ORIGINAL RESEARCH

Comparative Efficacy of Curative Effects of Sacubitril/Valsartan in HFpEF versus HFrEF Treatment

Yi Li, MM; Zifan Zhu, MM; Hongbin Liu, MD

ABSTRACT

Objective • This study aims to assess the differential efficacy of Sacubitril/Valsartan in treating heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), thereby enhancing medication guidance for heart failure management.

Methods • A retrospective cohort study was conducted, and a cohort of 89 patients, comprising 48 with HFrEF and 41 with HFpEF, treated at our hospital from February 2020 to January 2022, received Sacubitril/Valsartan. Adverse reactions were documented, and pre- and post-treatment cardiac and renal functions were evaluated. Mobility and quality of life were assessed using the 6-minute walk test (6MWT) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Patient outcomes were tracked for one year, measuring readmission and survival rates.

Results • The study found no significant difference in the overall incidence of adverse reactions or cardiac function before and after treatment between the two groups ($P > .05$). However, patients with heart failure with preserved ejection fraction (HFpEF) exhibited notably greater disparities in serum creatinine and blood urea nitrogen levels, as well as in 6MWT and MLHFQ scores before and after treatment compared to those with heart failure with reduced ejection fraction (HFrEF) ($P < .05$). Additionally, the HFpEF group showed a lower prognostic readmission rate compared to the HFrEF group, although the difference in prognostic survival was not statistically significant ($P > .05$).

Conclusions • Sacubitril/Valsartan demonstrates superior efficacy in improving renal function and enhancing quality of life in HFpEF patients while providing comparable prognostic benefits for HFrEF patients. This finding underscores its potential as a therapeutic foundation in the management of heart failure across ejection fraction categories. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Heart failure (HF) denotes the deterioration of cardiac function resulting from a variety of heart diseases, typically presenting as dyspnea, limited range of motion (LROM), and fluid retention.[1] HF primarily affects the elderly, with its risk escalating with age, culminating in a 5-year mortality rate of up to 50 percent.[2] Classifications of HF based on left ventricular ejection fractions (LVEF) include HF with reduced ejection fraction (HFrEF; LVEF <40%) or preserved ejection fraction (HFpEP; LVEF >50%).[3]

HFrEF also referred to as systolic HF, occurs when a patient's heart lacks the strength to contract effectively during blood pumping. On the other hand, HFpEP, known as diastolic HF, arises when the heart becomes excessively rigid, hindering proper relaxation and blood filling during pumping.[3,4] Recent years have seen a notable increase in the prevalence of both HFrEF and HFpEP, imposing a significant disease burden that warrants attention from healthcare professionals and patients.[5]

The treatment of these two types of HF has become a significant focus of clinical research in recent years. Previously, the renin-angiotensin-aldosterone system (RAAS) and sympathetic hyperactivation were considered the main pathological mechanisms driving cardiac remodeling.[5-6] However, recent research has underscored the significant role of the natriuretic peptide system (NPS) in

ventricular remodeling.[6] Sacubitril/Valsartan (S/V), comprising Sacubitril and Valsartan, targets both of these systems. Sacubitril regulates the NPS, while Valsartan exerts inhibitory effects on RAAS.[7]

Pharmacologically, S/V inhibits vasoactive peptides such as bradykinin and natriuretic peptides, which are upregulated by enkephalinase, by binding to the RAAS. This action leads to a reduction in blood pressure, vasodilation, and enhancement of myocardial function.[8,9] Furthermore, Valsartan, a component of S/V, improves cardiac function by regulating aldosterone levels and acting as an angiotensin receptor blocker. It also increases natriuretic peptide levels, reduces the body's reliance on diuretics, and rapidly corrects abnormal ejection fraction.[9]

Currently, S/V has been extensively utilized in the treatment of HF with notable success.[10] However, there is a paucity of literature addressing the differential treatment effects of S/V between HFpEF and HFrEF, leaving a void in reliable clinical medication guidance. Considering this gap, we conducted research and analysis to examine the changes in the long-term efficacy of S/V in treating HFrEF and HFpEF. Our objective was to furnish an effective reference for the future utilization of S/V in clinical practice.

DATA AND METHODS

Study Design

A retrospective cohort study was conducted that involved the selection of 89 patients diagnosed with either heart failure with HFrEF or HFpEF, with 48 patients in the HFrEF group and 41 patients in the HFpEF group. These patients received treatment at our hospital between February 2020 and January 2022. The treatment protocol was uniform across both groups, consisting of S/V therapy. This standardized approach allowed for a comparative analysis of the long-term efficacy of S/V in the treatment of HFrEF and HFpEF, providing valuable insights for future clinical practice.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) All patients included in the study met the diagnostic criteria for either HFrEF or HFpEF[11]; (2) exhibited good compliance; (3) provided complete data; and (4) provided informed consent either personally or through their families. Exclusion criteria encompassed individuals meeting at least one of the following conditions: (1) presence of other myocardial diseases; (2) liver or kidney dysfunction; (3) tumors, allergies to the medication or its constituents; (4) mental illness or communication disorders; (5) recent participation in relevant treatments; (6) dropouts from the study; and (7) patients experiencing gastrointestinal bleeding, dehydration, or metabolic abnormalities.

Treatment Protocol

Following the guidelines for chronic HF, both patient groups received standardized drug therapy, including β-receptor blockers, diuretics, and mineralocorticoid antagonists. Additionally, supportive treatments such as oxygen inhalation and adherence to low-salt and low-fat diets were implemented. Subsequently, Sacubitril/Valsartan (S/V; H20170344) was administered twice daily, initiating at a dosage of 50 mg per dose. The dosage was progressively increased, doubling every two weeks until reaching a maintenance dose of 100 mg per dose, also administered twice daily. Both groups underwent continuous treatment for a duration of 4 weeks.

Blood Sampling Procedure

Blood sampling was conducted both before and after treatment, wherein 4 mL of fasting venous blood was withdrawn from each patient into a pro-coagulation tube. Subsequently, the samples were allowed to stand at room temperature for 30 minutes before undergoing centrifugation to separate the plasma and serum for subsequent analysis.

Follow-Up Protocol

All patients underwent a follow-up period lasting 1 year, during which regular follow-up sessions were conducted. Each patient underwent a minimum of one review per month, resulting in a total of 12 follow-up sessions over the course of the year.

Outcome Measures

Adverse Reactions and Re-hospitalization/Mortality Rates. The study examined adverse reactions observed during treatment and assessed the rates of re-hospitalization and mortality over the 1-year follow-up period. This analysis was conducted to determine the safety and effectiveness of the treatment and to evaluate the long-term impact on patient outcomes.

Echocardiographic Parameters. Before and after treatment, the study compared echocardiographic indexes, including left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic diameter (LVESD). The comparison of echocardiographic indexes was performed to evaluate changes in cardiac structure and function after treatment with S/V.

Biochemical Analysis. Plasma levels of N-terminal B-type natriuretic propeptide (NT-proBNP), cardiac troponin I (cTnI), serum creatinine (Scr), and blood urea nitrogen (BUN) were measured using an automatic biochemical analyzer. Measurement of plasma biomarkers aimed to provide insights into the physiological response to treatment and to assess potential markers of cardiac function and injury.

Functional Capacity and Quality of Life Assessment. Patients' functional capacity and quality of life were evaluated through the six-minute walking test (6MWT)[12] and the Minnesota Living with Heart Failure Questionnaire (MLHFQ),[13] respectively. These assessments were conducted to evaluate the overall impact of treatment on patients' physical capabilities and their subjective perception of well-being and quality of life.

Statistical Analysis

The data analysis was performed using SPSS version 23.0 statistical software (International Business Machines, Corp., Armonk, NY, USA). Chi-square tests (χ^2) were conducted to compare categorical variables, expressed as percentages [n (%)]. Continuous variables, presented as mean ± standard deviation ($\bar{x} \pm s$), underwent paired t tests to evaluate intra-group differences pre- and post-treatment. Independent samples t tests were employed to assess inter-group differences. The statistical significance level was set at $P < .05$.

RESULTS

Comparison of Baseline Characteristics between the Two Groups

Prior to admission, demographic data, including age, body mass index (BMI), and gender, were collected for all patients. Statistical analysis indicated no significant differences in BMI or place of residence between the groups ($P > .05$). However, there were notable differences in age, New York Heart Association (NYHA) functional grade, and the proportion of female patients, with the HFpEF group exhibiting lower values compared to the HFrEF group ($P < .05$). Refer to Table 1.

Adverse Reactions During Treatment

Throughout the treatment period, both patient groups encountered adverse reactions, including nausea, vomiting, gastrointestinal discomfort, dizziness, and lethargy. The overall incidence of adverse reactions was 12.20% in the HFpEF group and 6.25% in the HFrEF group, with no statistically significant inter-group difference observed ($P > .05$), see Table 2.

Comparison of Echocardiographic Results

Before and after treatment, the differences in LVEF, LVEDD, and LVESD did not reach statistical significance when comparing the two groups ($P > .05$). However, after treatment, LVEF increased in both groups, while LVEDD and LVESD decreased significantly ($P < .05$). Furthermore, the disparities in LVEF, LVEDD, and LVSD remained statistically non-significant between the groups before and after treatment ($P > .05$), see Figure 1.

Comparison of Cardiac Function Markers

Following treatment, levels of cTnI and NT-proBNP in the HFpEF group decreased to (0.23±0.06) ng/mL and (632.30±66.22) pg/mL, respectively, while in the HFrEF group, they reduced to (0.26±0.04) ng/mL and (603.69±69.56) pg/mL, respectively. Notably, differences in pre- and post-treatment NT-proBNP and cTnI levels did not exhibit significant differences between the groups ($P > .05$); see Figure 2.

Comparison of Renal Function

Following treatment, both groups exhibited reductions in Scr and BUN levels ($P < .05$). However, the differences in pre- and post-treatment Scr and BUN were notably greater in

Table 1. Baseline Characteristics of Patients with Heart Failure

Characteristics	HFrEF Group (n=48)	HFpEF Group (n=41)	χ^2 or t	P value
Age	71.6±4.5	65.1±4.3	6.912	.001
BMI (Kg/m^2)	28.4±2.3	28.6±2.3	0.409	.684
NYHA Classification			4.048	.044
II	19(39.58)	25(60.98)		
III-IV	29(60.42)	16(39.02)		
Sex			5.024	.025
Male	19(39.58)	26(63.41)		
Female	29(60.42)	15(36.59)		
Place of Residence			0.327	.567
Urban	30(62.50)	28(68.29)		
Rural	18(37.50)	13(31.71)		
Ethnicity			0.748	.387
Han Chinese	45(93.75)	40(97.56)		
Ethnic Minority	3(6.25)	1(2.44)		

Note: Values presented as mean ± standard deviation ($\bar{x} \pm s$) or count [n (%)]. The chi-square test (χ^2) or independent samples t test (t) was used for statistical analysis. $P < .05$ are considered statistically significant.

Abbreviations: HFrEF, Heart Failure with Reduced Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction; BMI, Body Mass Index; NYHA, New York Heart Association.

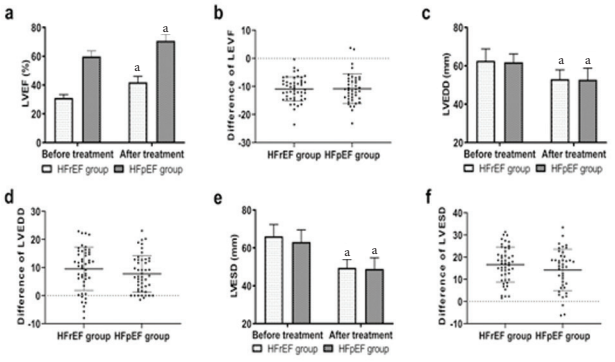
Table 2. Adverse Reactions During Treatment

Adverse Reactions	HFrEF Group (n=48)	HFpEF Group (n=41)	χ^2 or t	P value
Nausea and Vomiting	1(2.08)	1(2.44)		
Dizziness and Drowsiness	1(2.08)	2(4.88)		
Allergies	0(0)	1(2.44)		
Gastrointestinal Discomfort	1(2.08)	1(2.44)		
Total Incidence (%)	3(6.25)	5(12.20)	0.955	.328

Note: Values are presented as [n (%)]. The total incidence of adverse reactions was calculated for each group and expressed as a percentage of the total number of patients in the respective group. The chi-square (χ^2) test or t test (t) was used for statistical analysis, with significance set at $P < .05$.

Abbreviations: HFrEF, Heart Failure with Reduced Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction.

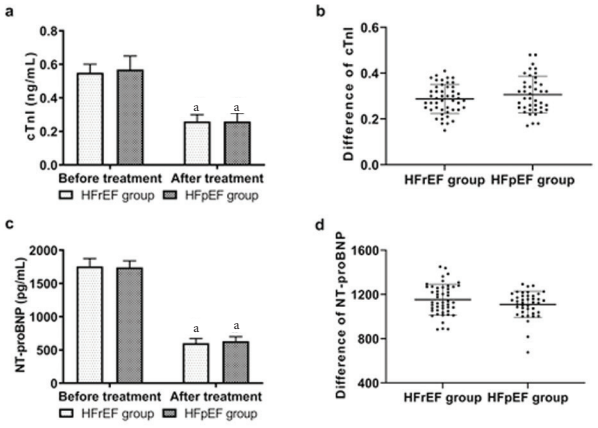
Figure 1. Echocardiographic Comparison between HFpEF and HFrEF Groups



[a]indicates statistical significance ($P < .05$) compared with pre-treatment.

Note: (a) Comparison of Left Ventricular Ejection Fraction (LVEF) before and after treatment in HFpEF and HFrEF groups. (b) Comparison of the difference in LVEF between the two groups before and after treatment. (c) Comparison of Left Ventricular End-Diastolic Dimension (LVEDD) before and after treatment in HFpEF and HFrEF groups. (d) Comparison of the difference in LVEDD between the two groups before and after treatment. (e) Comparison of Left Ventricular End Systolic Dimension (LVESD) before and after treatment in HFpEF and HFrEF groups. (f) Comparison of the difference in LVESD between the two groups before and after treatment.

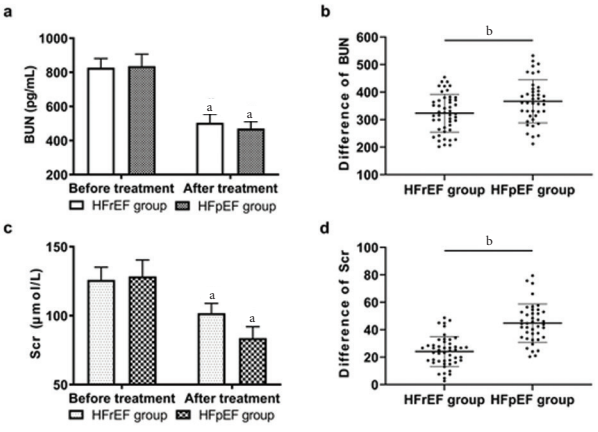
Figure 2. Comparison of Cardiac Function Markers between HFpEF and HFrEF Groups



[a]indicates statistical significance ($P < .05$) compared with pre-treatment.

Note: (a) Comparison of cardiac troponin I (cTnI) before and after treatment in HFpEF and HFrEF groups. (b) Comparison of the difference in cTnI between the two groups before and after treatment. (c) Comparison of N-terminal pro-B-type natriuretic peptide (NT-proBNP) before and after treatment in HFpEF and HFrEF groups. (d) Comparison of the difference in NT-proBNP between the two groups before and after treatment.

Figure 3. Comparison of Renal Function between HFpEF and HFrEF Groups



[a]indicates statistical significance ($P < .05$) compared with pre-treatment.
[b]indicates statistical significance ($P < .05$) for comparison between the two groups.

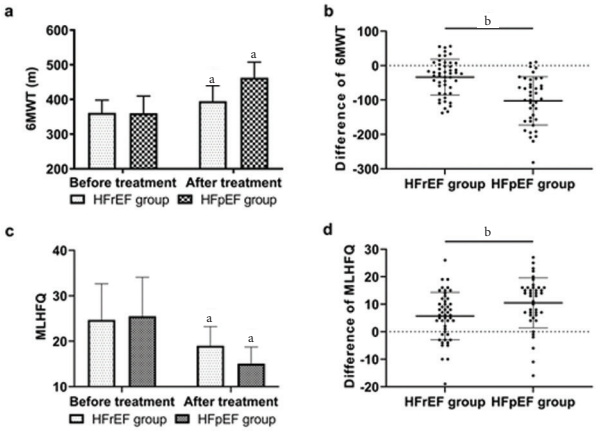
Note: (a) Comparison of blood urea nitrogen (BUN) before and after treatment in HFpEF and HFrEF groups. (b) Comparison of the difference in BUN between the two groups before and after treatment. (c) Comparison of serum creatinine (Scr) before and after treatment in HFpEF and HFrEF groups. (d) Comparison of the difference in Scr between the two groups before and after treatment.

the HFpEF group compared to the HFrEF group ($P < .05$), see Figure 3.

Comparison of Living Ability

After treatment, the 6MWT distance in the HFpEF group was (462.85±44.66) meters, and MLHFQ scores decreased to (15.05±3.67). The differences in pre- and post-

Figure 4. Comparison of Living Ability between HFpEF and HFrEF Groups



[a]indicates statistical significance ($P < .05$) compared with pre-treatment.
[b]indicates statistical significance ($P < .05$) for comparison between the two groups.

Note: (a) Comparison of the six-minute walk test (6MWT) before and after treatment in HFpEF and HFrEF groups. (b) Comparison of the difference in 6MWT between the two groups before and after treatment. (c) Comparison of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) before and after treatment in HFpEF and HFrEF groups. (d) Comparison of the difference in MLHFQ between the two groups before and after treatment.

Table 3. Prognostic Comparison between HFrEF and HFpEF Groups

Group	n	Readmission rate	Mortality
HFrEF Group (n=48)	48	20(41.67)	5(10.42)
HFpEF Group (n=41)	41	7(17.07)	3(7.32)
χ^2		6.328	0.260
P value		.012	.610

Note: Data presented as [n (%)]. Statistical analysis was conducted using the Chi-square (χ^2) test with a significance level set at $P < .05$.

Abbreviations: HFrEF, Heart Failure with Reduced Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction.

treatment values were (-102.56±70.21) and (10.46±9.11) respectively, which were higher than those observed in the HFrEF group (difference in pre- and post-treatment 6MWT: -33.50±(-8.63), the difference in pre- and post-treatment MLHFQ: 5.69±8.61) ($P < .05$), see Figure 4.

Comparison of Prognosis

During the 1-year follow-up period, all patients were successfully tracked. In the HFpEF group, the one-year readmission rate was 17.07%, significantly lower than the rate of 41.67% observed in the HFrEF group ($P < .05$). However, there were no significant differences between the two groups regarding prognostic survival ($P > .05$), see Table 3.

DISCUSSION

As socio-economic development continues and lifestyles evolve, the incidence of cardiovascular disease has seen a significant rise in recent years, making it a leading cause of human mortality.[14] HF represents a myocardial injury and signifies an advanced stage of cardiac insufficiency, with LVEF playing a crucial role.[15] HF is pathologically classified

into two categories based on LVEF levels: HFpEF and HFrEF. Both types pose significant threats to patient safety.[16] While the therapeutic efficacy of S/V in HF has been preliminarily established, the differential effects of S/V in treating HFpEF and HFrEF remain important areas of clinical interest.

In this study, it is evident that patients with HFrEF had significantly higher age and NYHA grades compared to HFpEF patients, along with a higher proportion of female patients. These findings align with the results of epidemiological studies[17,18] and the pathological characteristics of the two types of heart failure. Regarding therapeutic effects, no significant differences were observed in echocardiographic and clinical indexes before and after S/V therapy in both groups. This finding suggests the stable and excellent efficacy of S/V in treating both types of heart failure. The identical incidence of adverse reactions further underscores the high clinical safety profile of S/V. This is unsurprising, considering the well-established therapeutic effectiveness of S/V in treating heart failure.[19,20]

The unique drug structure of S/V contributes to its safety profile by enabling dual inhibition: (1) Valsartan serves as an angiotensin receptor inhibitor, effectively blocking angiotensin II receptors within the RAAS leading to decreased blood pressure and the reversal of left ventricular hypertrophy; (2) Sacubitril functions as an enkephalinase antagonist and it is effective in inhibiting the activity of NEP, consequently enhancing the levels of blood natriuretic peptides. This action facilitates water drainage, sodium excretion, vasodilation, and reduction of cardiac load. The combined effect of these pathways leads to enhanced vasodilation, improved myocardial condition, and reversal of cardiac remodeling.

We noted a more substantial difference before and after treatment in the HFpEF group compared to the HFrEF group when comparing renal function. This observation suggests that S/V exerts a more pronounced effect on enhancing renal function in HFpEF patients. Previous studies[21] have indicated that S/V has a protective effect on renal function. Its mechanism involves inhibiting or blocking sodium reabsorption in the distal/proximal kidney, thereby increasing urine flow and sodium excretion, ultimately aiding in the repair and enhancement of renal function.

The improved renal function observed in the HFpEF group after treatment may be attributed to the older age of patients in the HFrEF group, along with the presence of various underlying diseases, which could increase the likelihood of renal insufficiency. Considering that S/V is not specifically targeted for renal function repair, HFpEF patients with better baseline renal function may experience more favorable outcomes after treatment. Therefore, in the comparison of mobility, better treatment efficacy was observed in the HFpEF group, which we attribute to the superior baseline physiological activity of HFpEF patients.

Finally, during the prognostic follow-up, we noted that while HFrEF patients exhibited a higher readmission rate compared to HFpEF patients, there was no significant difference in mortality between the two groups. Considering the widely recognized high-risk nature of HFrEF in heart failure, it is commonly associated with a poorer prognosis, often resulting in significantly higher mortality rates compared to HFpEF.[22,23] After treatment with S/V, there was a notable improvement in the prognosis of HFrEF patients, a development of considerable significance for their overall outlook.

These results suggested that S/V treatment resulted in comparable therapeutic benefits in both groups, highlighting its effectiveness in improving cardiac function. Additionally, S/V exhibited a more pronounced impact on renal function improvement in HFpEF patients, suggesting its potential as a valuable treatment option for this subgroup.

Study Limitations

Although our study provides valuable insights, it is important to acknowledge its limitations. The relatively small sample size might have affected the precision of statistical analyses, potentially introducing a margin of error. Furthermore, the relatively short follow-up period may have limited our ability to fully assess the long-term prognostic impact of S/V on heart failure outcomes. Future research with larger sample sizes and longer follow-up durations is essential to provide more robust evidence regarding the efficacy and safety of S/V in HF management over extended periods.

CONCLUSION

In conclusion, our study highlights the significant therapeutic impact of S/V in managing both HFpEF and HFrEF, effectively improving cardiac function across patient cohorts. Notably, S/V exhibits notable efficacy in improving renal function and mobility among HFpEF patients, potentially attributed to their comparatively better baseline physiological status. Additionally, S/V demonstrates a pronounced enhancement in prognostic survival among HFrEF patients, offering promising long-term outcomes for this high-risk subgroup. Therefore, our findings underscore the clinical relevance of S/V as a pivotal intervention in HF treatment, advocating for its prevalent adoption to optimize patient outcomes and prognosis.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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None

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