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ORIGINAL ARTICLE

Comparison of Effectiveness of Sacubitril plus Valsartan versus Ramipril in Post MI Chronic Left Ventricular Systolic Heart Failure Patients with Reduced Ejection Fraction

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ABSTRACT

Background: *Heart failure is an increasing worldwide issue impacting 1–2% of the population and over 10% of older adults, resulting in high mortality rates. It is categorized by LVEF into HFrEF, HFmrEF, and HFpEF. Ramipril is effective but can lead to cough and kidney/electrolyte issues, whereas sacubitril+valsartan demonstrates improved results in HFrEF with increased hypotension. This study assesses both medications because of restricted local information.* ***Methods & Materials:*** *This study was a forward-looking comparative clinical trial carried out at Sir Salimullah Medical College and Mitford Hospital in Dhaka (January 2018–June 2019). A total of 100 post-MI HFrEF patients were randomly allocated to receive either sacubitril+valsartan or ramipril (50 each) and monitored for 3 months. Results showed enhancement in HF status and EF, with additional outcomes related to mortality, rehospitalization, medication discontinuation, and safety evaluation.* ***Results:*** *The baseline characteristics were comparable in both groups. Sacubitril+valsartan exhibited a more significant enhancement in NYHA class and EF, with fewer individuals in class III–IV (40% vs. 75%, p = 0.018) and an increased EF (34.96 ± 2.98 vs. 33.12 ± 3.32, p = 0.104). It also decreased rehospitalizations (6% compared to 22%, p = 0.018) and mortality rates (4% against 8%, p = 0.025), but resulted in higher hypotension incidence (18% compared to 8%). Other negative effects were reduced in the sacubitril+valsartan group (p = 0.027).* ***Conclusion:*** *Sacubitril+valsartan significantly improved NYHA functional class compared to ramipril after 3 months in post-MI HFrEF patients. It also showed lower rates of secondary outcomes and overall complications in patients received Sacubitril plus Valsartan.*

Keywords: *Sacubitril plus Valsartan, Ramipril, Post MI, Chronic Left Ventricular Systolic Heart Failure, Ejection Fraction*

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INTRODUCTION

Non-communicable illnesses, particularly high blood pressure and cardiovascular conditions, are rising worldwide. Heart failure impacts 1–2% of the general population, more than 10% of individuals over 70 years old, and carries a lifetime risk of 33% for men and 28% for women who are 55 years old [1]. Despite treatment advancements, 50% of patients die within 5 years of diagnosis of HF [2].

Heart failure (HF) has various origins that differ among populations. Cardiovascular and non-cardiovascular conditions both contribute to HF, with neurohormonal activation being a crucial factor in its progression and mortality [1]. Left ventricular ejection fraction (LVEF) is crucial for identifying and tracking heart failure. Heart failure is categorized according to LVEF into reduced ejection fraction (HFrEF, <40%), mildly reduced/mid-range ejection fraction (HFmrEF, 40–49%), and preserved ejection fraction (HFpEF, ≥50%) [3].

Dysregulation of neurohormones, especially concerning the renin–angiotensin–aldosterone and neprilysin–natriuretic peptide pathways, is crucial in the context of heart failure. Standard treatments like ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and β-blockers decrease the advancement of heart failure and lower mortality rates [1,4]. Ramipril has consistently been a successful remedy for heart failure. It enhances preload and afterload by lowering left ventricular filling pressure, pulmonary artery pressure, systemic blood pressure, and peripheral resistance while not impacting heart rate or cardiac output. In contrast to diuretics, ramipril reduces blood pressure without causing reflex tachycardia [5,6].

A new compound that combines the moieties of an ARB (valsartan) and a neprilysin (NEP) inhibitor (sacubitril) has recently been shown to be superior to ACEI in reducing the risk of death and of hospitalization for HF in a trial. Sacubitril+valsartan is therefore recommended to replace

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ACEIs in heart failure patients especially in ambulatory HFrEF patients [1,3, 7,8].

Natriuretic peptides control fluid equilibrium and blood pressure by enhancing vasodilation, diuresis, and natriuresis. They also suppress the release of renin and aldosterone, opposing angiotensin II, decreasing sodium and water retention, and ultimately lowering cardiac workload [2]. Neprilysin is a zinc-dependent enzyme responsible for breaking down natriuretic peptides and various vasoactive peptides. Its blockade boosts the positive effects of natriuretic peptides, making neprilysin inhibition a successful treatment approach for heart failure [2,9,10].

The objectives of heart failure therapy are to alleviate symptoms, enhance ejection fraction, boost functional capacity, and increase quality of life while decreasing hospitalizations and death rates. Sacubitril+valsartan has demonstrated superior effectiveness compared to ACE inhibitors like ramipril in reaching these results and is authorized for managing heart failure with reduced ejection fraction (HFrEF) [1,7,9,11]. Sacubitril+valsartan is often linked to hypotension, while ACE inhibitors like ramipril can result in dry cough, electrolyte disturbance, and kidney impairment. Sacubitril boosts natriuretic peptides while also elevating angiotensin II levels, necessitating the simultaneous inhibition of the renin–angiotensin–aldosterone system. Merging sacubitril with valsartan improves treatment advantages and lessens the likelihood of angioedema [12].

However, as Sacubitril-valsartan is a newer drug combination, it has not been widely tested, and its efficacy and safety profile are yet to be studied in our country. That's why the present study was designed to make a comparative evaluation of efficacy and safety between Sacubitril-valsartan and Ramipril in patients of chronic heart failure with reduced ejection fraction.

METHODS & MATERIALS

Study design: The present study was a prospective comparative clinical trial.

Place and period of study: The study was conducted in the Department of Cardiology, Sir Salimullah Medical College and Mitford Hospital, Mitford, Dhaka from January 2018 to June 2019.

Study population: Patients with chronic systolic heart failure (LVEF <40%) following myocardial infarction were included based on the established eligibility criteria. Despite the projected sample size being 125 patients, 100 qualified patients were included and evenly distributed between Group 1 and Group 2.

- Group 1- Patients received Sacubitril plus Valsartan (n=50)
- Group 2- Patients received Ramipril (n=50)

Selection criteria: Individuals between 25 and 65 years old who have chronic systolic heart failure post-myocardial infarction (LVEF <40%), NYHA class II–IV, systolic blood pressure over 100 mmHg, and normal levels of serum electrolytes and creatinine were included. Patients with LVEF >40%, NYHA category I, systolic blood pressure <100 mmHg, hyperkalemia, COPD, kidney issues, or valvular heart conditions were not included.

Study procedure: Following the acquisition of written informed consent, baseline clinical assessment, laboratory tests, ECG, chest X-ray, and echocardiography were conducted. The modified Simpson's method was utilized to measure left ventricular ejection fraction (LVEF). Patients were assigned to either sacubitril+valsartan (initial dose 50 mg twice daily) or ramipril (initial dose 2.5 mg once daily), with dosage modifications depending on clinical response, and were monitored for 3 months. Clinical and echocardiographic evaluations were conducted again at follow-up, and baseline and post-treatment results were compared between the two groups through suitable statistical analyses.

Data collection: Data was collected by using a predesigned structured data collection sheet containing variables of interest.

Statistical analysis: Data were processed and analyzed using SPSS (Statistical Package for Social Sciences), version 25.0. The test statistics used to analyze the data were unpaired t-Test and Chi-squared (χ^2) tests. While the data presented on continuous scale were compared between groups using unpaired t-Test, data presented on categorical scale were compared between groups using Chi-squared (χ^2) Test. The level of significance was set at 5% and p-value less than 0.05 was considered statistically significant.

Ethical considerations: The Ethical Review Committee of Sir Salimullah Medical College in Dhaka approved the study protocol. Informed consent in writing was acquired from all participants after clarifying the study's goals, processes, risks, and advantages in straightforward local language. The privacy of patient information was rigorously upheld during the study.

RESULTS

Table I indicates that the foundational demographic and clinical traits were similar across both study groups. The average age was comparable between Group 1 and Group 2 (53.83 ± 8.21 vs. 52.24 ± 7.94 years; p = 0.368), with most patients in both groups falling within the 56–65-year age range. The majority of participants were male (86.0% in Group 1 and 90.0% in Group 2). Businessmen made up the largest occupational category in both groups, and the occupation distribution showed no significant difference (p = 0.760). The occurrence of significant cardiovascular risk factors, such as hypertension, diabetes mellitus, smoking, and dyslipidemia, was similar across the groups (all p > 0.05). In general, there were no statistically meaningful differences in baseline demographic or clinical traits, suggesting that the two groups were adequately aligned prior to treatment.

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Table I: Baseline demographic and clinical characteristics of the study participants (*n* = 100)

Variable	Group 1 (Sacubitril+Valsartan) (n = 50),n(%)	Group 2 (Ramipril) (n = 50),n(%)	P value
Age (years), Mean ± SD	53.83 ± 8.21	52.24 ± 7.94	0.368
Age group			
25–35	1 (2.4)	0 (0.0)	
36–45	6 (14.3)	8 (19.0)	
46–55	17 (35.7)	19 (38.1)	
56–65	26 (47.6)	23 (42.9)	
Gender			>0.05
Male	43 (86.0)	45 (90.0)	
Female	7 (14.0)	5 (10.0)	
Occupation			0.760
Businessman	30 (60)	24 (48)	
Housewife	6 (12)	6 (12)	
Farmer	8 (16)	12 (24)	
Others	6 (12)	8 (16)	
Risk factors			
Diabetes mellitus	7 (14)	8 (16)	0.784
Hypertension	19 (38)	15 (30)	0.505
Smoking	12 (24)	10 (20)	0.804
Dyslipidemia	20 (40)	25 (50)	0.382

Values are expressed as mean ± SD or number (%). Group 1 received sacubitril+valsartan (n = 50), and Group 2 received ramipril (n = 50). Student's *t*-test was used for continuous variables and the Chi-square test for categorical variables. No statistically significant differences were observed between the two groups at baseline (all $p > 0.05$).

Table II presents at baseline, the NYHA functional classification was similar between both groups (p = 0.457), with the majority of patients in class III or IV. After 3 months, there was a notable improvement in functional status in the sacubitril+valsartan group compared to the ramipril group (p = 0.018), with a higher percentage of patients attaining NYHA class I–II and fewer staying in class III–IV.

Table II: Comparison of NYHA functional class at baseline and 3-month follow-up between the study groups

Assessment	NYHA Functional Class	Group 1,n(%)	Group 2,n(%)	P value
Baseline (n=50/group)	Class I	0 (0.0)	0 (0.0)	0.457
	Class II	4 (8.0)	4 (8.0)	
	Class III	26 (52.0)	20 (40.0)	
	Class IV	20 (40.0)	26 (52.0)	
3-month follow-up (Group 1, n=46; Group 2, n=36)	Class I	9 (19.6)	2 (5.6)	0.018
	Class II	19 (41.4)	7 (19.4)	
	Class III	14 (30.4)	18 (50.0)	
	Class IV	4 (8.7)	9 (25.0)	

Values are expressed as n (%). Baseline comparisons were performed using the Chi-square test, and 3-month comparisons using Fisher's exact test.

Table III shows at baseline, the two groups showed no significant differences in ejection fraction, LVIDd, or LVIDs (all p > 0.05). Following three months of treatment, the sacubitril+valsartan group demonstrated a more significant enhancement in ejection fraction and decreases in LVIDd and LVIDs when compared to the ramipril group; however, these differences between groups lacked statistical significance (all p > 0.05).

Table III: Comparison of echocardiographic parameters at baseline and 3-month follow-up between the study groups

Assessment	Variable	Group 1 (Sacubitril+Valsartan)	Group 2 (Ramipril)	P value
Baseline (n = 50/group)	Ejection fraction (%)	29.48 ± 3.32	30.54 ± 3.54	0.126
	LVIDd (mm)	59.14 ± 4.42	58.00 ± 3.93	0.072
	LVIDs (mm)	51.18 ± 4.43	49.50 ± 3.83	0.115
3-month follow-up(Group 1, n = 46; Group 2, n = 36)	Ejection fraction (%)	34.96 ± 2.98	33.12 ± 3.32	0.104
	LVIDd (mm)	56.24 ± 4.34	58.61 ± 4.84	0.108
	LVIDs (mm)	48.30 ± 4.41	50.66 ± 4.83	0.119

LVIDd: Left Ventricular Internal Diameter in Diastole; LVIDs: Left Ventricular Internal Diameter in Systole.

Values are expressed as mean ± SD. Comparisons between groups were performed using the independent Student's *t*-test.

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Table IV indicates that patients administered sacubitril+valsartan experienced notably improved clinical results compared to those receiving ramipril during the 3-month follow-up. The frequencies of recurrent hospital admissions (6.0% vs. 22.0%, p = 0.018), medication discontinuation (4.0% vs. 20.0%, p = 0.012), and mortality (4.0% vs. 8.0%, p = 0.025) were notably reduced in the sacubitril+valsartan group, suggesting better efficacy and tolerability than ramipril.

Table IV: Comparison of clinical outcomes between the study groups during the 3-month follow-up

Outcome	Group 1 (Sacubitril+Valsartan) (n = 50), n (%)	Group 2 (Ramipril) (n = 50), n (%)	Total (n = 100), n(%)	P value
Repeated hospital admission	3 (6.0)	11 (22.0)	14 (14.0)	0.018
Drug discontinuation	2 (4.0)	10 (20.0)	12 (12.0)	0.012
Death	2 (4.0)	4 (8.0)	6 (6.0)	0.025

Values are expressed as n (%). Comparisons between groups were performed using the Chi-square test or Fisher's exact test, as appropriate.Fisher's Exact Test was done to analyze the data.

Figure 1 show cough, Hyperkalemia and Renal Impairment were higher among Group 2 patients than Group 1 patients. Cough was among, 14% (7) vs 32% (16), Hypotension was among, 18% (9) vs 8% (4), Hyperkalemia was among, 8% (4) vs 20% (10) and renal impairment was among, 4% (2) vs 12% (6) of Group 1 and Group 2 patients respectively. Complications were significantly higher among Group 2 patients than Group 1 patients when compared as the p-value was < 0.05.

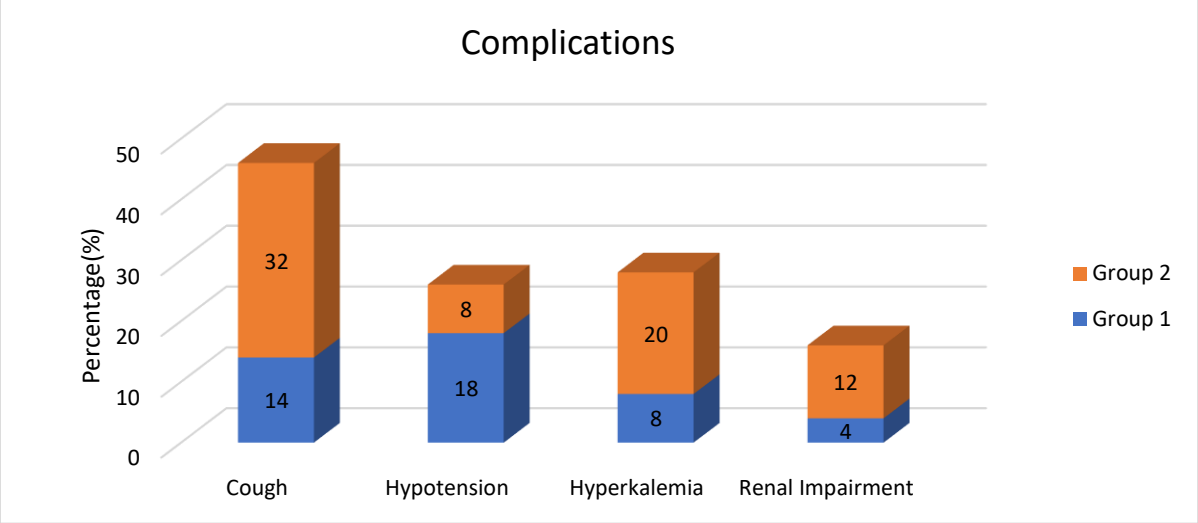


Figure 1 Distribution of studied patients regarding complications at 3 months follow up between groups (*n*=100)

DISCUSSION

In this study, baseline demographic and clinical traits were alike in the sacubitril+valsartan and ramipril groups, showing no significant differences in age, gender distribution, profession, or cardiovascular risk factors. The majority of patients were older men, with dyslipidemia and hypertension being the most prevalent risk factors. These results align with earlier studies indicating that ischemic heart disease and heart failure mainly impact older men and are closely linked to adjustable risk factors like dyslipidemia, hypertension, diabetes, and smoking. The current baseline comparability confirms the accuracy of additional outcome comparisons between the two treatment groups [13,14].

In our study, baseline NYHA classification was comparable in both groups, with the majority of patients in class III–IV. After 3 months, sacubitril+valsartan demonstrated a notably greater enhancement in NYHA class compared to ramipril, as more patients transitioned to class I–II, aligning with findings that sacubitril+valsartan offers better symptomatic and functional advantages in heart failure due to its combination of neprilysin inhibition and angiotensin receptor blocking [15].

Baseline echocardiographic measurements were alike in both groups. After 3 months, sacubitril+valsartan demonstrated a larger enhancement in ejection fraction and more beneficial alterations in LVIDd and LVIDs compared to ramipril, although the results were not statistically significant (p > 0.05). Comparable research has indicated enhanced left ventricular performance and reverse remodeling with sacubitril+valsartan over ACE inhibitors, which is linked to increased natriuretic peptide activity and diminished neurohormonal activation [16].

In the current study, at the 3-month follow-up, sacubitril+valsartan demonstrated superior secondary outcomes compared to ramipril, exhibiting fewer instances of repeated hospital admissions, lower drug discontinuation rates, and reduced mortality. Comparable results have been observed in earlier research, indicating fewer hospital admissions and better outcomes with sacubitril+valsartan in contrast to ACE inhibitors, probably owing to increased natriuretic peptide function and inhibition of harmful neurohormonal pathways [10,16].

In this study, ramipril showed increased incidence of cough, hyperkalemia, and renal impairment in contrast to sacubitril=valsartan, while sacubitril+valsartan led to greater hypotension. Comparable outcomes in earlier research also indicated that ACE inhibitors are more often related to cough, electrolyte disturbances, and renal impairment, whereas sacubitril+valsartan is more regularly associated with hypotension owing to its strong vasodilatory properties [10,16,17].

In summary, sacubitril+valsartan exhibited enhanced clinical effectiveness with greater functional enhancement and results, along with an acceptable safety profile when compared to ramipril in individuals with post-MI heart failure and reduced ejection fraction.

CONCLUSION

From the findings of the study, it appears that cases of heart failure status improved (from NYHA Class III and IV to NYHA Class II and Class 1) significantly following treatment with Sacubitril-valsartan than that of Ramipril. The EF also improved in the group 1 than that of group 2. The secondary outcome evaluation revealed that re-hospitalization and death were significantly lower in the Sacubitril-valsartan group than those of Ramipril group. While the complication like hypotension was significantly higher in sacubitril-valsartan than that in ramipril group, and the safety in terms of complications like intractable cough, renal impairment and hyperkalemia were significantly lower in the group 1. So, sacubitril plus valsartan is more effective and safer drug than ramipril in post MI chronic left ventricular systolic heart failure patients with reduced ejection fraction.

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