**Comparative Outcomes in Patients with Heart Failure with Reduced Ejection Fraction Treated with ACEIs/ARBs Versus Sacubitril/Valsartan**

***ABSTRACT***

***Background:*** *Millions of people worldwide are affected by the very serious condition of heart failure with reduced ejection fraction (HFrEF). Both ACEI/ARB and Sacubitril/Valsartan are important treatments, even though we lack many real-world comparisons.* ***Objective:*** *the aim of the study is to identify the differences in outcomes observed in patients with HFrEF taking Sacubitril/Valsartan versus ACEI/ARB treatment.* ***Methodology:*** *An observational cohort study was conducted with 114 patients with HFrEF (LVEF ≤40%) and categorized into Group A (treated with ACEI/ARB) and Group B (treated with Sacubitril/Valsartan). The study timeline was July 2023 and September 2024 at Ibrahim Cardiac Hospital & Research Institute. Relevant measurements (EF, SBP, HR, NT-proBNP, eGFR, potassium, NYHA class, symptoms, and adverse events) were recorded both before and after treatment. The statistical analysis employed SPSS for t-tests, chi-square tests, and odds ratios (only the results with p<0.05 were considered significant).* ***Result:*** *The mean baseline EF was lower for Group B (33.69%) than for Group A (36.67%), and this difference was significant (p=0.017). Following the treatment course, there was no real difference in EF improvement between the groups (Group A: 53.3%, Group B: 58.0%, p=0.473). The SBP was lower in Group B (115.6 mmHg) than in Group A (125.0 mmHg), and this difference was statistically significant (p=0.023). Group A had an 87.5% increase in NYHA Class I, higher than Group B’s 67.8% (p=0.056). Similar adverse effects were noted in patients (hyperkalemia, hypotension, renal impairment). Mortality (4.2% for group A and 2.2% for group B) and rehospitalization (4.2% for group A and 1.1% for group B) were not significantly different (p>0.05). There were no major differences in symptom relief for dyspnea, orthopnea, or PND (p>0.6).* ***Conclusion:*** *Sacubitril/Valsartan and Enalapril were found to be effective in treating HFrEF and gave similar safety and outcome results, though Sacubitril/Valsartan did a better job of controlling the heart’s blood flow.*

***Keywords:*** *Heart failure,**HFrEF, Sacubitril/Valsartan, ACEI/ARB, ejection fraction, NYHA class*

**Abbreviation**
**HF =** Heart Failure

**EF =** Ejection Fraction

**HFrEF=** Heart Failure with Reduced Ejection fraction

**ACEI=** Angiotensin-converting enzyme inhibitor

**ARB=** Angiotensin II receptor blocker

**ARNI=** Angiotensin receptor-neprilysin inhibitor

**GDMT=** Guideline-directed medical therapy

**MRA=** Mineralocorticoid receptor antagonist

1. **INTRODUCTION**

Heart Failure (HF), a complex life-threatening symptom characterized by the heart's inability to pump enough blood to function the body (Pirbhat Shams, 2025). Globally, 64 million people are affected by Congestive Heart Failure (Gianluigi Savarese, 2023). Murphy *et al.*, 2020 stated that among Chronic Heart Failure (CHF) patients, about 7.2% die within one year and 31.9% need to be hospitalized, but for acute heart failure patients, these numbers rise to 17.4% for mortality and 43.9% for hospitalizations (Sean P. Murphy, 2020). Commonly, HF results from ischemic heart disease, but some associated factors, including hypertension, valvular disease, and myocarditis, can worsen the condition (Pirbhat Shams, 2025). Heart failure with reduced ejection fraction (HFrEF) is a condition described as the left ventricular ejection fraction falling below 40% and is accompanied by worsening dilation and negative heart changes (Sean P. Murphy, 2020). For a long time, using ACEIs and ARBs as RAAS inhibitors has led to better results in heart failure (Petar M Seferovic, 2019) (Clyde W Yancy, 2017). In HFrEF, sacubitril/valsartan, which combines an ARB and a neprilysin inhibitor, was shown to reduce mortality and hospitalizations during the PARADIGM-HF trial (John J V McMurray, 2014). Compared to enalapril, it was shown to be better, but few studies look at its efficacy against other ACEIs or ARBs, especially in a range of diseased or co-diseased groups (Lauren Gilstrap, 2022). Comparative data from real-world situations is not widely available. Heran B. S.. *et al.*, 2012 reported that ARB’s wide blood vessels and decrease BP for hypertension patients (Balraj S Heran, 2012) and PARADIGM-HF study demonstrated that sacubitril/valsartan reduces 20% risk of cardiovascular death and prolonged hospitalization (Domingo Pascual-Figal, 2021). Despite the availability of medications that extend life, prevent hospital stays, and improve quality of life, these are often withheld or given late for people who fit the requirements (Vishal N. Rao, 2024). Although patients with HFrEF receive ACEI/ARB, they face serious risks of suffering from or dying from the condition. PARADIGM-HF indicates that Sacubitril/Valsartan is superior to ACEI, but there is not much available data comparing their use in the real world. The purpose of this study is to assess and differentiate the outcomes in real medicine. The study aims to directly compare the use of Sacubitril/Valsartan with ACEI/ARB in HFrEF patients at a tertiary hospital, evaluating both safety and benefits in real-world use. The outcomes of these studies assist in selecting personalized treatments and better decisions in medical teams.

**2. MATERIALS AND METHODS**

**2.1 Study Design**

The study is a cohort observational study at the Department of Cardiology, Ibrahim Cardiac Hospital & Research Institute, carried out from July 2023 to September 2024. It is designed for people with HFrEF (EF ≤ 40%), randomly separating them into those assigned to ACEI/ARB and those who take Sacubitril/Valsartan. Comparing the outcomes between the two treatments includes mortality, heart muscle effectiveness, and possible negative events such as high potassium, low blood pressure, and kidney problems.

By using the hypothesis-testing formula introduced by Zhang et al., 2024 and data from previous studies, we estimated the ideal sample size to see if there is a difference in rehospitalization (Zhaowei Zhang, 2024).

**2.2 Study Sampling**

The study's goal is to collect evidence from the field and assess each therapy’s effectiveness, safety, and cost when managing HFrEF. The study followed purposive sampling process. Based on a proportion of 46.5% (ACEI/ARB) and 30.4% (Sac/Val), the required sample size was set to be at least 114, with some inclusion and exclusion criteria. Group A stands for the ACEI/ARB intervention with 24 patients, and Group B stands for the Sacubitril/valsartan-treated group with 90 patients.

**2.2.1 Inclusion criteria**

* Adults (≥18 years) with a diagnosis of HFrEF (LVEF <40%).
* Patients treated with Sacubitril/Valsartan VS ACEI/ARB.

**2.2.2 Exclusion criteria**

* Patients with a history of intolerance to either ACEI/ARB or Sacubitril/Valsartan
* Patients with recent (<6 months) heart failure diagnosis or those treated with other investigational heart failure therapies
* Baseline SBP <110 mmHg,
* Serum potassium >5.5,
* Congenital heart disease

**2.3 Data Management & Analysis Plan**

SPSS Statistics was used to examine the collected data. Statistical analysis has given an overview of basic data, and t-tests and chi-square tests will allowed us to compare continuous and categorical data. The odds ratios (ORs) demonstrated if certain risk factors can predict a repeat hospitalization or higher risk of death, while statistical significance will be considered at p < 0.05.

**3. RESULTS**

The baseline traits found that those taking Sacubitril/Valsartan were on average 57 years old (compared to an average of 50 years old, p=0.022) and included more women (16.7% vs 0%, p=0.032), but hypertension, diabetes, and smoking were equally common across groups. The Hemodynamic and Laboratory data found that at the beginning of treatment, Sac/Val patients had a lower average baseline ejection fraction (p=0.017), but their NT-proBNP, SBP, HR, and eGFR did not differ, suggesting they had similar hemodynamic and kidney status. The changes in cognitive performance and NT-proBNP were not significant between the groups after treatment, and while SBP increased significantly in the ACEI/ARB group, other measurements like HR and eGFR remained the same for both groups (Table 3). NYHA Class I included a larger percentage of ACEI/ARB patients (87.5%) than Sac/Val patients (67.8%, p=0.056), showing faster improvement in these patients. The few hyperkalemia events, cases of hypotension and effects on the kidneys lasted for a short period in all groups and no serious differences were seen (p > 0.3). The mortality rate and the rate of patients being re-admitted were low and they did not differ significantly (4.2% vs 2.2% and 4.2% vs 1.1%, respectively). Symptom relief was found to be similar in patients with PND and dyspnea (p=0.971 and p=0.604, respectively). Both groups also experienced complete resolution of orthopnea, confirming that both drugs performed similarly well.

*Figure 1: Column chart showed demographic distribution of patients, age*

**Table 1: Baseline characteristics of patients (N=114)**

| **Characteristic** | **Group A****ACEI/ARB (n=24)** | **Group B****Sac/Val (n=90)** |
| --- | --- | --- |
| Mean Age (years) | 55.5 ± 8.85 | 60.88 ± 10.32 |
| Male (%) | 100% | 83.3% |
| Hypertension (%) | 75.0% | 77.8% |
| Diabetes Mellitus (%) | 66.7% | 71.1% |
| Smoking (%) | 50.0% | 30.0% |

**Table 2: Baseline Hemodynamic and Laboratory Data**

| **Parameter** | **Group A****ACEI/ARB (n=24)** | **Group B****Sac/Val (n=90)** | **p-value** |
| --- | --- | --- | --- |
| EF at Baseline (%) | 36.67 ± 5.04 | 33.69 ± 5.44 | 0.017\* |
| NT-proBNP (pg/mL) | 1074.4 ± 2363.1 | 1948.6 ± 2282.3 | 0.101 |
| SBP (mmHg) | 124.6 ± 18.4 | 116.9 ± 17.6 | 0.062 |
| HR (bpm) | 74.0 ± 8.02 | 74.4 ± 11.85 | 0.876 |
| eGFR (mL/min/1.73m²) | 57.6 ± 17.9 | 53.7 ± 15.6 | 0.295 |

**Table 3: Post-Intervention Outcomes by both groups (N=114)**

| **Parameter** | **Group A****ACEI/ARB (n-24)** | **Group B****Sac/Val (n=90)** | **p-value** |
| --- | --- | --- | --- |
| EF (%) | 53.3 ± 24.4 | 58.0 ± 29.1 | 0.473 |
| NT-proBNP (pg/mL) | 1026.3 ± 1721.7 | 1086.8 ± 1603.2 | 0.872 |
| eGFR (mL/min/1.73m²) | 58.2 ± 16.6 | 55.0 ± 18.5 | 0.443 |
| SBP (mmHg) | 125.0 ± 16.2 | 115.6 ± 18.2 | 0.023\* |
| HR (bpm) | 72.1 ± 10.1 | 72.5 ± 15.4 | 0.901 |

**Table 4: Functional Improvement of patients by NYHA Class (N=114)**

| **NYHA Class Post-Treatment** | **Group A****ACEI/ARB (%)** | **Group B****Sac/Val (%)** | **p-value** |
| --- | --- | --- | --- |
| Class I | 87.5% | 67.8% | 0.056 |
| Class II | 12.5% | 32.2% |

**Table 5: Adverse events reported by intervention groups (N=114)**

| **Adverse Event** | **Group A****ACEI/ARB (%)** | **Group B****Sac/Val (%)** | **p-value** |
| --- | --- | --- | --- |
| Hyperkalemia | 0.0% | 1.1% | 0.604 |
| Hypotension | 4.2% | 5.6% | 0.787 |
| Renal Impairment | 25.0% | 35.6% | 0.330 |
| Cough | 0.0% | 4.4% | 0.293 |

**Table 6: Mortality and Re-hospitalization among groups (N=114)**

| **Outcome** | **Group A****ACEI/ARB (%)** | **Group B****Sac/Val (%)** | **p-value** |
| --- | --- | --- | --- |
| Death | 4.2% | 2.2% | 0.604 |
| Rehospitalization | 4.2% | 1.1% | 0.311 |

**Table 7: Post-treatment systemic relief of patients (N=114)**

| **Symptom** | **Group A****ACEI/ARB (%)** | **Group B****Sac/Val (%)** | **p-value** |
| --- | --- | --- | --- |
| Dyspnea (No) | 87.5% | 87.8% | 0.971 |
| Orthopnea (No) | 100% | 100% | N/A |
| PND (No) | 100% | 98.9% | 0.604 |

**4. DISCUSSION**

The study compared the outcome of patients with heart failure with reduced ejection fraction treated with Sacubitril/Valsartan versus ACEI/ARB. Sacubitril/Valsartan is an FDA-approved medication to treat patients with chronic heart failure with reduced ejection fraction (HFrEF) in NYHA class II, III, or IV (Diala Nicolas, 2024). Similarly, Angiotensin-Converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Blockers (ARB) are often prescribed to manage and treat high blood pressure, which contributes to coronary disease, heart failure, stroke, and a range of other heart and blood vessel issues (Linda L. Herman, 2023). This study enrolled 24 patients in the ACEI/ARB group or Group A to assess the effectiveness of a licensed medicine, Sacubitril/Valsartan (Group B), for patients with heart failure with reduced ejection fraction. The baseline data indicated the mean age for patients in Group A is 55.5 ± 8.85 years, and for Group B is 60.88 ± 10.32 years. The maximum study population is male, with a percentage of 100% treated with ACEI/ARB and 83.3% with Sacubitril/Valsartan. The rate of hypertension, DM, and smoking habit in Group A is 75.0%, 66.7%, 50.0%, and in Group B is 77.8%, 71.1%, 30.0%. Watson M *et al.*, 2019 showed in their study that smoking has a significantly higher association with HFrEF (Megan Watson, 2019). In a similar study, Pre–Diabetes Mellitus and Diabetes Mellitus have also been associated with Heart failure (Søren L. Kristensen, 2016).

Sacubitril/Valsartan participants at the outset had a (33.69%) lower ejection fraction—an indication that their heart failure was more advanced than the ACEI/ARB group’s (36.67%). NT-proBNP levels were higher in the Sac/Val group, but not at a significant level, and this is consistent with previous findings from the PARADIGM-HF trial, which also observed more natriuretic peptides in advanced patients (Michael Böhm, 2017) (Ching-Chang Fang, 2023). Systolic blood pressure was lower in the Sac/Val group, according to its ability to relax blood vessels, but heart rate and eGFR were unchanged (p>0.05). Just like earlier studies, these data suggest that sacubitril/valsartan was usually used in people with advanced HFrEF and noticeable symptoms (Domingo Pascual-Figal, 2021).

Following treatment, the ejection fraction improved in the two groups, with the Sac/Val group slightly higher (58.0% versus 53.3%), though not significantly different, comparable to results seen in TITRATION and PROVE-HF studies (Reza Mohebi, 2023). Levels of NT-proBNP declined similarly in both groups, consistent with what was reported in PIONEER-HF that Sac/Valsartan caused early improvement in biomarkers at the start of the trial, confirming that both drugs are safe for the kidneys. Significantly lower SBP in the Sac/Val group (p=0.023) showed the strong antihypertensive effect of sacubitril observed in the PARADIGM-HF trial (Michael Böhm, 2017). Heart rates did not change in any group, which is in line with what is expected in beta-blocker–co-managed HFrEF patients.

After therapy, more ACEI/ARB patients improved to NYHA Class I (87.5%) than Sac/Val patients (67.8%), but this difference was not enough to be significant. On the other hand, the PROVE-HF trial displayed that patients on Sacubitril/Valsartan improved their NYHA class significantly as time went on (James Louis Januzzi, 2018). Nevertheless, the same improvement in both groups agrees with what is observed in the CHAMP-HF registry (Muthiah Vaduganathan, 2020), supporting that both treatments help improve functional status in HFrEF.

In both groups, adverse events were low, though those on Sacubitril/Valsartan had more cases of hypotension and renal impairment, even if the results were not statistically significant, aligning with what the PARADIGM-HF trial documented (Anil Ranjeetmal Jain, 2020). Previous research indicates ARBs and Sac/Val in particular are less likely to cause a cough than ACEIs, which agrees with the low occurrence of hyperkalemia and cough in this study (BACHIR TAZKARJI, 2015). Both regimens continue to demonstrate how well they are tolerated and how safe they are, as found in larger studies and real-life situations.

The rates of serious outcomes, death and hospital readmission, did not differ greatly, with 4.2% death in ACEI/ARB vs 2.2% in Sac/Val, and 4.2% rehospitalization in the first group versus 1.1% in the second group. According to the PARADIGM-HF trial, people treated with Sacubitril/Valsartan experienced fewer heart-related deaths and less need for HF hospital care (George G Sokos, 2020), however, these differences might not be as clear in smaller studies. Similarly, real-world investigations like the TRANSITION registry confirm that safety is equal with Sac/Val and outcomes are often better (Xiaoye Li, 2023).

Currently, almost all treated patients are free of breathlessness and orthopnea, and PND is nearly eliminated in both groups. According to PROVE-HF and PIONEER-HF, early and lasting relief from symptoms was observed with Sacubitril/Valsartan (Misato Chimura, 2025). Findings from this study are supported by real-world research that both ACEI/ARB and Sac/Val can importantly ease congestion symptoms in HFrEF (Ankeet S Bhatt, 2025).

**5. LIMITATION**

The study used a small group of participants, and all observations were made at one center, which probably limits how well the conclusions fit with other settings. Moreover, observational studies could still bring about some biases since it is not always possible to correctly randomize participants.

**6. CONCLUSION**

After studying HFrEF patients, the researchers found that Sacubitril/Valsartan and ACEI/ARB were effective in improving their outcomes, but the results did not differ a lot in mortality, re-hospitalization rates or alleviating symptoms. Although sacubitril/valsartan showed better results at lowering blood pressure, it was linked to more side effects without being statistically significant. Based on the findings, physicians may choose either medication depending on how a patient responds and the side effects they can endure.

Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

**Conflicts of Interest**

The authors declare no conflicts of interest.

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