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Original Article

Effect of sacubitril-valsartan on left ventricular remodeling and NT-proBNP in patients with heart failure complicated with hypertension and reduced ejection fraction

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Abstract: Objective: To analyze the effect of sacubitril-valsartan on left ventricular remodeling and NT-proBNP in heart failure patients with hypertension and reduced ejection fraction. Method: A retrospective analysis was conducted on 112 heart failure patients with reduced ejection fraction (HFrEF) and concomitant hypertension who were treated in Baoji Central Hospital from May 2019 to October 2021. Standard heart failure treatment was applied in both groups. Besides, the observation group (n=60) was additionally treated with sacubitril/valsartan (initial dose of 50 mg twice daily, adjusted every 2-4 weeks by doubling the dose to a maximum of 200 mg twice daily based on the patients' actual conditions and tolerance), and the control group (n=52) received valsartan (80 mg once daily). The treatment duration for both groups was 6 months. Therapeutic efficacy, blood pressure, echocardiographic parameters, N-terminal pro-brain natriuretic peptide (NT-proBNP) and left ventricular remodeling before and after treatment were recorded and compared between the two groups, as well as the adverse drug reactions during the treatment and life quality after treatment. Finally, multifactor regression analysis was performed to screen the independent risk factors affecting patient prognosis. Results: Compared with the CG, the overall response rate in the OG was evidently higher ($P < 0.001$); the improvements in blood pressure, NT-proBNP, interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT) and left ventricular mass index (LVMI) were more significant in the OG (all $P < 0.001$). Both groups showed marked improvements in left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD) and (left ventricular end-systolic diameter) LVESD compared to baseline, with more significant improvement in the OG compared with the CG (all $P < 0.001$). There was no significant difference in the incidence of adverse reactions between the two groups. However, post-treatment quality of life was much higher in the OG compared to the CG ($P < 0.001$). Comorbid diabetes and treatment regimen were identified as independent risk factors affecting patient prognosis. Conclusion: Sacubitril-valsartan can effectively improve blood pressure, cardiac function and ventricular remodeling in patients with HFrEF and hypertension without increasing adverse reactions. It is highly safe and worthy of clinical promotion.

Keywords: Sacubitril-valsartan, heart failure with reduced ejection fraction, hypertension, left ventricular remodeling, NT-proBNP

Introduction

Clinically, chronic heart failure (CHF) is a syndrome that primarily occurs as various heart diseases progress to advanced stages. The pathogenesis of CHF is intricate, potentially linked to myocardial remodeling and cardiac pathophysiology [1, 2]. Heart failure with reduced ejection fraction (HFrEF), a distinct subtype of heart failure, is characterized by patients having a left ventricular ejection fraction (LVEF) below 40%. Standard interventions involve medications such as cardiotonics, diuretics, and anticoagulants, yet the outcomes are often suboptimal [3]. Additionally, over half of heart failure patients in China concurrently experience hypertension [4]. Despite numerous studies and endeavors, the therapeutic effi-

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cacy for hypertensive patients with HFrEF remains discouraging, resulting in poor clinical outcomes, unsatisfactory prognoses, and an escalating mortality rate, imposing a substantial burden on society [5].

Sacubitril/valsartan, comprising sacubitril and valsartan in a 1:1 ratio, functions as an angiotensin receptor-neprilysin inhibitor (ARNI). It augments the natriuretic peptide system (NPS), fostering water and sodium excretion, vasodilation, and sympathetic activity antagonism, while inhibiting the renin-angiotensin-aldosterone system (RAAS). Additionally, it exhibits anti-inflammatory, anti-ventricular remodeling, and antihypertensive properties, thereby enhancing therapeutic outcomes and patient prognosis [6]. Recent studies have elucidated ARNI's role in ameliorating heart failure and its potential in blood pressure control [7]. Initially recommended as the primary treatment for heart failure with reduced ejection fraction (HFrEF), ARNI has gained approval for hypertension treatment in China based on substantial evidence [8]. Nevertheless, there is a scarcity of comprehensive studies addressing its role in HFrEF patients with hypertension.

In this study, we observed the changes of blood pressure, left ventricular remodeling and NT-proBNP in HFrEF patients with hypertension after ARNI treatment, so as to provide ideas for the development of medication regimens for patients in need.

Materials and methods

Clinical data

A retrospective analysis was conducted on a cohort of 112 heart failure patients presenting with reduced ejection fraction (HFrEF) complicated by hypertension, who sought medical attention at Baoji Central Hospital between May 2019 and October 2021. All patients were initially diagnosed with HFrEF and had not been treated before. All participants received standard heart failure treatment. Among them, 60 patients treated with sacubitril/valsartan were designated as the observation group (OG), while 52 patients treated with valsartan alone constituted the control group (CG).

The inclusion criteria: (1) Patients meeting the diagnostic criteria for HFrEF and presenting with hypertension as a newly diagnosed condition [9]; (2) Individuals aged ≥ 18; (3) Patients who tolerated the complete treatment course; (4) Patients with comprehensive clinical data available.

Exclusion criteria: (1) Presence of other heart diseases; (2) Significant dysfunction in vital organs such as the liver and kidney; (3) Severe infectious diseases and immune dysfunction; (4) Malignant tumors; (5) Unwillingness to participate in the study. All participants provided informed consent, and the study was approved by ethics committee of Baoji Central Hospital, adhering to the principles of the Helsinki Declaration. The research flow chart is shown in **Figure 1**.

Treatment method

Upon admission, both groups of patients received standard heart failure treatment, including tailored antihypertensive and diuretic therapy, adherence to a low-salt diet and adequate rest during the course of treatment. In the control group, patients received an additional dose of valsartan at 80 mg per administration, once daily. The observation group, on the other hand, was administered sacubitril/valsartan sodium (procured from Beijing Novartis Pharmaceutical Company, National Drug Approval H20170344) at an initial dose of 50 mg bid. The dosage was adjusted every 2-4 weeks based on the patient's actual condition and tolerance, doubling each time until reaching a final dosage of 200 mg bid. Both groups underwent a 6-month treatment period. The baseline measurements for all indicators were recorded at the time of admission and before the commencement of heart failure treatment.

Main observation indicators

(1) Ventricular remodeling related indexes were evaluated and compared between the two groups before and after treatment, including interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT), and left ventricular mass index (LVMI) levels. (2) N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were compared between the two groups before and after treatment.

Secondary observation indicators

(1) The treatment effect of patients was evaluated according to NYHA classification criteria:

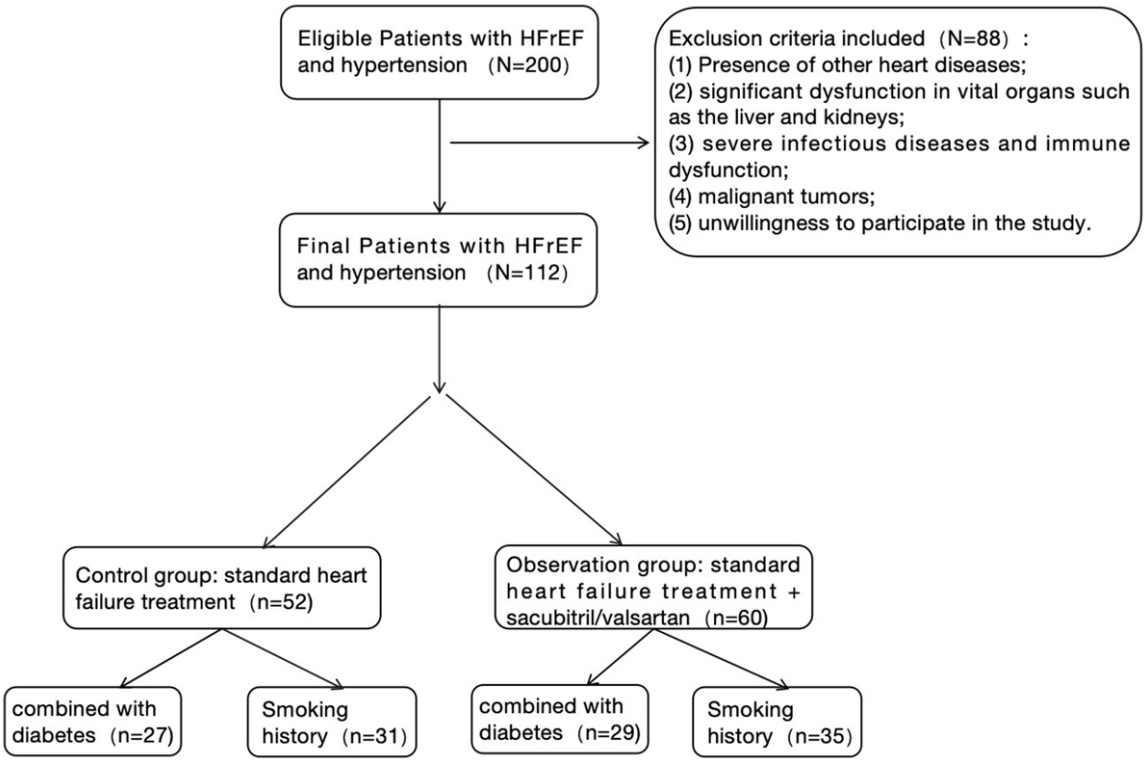

Figure 1. Research flow chart.

significantly effective (restoration to NYHA class I, or improvement from NYHA class IV to class II in cardiac function, with clinical symptoms and signs significantly relieved or even disappeared), effective (symptoms and signs were improved, and NYHA class was improved by one grade), ineffective (symptoms and signs were aggravated after treatment, with unchanged or deteriorated NYHA class). Response rate = (markedly effective + effective)/total number × 100%. (2) Blood pressure was recorded and compared between the two groups before and after treatment, including systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). (3) Cardiac function indexes, including left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD), were recorded and compared between the two groups before and after treatment. (4) According to the presence of rehospitalization for heart failure within 1 year after treatment, the patients were divided into a good prognosis group and a poor prognosis group, and Logistic multifactor analysis was performed to screen the independent risk factors for prognosis. (5) The incidence of adverse reactions during treatment was recorded and compared between the two groups, including hypotension, deterioration of renal function, hyperkalemia, and readmission for aggravated heart failure. (6) The Minnesota Living with Heart Failure Scale (MLHFQ) [10] was used to assess the life quality of the two groups of patients after treatment, including three domains: physical domain, emotional domain and other domains. The higher the score, the worse the quality of life.

Statistical methods

Collected data were processed and analyzed as well as visualized using SPSS 20.0 and GraphPad Prism 8. For measurement data, Student t-test and paired t-test were used for inter-group comparison and intra-group comparison, respectively, expressed as t; and chi-square test was used for enumeration data, expressed as x^2. Logistic multifactor regression analysis was used to analyze the independent risk factors for poor prognosis. Statistical differences were indicated when $P < 0.05$.

Table 1. Comparison of general data between two groups [n (%)]

Variable	Observation Group n=60	Control Group n=52	t/X^2	P
Gender			0.082	0.775
Male	33 (55.00)	30 (57.69)		
Female	27 (45.00)	22 (42.31)		
Age (years)			0.005	0.943
≥ 61	40 (66.67)	35 (67.31)		
< 61	20 (33.33)	17 (32.69)		
Body mass index (kg/m^2)			0.001	0.978
≥ 23	31 (51.67)	27 (51.92)		
< 23	29 (48.33)	25 (48.08)		
Smoking history			0.019	0.891
Yes	35 (58.33)	31 (59.62)		
No	25 (41.67)	21 (40.38)		
Alcohol history			0.010	0.919
Yes	41 (68.33)	36 (69.23)		
No	19 (31.67)	16 (30.77)		
Education Level			0.084	0.772
Primary school or below	40 (66.67)	36 (69.23)		
Primary school or above	20 (33.33)	16 (30.77)		
Combined diabetes			0.001	0.978
Yes	29 (48.33)	27 (51.92)		
No	31 (51.67)	25 (48.08)		

Table 2. Comparison of efficacy between the two groups [n (%)]

Therapeutic Efficacy	Observation Group n=60	Control Group n=52	X^2	P
Significantly effective	34 (56.67)	21 (40.38)	2.955	0.086
Effective	24 (40.00)	19 (36.54)		
Ineffective	2 (3.33)	12 (23.08)		
Overall response rate	58 (96.67)	40 (76.92)	9.928	0.002

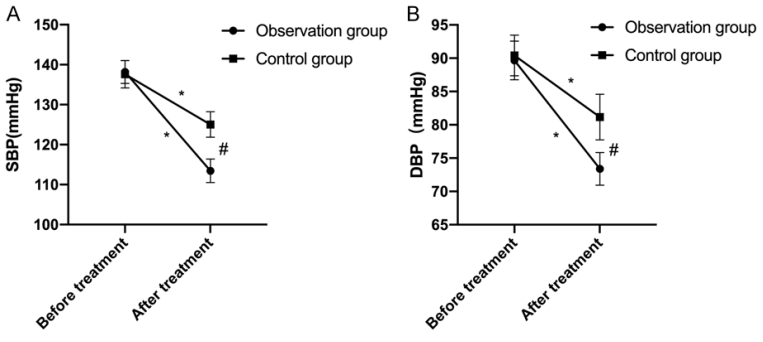

Figure 2. Comparison of blood pressure before and after treatment between the two groups. A: SBP, systolic blood pressure; B: DBP, diastolic blood pressure. * indicates P < 0.05 for comparison before and after treatment within the group; # indicates P < 0.05 for comparison between two groups after treatment.

Results

Comparison of general information between the two groups

There were no significant differences in gender, age, and BMI between the two groups (all P > 0.05), indicating the comparability between two groups, as shown in **Table 1**.

Comparison of treatment efficacy between the two groups

The numbers of patients achieved significantly effective, effective and ineffective treatment outcomes in the OG were 34, 24 and 2, respectively; and corresponding data in the CG were 21, 19 and 12, respectively. It is evident that the OG held a markedly higher overall response rate than the CG (X^2=9.928, P=0.002), **Table 2**.

Comparison of blood pressure before and after treatment between the two groups

Before treatment, no significant differences were identified in systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the two groups (both P > 0.05); while after treatment, the above indicators decreased significantly (both P < 0.05), and were both lower in the OG than in the CG (both P < 0.05), as shown in **Figure 2**.

Comparison of cardiac function before and after treatment between two groups

Before treatment, no evident differences were observed in LVEDD, LVESD and LVEF levels between two groups (all P > 0.05). While after treatment, LVEDD and LVESD levels decreased while LVEF level

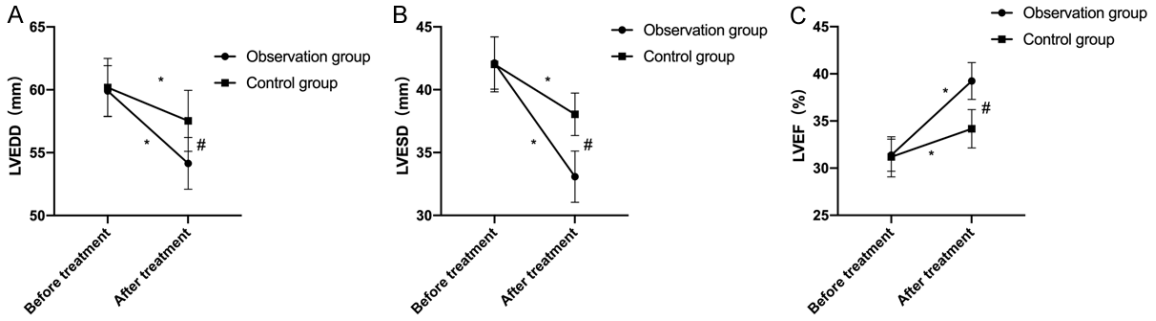

Figure 3. Comparison of cardiac function indexes before and after treatment between the two groups. A: LVEDD, left ventricular end-diastolic diameter; B: LVESD, left ventricular end-systolic diameter; C: LVEF, left ventricular ejection fraction. * indicates P < 0.05 for comparison before and after treatment within the group; # indicates P < 0.05 for comparison between two groups after treatment.

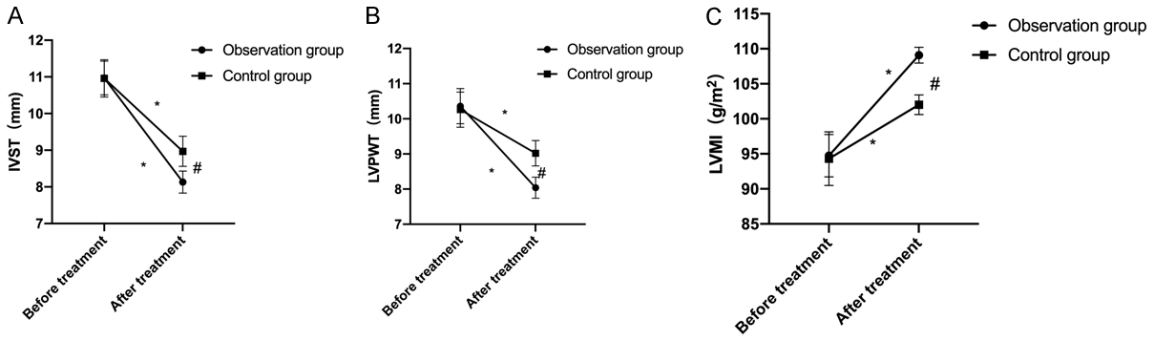

Figure 4. Comparison of ventricular remodeling indexes before and after treatment between the two groups. A: IVST, interventricular septum thickness; B: LVPWT, left ventricular posterior wall thickness; C: LVMI, left ventricular mass index. * indicates P < 0.05 for comparison before and after treatment within the group; # indicates P < 0.05 for comparison between two groups after treatment.

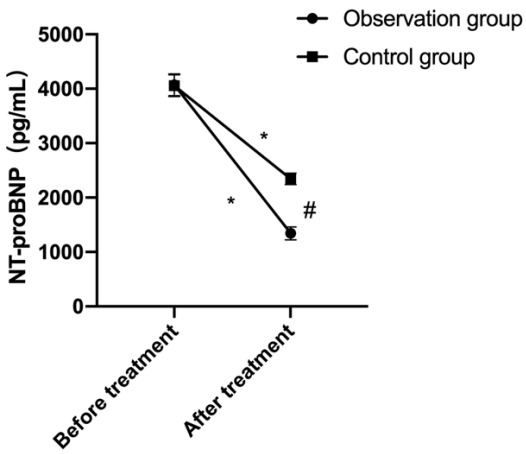

Figure 5. Comparison of NT-proBNP before and after treatment between the two groups. NT-proBNP, N-terminal pro-brain natriuretic peptide. * indicates P < 0.05 for comparison before and after treatment within the group; # indicates P < 0.05 for comparison between two groups after treatment.

increased significantly in both groups (all P < 0.001); and such changes were more prominent in the OG compared to the CG (all P < 0.001). Details are illustrated in **Figure 3**.

Comparison of ventricular remodeling indexes before and after treatment between the two groups

No marked differences were identified in IVST, LVPWT and LVMI levels between the two groups before treatment (all P > 0.05). While after treatment, the levels of IVST and LVPWT in the OG were lower than those in the CG, and its LVMI level was higher than that in the CG (all P < 0.001, **Figure 4**).

Comparison of NT-proBNP before and after treatment between the two groups

There was no significant difference in NT-proBNP level between the two groups before

Table 3. Comparison of adverse reaction between the two groups [n (%)]

Adverse Reaction	Observation Group n=60	Control Group n=52	X^2	P
Hypotension	3 (5.00)	2 (3.85)	0.087	0.768
Worsening of renal function	1 (1.67)	1 (1.92)	0.010	0.919
Hyperkalemia	1 (1.67)	1 (1.92)	2.372	0.124
Heart failure aggravated	2 (3.33)	1 (1.92)	0.213	0.645
Overall incidence ratio	7 (11.67)	5 (9.62)	0.123	0.726

Table 4. Comparison of MLHFQ scores after treatment between the two groups

Items	Observation Group n=60	Control Group n=52	t	P
Somatic domain	13.18±1.54	15.8±1.35	9.504	< 0.001
Emotion domain	8.14±0.39	9.9±0.35	24.97	< 0.001
Other domains	16.15±0.4	17.92±0.41	23.09	< 0.001

MLHFQ, Minnesota Living with Heart Failure Scale.

treatment, yet it was down-regulated in both groups after treatment (P < 0.001), and such decline was more prominent in the OG than in the CG (P < 0.001, **Figure 5**).

Comparison of the incidence of adverse reactions between the two groups

It was found that there was no significant difference in the incidence of adverse reactions between the two groups of patients (P=0.726, **Table 3**).

Comparison of MLHFQ scores after treatment between the two groups

After treatment, all quality-of-life scores in the OG were evidently lower than those in the CG, indicating better quality of life in the OG patients (P < 0.001, **Table 4**).

Analysis of risk factors affecting patient outcomes

Patients were categorized into a group with favorable prognosis (n=75) and a group with unfavorable prognosis (n=37) based on their prognosis. Univariate analysis revealed that underlying diseases and treatment regimens were both factors influencing the prognosis (**Table 5**). Subsequently, through assignment (**Table 6**), logistic regression analysis was conducted and underlined that diseases and treatment regimens were independent risk factors affecting the therapeutic efficacy of patients (all P < 0.001, **Table 7**).

Discussion

Heart failure is globally recognized for its high morbidity and mortality, with 5-year survival rates of less than 50% [11]. Hypertension serves as the primary "risk molecule" for heart failure, and the current treatment of hypertensive patients with heart failure often results in suboptimal clinical efficacy, poor prognosis, and high mortality [12]. Despite the availability of multiple antihypertensive treatment options, achieving and maintaining the target blood pressure is frequently challenging. Prolonged elevations in arterial blood pressure impose an increased pressure load on the ventricles, leading to compensatory left ventricular hypertrophy [13]. Left ventricular hypertrophy represents a significant manifestation of end-organ damage induced by hypertension and is associated with an elevated cardiovascular risk [14]. ACEI/ARB and β-blockers are the primary choices for treating HFrEF. Although they demonstrate good efficacy, there is still considerable room for improvement [15]. Therefore, the exploration of new treatment regimens is both necessary and urgent.

Sacubitril-valsartan functions as a dual angiotensin-receptor and neprilysin inhibitor. The PARADIGM-HF study [16] has validated the efficacy of sacubitril-valsartan in managing chronic heart failure. Nevertheless, its specific role in patients with heart failure and hypertension warrants further analysis. Our findings reveal that, post-treatment, the therapeutic impact on heart failure in the observation group (OG) was significantly superior to that in the control group (CG). Regarding blood pressure amelioration, while both groups exhibited improved blood pressure post-treatment, the OG demonstrated a notable reduction in systolic and diastolic blood pressure compared to pre-treatment levels, surpassing the reductions observed in CG patients. This implies that ARNI

Table 5. Univariate analysis of factors affecting patient prognosis

Variable	Good prognosis group (n=75)	Poor prognosis group (n=37)	X^2	P
Gender			0.108	0.742
Male (n=63)	43 (57.33)	20 (54.05)		
Female (n=49)	32 (42.67)	17 (45.95)		
Age			0.009	0.924
≥ 61 (n=75)	50 (66.67)	25 (67.57)		
< 61 (n=37)	25 (33.33)	12 (32.43)		
Body mass index			0.032	0.857
≤ 23 kg/m^2 (n=58)	38 (55.88)	20 (54.05)		
> 23 kg/m^2 (n=47)	30 (44.12)	17 (45.95)		
Smoking history			0.107	0.743
Yes (n=66)	45 (60.00)	21 (56.76)		
No (n=46)	30 (40.00)	16 (43.24)		
Whether combined with diabetes			15.57	< 0.001
Yes (n=66)	36 (42.35)	30 (81.08)		
No (n=56)	49 (57.65)	7 (18.92)		
Treatment programs			19.00	< 0.001
Valsartan (n=52)	24 (32.00)	28 (75.68)		
Sacubitril/valsartan sodium (n=60)	51 (68.00)	9 (24.32)		

Table 6. Assignment table

Factor	Assignment
Combined with diabetes	Yes =1, No =0
Treatment programs	Valsartan =1, Sacubitril/valsartan sodium =0

Table 7. Multivariate analysis of factors affecting patient prognosis

Variable	B	S.E	Wals	P	RR	95% C.I.	
						Lower limit	Upper limit
Combined with diabetes	1.732	0.682	5.502	0.005	5.128	1.364	18.221
Treatment programs	3.245	0.845	15.536	0.002	27.923	5.248	147.311

treatment more effectively lowered blood pressure in the OG, possibly attributed to the pharmacological mechanism of ARNI. As an innovative therapeutic agent, ARNI can rebalance the interplay between the renin-angiotensin-aldosterone system (RAAS) and the natriuretic peptide system (NPS) [17]. Sacubitril indirectly augments NPS effects by inhibiting neprilysin (NEP), leading to reduced peripheral vascular resistance, regulated water and sodium balance, lowered blood pressure, and RAAS inhibition. And this, in turn, reduces the heart's preload and afterload, resulting in decreased blood pressure and increased cardiac output [18]. In addition to its direct RAAS inhibition, valsartan can counteract the adverse effects of sacubitril on vasoconstrictor elevation and sympathetic activity [19]. These combined components contribute to vasodilation, exert a significant antihypertensive effect, and play a role in anti-ventricular remodeling, ultimately improving cardiac function.

Ventricular remodeling, resulting from myocardial damage, entails progressive alterations in the size, shape, structure, and function of the left ventricle. This process leads to ventricular chamber enlargement, diminished cardiac function, subsequent heart failure, resulting in high patient mortality [20]. Current therapeutic agents targeting ventricular remodeling, such as β-blockers, ACEI/ARB, spironolactone, and

trimetazidine do improve heart failure, but have limited effects [21]. Therefore, beyond blood pressure considerations, we compared cardiac function and ventricular remodeling-related indicators before and after treatment between two groups. The results demonstrated superior improvement in both parameters for the OG compared to the CG after treatment, indicating that ARNI not only effectively ameliorates heart failure but also contributes to the effective reversal of ventricular remodeling in patients.

The efficacy of ARNI in achieving these outcomes can be attributed to its role in maintaining stable blood pressure and water-salt balance. By inhibiting enkephalinase, ARNI reduces natriuretic peptide degradation, enhances water and sodium excretion, and mitigates excess "free water" accumulation in the body. This, in turn, reduces the left ventricle's preload, leading to enhanced relief of heart failure [22]. We postulate that the additional benefits of ARNI on ventricular remodeling primarily originate from the effects of sacubitril. Previous studies such as EVALUATE-HF [23] and PROVE-HF [24] have also demonstrated that ARNI rapidly and consistently improves cardiac remodeling in patients with HFrEF, aligning with our findings.

ARNI has demonstrated the ability to elevate BNP levels by inhibiting neprilysin (NEP), given NEP's role in the degradation of natriuretic peptides. Historically, natriuretic peptides, particularly atrial natriuretic peptide (ANP) and BNP, have been well-established for heart failure diagnosis and prognosis. Elevated ANP and BNP levels exhibit a positive correlation with left ventricular dysfunction and the degree of volume load [25]. Notably, NEP does not impact the degradation of NT-proBNP. In this study, NT-proBNP levels served as indicators reflecting changes in cardiac function and prognosis, revealing more pronounced improvement in the observation group compared to the control group after treatment. The significant reduction in NT-proBNP levels observed in the sacubitril/valsartan group aligns with the findings of Wang et al [26], underscoring consistency in our observations. Moreover, in terms of safety and improvements in quality of life, ARNI did not escalate the risk of hypotension or renal events. Instead, it effectively mitigated heart failure exacerbation and enhanced patient quality of life. Previous large-scale studies have also demonstrated the favorable tolerability and safety profile of sacubitril/valsartan [27, 28].

In conclusion, sacubitril/valsartan demonstrates superior efficacy in the treatment of patients with HFrEF and hypertension. It effectively improves blood pressure, heart failure, and ventricular remodeling indicators while maintaining a favorable safety profile. Its widespread adoption in clinical practice is warranted. However, this study still has certain limitations, including small sample size, short observation period, lack of historical data on hypertension and heart failure, absence of data from other dosage groups, and uncontrolled variables that may impact result accuracy. Therefore, extensive and long-term studies in the future are needed to validate these findings.

Disclosure of conflict of interest

None.

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