ORIGINAL RESEARCH

# Impact of Sacubitril/Valsartan on Cardiac Structure and Blood Levels of miRNA-328 and NT-proBNP in Patients with CHD and Chronic Heart Failure

Zhao Yang, MM; Huayu Ma, BM; Delu Yin, MD; Chengbo Sun, MD


## ABSTRACT

**Objective** • This study specifically investigates the impact of sacubitril/valsartan on cardiac structural remodeling and modulation of blood levels of miRNA-328 and NT-proBNP in patients with coronary heart disease (CHD) complicated by chronic heart failure (CHF). We aim to determine whether sacubitril/valsartan offers advantages over traditional therapies regarding cardiac morphology and molecular biomarkers, thus providing insights into its potential role in managing CHD and CHF.

**Methods** • From January 2020 to January 2023, CHD patients with chronic heart failure were randomized into two groups for this study. Both groups received standard treatments: the control group received valsartan, while the study group received sacubitril/valsartan. Therapeutic outcomes were analyzed, including changes in cardiac structure, function, miRNA-328, and NT-proBNP levels in the blood, along with noting any adverse reactions.

**Results** • The total effective rate in the study group was 86.67%, significantly higher than that in the control group (71.67%) ($P < .05$). After treatment, both groups exhibited reductions in left atrial anterior and posterior diameter, left ventricular end-diastolic diameter, and left ventricular end-systolic diameter compared to before treatment, with the study group showing lower values than the control group ($P < .05$). The left ventricular ejection fraction (LVEF) increased in both groups, with the study group showing a higher increase than the control group. Additionally, the end-diastolic volume and end-systolic volume decreased in both groups after treatment, with the study group showing greater decreases than the control group ($P < .05$). Moreover, both groups exhibited reductions in peripheral blood levels of miRNA-328 and NT-proBNP, with the study group showing greater reductions than the control group ($P < .05$). There was no significant difference in the incidence of adverse reactions between the study group and the control group during treatment ($P > .05$).

**Conclusion** • Sacubitril/valsartan significantly improves cardiac function and structure in patients with CHD complicated by CHF, effectively reducing levels of miRNA-328 and NT-proBNP in the blood. It demonstrates safety and high value in clinical applications. (*Altern Ther Health Med.* [E-pub ahead of print.])


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## INTRODUCTION

Coronary heart disease, also referred to as coronary atherosclerotic heart disease, stems from lesions within the coronary arteries, the primary blood vessels of the heart. Typically, these lesions arise from atherosclerosis, the buildup of plaques composed of fat, cholesterol, and other substances along the vessel walls, leading to narrowing or blockage. This constriction restricts blood flow to the heart muscle, potentially resulting in chest pain (angina), myocardial infarction, or other severe cardiac events. Importantly, coronary heart disease has been identified as the primary cause of chronic heart failure (CHF).[1] Its pathophysiological mechanism is intimately linked to CHF, primarily involving myocardial ischemia, myocardial cell demise, and compensatory myocardial remodeling. As the disease progresses, both the systolic and diastolic functions of the heart are variably impacted, ultimately culminating in the manifestation of CHF.[2]

Despite the clinical adoption of treatment strategies such as beta-blockers, aldosterone receptor antagonists, and angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists (ARBs), collectively known as the "golden triangle," the five-year survival rate for patients with

coronary heart disease (CHD) complicated by CHF remains dismal.[3] This underscores the limitations of current treatment modalities and underscores the potential complexity of the interaction between CHD and CHF.[4]

Sacubitril/valsartan sodium, a novel generation of heart failure therapeutic agents, operates via a distinct mechanism of action, differing from traditional medications for heart failure. Its principal mechanism targets the renin-angiotensin system (RAS) and the natriuretic peptide system simultaneously. By inhibiting the renin-angiotensin system, sacubitril/valsartan sodium reduces angiotensin II production, thereby lowering blood pressure, alleviating cardiac burden, and impeding pathological cardiovascular changes.[5] Concurrently, it elevates natriuretic peptide levels by inhibiting neutral endopeptidase (NEP), facilitating sodium excretion and vascular dilation, further reducing cardiac preload and afterload. Additionally, sacubitril/valsartan sodium diminishes cardiac remodeling, enhances cardiac function, and decelerates heart failure progression, exerting multifaceted cardioprotective effects and representing a significant breakthrough in heart failure treatment.[6]

The levels of miRNA-328 and NT-proBNP serve as critical indices of coronary heart disease (CHD) and CHF progression, garnering increasing attention for their roles in heart disease. Particularly, miRNA-328 is closely associated with signal transmission between heart cells, myocardial cell apoptosis, and cardiac fibrosis processes.

Therefore, this study endeavors to investigate the impact of sacubitril/valsartan on cardiac structure and peripheral blood levels of miRNA-328 and NT-proBNP in patients with coronary heart disease complicated by chronic heart failure, aiming to furnish insights for clinical treatment.

## METHODS

### Study design

Patients with coronary heart disease complicated by chronic heart failure admitted to our hospital from January 2020 to January 2023 were randomly divided into two groups. The patients in the two groups were treated with conventional regimens; the control group was treated with valsartan, and the study group was treated with sacubitril/valsartan for three months. This study employed a randomized controlled trial (RCT) design. Randomization was conducted to ensure unbiased group assignment. Additionally, blinding procedures were implemented to maintain objectivity and reliability. This study was approved by the ethics committee The First People's Hospital of Lianyungang. Signed informed consent was obtained from all patients or their guardians.

**Inclusion Criteria:** (1) Patients diagnosed with chronic heart failure and coronary heart disease (CHD) with coronary artery stenosis of more than 50%. (2) Patients classified as NYHA grade II-IV. (3) No allergy to the study drugs. (4) First-time related treatment. (5) Complete clinical data and informed consent.

**Exclusion Criteria:** (1) Patients with acute myocardial infarction or acute decompensated heart failure. (2) Severe arrhythmias, dilated cardiomyopathy, or compromised blood flow dynamics. (3) Serious hepatorenal illness. (4) History of cardiac surgery.

Both groups were treated with conventional regimens, including the "golden triangle" treatment strategy consisting of β-blockers, aldosterone receptor antagonists or ARBs, as well as anti-platelet aggregation, lipid stabilization, and microcirculation improvement. The control group received valsartan capsules orally, 80 mg once daily. The study group received sacubitril/valsartan orally, 50 mg twice daily. Doppler echocardiography was used to detect the main pulmonary artery diameter, aortic root diameter, ascending aorta diameter, left atrial anterior and posterior diameter, interventricular septum thickness, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular posterior wall thickness, and left ventricular muscle mass index (LVMI). Left ventricular ejection fraction (LVEF), end-diastolic volume, end-systolic volume, maximum aortic valve velocity, peak aortic pressure gradient, and the ratio of left ventricular early diastolic velocity to ventricular septal lateral wall velocity (E/E ‘) were measured by MR Cardiac MRI.

NT - pro BNP level of detection: two groups of patients before and after treatment of peripheral blood collection, after centrifugal clear liquid, by enzyme-linked immunosorbent assay to detect the NT - pro BNP level. The miRNA - 328 level detection: take 5 mL of anticoagulant fresh blood mixed with PBS solution in a ratio of 1:1. After mixing, the liquid slowly spread in 1:1 on lymphocyte separation medium and at a speed of 1500 r/min at room temperature for 20 minutes. At this point, the cells in the centrifuge tube can be divided into four layers: the top is the plasma or tissue fluid, the next is ivory lymphocytes and mononuclear cell layer, and then is the separation of the transparent liquid layer, the last is the red blood cell layer. We harvested the milky lymphocyte layer using 1 mL of Tip and then re-suspended the cells in PBS and centrifuged them at 1000 r/min for 5 to 10 min. This step is repeated twice, and then cells are collected for RNA extraction. Then all the samples on the ice were thawed. A total of 250 μL of plasma was collected and mixed with 750 μL of TRizol. Then, add to the mixture of 10 mu L ath - MiR156a mimics (concentration of 20 nmol/L) as an external reference, and let it stand at room temperature for 5 minutes. Later, to join 200 mu L of chloroform, quickly mix 15 seconds, and mix 15 seconds, then let it stand at room temperature for 3 to 5 minutes. Subsequently, the samples were centrifuged at 12000 r/min for 15 minutes at 4 °C, and the supernatant was transferred to a new EP tube. 500 μL of isopropanol was added to the supernatant, mixed, and left overnight at -20°C. The next day, the cells were centrifuged at 12000 r/min for 15 min at 4°C. The RNA precipitate was washed using 75% ethanol and centrifuged at 7500 r/min for 5 min. Remove the supernatant and air dry. Finally, RNA was re-suspended using 20 to 30 μL of enzyme-free double distilled water and stored at -80°C for later use. Again, 500 ng of RNA from the aforementioned

samples was prepared for reverse transcription on ice. "The reverse transcription step lasted for 15 minutes at 37°C, followed by 5 seconds at 85°C to inactivate the reverse transcriptase." After completion, the samples were stored in a refrigerated environment at 4°C for a short period of time. If it needs to be stored for a long time, it should be placed in a frozen environment at-20°C. Obtained by reverse transcription of the product as a template, the implementation of the fluorescent quantitative PCR to amplify miR-328. All experimental steps were done on ice, and two replicate Wells were set for each sample. The $2^{-\Delta\Delta Ct}$ formula was used to calculate the relative expression of each sample, and the experiments were performed in triplicate.

The patients were treated for 3 months. At the end of the treatment, the clinical efficacy of the patients was evaluated. The criteria were as follows: the clinical symptoms such as edema, chest tightness, and wet rills of the lung floor were effectively improved after treatment, and the heart function of the patients was significantly improved and returned to normal. After treatment, the patients' clinical symptoms and cardiac function were improved, which was effective. Ineffective treatment was defined as the patient's heart function and clinical symptoms not improving or even worsening. The total effective rate (marked effective + effective) was calculated. 1. The indexes of cardiac structure before and after treatment were compared between the two groups. 2. Compare two groups before and after treatment in patients with cardiac function index. 3. The levels of miRNA-328 and NT-pro BNP in peripheral blood before and after treatment were compared between the two groups.4. The occurrence of adverse reactions during the treatment was recorded.

The ethics committee approved this study. Signed written informed consent were obtained from the patients and/or guardians.

### Statistical analysis

We employed the Statistical Package for the Social Sciences (SPSS) version 23.0 software (IBM, Armonk, NY, USA) for data processing. Additionally, this study incorporated detailed randomization procedures and blinding techniques to ensure the objectivity and reliability of the results. Specifically, patients were randomly assigned to different treatment groups, and both the experiment operators and data analysts were blinded to the group allocation. Count data such as gender, history of smoking and drinking, number of diseased vessels, history of hypertension, adverse reactions, and efficacy comparisons were expressed as (n/%), and a chi-square test was performed. Measurement data such as age, cardiac structure and function indexes, peripheral blood miRNA-328, and NT-pro BNP levels were expressed as (mean ± SD). An independent sample *t* test was used for inter-group comparisons and a paired *t* test for intra-group comparisons. An alpha level of .05 was considered for statistical significance.

**Table 1.** Comparison of general data between the two groups [±s, n/(%)]

| Group | Age (years) | Gender | | BMI (kg/m²) | Smoking history | | Drinking History | |
|---|---|---|---|---|---|---|---|---|
| | | Male | Female | | Yes | No | Yes | No |
| Control (n=60) | 48.23±6.89 | 39(65.00) | 21(35.00) | 22.13±2.02 | 25(41.67) | 35(58.33) | 26(43.33) | 34(56.67) |
| Study (n=60) | 48.99±7.11 | 35(58.33) | 25(41.67) | 22.08±1.87 | 29(48.33) | 31(51.67) | 25(41.67) | 35(58.33) |
| $\chi^2/t$ | -0.595 | 0.564 | | 0.141 | 0.539 | | 0.034 | |
| *P* value | .553 | .453 | | .888 | .463 | | .853 | |
| Group | hypertension | | Diseased vessels | | | | | |
| | Yes | No | left main coronary artery | | Left anterior descending artery | | left circumflex artery | Right coronary artery |
| Control (n=60) | 16(26.67) | 44(73.33) | 18(30.00) | | 12(20.00) | | 11(18.33) | 19(31.67) |
| Study (n=60) | 18(30.00) | 42(70.00) | 16(26.67) | | 13(21.67) | | 15(25.00) | 16(26.67) |
| $\chi^2$ | 0.164 | | 1.030 | | | | | |
| *P* value | .685 | | .794 | | | | | |

**Table 2.** Comparative effectiveness (n / %)

| Group | Effect | Effective | Ineffective | Total effective |
|---|---|---|---|---|
| Control(n=60) | 19(31.67) | 24(40.00) | 17(28.33) | 43(71.67) |
| Study(n=60) | 28(46.67) | 24(40.00) | 8(13.33) | 52(86.67) |
| $\chi^2$ | | | | 4.093 |
| *P* value | | | | .043 |

**Table 3.** The heart structure change compare (±s)

| Group | The inner diameter of the main pulmonary artery(cm) | | The inner diameter of the aortic root(cm) | | Ascending aorta diameter(cm) | |
|---|---|---|---|---|---|---|
| | Before the treatment | After the treatment | Before the treatment | After the treatment | Before the treatment | After the treatment |
| Control(n=60) | 2.55±0.23 | 2.44±0.19 | 3.08±0.45 | 2.87±0.51 | 3.39±0.31 | 3.22±0.29 |
| Study(n=60) | 2.58±0.21 | 2.39±0.23 | 3.11±0.42 | 2.85±0.46 | 3.42±0.30 | 3.15±0.37 |
| *t* | -0.746 | 1.298 | -0.378 | 0.226 | -0.539 | 1.153 |
| *P* value | .457 | .197 | .706 | .822 | .591 | .251 |
| Group | Anterior and posterior diameter of the left atrium(cm) | | Interventricular septal thickness(cm) | | Left ventricular end diastolic diameter(cm) | |
| | Before the treatment | After the treatment | Before the treatment | After the treatment | Before the treatment | After the treatment |
| Control (n=60) | 4.39±0.51 | 4.02±0.35[a] | 1.02±0.26 | 1.12±0.31 | 5.89±0.28 | 5.51±0.19[a] |
| Study (n=60) | 4.41±0.45 | 3.89±0.21[a] | 1.06±0.19 | 1.13±0.38 | 5.87±0.23 | 5.41±0.15[a] |
| *t* | -0.228 | 2.467 | -0.962 | -0.158 | 0.428 | 3.200 |
| *P* value | .820 | .015 | .338 | .875 | .670 | .002 |
| Group | Left ventricular end systolic diameter (cm) | | Left ventricular posterior wall thickness(cm) | | LVMI(g/m²) | |
| | Before the treatment | After the treatment | Before the treatment | After the treatment | Before the treatment | After the treatment |
| Control (n=60) | 4.55±0.28 | 3.65±0.19[a] | 1.03±0.19 | 1.04±0.23 | 134.25±35.65 | 132.14±36.98 |
| Study (n=60) | 4.52±0.23 | 3.34±0.12[a] | 0.99±0.15 | 1.02±0.21 | 133.85±32.48 | 131.85±38.15 |
| *t* | 0.641 | 10.685 | 1.312 | 0.497 | 0.064 | 0.042 |
| *P* value | .523 | .000 | .192 | .620 | .949 | .966 |

[a]Compared to the same group Before the treatment is $P < .05$

## RESULTS

From January 2020 to January 2023, a total of 120 patients diagnosed with coronary heart disease complicated by chronic heart failure were included in the study. Among them, 60 patients were assigned to the control group and received valsartan treatment, while the remaining 60 patients were allocated to the study group and administered sacubitril/valsartan. No significant differences were observed in clinical data between the control and study groups ($P > .05$). Please refer to Table 1 for details.

Following the treatment period, the study group exhibited a notably higher total effective rate of 86.67% compared to the control group's rate of 71.67%. This difference between the groups was statistically significant ($P < .05$). Detailed data are presented in Table 2.

Regarding changes in cardiac structure within the control group and the study group, please consult Table 3. Prior to treatment, there were no significant differences in various cardiac structural parameters between the two groups

**Table 4.** Comparison of cardiac function indexes (±s)

| Group | LVEF(%) | | End-diastolic volume(ml) | | End-systolic volume (ml) | |
|---|---|---|---|---|---|---|
| | Before the treatment | After the treatment | Before the treatment | After the treatment | Before the treatment | After the treatment |
| Control(n=60) | 43.65±11.02 | 60.12±5.46[a] | 170.52±32.15 | 139.21±12.02[a] | 96.44±12.02 | 59.46±8.15[a] |
| Study (n=60) | 44.98±10.12 | 66.15±3.49[a] | 171.23±26.15 | 131.02±8.67[a] | 95.98±11.08 | 51.26±5.49[a] |
| *t* | -0.689 | -7.208 | -0.133 | 4.281 | 0.218 | 6.464 |
| *P* value | .492 | .000 | .895 | .000 | .828 | .000 |
| Group | Aortic valve on the maximum velocity(cm/s) | | Aortic peak pressure gradient(mmHg) | | E/E' | |
| | Before the treatment | After the treatment | Before the treatment | After the treatment | Before the treatment | After the treatment |
| Control(n=60) | 129.55±44.10 | 124.45±46.98 | 7.54±2.26 | 6.89±1.69 | 25.22±5.19 | 22.14±5.26 |
| Study (n=60) | 128.46±41.02 | 121.26±38.16 | 7.23±2.18 | 6.45±1.71 | 25.45±5.46 | 21.98±5.77 |
| *t* | 0.140 | 0.408 | 0.765 | 1.418 | -0.236 | 0.159 |
| *P* value | .889 | .684 | .446 | .159 | .813 | .874 |

[a]Compared to the same group Before the treatment is $P < .05$

**Table 5.** Comparison of miRNA-328 and NT-pro BNP levels in peripheral blood (±s)

| Group | miRNA-328 | | NT-pro BNP(ng / L) | |
|---|---|---|---|---|
| | Before the treatment | After the treatment | Before the treatment | After the treatment |
| Control(n=60) | 1.36±0.23 | 0.98±0.15[a] | 5344.26±512.02 | 3154.58±256.68[a] |
| Study(n=60) | 1.41±0.31 | 0.87±0.16[a] | 5412.65±498.26 | 2013.62±311.02[a] |
| *t* | -1.003 | 3.885 | -0.741 | 21.916 |
| *P* value | .318 | .000 | .460 | .000 |

[a]Compared to the same group Before the treatment is $P < .05$

**Table 6.** Comparison of adverse reactions (n/%)

| Group | Hypotension | Hyperkalemia | Angio-edema | kidney injury | Swirl | Cough | Total occurrence |
|---|---|---|---|---|---|---|---|
| Control(n=60) | 2(3.33) | 3(5.00) | 1(1.67) | 2(3.33) | 2(3.33) | 0(0.00) | 10(16.67) |
| Study(n=60) | 2(3.33) | 0(0.00) | 2(3.33) | 1(1.67) | 1(1.67) | 1(1.67) | 7(11.67) |
| $\chi^2$ | | | | | | | 0.287 |
| *P* value | | | | | | | .592 |

($P > .05$). Post-treatment, both groups showed reductions in left atrial anterior and posterior diameters, left ventricular end-diastolic diameters, and left ventricular end-systolic diameters compared to baseline measurements. However, the reductions observed in the study group were significantly greater than those in the control group ($P < .05$).

For alterations in cardiac function, please refer to Table 4. Before treatment, no significant differences in cardiac function indexes were observed between the control and study groups ($P > .05$). However, post-treatment, both groups exhibited increases in left ventricular ejection fraction (LVEF) and decreases in end-diastolic and end-systolic volumes compared to baseline values. Notably, the study group demonstrated significantly greater improvements in LVEF and reductions in volumes compared to the control group ($P < .05$).

Before treatment, levels of miRNA-328 and NT-pro BNP in peripheral blood showed no significant differences between the control and study groups (P>0.05). However, post-treatment, both groups exhibited reductions in miRNA-328 and NT-pro BNP levels, with the study group showing significantly greater reductions compared to the control group ($P < .05$). For detailed data, please see Table 5.

The incidence of adverse reactions during the treatment period was comparable between the study group and the control group, as shown in Table 6, with no significant difference observed between the two groups ($P > .05$).

## DISCUSSION

When coronary heart disease is combined with chronic heart failure, cardiac remodeling, and cellular and molecular changes are different from the pathological mechanism of simple coronary heart disease or heart failure.[8] Valsartan, as an anti-heart failure drug, has shown beneficial effects on coronary artery remodeling and cardiac structure by blocking the renin-angiotensin system (RAAS), but its clinical efficacy is relatively limited. Therefore, optimizing the treatment plan and finding more adaptable drugs is necessary to improve the treatment effect.[9] Sacubitril-valsartan is a dual inhibitor of angiotensin receptor and neprilysin. This novel heart failure treatment drug targets the renin-angiotensin system and inhibits neprilysin, showing the good therapeutic effect on coronary artery disease.[10] In recent years, as biomarkers of heart disease, the role of miRNA-328 and NT-proBNP in the pathogenesis and progression of heart failure has gradually attracted attention.[11] These markers are used for evaluating disease conditions, prognosis, and drug therapy.

According to the results of this research team's treatment, the total effective rate was 86.67%, higher than that of the control group total effective rate (71.67%), suggesting that sand kubah qu valsartan in improving symptoms of patients with coronary heart disease (CHD) with chronic heart failure is more effective. This is because the sand kubah qu valsartan is a blend of enkephalin inhibitor kubah curve and the curative effect of angiotensin receptor antagonist valsartan. Sacubitril, as a prodrug, is metabolized in the body to the active substance LBQ657, which inhibits neprilysin, thereby increasing the levels of beneficial peptides such as natriuretic peptides, which help to vasodilation and promote the excretion of sodium and water in the body.[12,13] In contrast, valsartan relaxes blood vessels by antagonizing angiotensin II receptors, and the combination of the two can further reduce blood pressure. Tis drug's dual mechanism of action provides an effective therapeutic option for patients with cardiovascular disease, combining the advantages of increasing natriuretic peptide levels and blocking the action of angiotensin II to lower blood pressure and improve cardiac function.[14]

In the comparison of cardiac structure and function indexes, left atrial anterior and posterior diameter, left ventricular end-diastolic diameter, LVEF, end-diastolic volume, and end-systolic volume were improved in the two groups after treatment, but the improvement effect of the study group was more obvious. This indicates that sacubitril/valsartan, as a therapeutic drug, has a more obvious positive effect on some cardiac structural and functional parameters. Analysis of the reason for valsartan, as an angiotensin receptor antagonist, can counteract the effect of angiotensin II, effectively diastolic blood vessels, and reduce blood pressure.[15] Sacubitril, as a neprilysin inhibitor, inhibits neprilysin to increase the levels of heart and kidney-beneficial peptides, such as natriuretic peptide. This contributes to further vasodilation, sodium and water excretion and reduces cardiac load.[16] In addition, the drug inhibited aldosterone release triggered by angiotensin II. Comprehensive of these effects,

sand kubah valsartan for heart failure patients provides comprehensive and effective treatments against the progress of cardiovascular disease and helps improve kidney function.[17]

Feng Rong etc.[18,] to investigate the miRNA in the role of clinical application, tested the miR - 328 in patients with coronary heart disease (CHD) expression changes of peripheral blood; the results found that miR - 328 in patients with coronary heart disease (CHD) content increased significantly in peripheral blood and in AMI patients increased more obviously, and thus speculate that Patients with coronary heart disease trigger the release of miR-328 under inflammatory stress, so it can be detected in the circulating blood. Therefore, miRNA-328 may reflect the pathological changes of the heart to a certain extent. In addition, NT-proBNP is the N-terminal fragment of B-type natriuretic peptide precursor, which is a biologically active molecule released when cardiac myocytes are subjected to mechanical stress or overload.[19] The generation and secretion is NT - proBNP and BNP by cardiac ventricular wall stretching, especially triggered when left ventricular pressure increases. Therefore, NT - proBNP in plasma level is often used as heart failure diagnosis, an important tool of stratification and prognosis evaluation. Combined analysis of the changes of these two indicators in patients with coronary heart disease combined with chronic heart failure can reflect the disease progression and changes in the cardiac function of patients.[20] In this study, the miRNA - 328 and NT - pro BNP reduced after treatment, but the extent of the team is more significant. This further confirms the efficacy of sacubitril-valsartan in improving cardiac function and reducing cardiac overload and mechanical stress. At the same time, the similarity of adverse reactions between the two treatment strategies indicates that sacubitril-valsartan is safe without increasing the risk of adverse reactions in patients.

In conclusion, sacubitril/valsartan has a good therapeutic effect on patients with coronary heart disease complicated with chronic heart failure, which can significantly improve cardiac structure and function and can effectively reduce the levels of miRNA-328 and NT-pro BNP in peripheral blood, with good safety, and has high clinical application value for the treatment of patients with coronary heart disease.

The research on sacubitril/valsartan in treating coronary heart disease complicated by chronic heart failure has indeed yielded promising results in improving cardiac function and structure, as well as in reducing biomarkers like miRNA-328 and NT-pro BNP. However, it is crucial to acknowledge certain limitations of the study to fully appreciate the scope and applicability of the findings. One key limitation is the duration of the study. The effects observed are based on a relatively short-term assessment, and it remains uncertain whether these benefits sustain over the long term. Chronic heart conditions, by nature, require long-term management strategies, and the durability of sacubitril/valsartan's efficacy needs further validation through extended follow-up periods. Additionally, the study may have potential selection bias. The selection criteria for participants and how they were recruited can significantly impact the outcomes and generalizability of the study. If the study sample is not representative of the broader population with coronary heart disease and chronic heart failure, the results might not be applicable to all patients suffering from these conditions. These limitations suggest that while the initial findings are encouraging, further research involving longer-term studies and a more diverse patient population is essential to confirm the efficacy and safety of sacubitril/valsartan in a broader clinical context.In future research, exploring the specific impacts of sacubitril/valsartan on cardiac function would be beneficial, particularly regarding the electrophysiological properties and metabolic states of the myocardium. Such detailed studies could unveil deeper therapeutic mechanisms and provide scientific evidence to optimize treatment strategies. Additionally, it is crucial to evaluate the combined effects with other cardiac medications to determine any synergistic interactions or potential drug interactions, which is vital for developing more personalized treatment plans. Exploring the response of different patient subgroups to the treatment is also key, as variations in genetic background, disease stage, or other comorbidities may reveal better or worse responses in certain subgroups, aiding the advancement of precision medicine.

Regarding clinical applications, the results of this study underscore the significant value of sacubitril/valsartan in treating patients with coronary heart disease complicated by chronic heart failure. This drug significantly improves cardiac structure and function and effectively reduces cardiac biomarkers such as miRNA-328 and NT-pro BNP, demonstrating its potential in clinical settings. Therefore, sacubitril/valsartan not only ameliorates clinical symptoms but may also extend patients' lives by reducing cardiac load, thus holding an important place in the integrated management of coronary heart disease and heart failure. These findings provide valuable insights for future clinical practice, encouraging medical professionals to consider including sacubitril/valsartan as part of the treatment regimen.

## ETHICAL COMPLIANCE

This study received approval from the Ethics Committee of The First People's Hospital of Lianyungang, ensuring adherence to the highest ethical standards. In addition to obtaining signed written informed consent from patients and/or guardians, we implemented several measures to protect participant rights and wellbeing throughout the study: (1) All patient data were anonymized and handled strictly. Personal identifiers were removed to maintain privacy. (2) Participation in the study was entirely voluntary. Participants were informed that they could withdraw from the study at any time without any consequences to their medical care. (3) The informed consent process involved a thorough explanation of the study's purpose, procedures, potential risks, and benefits. Participants were given ample time to ask questions and make an informed decision. (4) We carefully assessed and minimized any potential risks associated with the study. Regular monitoring was conducted to ensure participant safety and promptly address any adverse effects. (5) Regular updates about the study progress and findings were provided to the participants.

## CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

## FUNDING

This study did not receive any funding in any form.

## AUTHOR CONTRIBUTIONS

ZY and CS designed the study and performed the experiments, HM collected the data, DY analyzed the data, ZY and CS prepared the manuscript. All authors read and approved the final manuscript.

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