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Original Article

Empagliflozin combined with sacubitril/valsartan in hypertensive patients with heart failure: a retrospective study of efficacy and effect on blood pressure variability and cardiac function

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Abstract: Objective: To evaluate the efficacy of empagliflozin combined with sacubitril/valsartan in treating hypertensive patients with heart failure (HF), focusing on its effects on blood pressure variability (BPV) and cardiac function. Methods: This retrospective study included 101 patients with hypertension and heart failure with reduced ejection fraction treated at Baoji High-Tech Hospital from October 2021 to October 2023. Patients were divided into two groups: an observation group (n=51), treated with both empagliflozin and sacubitril/valsartan, and a control group (n=50), treated with sacubitril/valsartan alone. We compared the therapeutic effects, BPV (including 24-hour, daytime, and nighttime systolic and diastolic BPV), cardiac function indicators, levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) before and after treatment, and the incidence of adverse reactions between the groups. Independent risk factors affecting treatment efficacy were also analyzed. Results: The total effective rate of treatment in the observation group was significantly higher than in the control group ($P<0.05$). Both groups showed reductions in daytime and nighttime systolic and diastolic BPV after treatment, with the observation group displaying more pronounced improvements (all $P<0.05$). Enhancements in cardiac ultrasound measurements, NT-proBNP levels, and cTnI levels were more significant in the observation group compared to the control group post-treatment (both $P<0.05$). There was no significant difference in the incidence of adverse reactions during treatment between the two groups ($P>0.05$). Age and comorbid diabetes were identified as independent risk factors for poor prognosis, while treatment with empagliflozin combined with sacubitril/valsartan was a protective factor. Conclusion: Empagliflozin combined with sacubitril/valsartan significantly enhances treatment efficacy in hypertensive patients with heart failure, effectively improves cardiac function and BPV, and demonstrates good safety.

Keywords: Empagliflozin, sacubitril/valsartan, hypertension with heart failure, blood pressure variability, cardiac function

Introduction

Hypertension is a common chronic condition characterized by persistent elevation of blood pressure, influenced by factors such as age, mental state, genetics, lifestyle habits, and environment. The prevalence of hypertension increases with age [1]. Chronic hypertension can lead to increased left ventricular afterload, resulting in myocardial hypertrophy and progressive cardiac dysfunction, which may culminate in heart failure [2]. The concurrent presence of hypertension and heart failure significantly worsens cardiovascular outcomes, adversely affecting patient health and increasing the mortality rate [3]. Thus, identifying effective

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treatments that manage hypertension while improving cardiac function is crucial to improve outcome.

In standard clinical practice, treatment regimens for heart failure typically include inotropic agents, diuretics, and other medications aimed at alleviating symptoms, while active management of hypertension is also recommended [4]. However, the effectiveness of these conventional therapies is often limited, highlighting the need for optimized treatment strategies. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has demonstrated potential by enhancing the natriuretic peptide system and inhibiting the renin-angiotensin-aldosterone system. This dual action facilitates sodium and water excretion andvasodilation, and mitigates sympathetic activity, providing anti-inflammatory, anti-ventricular remodeling, and antihypertensive effects. These effects improve clinical outcome and prognosis [5, 6]. Approved in China for treating heart failure with reduced ejection fraction (HFrEF) and hypertension [7], sacubitril/valsartan still leaves some patients experiencing suboptimal responses.

Empagliflozin, a novel sodium-glucose cotransporter 2 inhibitor and antidiabetic agent, offers benefits including glycemic control, blood pressure reduction, and weight loss [8]. It has also been approved in China for the treatment of HFrEF, with studies confirming its effectiveness in managing blood pressure [9]. Despite these advancements, there is a lack of comprehensive analysis on the combined use of ARNI with empagliflozin in patients with both heart failure and hypertension. This warrants further investigation to optimize therapeutic outcomes for this patient group.

This study aims to assess the efficacy of empagliflozin combined with sacubitril/valsartan in patients with hypertension and heart failure, focusing on its impact on blood pressure variability and cardiac function, to provide evidence-based guidance for treatment strategies in this patient demographic.

Materials and methods

Clinical data

A retrospective review was conducted on 101 patients diagnosed with HFrEF and concurrent hypertension, hospitalized at Baoji High-Tech Hospital from October 2021 to October 2023. Patients were categorized into two groups: an observation group (n=51) treated with empagliflozin and sacubitril/valsartan, and a control group (n=50) treated solely with sacubitril/valsartan. Inclusion criteria included: (1) An initial diagnosis of HFrEF with concomitant hypertension [10]; (2) Availability of complete clinical data. Exclusion criteria: (1) Other cardiac diseases; (2) Significant organ dysfunction (e.g., liver, kidney); (3) Severe infectious diseases or immunodeficiency; (4) Malignant tumors; (5) Refusal to participate in the study. The study received ethical approval from the Ethics Committee of Baoji High-Tech Hospital and adhered to the Declaration of Helsinki principles.

Treatment methods

Upon admission, both groups received tailored treatments for underlying conditions, including management of blood pressure, blood glucose, and coronary atherosclerosis. Vasodilators, inotropic agents, and diuretics were administered as necessary. The control group received sacubitril/valsartan (Beijing Novartis Pharma Co., Ltd., National Drug Approval Number H20170344) with doses based on systolic blood pressure: 50 mg per dose for ≤100 mmHg and 100 mg per dose for >100 mmHg, administered twice daily. After 2-4 weeks, the dosage was uniformly increased to 100 mg twice daily. Additionally, the observation group received empagliflozin (Boehringer Ingelheim Pharma GmbH & Co. KG, National Medicine Approval No. HJ20170351) at 10 mg daily on an empty stomach. Treatment duration for both groups was 6 months, with all pre-treatment assessments conducted upon admission and before initiating heart failure treatment.

Primary outcome measures

(1) Treatment efficacy was assessed based on the New York Heart Association classification criteria [11]. Significant improvement was defined as a reduction in symptoms and a at least two grades of improvement in heart function. Effective treatment was characterized by a significant improvement in symptoms and a one-grade improvement in heart function. Treatments that did not meet these criteria were considered ineffective. The total effective

rate was calculated as follows: Total Effective Rate = (Number of significantly improved cases + Number of effective cases)/Total number of cases × 100%. The effectiveness rate was calculated as follows: Effectiveness Rate = (Significant improvement + Effective cases)/ Total number × 100%.

(2) Blood pressure variability (BPV) [12] was measured using a DM SABP-type ambulatory blood pressure monitor (manufactured by Dim Software (Beijing) Co., Ltd.). This included assessments of 24-hour, daytime, and nighttime systolic and diastolic BPV. Results were recorded for all measurements.

(3) Pre- and post-treatment cardiac function indicators were recorded and compared between the two groups, including left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD).

Secondary outcome measures

N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and cardiac troponin I (cTnI) levels were measured before and after treatment in both groups.

The incidence of adverse reactions during treatment was recorded and compared between the two groups. These included hypotension, worsening renal function, hyperkalemia, and heart failure readmission.

Post-treatment quality of life was evaluated using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) [13], encompassing physical, emotional, and other domains. Higher scores indicate poorer quality of life.

Patients were categorized into prognostically good or poor groups based on heart failure readmission within one year after treatment. Univariate and multivariate analyses using Cox proportional hazards models were performed to identify baseline variables associated with prognosis.

Statistical analysis

Data were analyzed using SPSS 20.0 software and visualized with GraphPad Prism 8. Continuous variables were presented as mean ± standard deviation, and group means were compared using the independent samples t-test. Categorical variables were expressed as n (%) and analyzed with the chi-square test. Statistical significance was set at $P<0.05$.

Results

Comparison of baseline data

There was no significant difference in gender, age, BMI, onset season, or rash severity between the two groups (all $P>0.05$). See **Table 1**.

Comparison of treatment efficacy between two groups

The observation group had 30 patients who were markedly effective, 19 effective, and 2 ineffective. Conversely, the control group had 21 markedly effective, 19 effective, and 10 ineffective. The total effective rate in the observation group was 96.08%, significantly higher than the 80.00% in the control group ($P <0.05$), as shown in **Table 2**.

Comparison of blood pressure variability between the two groups

Using the DMSABP type dynamic blood pressure monitor, we assessed the BPV of both groups. Prior to treatment, no significant differences were observed in 24-hour, daytime, or nighttime systolic and diastolic BPV (all $P>0.05$). After treatment, both groups showed reduced BPV across all periods, with the observation group exhibiting significantly lower BPV compared to the control group (all $P<0.05$), as illustrated in **Figure 1**.

Comparison of cardiac function indicators between the two groups before and after treatment

Before treatment, no significant differences were found in LVEDD, LVESD, or LVEF levels between the groups (all $P>0.05$). After treatment, both groups demonstrated reduced LVEDD and LVESD, and increased LVEF (all $P<0.001$). The improvements in the observation group were significantly better than those of the control group (all $P<0.001$), as depicted in **Figure 2**.

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

Before treatment, no significant differences were observed in the NT-proBNP and cTnI levels

Table 1. Comparison of baseline data

Factor	Observation group n=51	Control group n=50	t/X^2	P
Gender			0.081	0.776
Male	31 (60.78)	29 (58.00)		
Female	20 (39.22)	21 (42.00)		
Age			0.242	0.623
≥70	35 (68.63)	32 (64.00)		
<70	16 (31.37)	18 (36.00)		
Body mass index (kg/m^2)			0.011	0.915
≥23	24 (47.06)	23 (46.00)		
<23	27 (52.94)	27 (54.00)		
Smoking history			0.174	0.678
Yes	33 (66.00)	31 (62.00)		
No	17 (34.00)	19 (38.00)		
Drinking history			0.561	0.454
Yes	40 (78.43)	36 (72.00)		
No	11 (21.57)	14 (28.00)		
Combined with diabetes			0.082	0.774
Yes	30 (58.82)	28 (56.00)		
No	21 (41.18)	22 (44.00)		

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

Curative effect	Observation group n=51	Control group n=50	X^2	P
Markedly effective	30 (58.82)	21 (42.00)	2.859	0.091
Effective	19 (37.25)	19 (38.00)	0.006	0.938
Ineffective	2 (3.92)	10 (20.00)	9.928	0.002
Total Effective rate	49 (96.08)	40 (80.00)	6.234	0.013

between the two groups (both P>0.05). However, post-treatment levels of both markers were significantly reduced in both groups (both P<0.05), with the observation group showing significantly lower levels compared to the control group (both P<0.05), as shown in **Figure 3**.

Comparison of the incidence of adverse reactions between the two groups

There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). See **Table 3**.

Comparison of MLHFQ scores between two groups after treatment

After treatment MLHFQ scores were significantly lower in the observation group than in the control group, indicating a better quality of life (P<0.05), as indicated in **Table 4**.

Analysis of prognostic factors affecting patients

Univariate and multivariate Cox proportional hazards models were employed to analyze potential risk factors for patient prognosis, with heart failure rehospitalization within one year as the dependent variable. The multivariate analysis identified age and comorbid diabetes as independent risk factors for an adverse prognosis, while treatment with empagliflozin combined with sacubitril/valsartan was identified as a protective factor for patient prognosis (P<0.05), detailed in **Table 5**.

Discussion

Heart failure represents the terminal stage of various cardiovascular diseases. It is characterized by myocardial ischemia, a progressive decline in cardiac function, and reduced con-

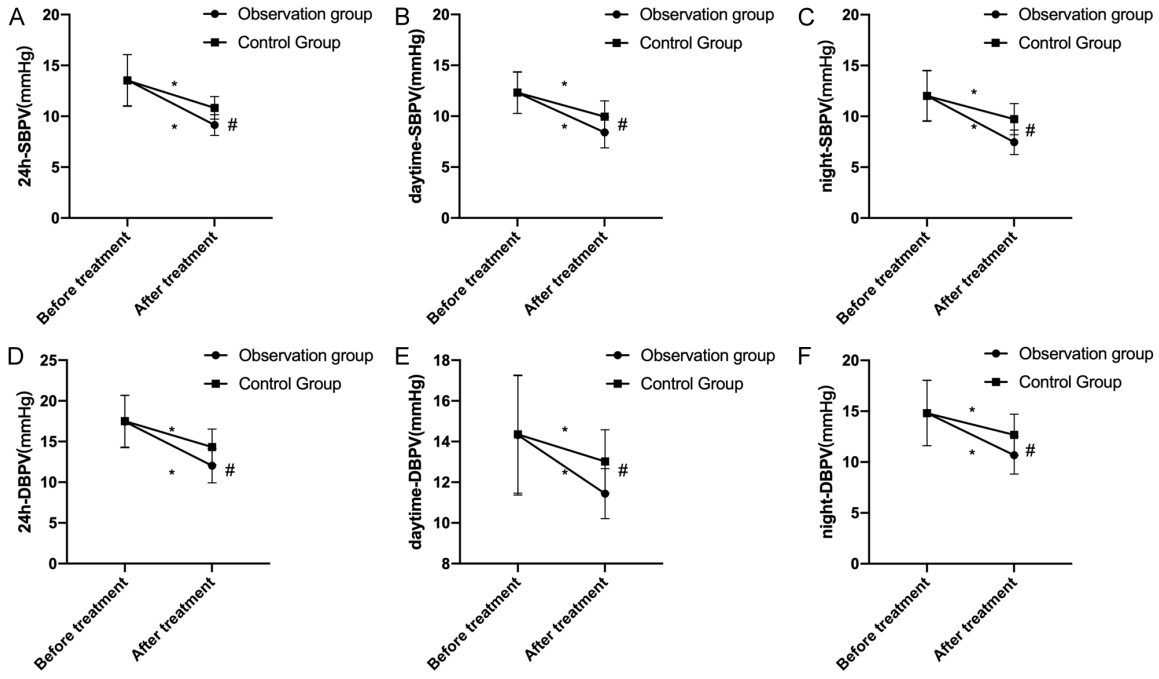

Figure 1. Comparison of blood pressure variability between two groups. A-C: Comparison of 24 h, daytime and nighttime SBPV between two groups; D-F: Comparison of 24 h, daytime and nighttime DBPV between the two groups. * indicates P<0.05 within the same group before and after treatment; # indicates P<0.05 between thr two groups after treatment. SBPV, systolic blood pressure variability; DBPV, diastolic blood pressure variability.

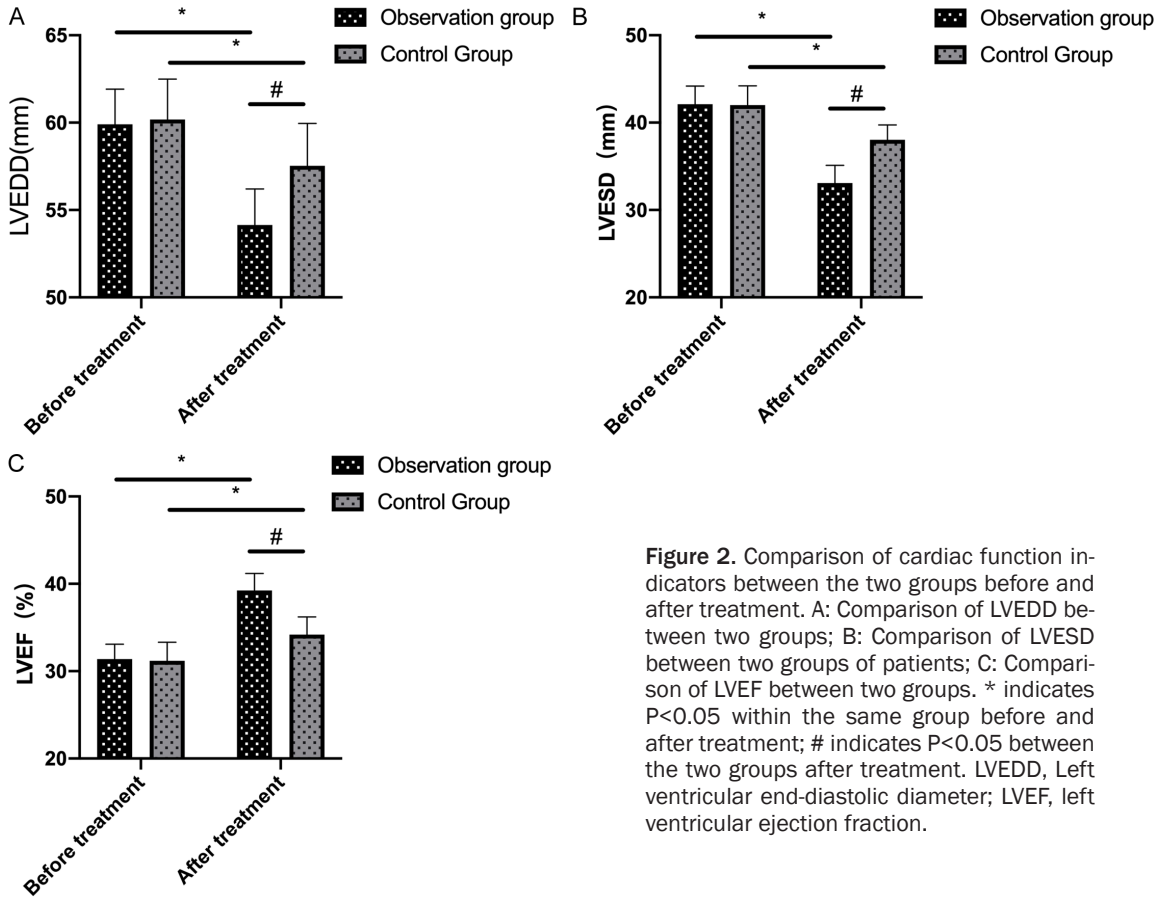

Figure 2. Comparison of cardiac function indicators between the two groups before and after treatment. A: Comparison of LVEDD between two groups; B: Comparison of LVESD between two groups of patients; C: Comparison of LVEF between two groups. * indicates P<0.05 within the same group before and after treatment; # indicates P<0.05 between the two groups after treatment. LVEDD, Left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

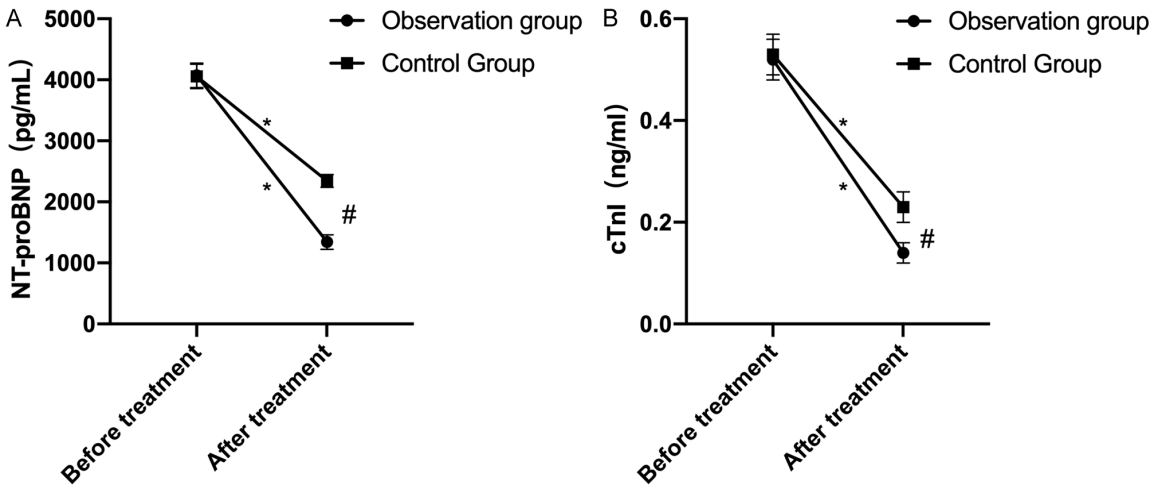

Figure 3. Comparison of NT-proBNP and cTnI levels between the two groups before and after treatment. A: Comparison of NT-proBNP levels between groups before and after treatment; B: Comparison of cTnI levels between groups before and after treatment. * indicates P<0.05 within the same group before and after treatment. # indicates P<0.05 between the two groups after treatment. NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I.

Table 3. Comparison of adverse reactions

Adverse reactions	Observation group n=51	Control group n=50	X^2	P
Hypotension	3 (5.88)	2 (4.00)	-	-
Worsening of kidney function	1 (1.96)	1 (2.00)	-	-
Hyperkalemia	1 (1.96)	1 (2.00)	-	-
Worsening of heart failure	1 (1.96)	3 (6.00)	-	-
Overall incidence	6 (11.76)	7 (14.00)	0.113	0.737

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

Project	Observation group n=51	Control group n=50	t	P
Somatic realm	13.15±1.02	15.94±1.29	12.07	<0.001
Emotional realm	8.09±0.36	10.06±0.42	25.33	<0.001
Other realm	16.07±0.37	18.38±0.32	33.53	<0.001

MLHFQ, Minnesota Living with Heart Failure Questionnaire.

tractility, significantly impairing patients' quality of life. In elderly individuals, the prevalence of concomitant hypertension compounds these challenges by increasing cardiac workload and accelerating the deterioration of cardiac function, complicating clinical management [14].

Sacubitril/valsartan, a novel therapeutic agent for heart failure, enhances cardiac function by inhibiting the degradation of natriuretic peptides. This increases serum levels of the peptides, improves sodium and water retention, reduces vascular smooth muscle contraction, and prevents myocardial interstitial cell remodeling [15]. Similarly, SGLT-2 inhibitors, primarily used for glycemic control, have demonstrated cardiovascular benefits, including reduced rates of heart failure hospitalization and cardiovascular mortality as evidenced by the EMPA-REG OUTCOME study in 2015 [16]. Notably, empagliflozin, a representative SGLT-2 inhibitor, has been shown to significantly reduce cardiovascular events, underscoring its myocardial protective effects [17].

Table 5. Univariate and multivariate Cox regression analysis of factors related to patient prognosis

Factor	Single factor		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender	1.17 (0.66-2.34)	0.679	-	-
Male (N=43)				
Female (N=39)				
Age	0.47 (0.35-0.82)	0.002	1.21 (1.07-1.15)	0.031
≤70 (n=35)				
>70 (n=47)				
Body mass index	0.98 (0.62-1.73)	0.823	-	-
≤23 kg/m^2 (n=44)				
>23 kg/m^2 (n=38)				
Smoking history	0.91 (0.55-1.33)	0.437	-	-
Yes (n=49)				
No (n=33)				
Combined with diabetes	1.89 (1.34-6.82)	0.019	2.23 (1.12-8.49)	0.027
Yes (n=53)				
No (n=29)				
Treatment programs	0.62 (0.41-0.98)	0.022	0.55 (0.75-0.92)	0.019
Sacubitril/valsartan (n=62)				
Empagliflozin combined with sacubitril/valsartan (n=20)				

In this study, we examined the efficacy of empagliflozin in patients with heart failure and hypertension. Results indicated that combining empagliflozin with sacubitril/valsartan significantly enhanced the total effective treatment rate to over 90%, confirming empagliflozin's therapeutic potential in treating HFrEF. Further, we observed notable improvements in BPV for both groups after treatment, with more pronounced improvements in the observation group. Prior research supports that SGLT-2 inhibitors are beneficial in managing diabetes with hypertension by improving dynamic blood pressure indicators and positively affecting patient prognosis [18]. The EMPA-REG blood pressure trial also reported that empagliflozin reduced average systolic blood pressure by 3-5 mmHg and diastolic by 1-2 mmHg at 12 weeks, which is consistent with our findings [19]. This effect is likely due to the osmotic diuresis-induced reduction in plasma volume, increased urinary sodium excretion, and weight loss facilitated by SGLT2 inhibition. Additionally, long-term blood pressure-lowering effects of SGLT-2 inhibitors may be linked to improved endothelial function [20].

This study is the first to demonstrate that adding empagliflozin to sacubitril/valsartan therapy can enhance blood pressure control in patients with heart failure and hypertension, indicating a synergistic effect of these medications. However, further systematic research is needed to elucidate the specific mechanisms underlying this enhanced efficacy.

As widely acknowledged, NT-proBNP and cTnI are critical biomarkers for heart failure, assisting clinicians in assessing the severity and prognosis of the condition [21-23]. In this study, these biomarkers were chosen as objective indicators. Our findings revealed that post-treatment serum levels of NT-proBNP and cTnI were significantly lower in the observation group than in the control group, further validating the effectiveness of combining empagliflozin with sacubitril/valsartan in treating HFrEF. Previous studies have demonstrated that empagliflozin improves cardiac function by enhancing hemodynamics, reducing myocardial fibrosis, and normalizing heart failure-related gene expression [24, 25]. Additionally, animal experiments have shown that empagliflozin enhances cardiac diastolic function and myocardial dynamics in non-diabetic HFrEF models by improving nitric oxide signaling and increasing cyclic GMP levels [26], aligning with our observations.

Moreover, we compared the incidence of adverse reactions and post-discharge quality of life between the two patient groups. The results indicated no significant difference in adverse reaction rates during the treatment period between the groups. However, quality of life scores were significantly better in the observation group than in the control group, suggesting that the combined treatment regimen is not only safe but also significantly enhances patients' quality of life. Previous large-scale studies have confirmed the safety and tolerability of combining sacubitril/valsartan with SGLT2 inhibitors [27, 28].

Our analysis of independent risk factors affecting patients' prognosis showed that age, comorbid diabetes, and treatment regimens were significant predictors of adverse patient outcome. This information is crucial for developing personalized treatment plans tailored to individual patient circumstances in the future.

In summary, the combined treatment of empagliflozin with sacubitril/valsartan in patients with hypertension and heart failure has shown substantial efficacy, significantly improving cardiac function and blood pressure variability. Moreover, it maintains a favorable safety profile, making it a viable clinical choice. However, this study has some limitations. The small sample size may introduce instability in the results, necessitating further validation in a larger multicenter study. Additionally, the retrospective nature of this study may introduce bias in sample inclusion, which should be addressed in future randomized controlled trials.

Disclosure of conflict of interest

None.

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