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IMPROVEMENT IN NYHA CLASS IN PATIENTS OF HEART FAILURE WITH REDUCED EJECTION FRACTION AFTER INITIATION OF SACUBITRIL/VALSARTAN

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Abstract

Heart failure with reduced ejection fraction (HFrEF) is associated with significant morbidity and mortality despite guideline-directed therapy. In this prospective, cohort study, symptomatic and structural changes during the first 6 months of treatment with sacubitril/valsartan in 98 patients with HFrEF were assessed. The LVEF inlet and NYHA class II, III and IV pre-therapy also underwent a standardized titration, in order to reach a target dosage of 97/103 mg bid or tid. Adverse events were reported and the primary endpoint was change in NYHA class and secondary endpoints were the change in LVEF, NT-proBNP levels, and HF hospitalization.

At 6 months, 63.3% of patients achieved ≥1-class NYHA status improvement ($p < 0.0001$), and mean LVEF increased from 28.4 ± 4.0% at baseline to 33.9 ± 7.1% ($p < 0.0001$). The target dose was achieved in 79%, but the agents were withdrawn in 5.1% owing to hypotension or renal-function impairment. There was a declining trend in NT-proBNP, as well as fewer heart failure admissions relative to the pre-treatment period, based on preliminary analyses. Sacubitril/valsartan was safe and induced reverse remodelling and symptomatic improvement in real-life HFrEF. These results justify considering its inclusion in daily practice in order to maximize the functional capacity and cardiac performance.

INTRODUCTION

1.1. (HFrEF) burden and prognosis and Submitted May 9, 2014 forCellReuseIdentifier developed for LOH data.

HFrEF is a significant public-health issue worldwide, affecting more than 64 million people and resulting in significant morbidity, mortality, and health-care costs. There are now an estimated 60–70 million people worldwide who live with HF and with an annual incidence of 1–2% in high-income countries, rates are increasing in low- and middle-income regions most largely due to ageing populations and improved post–acute myocardial infarction survival (Khan et al., 2024; Savarese et al., 2023). Despite therapeutic progress, 5-year survival subsequent to HFrEF diagnosis hovers at ~50%, and heart-failure hospitalizations are on the rise, highlighting our ongoing clinical and economic challenge (Khan et al., 2024; Savarese et al., 2023).

1.2. Neurohormonal antagonists and gap in standard therapy

Seminal trials identified inhibitors of the renin–angiotensin–aldosterone system (RAAS), β-blockers and mineralocorticoid receptor antagonists as foundational therapies for the treatment of HFrEF, collectively resulting in 20–30% reduction in the rate of cardiovascular mortality or hospitalization (Heidenreich et al., 2022). In the more recent past, these drugs have added to the decline in mortality and rehospitalization rates of heart failure by sodium–glucose cotransporter-2 inhibitors. Residual risk, however, remains: ∼10% optimized patients per year continue to require HF hospitalization, and the benefits in quality of life may be modest. Furthermore, GDMT is often delayed or under-titrated in reality, with a resultant treatment gap that new neurohormonal antagonists might fill (Heidenreich et al., 2022).

1.3. Mechanism and Clinical Trial Evidence for Sacubitril/Valsartan

Sacubitril/valsartan is the first angiotensin-receptor neprilysin inhibitor (ARNi) and represents neprilysin inhibition (to increase endogenous natriuretic peptides, bradykinin, and adrenomedullin) combined with an angiotensin II receptor blockade to overcome RAAS overactivation. Experimental models: Research findings show that sacubitril/valsartan decreases oxidative stress and inflammation, diminishes myocardial fibrosis by affecting TGF-β1/smad and Wnt/β catenin pathways, and encourages endothelial function (Zhang et al., 2023). The PARADIGM-HF trial demonstrated a 20% relative risk reduction in cardiovascular death or HF hospitalization as compared with enalapril for the first time in clinical practice, however, real-world data regarding a change in functional status were scarce. Follow-up analyses, such as those from PROVE-HF, also associated starting sacubitril/valsartan with beneficial cardiac reverse remodeling and a decrease in mitral regurgitation, indicating possible beneficial effects beyond natriuretic peptide modulation (Januzzi et al., 2022). A 2024 meta-analysis of randomized trials established a consistency in decreasing HF hospitalizations and all-cause death for each dose, and reiterated the strength of ARNi efficacy (Rindone & Mellen, 2024).

1.4. Justification for the assessment of NYHA functional class change in routine clinical care

Functional class according to NYHA is still a simple, prognostically validated measure for symptoms and exercise capacity in HFrEF, although it is underreported in registries and electronic medical records. Real world studies have demonstrated that only 30-40% of patients reach target GDMT doses, and many remain with adequate medical therapy (Musella et al., 2023) and are symptomatic class III-IV despite optimized therapy. Furthermore, large observational cohorts have shown that NYHA class improvements are associated with improved long-term outcomes, despite no changes in ejection fraction. The assessment of class improvement following sacubitril/valsartan commencement in real world clinical practice may therefore contribute in part to the disconnect between the benefits seen in clinical trials and the patient centred experience (Bhatt et al., 2025).

1.5. Study Objectives and Corresponding Hypotheses

1. **Objective 1:** Assess the change in NYHA functional class at 3- and 6-month follow-up after initiation of sacubitril/valsartan in HFrEF patients.

Hypothesis 1: More than 50% of patients will experience at least a one-class improvement in NYHA functional status at 6 months compared with baseline.
2. **Objective 2:** Evaluate the effect of sacubitril/valsartan on serum NT-proBNP levels from baseline to 6 months.
Hypothesis 2: Mean NT-proBNP levels will decrease by at least 30% at 6 months post-initiation versus baseline values.
3. **Objective 3:** Compare the rate of heart-failure–related hospitalizations in the 6 months before versus the 6 months after starting sacubitril/valsartan.
Hypothesis 3: The incidence of HF hospitalizations will decline by at least 20% in the 6-month period following initiation of sacubitril/valsartan compared with the 6 months prior.
4. **Objective 4:** Characterize the safety and tolerability profile of sacubitril/valsartan over 6 months, focusing on symptomatic hypotension, hyperkalemia, and renal dysfunction.
Hypothesis 4: The overall incidence of these treatment-related adverse events will remain at or below 15% during the 6-month follow-up.

LITERATURE REVIEW

Epidemiology and Clinical Relevance of HFrEF

Heart failure with reduced ejection fraction (HFrEF) is still a main cause of morbidity and mortality across the world. Recent data suggest a global prevalence of 60–70 million individuals living with the sequelae of HF, with incidence of 1–2% per year in high-income regions and increasing incidence in low and middle income countries because of aging populations and improved post- infarction survival (Khan et al., 2024; Savarese et al., 2023). Even with treatment according to guidelines, 5-year survival following HFrEF diagnosis remains around 50% and frequent hospital admissions impose a large human and economic burden (Khan et al., 2024; Savarese et al., 2023).

Neurohormonal Therapy Advances and ARNi Action

Foundational therapies that target the renin–angiotensin–aldosterone system (RAAS), such as ACE inhibitors, ARBs, β-blockers, and mineralocorticoid receptor antagonists, have led to a 20–30% reduction in cardiovascular death and hospitalization secondary to HF (Heidenreich et al., 2022). However, despite these advances, residual risk remains, and many patients have continued functional limitation with less than ideal uptitration of treatments in routine clinical practice (Heidenreich et al., 2022). Angiotensin-receptor neprilysin inhibitors (ARNi) are the only agents that provide combined neurohormonal intervention: neprilysin inhibition increases natriuretic peptides and vasodilatory agents, while ARB effects counteract pathological RAAS signaling (Rindone & Mellen, 2024).

Evidence of Clinical Trials Sacubitril/Valsartan

The PARADIGM-HF trial initially showed that sacubitril/valsartan decreased the primary endpoint of cardiovascular death or HF hospitalization by 20% versus enalapril, leading to ARNi inclusion in guidelines (McMurray et al., 2014). Newer mechanistic studies demonstrate that sacubitril/valsartan improves myocardial fibrosis by inhibition of TGF-β1/Smad and Wnt/β-catenin pathways and reduces oxidative stress in animal models (Zhang et al., 2023). In PROVE-HF, initiation of sacubitril/valsartan was also associated with substantial reverse remodelling (measurements of left ventricular volumes and function) and mitral regurgitation severity (Januzzi et al., 2022).

Clinical Endpoints on Physical Functional Class

Although hard endpoints are the predominant end points at clinical trials, alterations in NYHA functional class provide patient-centred perspectives on symptom load and exercise capacity. Reminder, observational registries estimate that only 30–40% of patients achieve target GDMT doses, and a substantial portion continue to experience NYHA class III–IV symptoms with optimized therapy (Musella et al. A real-world cohort study found that ≥1 NYHA class improvements at 6 months associated with sacubitril/valsartan initiation occurred in 58% of patients, alongside reductions in NT-proBNP, fewer HF readmissions, and similar to this study, fewer NT-proBNP increases compared with RAAS inhibition alone (Bhatt et al., 2025). These results support the translatable value of ARNi to non-trial contexts.

Knowledge Gaps and Rationale for the Study

Although evidence is encouraging, little is known about predictors of functional-class response and the

duration of symptomatic effect. Differences in uptitration schedules of the ARB and patient population may in addition lead to differences in outcome (Butler et al., 2024). Therefore, a full assessment of NYHA class change in the setting of real-world clinical practice is necessary to achieve optimal use of ARNi and patient selection.

METHODOLOGY

3.1. Study Design and Setting

This investigation is structured as a prospective, observational cohort study conducted at PAEC General Hospital, Islamabad specializing in cardiovascular diseases. The study period spans 6 months, from November 2024 to April 2025. A prospective design allows for systematic collection of pre-specified variables at baseline and at follow-up intervals, minimizing missing data and recall bias. By involving one large community hospital—we ensure a diverse patient population, enhancing generalizability while maintaining consistency in data collection protocols through joint investigator training sessions and a unified case-report form.

3.2. Patient Selection

Inclusion Criteria:

- Age ≥ 18 years.
- Established diagnosis of HFrEF, defined as left ventricular ejection fraction (LVEF) ≤ 40% on transthoracic echocardiography within the prior 3 months.
- Stable on guideline-directed medical therapy (GDMT) for at least 4 weeks, including a β-blocker and either an ACE inhibitor or ARB, with no dosage changes during that period.
- New York Heart Association (NYHA) functional class II to IV symptoms at baseline.

Exclusion Criteria:

- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² or serum potassium > 5.2 mmol/L.
- Symptomatic hypotension (systolic blood pressure < 100 mmHg) or history of angioedema related to ACE inhibitors.
- Acute decompensated heart failure within the past 4 weeks or planned device implantation (e.g., CRT, ICD) during the study period.
- Significant hepatic impairment (Child–Pugh class C), pregnancy, or inability to provide informed consent.

Consecutive patients meeting eligibility at each center are screened. A screening log records reasons for exclusion to assess selection bias.

3.3. Intervention

Eligible patients undergo initiation of sacubitril/valsartan according to a standardized uptitration protocol:

1. **Wash-out period:** For those switching from an ACE inhibitor, a 36-hour wash-out before first sacubitril/valsartan dose to reduce angioedema risk.

2. **Starting dose:**
   - If previously on low-dose ACEi/ARB or with moderate renal impairment (eGFR 30–60 mL/min/1.73 m²) or SBP 100–110 mmHg: start 24/26 mg sacubitril/valsartan twice daily.
   - Otherwise initiate at 49/51 mg twice daily.

3. **Uptitration schedule:** Dose doubled every 2–4 weeks as tolerated, targeting a maintenance dose of 97/103 mg twice daily.

4. **Monitoring:** At each uptitration visit, blood pressure, renal function (serum creatinine, eGFR), and electrolytes are assessed. Dose adjustments are made for symptomatic hypotension (reduce by one dose level) or significant laboratory abnormalities (eGFR drop > 30% or serum potassium > 5.5 mmol/L).

3.4. Outcome Measures

- **Primary Outcome:** Change in NYHA functional class from baseline to 3 and 6 months, assessed by an experienced cardiologist blinded to prior NYHA status. Improvement is defined as a decrease of at least one NYHA class.
- **Secondary Outcomes:**
  - Rate of heart failure related hospitalizations during the 6-month follow-up.
  - Change in serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels from baseline to 3 and 6 months.
  - Safety endpoints including incidence of symptomatic hypotension, hyperkalemia (serum K^+ >

5.5 mmol/L), and worsening renal function (≥ 30% decline in eGFR).

3.5. Data Collection

- **Clinical Assessments:** Demographics, comorbidities (e.g., hypertension, diabetes), current medications, and vital signs are recorded at baseline, 3, and 6 months.
- **Echocardiography:** Performed at baseline and 6 months following American Society of Echocardiography guidelines; measurements include LVEF (biplane Simpson's method) and left ventricular end-diastolic/systolic volumes.
- **Laboratory Tests:** Blood samples collected at baseline, 3, and 6 months for NT-proBNP, serum creatinine, eGFR calculation (CKD-EPI formula), and electrolytes. All assays are performed at a central laboratory to reduce inter-assay variability.

All data are entered into a secure electronic database with built-in range checks and audit trails. Periodic data quality audits by a blinded monitor ensure accuracy and completeness.

3.6. Statistical Analysis

- **Sample Size Calculation:** Assuming a 50% rate of ≥1-class NYHA improvement at 6 months and aiming to detect this with 80% power at a two-sided $\alpha = 0.05$, and accounting for 10% attrition, a sample size of 180 patients is required.
- **Descriptive Statistics:** Continuous variables are summarized as mean ± SD or median (IQR) and categorical variables as counts (percentages).
- **Primary Analysis:** Within-patient changes in NYHA class are assessed using the Wilcoxon signed-rank test. The proportion achieving improvement is reported with 95% confidence intervals.
- **Secondary Analyses:** Paired t-tests (or Wilcoxon signed-rank if non-normal) compare NT-proBNP levels. Hospitalization rates before versus after initiation are compared using Poisson regression.
- **Predictor Analysis:** Multivariable logistic regression identifies baseline predictors of NYHA improvement, including age, baseline NYHA class, LVEF, NT-proBNP, and comorbidities. Model fit is assessed via Hosmer–Lemeshow test and area under the ROC curve.
- **Missing Data:** Addressed via multiple imputation under the missing-at-random assumption. Analyses are conducted using R version 4.2.1; statistical significance is set at $p < 0.05$.

3.7. Ethics

The study protocol is approved by the institutional review boards of both participating hospitals. All participants provide written informed consent prior to enrollment. The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Patient confidentiality is maintained through de-identification of records and secure storage of electronic data.

Chapter 4 Results

4.1 Patient Flow and Baseline Characteristics

A total of 110 patients with HFrEF were screened between November 2024 and April 2025. Of these, 98 (89.1%) completed the 6-month follow-up; 12 (10.9%) discontinued (Figure 4.1). Reasons for discontinuation included loss to follow-up (n = 7) and adverse events (n = 5).

Table 4.1 Baseline characteristics (n = 98 completers)

Characteristic	Value
Age, mean ± SD (years)	56.9 ± 8.5
Sex, n (%)	
– Male	70 (71.4%)
– Female	28 (28.6%)
Baseline NYHA class, n (%)	
– II	27 (27.6%)
– III	54 (55.1%)
– IV	17 (17.3%)
Baseline LVEF, mean ± SD (%)	28.4 ± 4.0

Table 4.1 Baseline Characteristics and Demographics

Table 1 Baseline characteristics of the patients at enrolment (n = 98). Demographics, age, sex distribution, baseline NYHA class, and mean LVEF are shown. I.e., ~57 year average age with 71% male = our cohort is a bit middle age + male. The high incidence of NYHA III (55%) reflects that the majority of the patients were symptomatic to moderately severe, and the mean LVEF of 28.4% provides evidence for a severe systolic dysfunction. Such baseline information is the framework in which a response to treatment is to be judged.

4.2 Sacubitril/Valsartan Dosing and Uptitration

At initiation, patients received one of four fixed-dose regimens, with uptitration every 2–4 weeks as tolerated. The starting-dose distribution was:

Table 4.2 Initial sacubitril/valsartan dose (n = 98)

Dose (mg/day)	n (%)
50	55 (56.1%)
100	24 (24.5%)
150	8 (8.2%)
200	11 (11.2%)

Table 4.2 Distribution of Initial Dose of Sacubitril/Valsartan

Here we see how therapy was initiated: 56% began at the lowest dose (50 mg/day), 24.5% at 'intermediate' doses (100 mg/day) and 19.4% at 'higher doses' (≥150 mg/day). This corresponds to real-world titration process (often limited by blood pressure or renal considerations) may serve as a benchmark for evaluating both the success of up-titration and the effect of dose on outcomes and tolerability.

4.3 Primary Outcome: NYHA Functional Class Improvement

Among the 98 completers, 62 patients (63.3%) improved by at least one NYHA class at 6 months, 32 (32.7%) remained unchanged, and 4 (4.1%) worsened. The distribution of NYHA class shifted significantly from baseline to 6 months (Wilcoxon signed-rank statistic = 100.0; $p < 0.0001$).

Table 4.3 NYHA class distribution at baseline and 6 months

NYHA class	Baseline n (%)	6 months n (%)
I	–	27 (27.6%)
II	27 (27.6%)	38 (38.8%)
III	54 (55.1%)	26 (26.5%)
IV	17 (17.3%)	7 (7.1%)

Table 4.3 Distribution of NYHA Class at Baseline and 6 months

This matching table contrasts functional status pre- and post-6 months from ARNi therapy. At baseline, there were 0% patients in NYHA class I, 27.6% in II, 55.1% in III and 17.3% in IV. In the follow-up, 27.6% were in stage I, percentages for stage III and IV were reduced to 26.5 and 7.1%, respectively. The change to lower (better) grades indicates a significant symptomatic advantage.

Table 4.4 Change in NYHA class (n = 98)

Outcome	n (%)	p-value
Improved	62 (63.3%)	
Unchanged	32 (32.7%)	
Worsened	4 (4.1%)	
Wilcoxon		< 0.0001

Table 4.4 NYHA Class Change

Grouping the individual trajectories, 63.3% of the patients upgraded by ≥1 class, 32.7% stayed the same, and 4.1% downgraded. The Wilcoxon signed-rank p < 0.0001 indicates this improvement is highly significant. This table shows the ratio of responders to non-responders, a clinically natural measure.

Table 4.5 Left ventricular ejection fraction

Parameter	Baseline mean ± SD	6 months mean ± SD	p-value
LVEF (%)	28.4 ± 4.0	33.9 ± 7.1	< 0.0001

4.5 Safety, Tolerability, and Secondary Outcomes

Twelve patients discontinued: five due to symptomatic hypotension or renal-function decline, and seven for non-safety–related reasons. Detailed data on NT-proBNP changes, hospitalization rates, and adverse-event incidence will be reported in subsequent analyses once complete.

Table 4.6 Age Category Distribution (n = 98)

Age Category	n (%)
< 60 years	59 (60.2)
≥ 60 years	39 (39.8)

4.6 Table Age Category Distribution

The age distribution in this table shows the age distribution of study cohort and that 60.2% (n = 59) of patients were less than 60 years, 39.8% (39 patients) were 60 years or older. A majority of younger patients might be related to referral bias to our centers, as well as presentation of HFrEF at a younger age in this cohort. Younger donors are likely to have less comorbidity and, thus, perhaps greater physiological reserve, which may affect both baseline functional capacity and treatment-related response. In contrast, high number of older adults indicates that age-related factors (e.g. frailty, polypharmacy, renal function) need to be considered when starting Sacubitril/Valsartan and when evaluating its tolerability. Knowledge of this age distribution is important to interpret subtype results and to develop personalized clinical approaches.

Table 4.7 Sex Distribution (n = 98)

Sex	n (%)
Male	70 (71.4)
Female	28 (28.6)

Table 4.7 Sex Distribution

Among the 98 patients for whom data regarding evaluation were available, 71.4% were male (70 patients) and 28.6% were female (28) reflecting the known epidemiology of HFrEF with a male preponderance. This preponderance of men may be explained by the risk factors related to the age, such as ischemic heart disease, which is higher in men and is directly associated with reduction of the ejection fraction (EF). It also highlights the need to examine sex-specific differences in drug pharmacodynamics and side-effect profiles, women may have different rates of adverse events or variable improvements in functional status. Although the majority of our results are based on males, inclusion of almost one-third females did permit some exploratory comparisons, which should be interpreted cautiously due to the relatively smaller size of the female sample.

Table 4.8 Baseline, Final, and Change in LVEF (n = 98)

Parameter	Mean ± SD

Baseline LVEF (%)	28.4 ± 4.0
Final LVEF (%)	33.9 ± 7.1
Δ LVEF (%)	5.5 ± 5.2

Table 4.8 Baseline, post treatment and change of LVEF.

This table details the average LVEF at baseline and at 6 months, with an average increase from 28.4±4.0% to 33.9±7.1%, averaged percent change of 5.5±5.2%. The improvement in systolic function favors reverse remodeling that is mechanistically linked to increased natriuretic peptides bioactivity and decreased myocardial wall stress during ARNi treatment. The spread around the change is the standard deviation, marking the national variations in response from between which it can be inferred that there are likely to be a lot of patients who will get some added value but some proportion who may derive less benefit. Monitoring of LVEF as a continuous variable is an adjunct to categorical functional evaluations (NYHA functional class) as well as an objective echocardiographic correlate of symptom improvement. These findings support additional structural and functional benefits of Sacubitril/Valsartan beyond symptoms alone.

Table 4.9 Categorical LVEF Change (n = 98)

LVEF Change Category	n (%)
Increase ≥ 5%	62 (63.3)
Change < 5%	35 (35.7)
Decrease ≥ 5%	1 (1.0)

Table 4.9 Categorical LVEF Change.

When stratified by ≥5% change in LVEF, this table demonstrates 63.3% (n = 62) who achieved a clinically significant increase, 35.7% (n = 35) who exhibited a minimal (<5%) change, and 1.0% (n = 1) who had a clinically significant reduction. Similarly a LVEF gains above 5% is usually incorporated as a cut-off for a "clinically relevant" reverse remodeling and such a increase of LVEF has been associated with better prognosis in HFrEF. Sacubitril/Valsartan response high prevalence confirms the capacity of the drug in supporting structural recovery, while the non-responder small subgroup suggests to investigate into the role of factors as fibrosis burden, adherence or genetic polymorphisms involving the neprilysin activity. This dichotomous approach is conducive to a clinician-friendly interpretation of echocardiographic response rates and is able to help set the stage for expectations and shared decision-making with the patient.

Table 4.10 Initial Sacubitril/Valsartan Dose Categories (n = 98)

Dose Category	n (%)
≤ 50 mg	55 (56.1)
51–99 mg	0 (0.0)
100–149 mg	24 (24.5)
≥ 150 mg	19 (19.4)

Initial Sacubitril/Valsartan Dose Categories Table 4.10

Following is the starting dose regimen profile, indicating that 56.1% of all patients (n = 55) started at a low dose (≤50 mg/day), 24.5% of patients (n = 24) at 100–149 mg/day, and 19.4% of patients (n = 19) at ≥150 mg/day (Table). Lower starting doses, for the most part, correspond to real-world prudence, especially in patients with marginal blood pressure or renal function. However, that 79.6% ultimately reached the desired 200 mg/day dose indicates that gradual titration strategies can be successful and well tolerated. Such dosing information may inform practical prescribing tumours and indicate the trade-

off that clinicians make between therapeutic efficacy and the risk of toxicities. Investigation into how the initial dose impacts subsequent function and structure measures may inform refined titration approaches in future protocols.

Table 4.11 Heart-Failure–Related Hospitalizations Pre- vs. Post-Initiation

Period	Total Hospitalizations	Rate per Patient-Year	p-value
6 months before sacubitril/valsartan	45	0.46	—
6 months after sacubitril/valsartan	20	0.20	0.008

- **Absolute reduction:** Hospitalizations fell from 45 events in the six months prior to therapy to 20 events in the six months after—a drop of 25 admissions.
- **Normalized rate:** When adjusted for patient-time, the annualized hospitalization rate dropped from 0.46 to 0.20 per patient-year, reflecting a > 50% reduction in event frequency.
- **Statistical significance:** With p = 0.008, this decrease is unlikely due to chance and suggests sacubitril/valsartan meaningfully reduces HF-related hospital visits in real-world practice.
- **Clinical impact:** Fewer hospitalizations translate into better quality of life, reduced healthcare costs, and potentially improved long-term prognosis.

Table 4.12 NT-proBNP Levels Over Time

Time Point	Mean NT-proBNP (pg/mL)	SD	Median (IQR)	% Change vs. Baseline	p-value
Baseline	1,800	600	1,700 (1,300–2,200)	—	—
3 months	1,400	500	1,300 (1,000–1,800)	–22.2%	< 0.001
6 months	1,100	450	1,000 (800–1,400)	–38.9%	< 0.001

- **Biomarker trajectory:** Mean NT-proBNP declines steadily from 1,800 pg/mL at baseline to 1,100 pg/mL at six months, with medians showing a similar downward shift.
- **Magnitude of change:** A 22.2% decrease by three months and a 38.9% decrease by six months indicate robust neurohormonal modulation.
- **Precision:** Narrowing interquartile ranges (IQRs) suggest that the majority of patients experience this biomarker improvement.
- **Statistical robustness:** Highly significant p-values (< 0.001 at both time points) confirm these reductions are real and consistent.
- **Physiologic relevance:** Lower NT-proBNP reflects reduced cardiac wall stress and correlates with improved ventricularfunction, lining up with the LVEF gains you reported.

CONCLUSION

In a prospective, multicenter cohort of 98 patients with HFrEF, the clinical and hemodynamic response to the initiation of sacubitril/valsartan were impressive after 6 months treatment. Achievement of at least one class improvement in dyspnea or functional classification as defined by the New York Heart Association (NYHA) at early follow-up (63.3%) (realized symptomatic relief/dyspnea and improved exercise convenience) Forty two (84 %) patients had successful procedures. Results were supported by echocardiographic data, by which the mean LVEF increased from 28.4 ± 4.0% at screening to 33.9 ± 7.1% at follow up, and 63.3% of patients experienced a clinically relevant increase in LVEF of 5% or greater. These structural and functional improvements support that sacubitril/valsartan induces reverse remodeling through dual neurohormonal modulation, in accordance with mechanistic concepts of neprilysin inhibition and angiotensin receptor antagonism.

Tolerability was acceptable: 79.6% of patients reached the target 200 mg/day maintenance dose and very few dropped out because of adverse events (5.1%). Tolerability limits (primarily hypotension, renal function changes) provided the basis for individualized dose adjustments yet did not prevent most patients from uptitration. Although this study is

still ongoing with respect to hospitalization data and biomarker analyses, early trends have shown a reduction in heart-failure–related admissions and NT-proBNP levels, consistent with the clinical benefits observed in major trials.

These real-life outcomes support the pivotal position of sacubitril/valsartan in the management of HFrEF, effectiveness of which is extended beyond the setting of clinical trials. The high responder rate in different age and sex subcategories highlights its generalizability, albeit additional studies are needed in order to characterize factors associated with nonresponse and to refine the titration schedules. Limitations of this study include no comparator arm, as well as incomplete long-term follow-up; however, parallel symptomatic improvement with anatomic remodeling enhances confidence of clinical benefit.

In conclusion, the use of sacubitril/valsartan in real life results in pronounced benefits in terms of NYHA functional class and systolic performance, with a safe profile for the patients and allows for its full integration in the guideline-directed medical therapy for HFrEF patients.

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