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Original Article

Sacubitril/valsartan plus dapagliflozin improves cardiac function and reduces MACE and rehospitalization in hFrEF: a retrospective study

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Abstract: Objective: To evaluate the efficacy and safety of sacubitril/valsartan combined with dapagliflozin in heart failure with reduced ejection fraction (HFrEF). Methods: A retrospective study included 400 HFrEF patients (control group: sacubitril valsartan, n=200; observation group: add dapagliflozin, n=200) treated for 6 months. Cardiac function, NT-proBNP, 6MWT, MACE, readmission rate, and adverse reactions were compared. Results: After treatment, LVEF increased in both groups (control: 32.5 ± 5.6% to 38.6 ± 6.2%; observation: 32.8 ± 5.4% to 42.3 ± 6.5%, P<0.05), with greater improvement observed in observation group. LVEDD, LVESD, and NT-proBNP decreased, while 6MWT increased in both groups (all P<0.05), with superior changes in observation group. Readmission rate (8.5% vs. 16.0%, P=0.022) and MACE (6.0% vs. 9.5%, P=0.040) were significantly lower in observation group. No significant differences in adverse reactions between groups (all P>0.05). Conclusion: Sacubitril valsartan combined with dapagliflozin improves cardiac function, reduces NT-proBNP, enhances exercise tolerance, and lowers readmission and MACE rates without increasing adverse reactions, offering better clinical net benefit than sacubitril valsartan alone.

Keywords: Heart failure, sacubitril valsartan, dapagliflozin, clinical efficacy, adverse reactions

Introduction

Heart failure (HF) is a serious manifestation or advanced stage of various heart diseases and has become an important public health problem worldwide, affecting approximately 26 million people globally and contributing to substantial healthcare expenditures [1, 2]. Heart failure with reduced ejection fraction (HFrEF) is the main type of heart failure, accounting for approximately 50% of all heart failure cases. Its incidence has been increasing annually due to population aging. The prognosis of patients is poor, with a 5-year mortality rate approaching 50%, a rate worse than that of many common malignancies [3, 4]. Although traditional anti-heart failure treatment (e.g., angiotensin converting enzyme inhibitors, beta blockers, aldosterone receptor antagonists) has improved the clinical symptoms and survival of patients to a certain extent, a considerable proportion of patients still face the risk of repeated hospitalization, poor quality of life and adverse cardiovascular events [5].

In recent years, the advent of angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter 2 inhibitor (SGLT2i) has brought a revolutionary breakthrough in the treatment of HFrEF [6]. As the world's first ARNI drug, sacubitril/valsartan exerts multiple effects, including vasodilation, diuresis, and antifibrotic actions, by simultaneously inhibiting neprilysin and blocking angiotensin II receptors. The landmark PARADIGM-HF trial demonstrated that sacubitril valsartan significantly reduced the risk of cardiovascular death and heart failure hospitalization in patients with HFrEF compared with enalapril, establishing it as a cornerstone therapy for HFrEF [7]. As a SGLT2 inhibi-

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tor, dapagliflozin was originally used for the treatment of type 2 diabetes. Subsequent landmark trials including DAPA-HF have confirmed that dapagliflozin can significantly improve the clinical outcome of patients with HFrEF, reducing heart failure hospitalization and cardiovascular mortality, regardless of diabetes status [8].

Current studies have confirmed that excessive activation of the neuroendocrine system and hemodynamic abnormalities are the core pathophysiological mechanisms underlying the development of HFrEF, while sacubitril/valsartan and dapagliflozin exert synergistic therapeutic effects from the two dimensions of neuroendocrine regulation and hemodynamic improvement by modulating the natriuretic peptide system and inhibiting glucose reabsorption in the renal proximal tubules [9]. Several studies have shown that sacubitril valsartan combined with dapagliflozin can further improve left ventricular remodeling and quality of life in patients with HFrEF compared with sacubitril valsartan alone [10].

Despite these advances, several important research gaps remain to be addressed. First, although randomized controlled trials have demonstrated the efficacy of sacubitril valsartan and dapagliflozin individually, real-world evidence regarding the combination therapy in routine clinical practice is still limited. Second, the potential synergistic benefits of combining these two agents - one targeting neurohormonal modulation (sacubitril/valsartan) and the other targeting metabolic and hemodynamic pathways (dapagliflozin) - have not been fully elucidated in large-scale retrospective studies. Third, long-term safety data of the combination therapy, particularly regarding renal function, electrolyte balance, and symptomatic hypotension, remain insufficient. Fourth, the comprehensive impact of combination therapy on major adverse cardiovascular events (MACE), heart failure readmission rates, and quality of life in Chinese HFrEF patients requires further investigation. Therefore, more clinical evidence is urgently needed to support whether the combination of these two agents can provide better net clinical benefits on the basis of conventional anti-heart failure treatment, as well as to establish its long-term safety profile. Based on this, this study retrospectively analyzed the clinical data of patients with HFrEF, and compared the clinical efficacy and safety of sacubitril valsartan combined with dapagliflozin versus sacubitril/valsartan alone, in order to provide evidence-based basis for the optimal combined treatment of HFrEF.

Materials and methods

Patient selection and search strategy

This retrospective study was conducted at the First Affiliated Hospital of Jinzhou Medical University. Using the hospital's electronic medical record system, we searched for patients diagnosed with HFrEF who were admitted to the Department of Cardiology between January 2023 and December 2024. The search strategy employed the following keywords: "heart failure", "reduced ejection fraction", "sacubitril valsartan", and "dapagliflozin".

Treatment decisions were made by attending cardiologists based on the 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guideline and individual patient conditions. Before treatment initiation, all patients or their legal guardians were fully informed of the potential benefits, risks, and alternatives of each treatment regimen, and signed a written informed consent for the clinical treatment (not for study participation). Treatment allocation was not randomized; patients in the control group received sacubitril valsartan alone, and those in the observation group received sacubitril valsartan plus dapagliflozin, based on clinical judgment, drug availability, and patient preferences after full discussion.

Inclusion criteria: (1) Patients who met the diagnostic criteria for heart failure according to the *2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure* and the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure*, with left ventricular ejection fraction (LVEF) <40% confirmed by echocardiography using the Simpson biplane method [11]. (2) New York Heart Association (NYHA) functional class II, III, or IV at the time of enrollment. (3) Clinically stable for at least 4 weeks prior to enrollment, receiving standardized and optimized anti-heart failure treatment (including

β-blockers, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI), and/or aldosterone receptor antagonists at stable doses for ≥4 weeks). (4) Age ≥18 years. (5) First-time initiation of sacubitril/valsartan. (6) Complete clinical, laboratory, and echocardiographic data available for review. (7) Treatment duration of at least 6 months with complete follow-up records.

Exclusion criteria: (1) Heart failure secondary to reversible causes, including severe valvular heart disease, pericardial disease, myocarditis, or uncorrected congenital heart disease. (2) Acute coronary syndrome within 3 months prior to enrollment. (3) Severe arrhythmias (atrial fibrillation/flutter with ventricular rate >130 bpm, sustained ventricular tachycardia, or high-degree atrioventricular block without pacemaker). (4) Uncontrolled hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg. (5) Severe hepatic insufficiency: Child-Pugh class C or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3 times the upper limit of normal. (6) Severe renal insufficiency: estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. (7) Type 1 diabetes mellitus or history of diabetic ketoacidosis. (8) Known hypersensitivity or contraindication to ARNI or SGLT2i. (9) Pregnant or lactating women. (10) Participation in other interventional clinical trials within 3 months. (11) Life expectancy <6 months due to non-cardiovascular disease. (12) Inability to comply with study procedures or provide complete medical records.

Based on their actual treatment regimens, patients who received sacubitril valsartan combined with conventional anti-heart failure therapy but without dapagliflozin were assigned to the control group (n=200). Patients who received sacubitril valsartan combined with conventional anti-heart failure therapy plus dapagliflozin were assigned to the observation group (n=200). The study was approved by ethics committee of the First Affiliated Hospital of Jinzhou Medical University (ethics number: KYLL20240615). Due to the retrospective nature and anonymization of patient information, the requirement for written informed consent was waived (**Figure 1**).

Data extraction and validation

Two independent investigators extracted data from the electronic medical records using a standardized data collection form. Data extracted included: (1) baseline characteristics (age, sex, body mass index [BMI], NYHA class, vital signs); (2) laboratory parameters (N-terminal pro-brain natriuretic peptide [NT-proBNP], eGFR, creatinine [Cr], urea nitrogen [BUN], serum potassium); (3) echocardiographic parameters (LVEF, ventricular end-diastolic diameter [LVEDD], left ventricular end-systolic diameter [LVESD]); (4) treatment information (medication types, doses, duration); (5) outcome events (MACE, heart failure readmission, mortality); (6) adverse events (hypotension, urinary tract infection, etc.).

Data validation was performed by a third investigator who randomly selected 20% of the patients and re-extracted the data. The interobserver agreement was >95% for key variables. Discrepancies were resolved by consensus or referral to a senior cardiologist.

Echocardiography was performed using a Vivid E95 color Doppler ultrasound diagnostic instrument (GE Healthcare, USA). Serum NT-proBNP levels were detected by electrochemiluminescence using a Cobas e801 automatic analyzer with Roche diagnostic kits (Roche Diagnostics, Germany). Medications used in this study included sacubitril/valsartan (Novartis Pharma Schweiz AG, Switzerland), dapagliflozin (AstraZeneca AB, Sweden), metoprolol (AstraZeneca Pharmaceutical Co., Ltd., China), bisoprolol (Merck KGaA, Germany), furosemide (Shandong Xinhua Pharmaceutical Co., Ltd., China), torasemide (Zhejiang Tiantai Pharmaceutical Co., Ltd., China), and spironolactone (Hangzhou MSD Pharmaceutical Co., Ltd., China). Blood pressure was measured using an HEM-7121 electronic sphygmomanometer (Omron Healthcare, Japan), and electrocardiography was performed using a MAC 2000 electrocardiograph (GE Healthcare, USA).

Outcome measures

Primary outcome measures: Changes in cardiac function indices (LVEF, LVEDD, LVESD) from baseline to 6 months; Changes in serum NT-proBNP levels from baseline to 6 months;

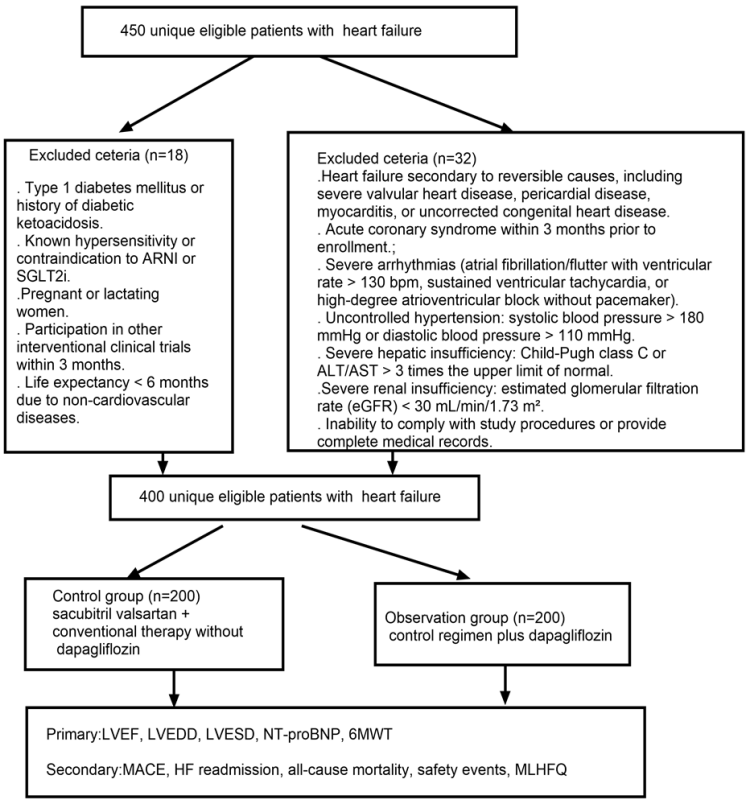

Figure 1. Patient enrollment flowchart.

Changes in 6-minute walking test (6-MWT) distance from baseline to 6 months [12].

Secondary outcome measures: MACEs: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; Heart failure readmission rate; All-cause mortality; Safety outcomes: symptomatic hypotension, renal dysfunction, hyperkalemia, reproductive urinary tract infection, and other adverse reactions; Quality of life assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. Normally distributed continuous variables were expressed as mean ± standard deviation (SD); comparisons between two groups were performed using the independent samples t-test, and pre-post comparisons within groups were performed using the paired t-test. Non-normally distributed continuous variables were expressed as median (interquartile range, IQR) [M (P25, P75)]; comparisons between groups were performed using the Mann-Whitney U test. Categorical variables were expressed as number of cases and percentage [n (%)]; comparisons between groups were performed using the chi-square test or Fisher's exact test (when expected frequency <5). Repeated measures analysis of variance was used to compare changes in cardiac function indices and scale scores over time between the two groups. Multivariable Cox proportional hazards regression analysis was performed to identify independent factors associated with heart failure readmission and MACE. Variables with P<0.10 in univariate analysis were entered into the multivariable model, including age, sex, BMI, NYHA class, comorbidities (hypertension, diabetes, coronary heart disease, atrial fibrillation, chronic kidney disease), baseline medications (β-blockers, diuretics, aldosterone receptor antagonists), and treatment group (control vs. observation). Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). All tests were two-sided, and a *P* value <0.05 was considered statistically significant.

Result

Comparison of baseline characteristics between the two groups

All 200 in each group completed the study; no patients were lost to follow-up. Before treatment, there were no significant differences in age, sex, BMI, NYHA cardiac function classification, LVEF, etiology of heart failure, comorbidities (hypertension, diabetes, coronary heart disease, atrial fibrillation, chronic kidney disease) and basic medication (β-blockers, diuretics, aldosterone receptor antagonists) between the two groups (P>0.05; **Table 1**).

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

After 6 months of treatment, LVEF significantly increased in both groups compared with base-

Table 1. Comparison of baseline data between the two groups of patients

Project	Control group (n=200)	Observation group (n=200)	χ^2/t value	*P* value
Age (years, $\bar{x} \pm s$)	65.8 ± 10.2	66.3 ± 9.8	0.502	0.616
Gender [n (%)]			0.101	0.751
Male	118 (59.0)	115 (57.5)		
Women	82 (41.0)	85 (42.5)		
BMI (kg/m^2, $\bar{x} \pm s$)	24.5 ± 3.2	24.8 ± 3.5	0.891	0.374
NYHA cardiac function classification [n (%)]			0.447	0.800
Grade II	72 (36.0)	68 (34.0)		
Grade III	98 (49.0)	104 (52.0)		
Grade IV	30 (15.0)	28 (14.0)		
Etiology [n (%)]			0.312	0.856
Dilated cardiomyopathy	86 (43.0)	82 (41.0)		
Hypertensive heart disease	64 (32.0)	68 (34.0)		
Ischemic cardiomyopathy	42 (21.0)	44 (22.0)		
Other	8 (4.0)	6 (3.0)		
Complications [n (%)]				
Hypertension	112 (56.0)	108 (54.0)	0.160	0.689
Diabetes	68 (34.0)	72 (36.0)	0.176	0.675
Coronary heart disease	96 (48.0)	100 (50.0)	0.160	0.689
Atrial fibrillation	52 (26.0)	48 (24.0)	0.213	0.644
Chronic kidney disease	24 (12.0)	26 (13.0)	0.091	0.763
Medication [n (%)]				
β-blockers	178 (89.0)	182 (91.0)	0.437	0.509
Diuretics	156 (78.0)	160 (80.0)	0.244	0.622
Aldosterone receptor antagonists	142 (71.0)	146 (73.0)	0.200	0.655

Note: BMI: body mass index; nYHA: New York Heart Association; lVEF: left ventricular ejection fraction. Independent sample t test or χ^2 test was used for comparison between groups. P>0.05 indicated that the baseline data of the two groups were comparable.

Table 2. Comparison of cardiac function indexes between the two groups before and after treatment ($\bar{x} \pm s$)

Groups	Time	LVEF (%)	LVEDD (mm)	LVESD (mm)
Control group (n=200)	Before treatment	32.5 ± 5.6	62.5 ± 6.8	52.3 ± 6.2
	After treatment	38.6 ± 6.2*	58.2 ± 6.1*	48.5 ± 5.8*
Observation group (n=200)	Before treatment	32.8 ± 5.4	62.9 ± 6.5	52.6 ± 5.9
	After treatment	42.3 ± 6.5$^{*,\#}$	54.6 ± 5.8$^{*,\#}$	44.2 ± 5.5$^{*,\#}$

Note: LVEF: left ventricular ejection fraction; lVEDD: left ventricular end-diastolic diameter; lVESD: left ventricular end-systolic diameter. Paired t test was used for intra-group comparison, and independent sample t test was used for inter-group comparison. *P<0.05, compared with the same group before treatment; $^\#$P<0.05, compared with the control group after treatment; *P<0.05, compared with before treatment (paired t-test); $^\#$P<0.05, compared with control group after treatment (independent samples t-test). Within-group comparison: control group (LVEF: t=10.234, P<0.001; LVEDD: t=6.456, P<0.001; LVESD: t=6.123, P<0.001); observation group (LVEF: t=15.678, P<0.001; LVEDD: t=12.345, P<0.001; LVESD: t=13.456, P<0.001). Between-group comparison after treatment (LVEF: t=5.678, P<0.001; LVEDD: t=5.123, P<0.001; LVESD: t=6.789, P<0.001).

line, and the LVEDD and LVESD significantly decreased. The improvement of the above indexes in the observation group was significantly better than that in the control group, and the difference was statistically significant (P<0.05). See **Table 2** and **Figure 2**.

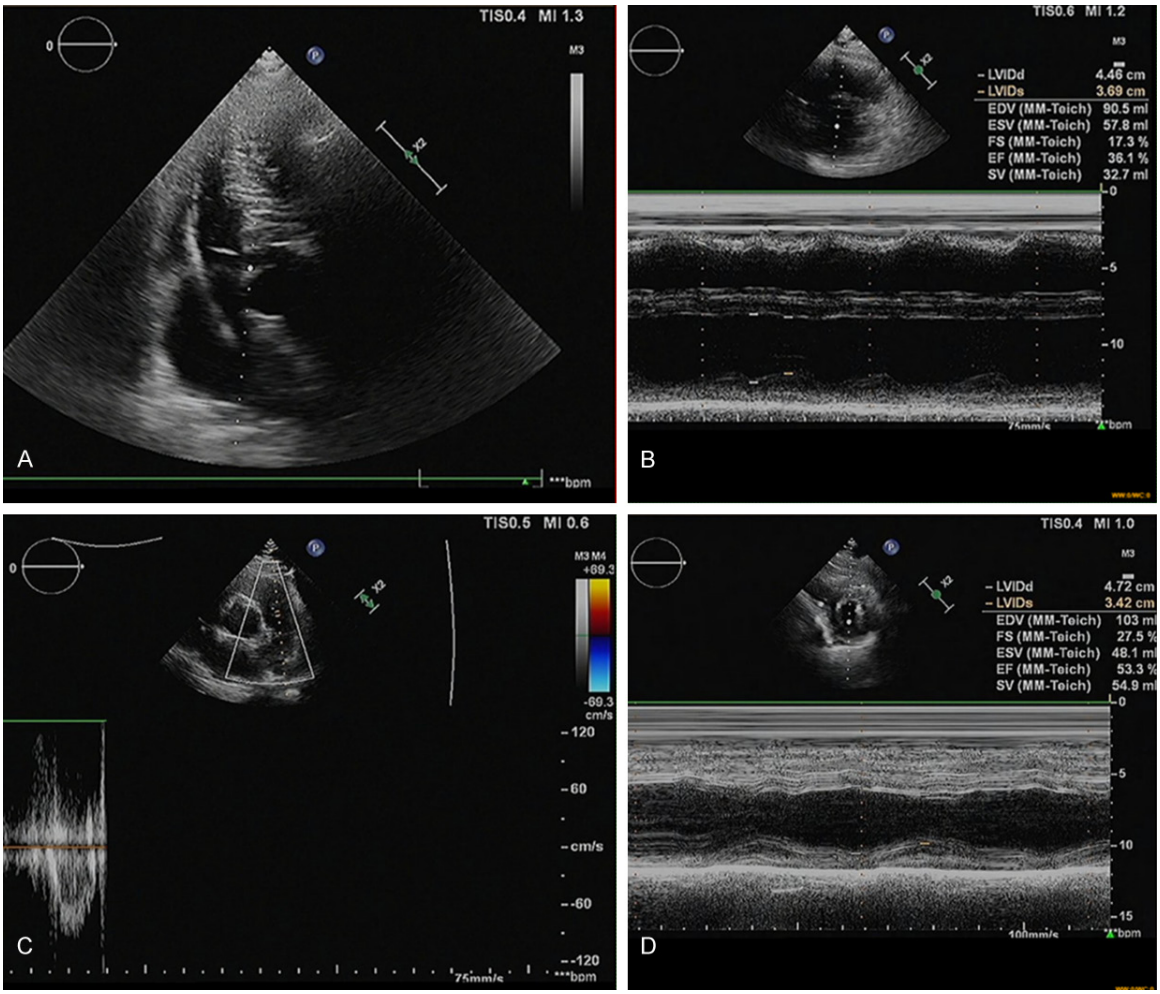

Figure 2. Representative echocardiographic images. A, B. Before treatment; C, D. After treatment.

Comparison of 6MWT and NT-proBNP between the two groups before and after treatment

After 6 months of treatment, the 6-MWT of the two groups was significantly longer, and the serum NT-proBNP level was significantly lower compared with baseline. The improvement of the above indicators in the observation group was significantly better than that in the control group (P<0.05; **Table 3**).

Comparison of clinical outcome events between the two groups of patients with heart failure

During 6 months of treatment, the heart failure rehospitalization rate in the observation group (8.5%) was significantly lower than that in the control group (16.0%), and the overall incidence of MACE in the observation group (6.0%) was also statistically lower than that in the control group (9.5%) (both P<0.05; **Table 4**).

Comparison of blood pressure and incidence of symptomatic hypotension between the two groups

After 6 months of treatment, the systolic blood pressure of the two groups was slightly lower than that before treatment (P>0.05). The incidence of symptomatic hypotension was 4.5% in the observation group and 5.0% in the control group (P>0.05; **Table 5**).

Comparison of renal function between the two groups before and after treatment

After 6 months of treatment, the levels of eGFR, Cr, BUN, and serum potassium in the two

Table 3. Comparison of 6MWT and NT-proBNP between the two groups before and after treatment

Group	Time	6MWT (m, $\bar{x} \pm s$)	Statistics	NT-proBNP (pg/mL, M (IQR))	Statistics
Control (n=200)	Before	285.5 ± 65.3		2850 (1850, 4250)	
	After	335.8 ± 58.6	t=8.234, P<0.001[1]	1850 (1200, 2850)	Z=6.789, P<0.001[2]
Observation (n=200)	Before	290.2 ± 62.8		2790 (1820, 4180)	
	After	368.5 ± 55.2	t=12.456, P<0.001[1]	1280 (850, 1950)	Z=9.123, P<0.001[2]
Between-group (after treatment)			t=4.567, P<0.001[3]		Z=5.432, P<0.001[4]

Note: [1]Paired t-test; [2]Wilcoxon signed-rank test; [3]Independent samples t-test; [4]Mann-Whitney U test. 6MWT: 6-minute walking test; NT-proBNP: N-terminal pro-brain natriuretic peptide; IQR: interquartile range.

Table 4. Comparison of clinical outcomes between the two groups [n (%)]

Groups	Number of cases	Heart failure rehospitalization rate	Total incidence of MACE	All-cause mortality
Control group	200	32 (16.0)	19 (9.5)	11 (5.5)
Observation group	200	17 (8.5)	12 (6.0)	6 (3.0)
χ^2 value		5.236	4.236	1.529
P value		0.022	0.040	0.216

Note: MACE: major adverse cardiovascular events.

groups were not significantly different from those before treatment (P>0.05). The comparison between the two groups showed that there was no significant difference in the above indexes between the two groups after treatment (P>0.05), indicating that the addition of dapagliflozin had no significant effect on renal function and electrolyte. Details are shown in **Table 6**.

Comparison of the incidence of adverse reactions between the two groups of patients

The incidence of adverse reactions during treatment was low in both groups. The incidence of urinary tract infection in the observation group was 2.0% (4/200), which was slightly higher than 1.0% (2/200) in the control group (χ^2=0.671, P=0.410). There was no significant difference in the incidence of cough (1.0% vs. 1.5%) and rash (1.0% vs. 0.5%) between the two groups (P>0.05). The total incidence of adverse reactions was 10.0% (20/200) in the observation group and 9.0% (18/200) in the control group, and the difference was not statistically significant (χ^2=0.117, P=0.732; **Table 7**).

Comparison of quality of life between the two groups before and after treatment

Before treatment, there was no significant difference in the MLHFQ score between the two groups (P>0.05). After 6 months of treatment, the MLHFQ scores of the two groups were significantly decreased compared with baseline (P<0.001), indicating improved quality of life. Comparison between groups showed that the MLHFQ score after treatment of the observation group was significantly lower than that of the control group (36.5 ± 7.5 vs. 42.8 ± 8.6, P<0.001), and the reduction in MLHFQ score was significantly greater in the observation group than in the control group (16.3 ± 5.8 vs. 9.7 ± 5.2, P<0.001; **Figure 3**), indicating that the combined treatment further improved the quality of life in patients with HFREF.

Multivariable Cox regression analysis

Multivariable Cox regression analysis was performed to identify independent factors associated with heart failure readmission and MACE. As shown in **Table 8**, after adjusting for potential confounders (age, sex, BMI, NYHA class, comorbidities, and baseline medications), combination therapy (sacubitril valsartan + dapagliflozin) remained an independent protective factor for heart failure readmission (HR=0.52, 95% CI: 0.35-0.78, P=0.001) and MACE (HR=0.61, 95% CI: 0.42-0.89, P=0.010). Other independent predictors included older age, higher NYHA class, chronic kidney disease, diabetes, and prior heart failure hospitalization (all P<0.05).

Discussion

Heart failure is the end-stage manifestation of various heart diseases, among which HFrEF is the main type, and such patients have a high risk of malignant arrhythmia, a high rate of repeated hospitalization, and even lead to death

Table 5. Comparison of systolic blood pressure and incidence of symptomatic hypotension between the two groups before and after treatment

Groups	n	Systolic blood pressure (mmHg)		Hypotension [n (%)]
		Before treatment	After treatment	
Control group	200	128.5 ± 12.5	118.5 ± 10.2*	10 (5.0)
Observation group	200	127.8 ± 12.0	116.2 ± 10.5*	9 (4.5)
Comparison			Statistical value	*P* value
Between-group (before treatment)			t=0.568	0.570
Between-group (after treatment)			t=2.211	0.128
Between-group (hypotension)			χ^2=0.058	0.810
Control group (before vs. after)			t=8.456	<0.001
Observation group (before vs. after)			t=9.123	<0.001

Note: *P<0.05, compared with the same group before treatment.

Table 6. Comparison of renal function and serum potassium indices between the two groups before and after treatment

Indicator	Time	Control group (n=200)	Observation group (n=200)	Within-group t/P	Between-group t/P
eGFR (mL/min/1.73 m^2)	Before	72.5 ± 15.6	73.2 ± 14.8		t=0.458, P=0.647
	After	71.8 ± 14.5	72.5 ± 14.2	t=0.456, P=0.649	t=0.485, P=0.628
Cr (μmol/L)	Before	85.6 ± 18.5	84.9 ± 19.2		t=0.369, P=0.712
	After	86.2 ± 17.8	85.5 ± 18.5	t=0.325, P=0.745	t=0.382, P=0.703
BUN (mmol/L)	Before	6.8 ± 1.8	6.9 ± 1.9		t=0.531, P=0.596
	After	6.9 ± 1.7	7.0 ± 1.8	t=0.542, P=0.588	t=0.560, P=0.576
Serum potassium (mmol/L)	Before	4.2 ± 0.4	4.2 ± 0.4		t=0.000, P=1.000
	After	4.3 ± 0.4	4.3 ± 0.4	t=0.456, P=0.649	t=0.000, P=1.000

Table 7. Comparison of adverse events between the two groups

Adverse reactions	Control group (n=200)	Observation group (n=200)	χ^2 value	*P* value
Reproductive urinary tract infection	2 (1.0)	4 (2.0)	0.671	0.410
Cough	3 (1.5)	2 (1.0)	0.205	0.651
Rash	1 (0.5)	2 (1.0)	0.338	0.561
Any adverse reactions	18 (9.0)	20 (10.0)	0.117	0.732

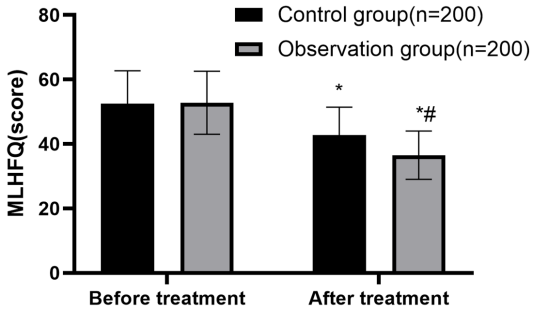

Figure 3. Comparison of MLHFQ scores between the two groups before and after treatment. MLHF: Minnesota Living with Heart Failure Questionnaire. *P<0.05, compared with before treatment in the same group; #P<0.05, compared with the control group after treatment.

[13, 14]. Therefore, how to optimize the HFrEF treatment plan, improve the cardiac function and quality of life of patients, and reduce the incidence of adverse cardiovascular events has important clinical significance.

At present, the treatment strategies of HFrEF mainly include drug therapy, device therapy and cardiac rehabilitation. Among them, sacubitril/valsartan has demonstrated substantial clinical benefits through inhibition of neprilysin and blockade of the angiotensin II receptor, exerting multiple effects such as vasodilation, diuresis and anti-myocardial fibrosis [15, 16]. Dapagliflozin exerts an osmotic diuretic effect by inhibiting glucose reabsorption in the renal proximal

Table 8. Multivariable Cox regression analysis for predicting heart failure readmission and MACE

Outcome	Variable	HR	95% CI	*P* value
Heart failure readmission	Combination therapy (vs. control)	0.52	0.35-0.78	0.001
	Age (per 1 year)	1.03	1.00-1.06	0.033
	NYHA class (III/IV vs. II)	1.67	1.16-2.40	0.006
	Chronic kidney disease	1.80	1.11-2.91	0.017
MACE	Combination therapy (vs. control)	0.61	0.42-0.89	0.010
	Age (per 1 year)	1.04	1.01-1.08	0.023
	Diabetes	1.61	1.09-2.38	0.016
	Prior heart failure hospitalization	1.69	1.11-2.57	0.015

Note: Adjusted for age, sex, BMI, NYHA class, comorbidities, and baseline medications. HR: hazard ratio; CI: confidence interval; NYHA: New York Heart Association; MACE: major adverse cardiovascular events.

tubules, while also improving myocardial energy metabolism and reducing cardiac load. The results of this study showed that the cardiac function indexes (LVEF, LVEDD, LVESD), exercise tolerance (6MWT) and heart failure load index (NT-proBNP) of the two groups of patients were significantly improved after treatment, and the observation group treated with sacubitril valsartan combined with dapagliflozin showed better improvement in the above indexes. The potential mechanism may be as follows: single sacubitril/valsartan treatment mainly inhibites neprilysin, increases endogenous natriuretic peptide level, promotes vasodilation and urinary sodium excretion, and blocks angiotensin II receptor, inhibits myocardial fibrosis and ventricular remodeling, so as to improve cardiac function and reduce NT-proBNP level; dapagliflozin exerts osmotic diuretic effect by increasing urinary glucose excretion, reducing cardiac preload and afterload, improving myocardial energy metabolism, promoting cardiomyocyte autophagy, inhibiting myocardial fibrosis, and forming a complementary mechanism with sacubitril valsartan. The synergistic effect further optimizes the therapeutic effect, which is consistent with previous findings [10, 17]. Compared with the DAPA-HF trial (HR for worsening HF or cardiovascular death: 0.74, 95% CI: 0.65-0.85), our study showed a more pronounced reduction in heart failure readmission (HR=0.52, 95% CI: 0.35-0.78). This discrepancy may be attributed to the synergistic effect of combining sacubitril valsartan with dapagliflozin, whereas the DAPA-HF trial mainly evaluated dapagliflozin added to standard therapy (including ACEI/ARB but not ARNI in most patients). In addition, the increase of 6MWT in the observation group was greater and the decrease of NT-proBNP was more significant, indicating that the addition of dapagliflozin could make up for the deficiency of single sacubitril valsartan in metabolic regulation and energy metabolism optimization, further improve the intervention efficiency and enhance the therapeutic effect. Similar studies have been reported in the past [18].

Previous studies have shown that HFrEF patients are often accompanied by a significant decline in quality of life and reduced exercise tolerance. The two interact with each other to form a vicious circle. The decline in cardiac function will aggravate the decrease in activity endurance, and the decline in activity ability will further affect the patient's emotional state and daily living ability, leading to the aggravation of heart failure symptoms and the continuous reduction of quality of life [19, 20]. The results of this study showed that the MLHFQ scores of the two groups were significantly reduced and the 6MWT was significantly improved after treatment, and the improvement of the observation group was significantly better than that of the control group. To a certain extent, it suggested that both treatment regimens could effectively improve the quality of life and exercise tolerance of patients, and the effect of sacubitril valsartan combined with dapagliflozin intervention was more advantageous. Our findings are consistent with those of the EMPEROR-Reduced trial, which demonstrated that SGLT2 inhibitors improved quality of life in HFrEF patients [21]. However, the magnitude of improvement in our study (MLHFQ reduction: 16.3 ± 5.8 vs. 9.7 ± 5.2, P<0.001) was larger than that reported in previous studies, possibly due to the longer treatment duration (6 months)

and the combination therapy effect. The reasons for the analysis are as follows: the improvement of cardiac function and the decrease of NT-proBNP level are the core determinants of improved exercise tolerance and quality of life. After treatment, LVEF increased significantly, LVEDD and LVESD decreased significantly, and cardiac pumping function recovered, effectively improving the body's tissue perfusion and reducing the accumulation of heart failure symptoms. At the same time, the decrease of NT-proBNP level reflects the reduction of heart failure load, thereby improving the patient's daily living ability and quality of life, which is consistent with the previous research results [21, 22]. The improvement of cardiac function and NT-proBNP in the observation group was more significant, and dapagliflozin could improve patients' exercise tolerance, reduce myocardial cell oxidative stress, further protect myocardial function. In addition, the improvement of quality of life can also reduce the negative emotions of patients due to decreased activity ability, thus enhancing treatment compliance and forming a virtuous circle, which is an important reason for better improvement observed in the observation group, consistent with previous reports [23, 24].

Clinical outcomes are key indicators for evaluating heart failure treatment, and the rate of rehospitalization and the incidence of MACE directly reflect the long-term benefits and risks of the treatment [25]. The results of this study showed that the rehospitalization rate of heart failure in the observation group (8.5%) was significantly lower than that in the control group (16.0%), and the total incidence of MACE (6.0%) was also significantly lower than that in the control group (9.5%). Although the all-cause mortality rate was lower than that of the control group, the difference was not statistically significant, suggesting that combined with dapagliflozin treatment can more effectively reduce the risk of short-term adverse events in patients with HFrEF and improve clinical outcomes. Compared with the PARADIGM-HF trial (sacubitril valsartan vs. enalapril, HR for cardiovascular death or HF hospitalization: 0.80), our study demonstrated a more favorable outcome (HR=0.52 for HF readmission), suggesting that adding dapagliflozin on top of sacubitril valsartan provides additional clinical benefits beyond sacubitril valsartan alone [7]. This may be attributed to multiple mechanisms. Dapagliflozin improves the clinical outcomes through several complementary pathways: first, its osmotic diuretic effect can effectively reduce cardiac load, reduce the risk of pulmonary congestion and peripheral edema, and reduce the risk of acute heart failure exacerbation; second, dapagliflozin improves myocardial energy metabolism, inhibit myocardial fibrosis, and delay the process of ventricular remodeling, thereby reducing the risk of MACE [19]. In addition, subgroup analysis showed that in patients with NYHA IV and diabetes, the increase of LVEF and the decrease of heart failure rehospitalization rate in the observation group were more significant, suggesting that severe patients and patients with metabolic abnormalities may benefit more from combined treatment, which provides a reference for clinical individualized treatment [26].

Safety is an important prerequisite for the selection of clinical treatment options. In particular, HFrEF patients are mostly middle-aged and elderly people, often accompanied by liver and kidney dysfunction, poor tolerance to drugs, and the risk of adverse reactions needs to be focused on [27]. The results of this study showed that no severe renal impairment, severe hyperkalemia or angioedema occurred in the two groups of patients during the treatment period. The incidence of adverse reactions such as symptomatic hypotension, reproductive urinary tract infection, cough and rash was low, and there was no significant difference between the two groups. It is suggested that the combination of sacubitril valsartan and dapagliflozin has high safety compared with sacubitril valsartan alone. The addition of dapagliflozin does not increase the risk of adverse reactions such as hypotension, renal impairment, hyperkalemia and reproductive urinary tract infection, which is consistent with the conclusions of previous scholars [28]. It is worth noting that the incidence of genitourinary tract infection in the observation group (2.0%) was slightly higher than that in the control group (1.0%), which was consistent with the known adverse event profile of dapagliflozin, but the difference was not statistically significant. All of them were mild infections, which were improved after symptomatic treatment and did not lead to drug reduction or withdrawal [29].

This study has several limitations. First, as a retrospective study, this study may subject to certain selection bias and information bias. The generalizability of our findings needs further verification. Second, the sample size of this study is limited, and there is no stratified analysis of patients (such as stratification by age, etiology, and comorbidities), which may reduce the accuracy of the research results. It is necessary to expand the sample size and carry out multi-center prospective studies to supplement and improve. Third, although we performed multivariable regression analysis to adjust for potential confounders, residual confounding due to unmeasured variables (such as socioeconomic status, medication adherence, and lifestyle factors) may still exist. Fourth, the follow-up time of this study was 6 months, and the patients were not followed up for a long time. It was not possible to clarify the long-term efficacy of the combined treatment and its effect on all-cause mortality, nor to observe the long-term dynamic evolution trajectory of cardiac function in patients. It is necessary to extend the follow-up time for further study. Fifth, this study did not detect objective indicators such as cardiac magnetic resonance and myocardial biopsy in patients, and the discussion of the treatment mechanism was not deep enough. In the follow-up, relevant detection indicators can be added to further clarify the mechanism of combined treatment. Sixth, the generalizability of our findings may be limited because all patients were from a single center in China, and the results may not be directly applicable to other populations or healthcare settings.

Conclusion

In summary, sacubitril/valsartan combined with dapagliflozin can significantly improve the cardiac function of patients with HFrEF, reduce the level of NT-proBNP, improve exercise tolerance and quality of life, and significantly reduce the rehospitalization rate of heart failure and the incidence of MACE, without increasing the risk of hypotension, renal dysfunction and hyperkalemia. It has good safety and better clinical net benefit than sacubitril valsartan alone, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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