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ARTICLE

Efficacy of Sacubitril/Valsartan Combined With Metoprolol on Cardiac Function, Cardiac Remodeling, and Endothelial Function in Patients With Coronary Heart Disease and Heart Failure

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Abstract

Aims/Background Coronary heart disease (CHD) combined with heart failure results in a rapidly progressing disease with an acute onset, posing a significant threat to a patient's survival. Metoprolol, a β-blocker, is effective in treating heart failure; however, due to its complex pathogenesis, the efficacy of monotherapy in managing disease progression remains suboptimal. Sacubitril/valsartan, an angiotensin II receptor antagonist, is another widely used drug for treating heart failure. The combination of the two drugs may play a synergistic role in effectively managing heart failure through different mechanisms. This study aims to investigate the effects of sacubitril/valsartan combined with metoprolol on cardiac function, cardiac remodeling, and endothelial function in patients with CHD and heart failure.

Methods This retrospective analysis included 138 CHD patients combined with heart failure who received care at Linhai Hospital of Traditional Chinese Medicine between January 2022 and January 2024. Based on the treatment regimen, patients were divided into two groups. Patients receiving metoprolol monotherapy were included in the Metoprolol group (n = 61), while those receiving a combination of sacubitril/valsartan and metoprolol were assigned to the Combination group (n = 77). The cardiac function [New York Heart Association (NYHA) cardiac function classification], myocardial injury markers [serum cardiac troponin I (cTnI), N-terminal pro-brain natriuretic peptide (NT-proBNP)], cardiac remodeling function [left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD)], endothelial function [serum endothelin-1 (ET-1), nitric oxide (NO)] were compared between these two groups before treatment and 3 months post-treatment. Additionally, the two groups were comparatively assessed for the incidence of adverse reactions during the treatment period.

Results Following treatment, the NYHA cardiac function grading was significantly improved in the Combination group than in the Metoprolol group ($p = 0.014$). After treatment, the Combination group demonstrated significantly lower serum cTnI and NT-proBNP levels than the Metoprolol group ($p < 0.05$). After treatment, the Combination group had substantially higher LVEF and lower LVEDD and LVESD than the Metoprolol group ($p < 0.05$). Furthermore, the Combination group showed a significant decrease in serum ET-1 levels and an increase in serum NO levels compared to the Metoprolol group ($p < 0.05$). During the treatment period, there was no significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$).

Conclusion Sacubitril/valsartan combined with metoprolol is a safe, effective, and viable treatment option for patients with CHD combined with heart failure. This combination therapy may further improve cardiac and endothelial function by reducing cardiac remodeling, without increasing the risk of adverse reactions. This study offers a new drug combination regimen (sacubitril/valsartan combined with metoprolol) for patients with CHD combined with heart failure. This regimen further improves the cardiac and endothelial function, inhibits cardiac remodeling, and has good safety.

Key words: sacubitril/valsartan sodium hydrate drug combination; metoprolol; coronary disease; heart failure; heart function tests; ventricular remodeling; atrial remodeling; endothelium

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Introduction

As a primary type of cardiomyopathy, coronary heart disease has a complex pathogenesis with incompletely defined etiology, and is mainly manifested as single left ventricular dilatation, single right ventricular dilatation, or biventricular dilatation and may progress to heart failure as the disease advances (Lala and Desai, 2014; Nichols et al, 2021; Velagaleti and Vasan, 2007). Coronary heart disease (CHD) complicated by heart failure results in a rapidly progressing syndrome with an acute onset. Without timely treatment, it not only affects the quality of life but also poses a significant threat to patients' survival and imposes a substantial burden on the healthcare system (Feingold and DeNofrio, 2003).

Metoprolol, a commonly used β-blocker, inhibits the central nervous β receptor, thereby reducing vasoconstriction, atrioventricular conduction resistance, and myocardial excitability, which in turn improves left ventricular hypertrophy, increases coronary blood flow, facilitates oxygen supply to the heart, ultimately preventing sustained myocardial damage (Grassi, 2018; Prakash and Markham, 2000). As early as 1994, Fisher et al (1994) proposed that metoprolol was safe and effective in treating CHD complicated by heart failure. Subsequent studies supported this finding; for example, Gattis (2001) revealed that metoprolol improved survival rates and reduced hospital stays of patients with heart failure, while Maack et al (2003) confirmed its role in improving prognosis in chronic heart failure. De Freitas et al (2006) observed metoprolol as a safe and viable option for patients with both diabetes and heart failure. A meta-analysis by Briasoulis et al (2015) demonstrated that metoprolol effectively reduced all-cause mortality in heart failure patients. Similarly, Cheng et al (2020) investigated 154 patients with chronic heart failure and found that metoprolol significantly improved their cardiac index, motor function, and overall quality of life. Furthermore, Cheng and Xu (2023) reported that combining metoprolol with percutaneous coronary intervention (PCI) further improves endothelial and cardiac function in CHD patients.

While research has demonstrated the beneficial effects of metoprolol in heart failure treatment, the pathogenesis of heart failure remains relatively complex, and the effectiveness of monotherapy in controlling disease progression is often suboptimal. Sacubitril/valsartan, an angiotensin II receptor antagonist, has been widely used in clinical practice for heart failure management (Khder et al, 2017; Sauer et al, 2019). Heyse et al (2019) reported that sacubitril/valsartan is a safe and viable option for patients with severe heart failure undergoing hemodialysis. Similarly, Solomon et al (2020) found that sacubitril/valsartan significantly reduced all-cause mortality in hospitalized patients with heart failure. Wachter et al (2019) revealed that it can also be administered to patients in stable condition after acute heart failure. Lee et al (2020) found that sacubitril/valsartan significantly improved cardiovascular biomarkers in heart failure patients. Furthermore, Kang et al (2020), through a meta-analysis, observed it to be beneficial for cardiovascular and renal function in patients with heart failure and chronic kidney disease. Recently, Zhang et al (2022a) underscored the favorable safety and tolerability profile, considering it a promising therapeutic option for heart failure treatment.

With the increasing proportion of elderly patients, the occurrence of various underlying diseases has elevated the demand for optimal treatment approaches. Conservative drug treatment has become the primary, and often the only, treatment choice for elderly patients with CHD and heart failure. However, factors such as disease complexity, drug toxicity, dose dependence, and individual differences can limit the efficacy of long-term monotherapy, resulting in poor outcomes. To improve the treatment efficacy and reduce the risk of drug resistance, combination therapy provides a potential solution. Pieces of evidence suggested that metoprolol, a β-blockers, and sacubitril/valsartan, an angiotensin II receptor antagonist, function through different mechanisms of action in heart failure treatment. Therefore, we hypothesize that their combined use may have a synergistic effect in treating heart failure. However, while the existing research has investigated the use of sacubitril/valsartan or metoprolol individually, there is currently no study on their combination. Moreover, most of the previous studies investigated patients with either heart failure or CHD, even though CHD and heart failure are closely correlated, and their coexistence is relatively common in clinical practice.

To address this knowledge gap, this study retrospectively analyzed patients with CHD complicated by heart failure who underwent treatment at Linhai Hospital of Traditional Chinese Medicine between January 2022 and January 2024. We compared the effects of sacubitril/valsartan combined with metoprolol versus metoprolol alone on cardiac function, cardiac remodeling, and endothelial function in these patients. This study aims to provide valuable insights to support the formulation of more effective treatment approaches for CHD complicated by heart failure.

Methods

Study Participants

This retrospective study analyzed 210 CHD and heart failure patients who received treatment at Linhai Hospital of Traditional Chinese Medicine between January 2022 and January 2024. Following predetermined inclusion and exclusion criteria, 138 cases were ultimately included in the final analysis. Patients receiving metoprolol monotherapy were included in the Metoprolol group (n = 61), and those administered sacubitril/valsartan and metoprolol were assigned to the Combination group (n = 77). The patient selection process is shown in Fig. 1.

Inclusion and Exclusion Criteria

The inclusion criteria for patient selection were as follows: (1) Patients meeting the diagnostic criteria for coronary heart disease (Knuuti et al, 2020); (2) Those meet the diagnostic criteria for heart failure (Ponikowski et al, 2016); (3) Presence of no other heart disease; (4) Patients with New York Heart Association (NYHA) cardiac functional grade II–IV (Fisher , 1972); (5) Heart failure with reduced ejection fraction (HFrEF) or heart failure with mildly reduced ejection fraction (HFmrEF); (6) All patients received standard treatments, such as diuretics, beta-blockers, mineralocorticoid receptor antagonists, and sodium-dependent glucose transporters 2 (SGLT2) inhibitors. Additionally, patients in the Metoprolol group received

angiotensin-converting enzyme inhibitors; (7) Those with clear consciousness and availability of complete clinical data.

The exclusion criteria were set as follows: (1) Heart failure caused by long-term drug use; (2) Those with severe mental illness; (3) Patients with malignant tumors; (4) Patients with severe liver and kidney dysfunction; (5) Patients with concurrent systemic infection; (6) Patients with coagulation diseases; (7) Those with a history of allergies; (8) Patients with incomplete or abnormal clinical data.

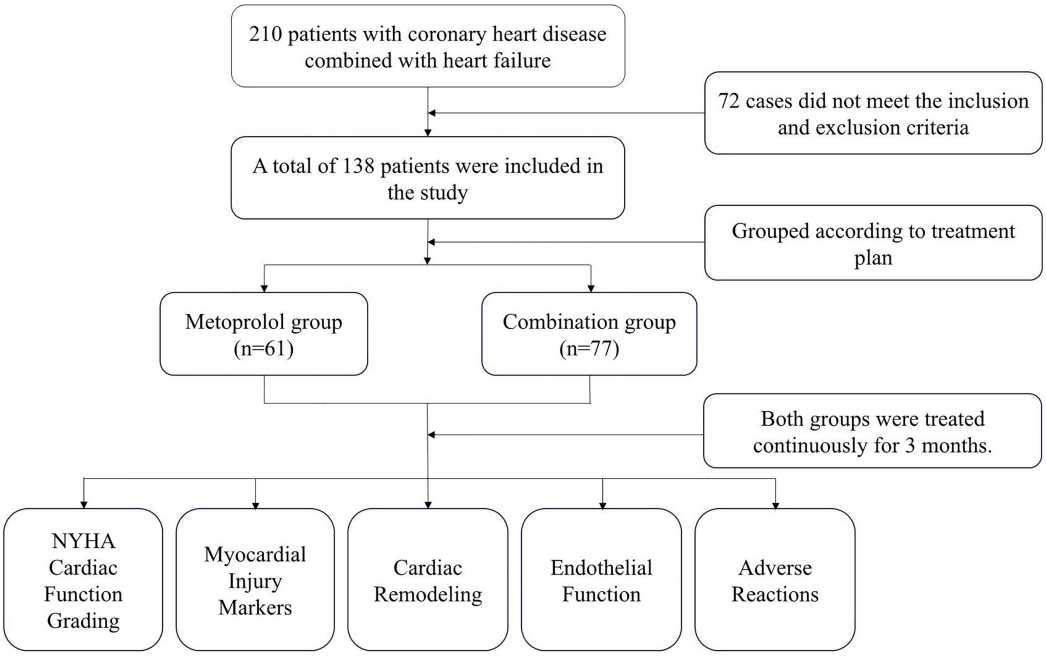

Fig. 1. A flow chart of patient selection process. NYHA, New York Heart Association.

Patient Treatment Protocols

Based on their treatment plan, patients were divided into two groups. Those receiving metoprolol monotherapy were included in the Metoprolol group (n = 61), where the patients were administered oral metoprolol succinate sustained-release tablets (SFDA approval number HJ20140779, AstraZeneca AB, Södertälje, Sweden). The initial dose was 23.75 mg once/day. After 2 weeks, the dose could be increased to 47.5 mg once daily if the symptoms do not worsen and the resting heart rate remains above 80 beats/min. Depending on the patient's tolerance, the dose could be further increased to 95 mg once/day.

Patients receiving sacubitril/valsartan combined with metoprolol were included in the Combination group (n = 77). Metoprolol dosing followed the same protocol as above. Additionally, sacubitril/valsartan sodium tablets (SFDA approval number HJ20170363, Novartis Singapore Pharmaceutical Manufacturing Private Ltd., Singapore, Republic of Singapore) were administered orally with warm water. The initial dose was 25 mg twice/day, and if there was no symptomatic hyperkalemia or hypotension, the dose was gradually increased to a maintenance dose of 100 mg twice daily.

All patients received routine treatment, such as diuretics, cardiotonic drugs, vasodilators, and other basic supportive treatments, along with adequate bed rest and a low-fat, low-salt diet. Both groups were treated continuously for 3 months.

Observation Indicators

Observational indicators included in this analysis were as follows:

(1) Baseline characteristics: Basic data were collected from electronic medical records of the patients, including age, body mass index (BMI), course of coronary heart disease, number of coronary artery lesions, course of heart failure, forms of heart failure, presence of hypertension (defined as systolic blood pressure $>$140 mmHg and/or diastolic blood pressure $>$90 mmHg), diabetes mellitus (defined as fasting blood glucose level $\geq$7.0 mmol/L and/or random blood glucose level $\geq$11.1 mmol/L and/or glycosylated hemoglobin $\geq$6.5%), smoking history (continuous or cumulative smoking for at least 6 months) and drinking history (drinking for $>$90 days).

(2) Cardiac function evaluation: Cardiac function was assessed before treatment and 3 months after treatment employing the NYHA classification (White and Myers, 1921). Grade I meant no limitations in daily activities; normal physical activities did not cause excessive fatigue, palpitations, asthma, or angina. Grade II refers to patients with mild limitations of physical activity, and no conscious symptoms at rest, but general physical activity may cause excessive fatigue, palpitations, asthma, or angina. Grade III refers to patients with significant limitations in physical activity, that is, no symptoms at rest, but even mild activity can induce excessive fatigue, palpitations, asthma, or angina. Grade IV refers to severe functional impairment, where patients are unable to engage in any physical activity. They also experience symptoms of heart failure even at rest, such as chest tightness, palpitations, and fatigue, and symptoms worsen with any physical activity.

(3) Myocardial injury markers: Serum myocardial injury markers were evaluated before and 3 months after treatment. Cardiac troponin I (cTnI) levels were measured using a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA). The assay kit was purchased from Shanghai Enzyme-Linked Biotechnology Co., Ltd. (item number ml105042, Shanghai, China). N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were assessed using a chemiluminescence immunoassay (Shanghai Yaji Biotechnology Co., Ltd., item number CL01163, Shanghai, China).

(4) Cardiac remodeling evaluation: Cardiac remodeling indicators were assessed before treatment and 3 months after treatment employing the APOGEE-800 PLUS color Doppler ultrasonic diagnostic system (Advanced Technology Laboratories, Bosell, WA, USA). The evaluation included left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD). A 2.5 MHz probe was applied for the assessments.

(5) Endothelial function: Endothelial function was assessed before treatment and 3 months after treatment. Serum endothelin-1 (ET-1) levels were determined using the nitrate reductase method with a detection kit purchased from Shanghai Baiyi Biotechnology Co., Ltd. (item number P91231T, Shanghai, China). Moreover,

serum nitric oxide (NO) levels were measured using the colorimetric method with the detection kit obtained from Shanghai Xuanya Biotechnology Co., Ltd. (item number XY-SHSJH-1032, Shanghai, China).

(6) Adverse reactions: The incidence of adverse reactions during treatment was analyzed, such as diarrhea/abdominal pain, rash, dizziness/headache, and nausea/vomiting.

Statistical Analysis

Data entry followed a double-blind method, with two personnel independently entering the data in parallel. After data entry, a designated person conducted a verification check. Statistical analysis was performed using SPSS 23.0 software (IBM Corp, Armonk, NY, USA). Categorical variables (e.g., hypertension, diabetes mellitus, smoking history, drinking history, NYHA cardiac function grading, and adverse reactions) were expressed as counts and percentages [n (%)], with comparisons made using the chi-square or Fisher-Freeman-Halton exact test. All measurement data (such as age, BMI, course of coronary heart disease, course of heart failure, cTnI, N-terminal pro-brain natriuretic peptide (NT-proBNP), LVEF, LVEDD, LVESD, ET-1, and NO) were evaluated for normality using the Kolmogorov-Smirnov normality test. Since continuous variables followed a normal distribution, they were expressed as $\bar{x} \pm s$ and compared using the t-test. A p-value < 0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics Between the Combination and Metoprolol Groups

Both groups demonstrated no significant differences in baseline characteristics, such as age, BMI, course of coronary heart disease, number of coronary artery lesions, course of heart failure, forms of heart failure, hypertension, diabetes mellitus, smoking history, and drinking history ($p > 0.05$, Table 1).

Comparison of NYHA Cardiac Function Grading Between the Two Groups

At baseline, the NYHA cardiac function grading was comparable between the two groups ($p > 0.05$). Following treatment, the NYHA cardiac function grading was significantly improved in the Combination group than in the Metoprolol group ($p < 0.05$, Table 2).

Comparison of Myocardial Injury Markers Between the Two Groups

Before treatment, there was no significant difference in serum cTnI and NT-proBNP levels between the two groups ($p > 0.05$). After treatment, both groups exhibited a significant decrease in serum cTnI and NT-proBNP levels compared to the baseline ($p < 0.05$). Moreover, the Combination group had significantly lower serum cTnI and NT-proBNP levels than the Metoprolol group ($p < 0.05$, Table 3).

Table 1. Comparison of baseline characteristics between the two groups.

Baseline characteristics	Combination group (n = 61)	Metoprolol group (n = 77)	χ^2/t	*p*-value
Age (years)	67.97 ± 7.11	66.55 ± 7.83	1.103	0.272
BMI (kg/m^2)	21.89 ± 2.14	21.98 ± 2.20	0.241	0.810
Course of coronary heart disease (months)	53.11 ± 10.71	52.56 ± 11.06	0.297	0.767
Number of coronary artery lesions [n (%)]			0.235	0.628
Single vessel	19 (31.15)	27 (35.06)		
Double vessels	42 (68.85)	50 (64.94)		
Course of heart failure (months)	35.21 ± 8.32	35.97 ± 8.06	0.543	0.588
Forms of heart failure [n (%)]			0.560	0.454
HFrEF	35 (57.38)	49 (63.64)		
HFmrEF	26 (42.62)	28 (36.36)		
Hypertension [n (%)]			0.016	0.900
Yes	26 (42.62)	32 (41.56)		
No	35 (57.38)	45 (58.44)		
Diabetes mellitus [n (%)]			0.001	0.973
Yes	16 (26.23)	20 (25.97)		
No	45 (73.77)	57 (74.03)		
Smoking history [n (%)]			0.079	0.778
Yes	22 (36.07)	26 (33.77)		
No	39 (63.93)	51 (66.23)		
Drinking history [n (%)]			0.058	0.810
Yes	25 (40.98)	30 (38.96)		
No	36 (59.02)	47 (61.04)		

Notes: BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction.

Comparison of Cardiac Remodeling Between the Two Groups

There were no statistically significant differences between the two groups in baseline levels of LVEF, LVEDD, and LVESD ($p > 0.05$). After treatment, both groups exhibited significant increases in LVEF as well as decreases in LVEDD and LVESD compared to baseline ($p < 0.05$). The Combination group had significantly higher LVEF and significantly lower LVEDD and LVESD than the Metoprolol group ($p < 0.05$, Table 4).

Comparison of Endothelial Function Between the Two Groups

Baseline serum ET-1 and NO levels were similar between the two groups ($p > 0.05$). After treatment, both groups experienced significant reductions in serum ET-1 levels ($p < 0.05$) along with substantial increases in serum NO levels ($p < 0.05$). The Combination group had significantly lower serum ET-1 levels and higher serum NO levels than the Metoprolol group ($p < 0.05$, Table 5).

Table 2. Comparison of NYHA cardiac function grading between the two groups before and after treatment.

Group	n	Before treatment				After treatment			
		Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV
Combination group	61	0 (0.00)	13 (21.31)	33 (54.10)	15 (24.59)	30 (49.18)	26 (42.62)	5 (8.20)	0 (0.00)
Metoprolol group	77	0 (0.00)	16 (20.78)	44 (57.14)	17 (22.08)	19 (24.68)	45 (58.44)	11 (14.29)	2 (2.60)
Fisher-Freeman-Halton exact test		0.159				9.542			
p-value		0.946				0.014			

Notes: Fisher's exact test was used for analysis; NYHA, New York Heart Association.

Table 3. Comparison of myocardial injury markers between the two groups before and after treatment ($\bar{x} \pm s$).

Group	n	cTnI (μg/L)		NT-proBNP (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Combination group	61	0.55 ± 0.07	0.15 ± 0.04*	770.76 ± 104.01	423.82 ± 72.45*
Metoprolol group	77	0.55 ± 0.07	0.18 ± 0.04*	787.90 ± 107.61	472.09 ± 69.30*
t-value		0.612	5.599	0.943	3.983
p-value		0.542	<0.001	0.347	<0.001

Notes: "*" indicates that a significant difference existed in the comparison of data before and after treatment in the same group ($p < 0.05$); cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 4. Comparison of cardiac remodeling-related indicators between the two groups before and after treatment ($\bar{x} \pm s$).

Group	n	LVEF (%)		LVEDD (mm)		LVESD (mm)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	61	39.11 ± 3.08	46.73 ± 4.23*	65.88 ± 4.45	57.23 ± 4.44*	56.44 ± 2.56	43.44 ± 2.21*
Metoprolol group	77	38.38 ± 2.63	44.81 ± 3.88*	66.86 ± 4.91	61.67 ± 4.64*	56.27 ± 2.37	47.60 ± 2.13*
t-value		1.497	2.780	1.214	5.685	0.405	11.203
p-value		0.137	0.006	0.227	<0.001	0.686	<0.001

Notes: "*" indicates that a significant difference existed in the comparison of data before and after treatment in the same group ($p < 0.05$); LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

Table 5. Comparison of endothelial function between the two groups before and after treatment ($\bar{x} \pm s$).

Group	n	ET-1 (ng/L)		NO (μmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Combination group	61	56.74 ± 6.12	44.58 ± 4.83*	51.14 ± 4.96	82.16 ± 7.37*
Metoprolol group	77	57.61 ± 6.49	49.04 ± 5.83*	50.85 ± 5.10	73.84 ± 7.98*
t-value		0.797	4.806	0.339	6.298
p-value		0.427	<0.001	0.735	<0.001

Notes: "*" indicates that a significant difference existed in the comparison of data before and after treatment in the same group ($p < 0.05$); ET-1, endothelin-1; NO, nitric oxide.

Table 6. Comparison of adverse reactions between the two groups before and after treatment.

Group	n	Diarrhea/abdominal pain	Rash	Dizziness/headache	Nausea/vomiting	Total	χ^2	*p*-value
Combination group	61	2 (3.28)	2 (3.28)	1 (1.64)	1 (1.64)	6 (9.84)	0.518	0.472
Metoprolol group	77	1 (1.30)	2 (2.60)	2 (2.60)	0 (0.00)	5 (6.49)		

Comparison of Adverse Reactions Between the Two Groups

As shown in Table 6, there was no significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$).

Discussion

Our study compared the efficacy and safety of different treatment regimens for coronary heart disease combined with heart failure and found that, compared to metoprolol monotherapy, the combination of sacubitril/valsartan is beneficial to further improve cardiac function (NYHA cardiac function grade), myocardial injury markers (cTnI, NT-proBNP), cardiac remodeling function (LVEF, LVEDD, LVESD), and endothelial function (ET-1, NO), without increasing the risk of adverse reactions.

The NYHA cardiac function grade, cTnI and NT-proBNP are currently the primary methods for evaluating the degree of cardiac function impairment, which are essential for determining disease severity, selecting treatment plans, and assessing the prognosis of patients with cardiovascular diseases (Bredy et al, 2018; Cao et al, 2019; Park et al, 2017). In our study, we selected these three methods to evaluate the cardiac function of patients with CHD combined with heart failure before and after treatment. We observed that the combination of sacubitril/valsartan further improved cardiac function. This improvement is due to sacubitril, an enkephalin inhibitor, and valsartan, an angiotensin II (AngII) receptor antagonist. They work together to reduce the burden on the heart and improve heart function by inducing vasodilating, lowering blood pressure, reducing aldosterone secretion, reducing myocardial contractility, and decreasing myocardial oxygen consumption (Fonseca et al, 2019; Kido et al, 2022).

Furthermore, Pieske et al (2021) reported that after 12 weeks of treatment with sacubitril/valsartan, both NYHA cardiac function grade and plasma NT-proBNP levels improved significantly in patients with chronic heart failure. Morrow et al (2024) observed that sacubitril/valsartan significantly reduced plasma NT-proBNP levels in heart failure patients, improving therapeutic outcomes. Wang et al (2017) found that after receiving sacubitril/valsartan treatment for 28 days, serum NT-proBNP levels in hypertensive patients were significantly reduced. Moreover, similar results were observed by Heyse et al (2019) in patients with heart failure and end-stage renal disease. Zhao et al (2022) also found that sacubitril/valsartan treatment substantially improved cTnI and NT-proBNP levels in hemodialysis patients. Furthermore, Fan et al (2024) investigated hypertensive heart failure patients undergoing PCI surgery and highlighted that sacubitril/valsartan reduced cTnI and NT-proBNP levels in the first week after surgery. These results are consistent with the present study; however, it differs in that the subjects in our study were patients with CHD combined with heart failure, and the above studies focused on the application of sacubitril/valsartan. However, our study is the first to report the positive effect of combining sacubitril/valsartan with metoprolol in improving heart function.

Cardiac remodeling is a key pathological mechanism in the occurrence and progression of heart failure (Bertero and Maack, 2018). In this study, LVEF, LVEDD and LVESD significantly improved after treatment in both groups compared to before treatment, with the Combination group exhibiting greater improvements, suggesting that sacubitril/valsartan further inhibits cardiac remodeling. Mustafa et al (2022) summarized the mechanism through which sacubitril/valsartan inhibits cardiac remodeling, underscoring its positive effects on mitochondrial function, apoptosis, oxidative stress, inflammation, fibrosis, and matrix remodeling. Januzzi et al (2019) investigated patients with heart failure and reported that reverse cardiac remodeling occurred in patients treated with sacubitril/valsartan. By establishing an animal model, Zhang et al (2022b) found that sacubitril/valsartan improved heart failure by inhibiting cardiac remodeling through the Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase signaling pathway. Similarly, Khan et al (2021) reported that sacubitril/valsartan promotes reverse myocardial remodeling and improves prognosis in patients with heart failure. Yang et al (2023) investigated patients with acute myocardial infarction and demonstrated that sacubitril/valsartan effectively treats cardiac remodeling and prevents heart failure. Furthermore, similar findings were reported by Januzzi et al (2020) and Yamamoto et al (2023), although their research participants and drug treatment plans differed from the present study.

After the occurrence of heart failure, there is an increased activity of the nervous system, an aggravation of the inflammatory response, and oxidative stress, all of which lead to endothelial dysfunction. Furthermore, the abnormal endothelial function can lead to increased coronary blood flow resistance and decreased body blood flow, resulting in further peripheral vascular dilation and increased cardiac load (De Keulenaer et al, 2017; Paulus and Tschöpe, 2013). In our study, the serum ET-1 levels in the Combination group were lower than before treatment and in the Metoprolol group, while the level of NO was higher than before treatment and in the Metoprolol group. The mechanism behind this is assumed to be that sacubitril/valsartan increases the level of natriuretic peptide in the body by inhibiting endogenous neurokinin activity. It can inhibit the release of inflammatory factors, reduce the damage of vascular endothelial cells, and protect the integrity and function of vascular endothelial cells. Li et al (2021) investigated chronic heart failure patients and reported that sacubitril/valsartan improved endothelial and cardiac functions. Du et al (2022) also found that sacubitril/valsartan effectively improved endothelial function in patients with chronic heart failure. In a study on patients with dilated cardiomyopathy, Amore et al (2022) found that sacubitril/valsartan improved endothelial and left ventricular function. Cassano et al (2022) observed that sacubitril/valsartan can improve endothelial dysfunction and arterial stiffness by reducing oxidative stress, platelet activation, and inflammatory cycle biomarkers. Regarding safety, we found that the risk of adverse effects did not increase in the Combination group during treatment. Similarly, Berg et al (2021) highlighted that sacubitril/valsartan treatment was well tolerated in patients with stable acute heart failure, which aligns with the results of our study.

Limitations and Prospects

Firstly, this study is a single-center trial with inherent limitations, such as a small sample size and participants from the same region. These factors may limit the representativeness of the target population, potentially affecting the generalizability of the research results. Secondly, as a retrospective analysis, our data relies on existing electronic medical records, which may introduce a time lag and some unnoticed confounding factors, thereby impacting the applicability of the results to the broader target population. Additionally, Endothelial-specific molecule-1 (ESM-1) is a commonly used and classical marker of endothelial function, and inflammatory reactions significantly affect endothelial function. However, as a retrospective study design, we did not include these indicators in this analysis. In future research, we aim to expand the sample size and geographic diversity, eliminate confounding factors, conduct a stratified analysis of potential factors that may affect the results, incorporate additional observation indicators, and optimize experimental design. Further investigation of the intrinsic mechanism of combination therapy will improve the accuracy and generalizability of research findings.

Innovation of the Study

This study is the first to assess the combination of sacubitril/valsartan and metoprolol for the treatment of CHD with heart failure. The findings confirm that combination therapy is safe and effective, providing a promising option for enhancing patient outcomes.

Conclusion

The combination of sacubitril/valsartan and metoprolol is an effective and viable treatment option for patients with CHD and heart failure. This therapy may further improve cardiac and endothelial function by inhibiting cardiac remodeling, without increasing the risk of adverse reactions. These results provide valuable insights for doctors when making treatment decisions. However, it is worth noting that combination therapy may lead to higher treatment costs, potentially increasing the economic burden on patients.

Key Points

- Sacubitril/valsartan combined with metoprolol promotes the recovery of cardiac function in patients with CHD and heart failure.
- Combination of sacubitril/valsartan with metoprolol effectively improves myocardial injury markers in patients with CHD and heart failure.
- This combination therapy effectively inhibits cardiac remodeling in patients with CHD and heart failure.
- Sacubitril/valsartan combined with metoprolol improves endothelial function in patients with CHD and heart failure.
- The combination of metoprolol and sacubitril/valsartan does not increase the risk of adverse reactions in patients with CHD and heart failure.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

TYZ and YJS designed the research study and wrote the first draft. TYZ and YJS performed the research. TYZ and YJS analyzed the data. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Linhai Hospital of Traditional Chinese Medicine Ethics Review Committee (Approval No.: L-2025-01-01) and strictly adheres to the Declaration of Helsinki. The patients themselves or their guardians included in the study signed the informed consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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