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Clinical efficacy of sacubitril/valsartan combined with cardiac rehabilitation in patients with heart failure after acute myocardial infarction: a single-center randomized trial

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Abstract

Objective To investigate the effect of sacubitril/valsartan (ARNI) combined with cardiac rehabilitation (CR) in patients with heart failure (HF) after acute myocardial infarction (AMI).

Methods A total of 118 patients with HF after AMI were screened and randomly divided into an experimental group and a control group. The control group was given ARNI. The experimental group received CR treatment in addition to the control treatment. The primary endpoint was cardiorespiratory fitness as measured by the cardiopulmonary exercise test (CPET). The secondary endpoints included cardiac remodeling detected by NT-ProBNP and cardiac ultrasound. All participants were assessed by CPET, NT-ProBNP, and cardiac ultrasound at baseline and after treatment.

Results After treatment, the changes in the left ventricular ejection fraction (LVEF), anaerobic threshold (AT), oxygen uptake peak (VO_2 peak), and metabolic equivalents (METs) in the experimental group were significantly greater than those in the control group (all $P < 0.05$). However, there was no significant difference in BNP, Left atrial diameter (LA) or Left ventricular end diastolic diameter (LVD) between the two groups ($P > 0.05$).

Conclusions Patients with HF after AMI could benefit from combined ARNI and CR.

Trial registration http://www.chictr.org.cn, ChiCTR2400093772 (11/12/2024). Retrospectively registered.

Keywords Cardiac rehabilitation, Sacubitril/valsartan, Acute myocardial infarction, Heart failure

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Introduction

Background

Acute myocardial infarction (AMI) is one of the most common causes of hospitalization for heart disease [1]. As the population ages and the global prevalence of diabetes increases, the overall incidence of AMI is expected to continue to rise in the coming decades. Moreover, the incidence of heart failure (HF) after AMI continues to rise [2]. AMI patients experience pathological changes such as myocardial injury and poor adaptation of the surviving myocardium, leading to cardiac remodeling and a significantly increased risk of HF events. AMI significantly increases the proportion of patients with a left ventricular ejection fraction (LVEF) of ≤ 40%, leading to a significant increase in heart failure morbidity and mortality [3].

The factors that induce cardiac remodeling are activated within a few hours after AMI. Changes in myocardial load conditions and neurohumoral system disorders alter the shape and function of the left ventricle, leading to cardiac remodeling. The main treatment for heart failure after myocardial infarction is drug therapy. Traditional drugs include beta blockers, aldosterone receptor antagonists, and angiotensin II receptor blocker (ARB)/angiotensin-converting enzyme inhibitor (ACEI) drugs. Previous studies have shown that ACEIs can reverse pathological structural remodeling and increase survival rates in patients with HF after AMI [4, 5]. Multiple lines of evidence suggest that in patients with AMI, increasing the level of natriuretic peptide in addition to inhibiting the renin–angiotensin system (RAS) may provide greater benefits than inhibiting the RAS alone [6]. Moreover, patients with HF benefit more from the use of sacubitril/valsartan (ARNI), which can improve quality of life, ameliorate arrhythmia, and regulate metabolism [7–12]. ARNI is an enkephalin inhibitor/angiotensin II type I receptor blocker that simultaneously inhibits enkephalin and blocks the action of angiotensin type I receptors. The PARADIGM-HF study evaluated the efficacy and safety of ARNI titration to a target dose of 200 mg twice daily in patients with chronic heart failure and a reduced ejection fraction (HFrEF). Research has shown that, compared with enalapril, the ARNI reduces endpoint events such as cardiovascular death and HF hospitalization [13]. The results of a study on non -responders after CRTd for HF treated with ARNI showed that the effects ARNI induced might influence the epigenetic mechanisms modulating and also in adverse cardiac remodeling responses to CRTd [14].

Cardiac rehabilitation (CR) can reduce the incidence, mortality and hospitalization rates of cardiovascular disease [15, 16]. Patients with AMI combined with HF often rely on bed rest in the early stages due to the severity of their condition. However, long-term bed rest can lead to decreased exercise tolerance, decreased blood volume and thromboembolic complications in patients. Early bedside phase I cardiac rehabilitation can shorten the hospitalization time and promote the recovery of daily living and exercise abilities [17, 18].

A study shows that the combination therapy of two drugs can reduce the incidence of cardiovascular events in patients with AMI [19]. The previous research only focusing on either ARNI or CR [20, 21]. However, there is still limited research on the effects of combining CR and ARNI in patients with HF after AMI. At present, there are relatively few studies on whether the prognosis of ARNI combined with CR therapy for patients with HF after AMI is better than using ARNI or CR alone. This study focuses on the combination therapy and further evaluates the efficacy by cardiopulmonary exercise test (CPET).

Objectives

The aim of this study was to analyze the clinical efficacy of ARNI combined with CR in patients with AMI complicated with HF and thereby provide clinical evidence for the treatment plan of patients who have AMI complicated with HF.

Methods

Trial design

This was a randomized controlled trial. Participants who fulfilled all inclusion criteria and had no exclusion criteria were randomly assigned to experimental and control groups in a 1:1 ratio. Both groups received routine treatments. The experimental group underwent sacubitril/valsartan combined with cardiac rehabilitation treatment. while the control group underwent sacubitril/valsartan treatment.

Ethical approval and trial registration

This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Guangxi Medical University (YLSY-IRB-SR-2021035) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The study adhered to the CONSORT guidelines for reporting randomized trials. Trial registration: http://www.chictr.org.cn, ChiCTR2400093772 (11/12/2024).

Participants

A total of 118 patients with HF after AMI in our hospital from September 2021 to August 2022 were screened for inclusion. Patients who met the following criteria were included: were diagnosed with heart failure (HF) after acute myocardial infarction (AMI) through electrocardiogram (ECG), were aged 18 years or older, and had no new or recurrent chest pain within the past 8 h. The

study exclusion criteria included HF caused by cardiomyopathy, myocarditis, severe arrhythmia, papillary muscle dysfunction, ventricular septal perforation, and isolated ventricular aneurysm. Patients with aortic dissection, severe aortic valve stenosis, or severe liver and kidney dysfunction were also excluded. Patients with past hemodynamic instability or a previous history of myocardial infarction were excluded.

Intervention

Both groups received routine treatments such as diuresis, antiplatelet aggregation, anticoagulation, lipid-lowering, and beta blocker drugs. The control group was given an initial dose of 50 mg of sacubitrile valsartan tablets (specification 100 mg twice a day, doubling the dose at an interval of 2 weeks, with a maximum dose not exceeding 400 mg/d. In addition to the control treatment the experimental group underwent phase I and phase II cardiac rehabilitation under the evaluation of a specialist doctor. Phase I cardiac rehabilitation includes passive joint movements such as toe flexion and ankle dorsiflexion, which gradually increase to daily activities and include inspiratory muscle training, rehabilitation exercises, resistance training, balance training, endurance training, and interval aerobic training. The phase II rehabilitation plan included moderate-intensity exercise 3 times a week for 4 consecutive weeks, including aerobic exercise at an intensity of 40-60% of the heart rate reserve, resistance exercise and flexibility training.

Endpoint events observed in the study (Outcomes)

The primary endpoint was cardiorespiratory fitness as measured by the CPET. The secondary endpoints included cardiac remodeling detected by NT-ProBNP and cardiac ultrasound. All participants were assessed by CPET, NT-ProBNP, and cardiac ultrasound at baseline and at 3 month. We evaluated left ventricular function, including the left ventricular ejection fraction (LVEF), left atrial diameter (LA), and left ventricular end-diastolic diameter (LVD), through cardiac ultrasound.

CPET

The CPET was performed by a MasterScreen CPX tester from German Yeger and included rest, warm-up, and exercise phases. Then, experienced medical staff calculated indices such as the VO_2 anaerobic threshold (AT), oxygen uptake peak (VO_2 peak), and metabolic equivalents (METs) on the basis of the experiments.

Sample size

The PASS software (version 2011) was used to calculate the sample size. A total of 120 patients were required to test for a power of at least 80% for group comparison with a loss-to-follow-up rate of 20% ($\alpha = 5\%$). Consequently, 60 patients in each group were intended to include in our study. This study is a parallel group design, whose primary endpoint is the difference in the cardiorespiratory fitness as measured by the CPET at 3 month compared with baseline.

Sequence generation

Randomization was performed using a random number by the SPSS 23.0. The randomized allocation sequence was generated at a 1:1 ratio.

Concealment mechanism and implementation

The statistician generated a random allocation sequence, the investigators recruited participants, and the clinical physician assigned intervention measures to the participants. The main investigators will not have permission to view the allocation.

Blinding

Study participants and all staff, including investigators, clinical care providers, statisticians, and personnel who recruit, follow-up with participants, and collect data are blinded to the randomizations.

Statistical analysis

Normally distributed values are presented as the mean ± standard deviation (SD), and a t test was used to compare the differences between the two groups. Count data are expressed in terms of the number of patients and percentage (%). The chi square test was used for intergroup comparisons. Otherwise, the median (interquartile range), Mann–Whitney U test and Kruskal–Wallis test were used. All data analysis was conducted via SPSS 23.0, and values with $P < 0.05$ in the two-sided test were considered statistically significant.

Results

Patient characteristics

Overall, a total of 150 patients with HF after AMI were assessed for eligibility. We selected 120 patients on the basis of the inclusion criteria and randomly divided them into an experimental group and a control group. Two patients in the control group were lost to follow-up. A total of 118 patients were included in the analysis. The patients underwent at least basal CPET, and at least 1 follow-up CPET was available (Fig. 1). The average age was 57.1 ± 11.3 years, and 89.9% of the patients were male, 36.4% had hypertension, and 22.9% had diabetes. The two groups were well balanced in sex, BMI, smoking history, hypertension status, diabetes status, total cholesterol, triglycerides, creatinine, uric acid, or number of diseased vessels (Table 1).

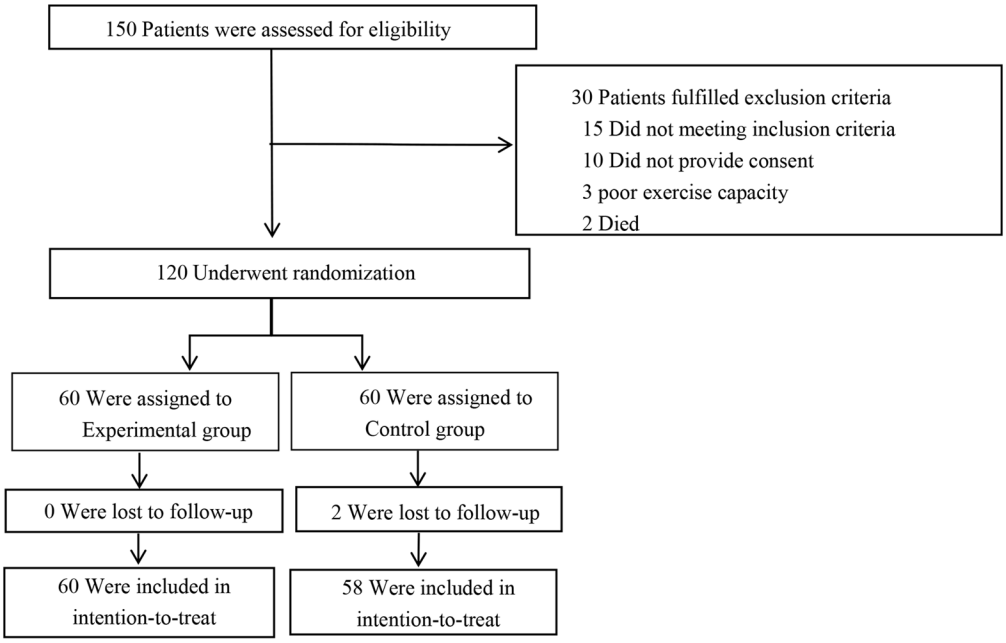

Fig. 1 Flow diagram of our study (CONSORT 2010)

Table 1 Basic data of the patients

Clinical data	Totol (*n* = 118)	Experimental group (*n* = 60)	Control group (*n* = 58)	*P*
Age (years)	57.1 ± 11.3	54.2 ± 10.4	60.1 ± 11.4	0.004
Male [n (%)]	106(89.8)	57(95.0)	49(84.5)	0.072
Smoking history [n (%)]	64(54.2)	36(60.0)	28(48.3)	0.267
BMI (kg/m^2)	24.79 ± 3.32	24.97 ± 3.18	24.60 ± 3.49	0.547
Hypertension [n (%)]	43(36.4)	20(33.3)	23(39.7)	0.567
Diabetes [n (%)]	22(22.9)	10(16.7)	18(31.0)	0.084
TC (mmol/L)	4.63 ± 1.00	4.61 ± 0.90	4.64 ± 1.10	0.882
TG (mmol/L)	1.86 ± 1.19	1.66 ± 1.04	2.07 ± 1.29	0.063
HDL(mmol/L)	0.97 ± 0.24	0.98 ± 0.24	0.97 ± 0.25	0.853
LDL(mmol/L)	3.07 ± 0.88	3.17 ± 0.75	2.96 ± 0.98	0.201
CR (μmol/L)	92.70 ± 23.22	90.7 ± 17.0	94.7 ± 28.2	0.351
UA (μmol/L)	382.7 ± 96.6	390.6 ± 92.8	374.5 ± 100.5	0.367
Number of diseased vessels				0.988
One	14(11.9)	7(11.7)	7(12.1)	
Two	36(30.5)	18(30.0)	18(31.0)	
Three	68(57.6)	35(58.3)	33(56.9)	

BMI body mass index, TG triglycerides, TC total cholesterol, HDL High density lipoprotein, LDL Low density lipoprotein, UA uric acid, Cr serum creatinine

Outcomes in the study population

All participants were assessed for CPET, NT-ProBNP, and left ventricular function at baseline and after cardiac rehabilitation. After treatment, all patients showed improvement in cardiac function compared to the baseline. The baseline BNP was 1253 (590, 2264), the EF was 48.6 ± 10.0, the VO_2 AT was 13.57 ± 2.93, the VO_2 peak was 16.48 ± 3.71, and the METS was 4.81 ± 0.93. After treatment, the follow-up BNP was 310 (126, 1033), the EF was 54.8 ± 10.8, the VO_2 AT was 14.48 ± 3.25, the VO_2 peak was 19.48 ± 4.73, and the METS was 5.43 ± 1.07 (Table 2).

Primary endpoint outcomes in the experimental and control groups

There was no significant difference in the VO_2 AT, VO_2 peak, or MET between the experimental group and the control group at baseline. After treatment, the VO2 AT, VO2 peak, and METS of the experimental group were significantly greater than those of the control group (all $P < 0.05$) (Table 3).

The secondary endpoint outcomes in the experimental and control groups

There was no significant difference in BNP or left ventricular function between the experimental group and the control group at baseline. After treatment, the BNP level in the experimental group was significantly lower than that in the control group ($P < 0.05$). The EF In the experimental group was greater than that in the control group, but the difference was not statistically significant. (Table 4).

Percentage changes in outcome indicators between the experimental group and the control group

After treatment, the changes in the EF, VO_2 AT, VO_2 peak, and METS in the experimental group were

Table 2 CPET, NT-ProBNP, and left ventricular function in the study population

	Total ($n = 118$)
Baseline	
NT-ProBNP	1348 (587, 2234)
LVEF [(%)]	48.6 ± 10.0
LA	32.9 ± 5.1
LVD	47.9 ± 6.0
VO_2 AT(ml/min/kg)	13.57 ± 2.93
VO_2 peak(ml/min/kg)	16.48 ± 3.71
METs	4.81 ± 0.93
Heart Function class	
Weber A	46 (39.0)
Weber B	41 (34.7)
Weber C	31 (26.3)
Follow-up	
NT-ProBNP	315 (121, 1033)
LVEF [(%)]	54.1 ± 10.7
LA	33.5 ± 4.7
LVD	48.8 ± 5.4
VO_2 AT(ml/min/kg)	15.90 ± 3.72
VO_2 peak(ml/min/kg)	19.48 ± 4.73
METs	5.43 ± 1.07
Heart function class	
Weber A	64 (54.2)
Weber B	37 (31.4)
Weber C	17 (14.4)

LVEF left ventricular ejection fraction, LA Left atrial diameter, LVD Left ventricular end diastolic diameter, AT anaerobic threshold, VO_2 oxygen uptake, peak VO_2 peak oxygen uptake, METs metabolic equivalents

Table 3 The primary endpoint outcomes in the experimental and control group

	Experimental group ($n = 60$)	Control group ($n = 58$)	*P*
Baseline			
VO_2 AT(ml/min/kg)	13.76 ± 3.00	13.36 ± 2.87	0.461
VO_2 peak(ml/min/kg)	16.72 ± 3.88	16.22 ± 3.53	0.469
METs	4.96 ± 0.87	4.65 ± 0.97	0.067
Heart Function class			0.869
Weber A	23 (38.3)	23 (39.7)	
Weber B	20 (33.3)	21 (36.2)	
Weber C	17 (28.3)	14 (24.1)	
Follow-up			
VO_2 AT(ml/min/kg)	17.07 ± 4.00	14.68 ± 2.98	<0.001
VO_2 peak(ml/min/kg)	20.78 ± 4.93	18.11 ± 4.15	0.002
METs	5.74 ± 0.92	5.12 ± 1.13	0.001
Heart Function class			0.419
Weber A	36 (60.0)	28 (48.3)	
Weber B	17 (28.3)	20 (34.5)	
Weber C	7 (11.7)	10 (17.2)	

AT anaerobic threshold, VO_2 oxygen uptake, peak VO_2 peak oxygen uptake, METs metabolic equivalents

Table 4 The secondary endpoint outcomes in the experimental and control group

	Experimental group ($n = 60$)	Control group ($n = 58$)	*P*
Baseline			
NT-ProBNP	1238 (521, 2059)	1477 (797, 2903)	0.313
LVEF [(%)]	47.8 ± 8.7	49.4 ± 11.3	0.407
LA	33.4 ± 4.9	32.5 ± 5.2	0.328
LVD	48.0 ± 5.8	47.7 ± 6.3	0.793
Follow-up			
NT-ProBNP	195 (103, 628)	659 (178, 1327)	0.002
LVEF [(%)]	55.4 ± 10.5	52.7 ± 10.8	0.177
LA	33.4 ± 4.6	33.6 ± 4.9	0.877
LVD	48.5 ± 5.6	49.1 ± 5.2	0.527

LVEF left ventricular ejection fraction, LA Left atrial diameter, LVD Left ventricular end diastolic diameter

Table 5 Percentage changes in outcome indicators between the experimental group and the control group

	Experimental group ($n = 60$)	Control group ($n = 58$)	P值
Percentage changes (follow up/baseline)			
NT-ProBNP	0.68 ± 1.40	0.74 ± 0.99	0.762
LVEF [(%)]	1.18 ± 0.27	1.09 ± 0.19	0.027
LA	1.01 ± 0.13	1.05 ± 0.17	0.151
LVD	1.02 ± 0.12	1.04 ± 0.12	0.313
VO_2 AT(ml/min/kg)	1.28 ± 0.40	1.12 ± 0.21	0.005
VO_2 peak(ml/min/kg)	1.33 ± 0.62	1.12 ± 0.14	0.014
METs	1.17 ± 0.20	1.11 ± 0.15	0.047

LVEF left ventricular ejection fraction, LA Left atrial diameter, LVD Left ventricular end diastolic diameter, AT anaerobic threshold, VO_2 oxygen uptake, peak VO_2 peak oxygen uptake, METs metabolic equivalents

significantly greater than those in the control group (all $P < 0.05$). However, there was no significant difference in BNP, LA or LVD between the two groups (Table 5; Fig. 2).

Discussion

AMI is the main cause of heart failure. The main reason is the loss of active myocardium after large-area myocardial infarction and myocardial remodeling involving various neurohumoral factors [22]. Our study revealed that ARNI combined with CR can increase exercise endurance and improve heart function in patients with HF after AMI. However, the results revealed no significant improvement in BNP in the short term. In summary, these findings demonstrated the efficacy and safety of ARNI combined with CR for patients with HF after AMI.

The traditional "golden triangle" drugs ACEI/ARB, β-receptor blockers and aldosterone receptor antagonists are the main drugs used for treating heart failure and preventing myocardial remodeling after myocardial infarction [23]. The latest research shows that ARNI is superior to traditional ACEI/ARB drugs in the treatment of heart

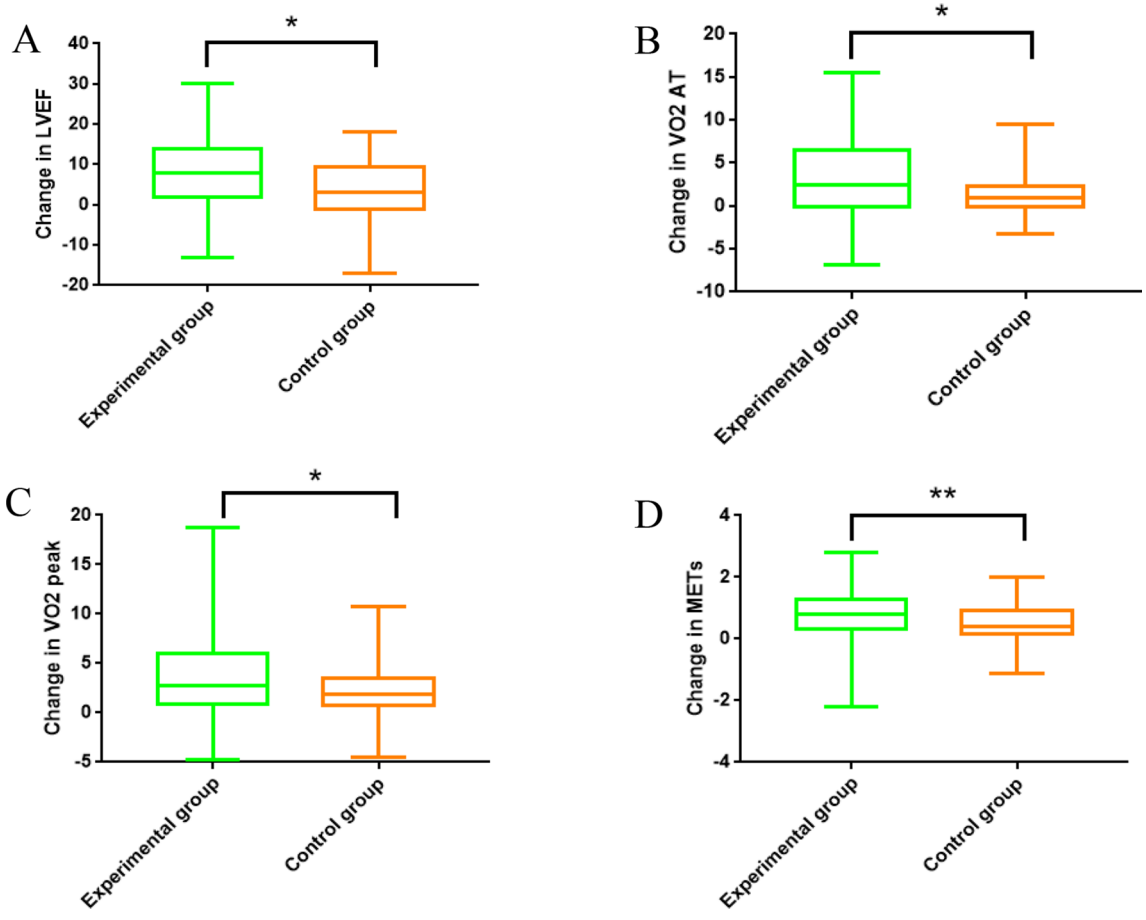

Fig. 2 Changes in outcome indicators between the experimental and control groups. (**A**): Changes in LVEF; (**B**): Changes in VO2 AT; (**C**): Changes in VO2 peak; (**D**): Changes in METs

failure [24, 25]. In patients with HF after AMI, ARNI can effectively improve cardiac function and reduce the incidence of major cardiovascular adverse events [2, 26]. An observational study revealed that ARNI can increase exercise tolerance and improve cardiopulmonary exercise indicators measured after six months of follow-up [20]. In this study, patients with HF after acute myocardial infarction were selected as the study objects, and patients with past hemodynamic instability and a previous history of myocardial infarction were excluded. All study subjects were treated with ARNI. After treatment, the symptoms of HF patients improved significantly and their heart function significantly improved. The incidence of HF remains high in patients with AMI even after PCI treatment, mainly because of the activation of the renin angiotensin aldosterone system (RAAS), sympathetic nervous system, and natriuretic peptide system. ARNI is composed of valsartan and the enkephalin inhibitor sacubitril at a 1:1 molar ratio. It can counteract the RAAS system, increase the levels of natriuretic peptide in the body, and delay ventricular remodeling [6, 27].

CR is highly beneficial for patients with HF and AMI. However, at present, there is still limited research on the combination of ARNI and CR for the treatment of HF after AMI. A study suggests that although Optimal medical therapy including ARNI can provide significant benefits to patients with HF. CR also play a pivotal role in treatment. Combination therapy with CR has better benefits for patients [28, 29]. However, previous study only analyzed cardiac ultrasound and 6-minute walk test [29], while our study used CPET to further analyze cardiopulmonary function. In this study, patients were divided into an experimental group and a control group. The control group was given ARNI. The experimental group received the same ARNI treatment combined with CR treatment. Compared with the use of ARNI alone, the combination of ARNI with CR is effective and can improve cardiac function better. Patients in the experimental group showed significant improvements in NT-ProBNP and EF. Moreover, the improvements in the VO_2 AT, VO_2 peak, and METS results in the experimental group were significantly greater than those in the control group. A study on combination therapy including ARNI and CR

for HF after AMI also revealed that combination therapy can improve heart function and reduce the occurrence of adverse cardiac events [30].

Our study found that there was a certain improvement in NT-ProBNP levels between the two groups of patients after treatment. But there was no significant difference between the two groups. This may be related to the influence of obesity, renal function, and different detection methods on NT-ProBNP. Short term follow-up with a small sample size also has an impact. This study evaluated the LVEF, LA and LVD of patients using echocardiography. The results indicate that after intervention, the LVEF of the experimental group and the control group has improved. The experimental group have a greater improvement than the control group. Combination therapy significantly improves heart pump function in patients. But there was no difference in LA and LVD between the two groups. Combination therapy does not significantly reverse cardiac remodeling function in the short term.

It still had the following limitations in the research. The study was a single-center trial with a small sample size and larger trials with longer follow-up will be necessary to confirm these findings. Future studies of longer duration and multi center designs should explore the impact of treatment on this endpoint.

In summary, ARNI combined with CR has a good effect on patients with HF after AMI and can improve heart function and enhance cardiopulmonary exercise indicators.

Conclusion

Patients with HF after AMI could benefit from ARNI and CR, and the combined therapy should be initiated as early as possible.

Abbreviations

AMI	Acute myocardial infarction
ARNI	Sacubitril/Valsartan
PCI	Percutaneous coronary intervention
CPET	Cardiopulmonary exercise testing
CR	Cardiac rehabilitation
AT	Anaerobic threshold
METs	Metabolic equivalents
VO_2 peak	Peak oxygen uptake
LVEF	Left ventricular ejection fraction
LA	Left atrial diameter
LVD	Left ventricular end diastolic diameter
BMI	Body mass index
TG	Triglycerides
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
UA	Uric acid
Cr	Serum creatinine

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04682-z.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

Yan-Mei Zhao and Jun-Ting Luo conceived the study. Jun-Ting Luo analysis and interpretation. Jun-Ting Luo and Yan-Mei Zhao contributed equally to this work. Kai-Fang Pang and Jian-Ping Tan contributed to data collection. Ying Feng and Ming Liu contributed to the study design. Zhi-Hai Lin contributed to the study conceptions. All authors read and approved the final version of the manuscript.

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Data availability

Data is provided within the supplementary information files.

Declarations

Ethic approval and consent to participate

This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Guangxi Medical University (YLSY-IRB-SR-2021035) and conducted in accordance with the Declaration of Helsinki. All procedures were performed in accordance with ethical standards. Written consent was obtained from all participants after they had been informed of the objectives, benefits, medical items and confidentiality agreement regarding their personal information.

Competing interests

The authors declare no competing interests.

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