observational studies.

In the PARADIGM-HF trial, sacubitril/valsartan significantly reduced the risk of cardiovascular death or heart failure hospitalization by 20% compared with enalapril (McMurray et al., 2014). Our study similarly showed a notable reduction in NT-proBNP levels—from 2867.15 pg/mL to 938.41 pg/mL ($p< .001$)—a key biomarker predictive of prognosis in HFrEF. Furthermore, 85% of patients demonstrated an improvement in NYHA class, indicating significant symptomatic benefit.

The present findings align with real-world evidence. For example, Amitabh et al. (2019) reported a significant reduction in NT-proBNP (3703 to 1478 ng/mL, $p < .01$) among patients in California on very low doses of sacubitril/valsartan. In Korea, Hyoeun et al. (2019) observed a similar NT-proBNP decline (2594 to 2199 pg/mL, $p < .001$), with no differences in outcomes between standard and very low-dose groups. These studies also reported improvement in NYHA functional class, consistent with our observations.

Jingwen et al. (2019) found a reduction in NT-proBNP (from 2495 to 943 pg/mL, $p < .001$), a rise in LVEF (from 35.4% to 43.0%, $p < .001$), and a decrease in LVEDD (from 63.7 to 60.4 mm, $p < .01$), mirroring our findings (LVEF: 34.80% to 39.20%, $p < .001$; LVEDD: 60.26 to 57.34 mm, $p < .001$).

Renal and electrolyte safety were also observed in our cohort. While Amitabh et al. (2019) noted a non- significant rise in serum creatinine and potassium, our study revealed a statistically significant reduction in serum creatinine (1.24 to 1.18 mg/dL; $p < .001$), with no significant changes in potassium levels. These findings are in line with those from Jingwen et al. (2019), who reported no significant changes in creatinine or potassium levels.

Adverse events in our study were infrequent and generally mild. Tolerable cough was most commonly reported (16.5% at baseline, declining to 9.6% at 12 weeks), followed by hypotension (6.6% to 3.4%) and angioedema (1.4% to 0.8%). Jingwen et al. (2019) reported hypotension in 60% of patients during up-titration, with minimal cough and no angioedema. Similarly, Hyoeun et al. study showed, the most common adverse event was hypotension, but there was no significant difference in the adverse events between the two dose-groups. The most common cause for intolerance during up-titration was dizziness, and more patients complained of dizziness in the SD group compared to the VLD group.

Across various clinical trials and real-world studies, the tolerability and discontinuation rates of sacubitril/valsartan have shown notable variation. In PARADIGM-HF and PARAGON-HF, discontinuation due to adverse events occurred in 10.7% and 25.3% of patients, respectively (McMurray et al., 2014; Solomon et al., 2019). The TRANSITION study showed lower discontinuation rates when therapy was initiated in-hospital (7.1% pre-discharge, 5.6% post-discharge) (Welsh et al., 2019). In contrast, real-world discontinuation rates are generally lower. For instance, Jin Joo et al. (2019) reported a 5.2% rate, Alberto et al. (2018) reported none, and Muhammad et al. (2020) reported a higher rate (19.4%) related to dose adjustments. Remarkably, in our study, no patient discontinued sacubitril/valsartan therapy during the follow-up period, indicating excellent tolerability and adherence.

Importantly, our cohort was initiated on sacubitril/valsartan without a run-in phase or prior tolerance of high-dose ACE inhibitors, unlike the PARADIGM-HF protocol. This deviation was necessitated by the clinical characteristics of our population, which included lower average BMI, higher baseline hypotension, and frequent comorbidities (e.g., diabetes, hypertension). These factors may explain both the need for low-dose initiation and the observed high tolerability.

Limitations and Future Directions

This study has several limitations. First, the absence of a control group limits causal inference, as improvements cannot be definitively attributed to sacubitril/valsartan alone. Second, observational design is subject to potential confounders, such as variability in physician decision-making and adherence. Third, although multicenter, the study population was limited to Bangladesh, potentially reducing generalizability to broader populations. Fourth, the follow-up duration (12 weeks) may not capture long-term outcomes, including mortality and rehospitalization rates. Fifth, the use of echocardiography and laboratory parameters without centralized adjudication may introduce measurement bias.

Conclusion

The findings of this study support the therapeutic potential of initiating sacubitril/valsartan at a very low dose in patients with HFrEF, particularly in real-world clinical settings. Significant improvements in NT-proBNP levels, left ventricular function, and symptom burden, coupled with favorable tolerability, underscore the viability of low-dose initiation strategies—especially for patient populations with heightened sensitivity to standard dosages. Moreover, the enhanced tolerability profile may facilitate better treatment adherence. Nonetheless, these findings should be interpreted within the context of an observational design. Future randomized controlled trials are warranted to confirm the long-term efficacy, safety, and optimal dosing strategies of sacubitril/valsartan in diverse clinical populations.

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Conflict of Interest

The authors declare no conflicts of interest.

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