Am J Transl Res 2026;18(4):3201-3210
www.ajtr.org /ISSN:1943-8141/AJTR0170677

Original Article

Effects of sacubitril/valsartan combined with ivabradine in treating cardiorenal syndrome

Guilan Li[1*], Hongxia Liu[2*], Siying Zhou[3], Wen Xiong[3]

[1]Jishou University School of Medicine, Jishou 416000, Hunan, China; [2]Department of Cardiovascular Medicine, First Affiliated Hospital of Jishou University, Jishou 416000, Hunan, China; [3]Department of Nephrology, First Affiliated Hospital of Jishou University, Jishou 416000, Hunan, China. [*]Equal contributors and co-first authors.

Received December 11, 2025; Accepted March 8, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: Objective: To investigate the effects of sacubitril/valsartan combined with ivabradine in treating cardiorenal syndrome (CRS). Methods: Information from 120 selected participants was retrospectively analyzed and divided into an experimental group (n=60) and a control group (n=60). The control group received sacubitril/valsartan alone, while the experimental group received sacubitril/valsartan plus ivabradine. Clinical efficacy, blood lipids, cardiac and renal function, and oxidative stress were observed in both groups. Results: The experimental group showed better clinical efficacy, lipid metabolism, cardiac function, renal function, and oxidative stress than the control group, and a lower incidence of major adverse cardiovascular events (MACE) (all P<0.05). Conclusion: Sacubitril/valsartan combined with ivabradine is effective in treating CRS patients, with superior efficacy across various indicators and its usage has a lower incidence of MACE.

Keywords: Sacubitril-valsartan, ivabradine, cardiorenal syndrome, oxidative stress response, retrospective analysis

Introduction

Cardiorenal syndrome (CRS) is a disease in which the heart and kidneys interact and affect each other's functions. The pathogenesis of CRS mainly involves the interaction between the circulatory system and the kidneys. For example, increased blood pressure and decreased cardiac output caused by heart disease may lead to a decrease in renal perfusion pressure and glomerular filtration rate, thereby affecting renal function; decreased glomerular filtration rate and water and electrolyte disturbances caused by kidney disease may also have a negative impact on cardiac function [1]. With the increase in the incidence of cardiovascular disease and chronic kidney disease, the incidence of CRS has also gradually increased, especially in the elderly population. It has been reported that the incidence of CRS is high in patients with heart disease and chronic kidney disease, reaching 30%-60% [2]. CRS occurs worldwide, especially in the elderly population in developed countries and regions. In China, with the increasing trend of population aging and the high incidence of cardiovascular disease and chronic kidney disease, the incidence of CRS is also gradually increasing.

The treatment of CRS is multifaceted, mainly using comprehensive treatment, aiming to protect the function of the heart and kidneys and prevent mutual damage [3]. Generally, treatment includes controlling blood pressure to reduce the burden on the heart and kidneys; controlling blood sugar to reduce damage to the heart and kidneys; maintaining water and electrolyte balance, which is crucial for both the heart and kidneys; limiting salt intake to help control blood pressure and fluid balance; and medication. Medications used include diuretics, antihypertensives, anticoagulants, nephroprotective agents, calcium channel blockers, angiotensin receptor antagonists, and beta-blockers. Commonly used medications for CRS include sacubitril/valsartan, ivabradine, dapagliflozin, tolvaptan, and novitor. Sacubitril/valsartan is an angiotensin receptor antagonist, and ivabradine is a heart rate lowering agent. This study adopted a retrospective analysis to

https://doi.org/10.62347/DOWT1981

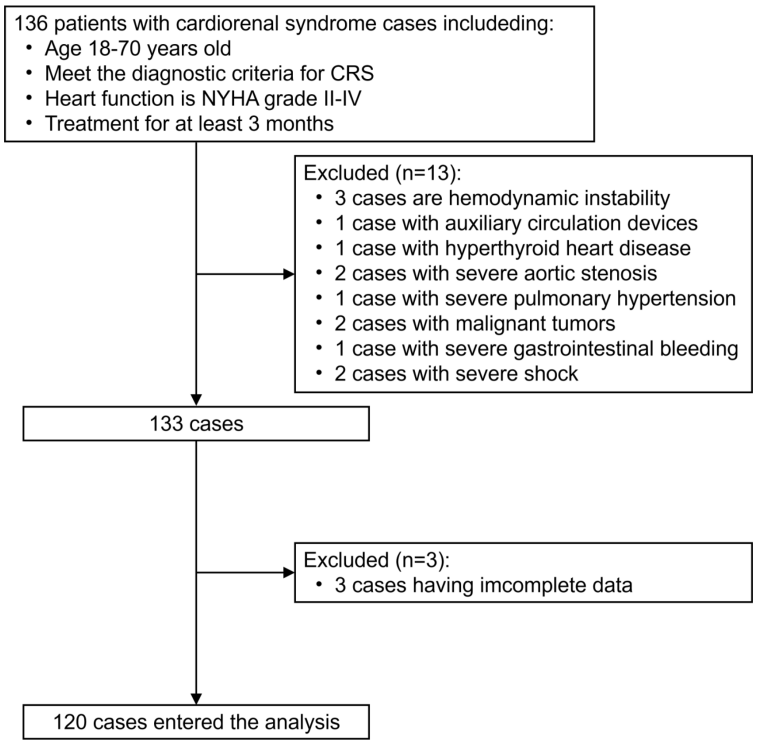

Figure 1. Flow diagram. CRS, cardiorenal syndrome; NYHA, New York Heart Association.

investigate the therapeutic effects of these two drugs.

Materials and methods

General information

This study included data from 120 CRS patients treated in the First Affiliated Hospital of Jishou University from January 2023 to January 2024. According to the actual medication use, patients were divided into an experimental group (n=60) and a control group (n=60). The experimental group received sacubitril/valsartan plus ivabradine, while the control group received only sacubitril/valsartan. Since the data was collected retrospectively and de-identified, no approval from the ethics review committee was required.

Inclusion criteria

Inclusion criteria: Age 18-70 years; meeting the diagnostic criteria for CRS as defined in the "Clinical Practice Guidelines for the Diagnosis and Treatment of Cardiorenal Syndrome (2023 Edition)"; cardiac function class II-IV of the New York Heart Association (NYHA); treatment duration of at least 3 months. Exclusion criteria: hemodynamic instability; patients using circulatory support devices; patients with hyperthyroid heart disease, myocardial amyloidosis, severe aortic stenosis, severe pulmonary hypertension, malignant arrhythmia, cardiogenic shock, or malignant tumors; patients with severe hypovolemia such as gastrointestinal bleeding, severe dehydration, or shock (**Figure 1**).

Methods

Both groups received routine treatment, including bed rest, oxygen therapy, a low-sodium diet, and the use of diuretics, cardiotonics, and vasodilators, along with improvements in neuroendocrine function and myocardial energy metabolism, as well as ventricular rate control.

In the control group, Sacubitril/valsartan was administered at an initial dose of 50-100 mg twice daily, depending on the patient's blood pressure and renal function. Patients at high risk of hypotension (blood pressure <110 mmHg) or impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m^2) received 50 mg per dose; other patients received 100 mg per dose. After 2-4 weeks of treatment, the dose was gradually increased based on patient tolerance, with a maximum dose of 400 mg daily. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were discontinued 36 hours before treatment, followed by the addition of sacubitril/valsartan.

In the experimental group, Sacubitril/valsartan was combined with ivabradine, with an initial dose of 2.5 mg orally twice daily. After two weeks of treatment, the dosage was adjusted based on heart rate control. If the patient's resting heart rate remained above 60 beats/minute, the dose was increased to 5 mg twice daily; if the patient's resting heart rate was 50-60 beats/minute, the current dose was

maintained; if the patient's resting heart rate remained below 50 beats/minute, or symptoms related to bradycardia appeared, the dose was reduced or the medication was discontinued. The maximum dose was 7.5 mg twice daily, with the goal of controlling the resting heart rate at 55-60 beats/minute.

Observation indicators

Clinical efficacy: Clinical efficacy was assessed based on the improvement in the New York Heart Association (NYHA) functional classification, categorized as markedly effective, effective, and ineffective. Markedly effective: complete recovery of clinical symptoms and signs, or improvement of ≥2 grades in the functional classification compared to pre-treatment. Effective: improvement in clinical symptoms and signs, and improvement of ≥1 grade in the functional classification compared to pre-treatment. Ineffective: no significant change or worsening of symptoms after treatment. Total effective rate = markedly effective rate + effective rate.

Blood lipids: Blood lipid indicators include triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Renal function: Blood was drawn venously by the laboratory to test urobilinogen (BUN), serum creatinine (Cr), serum potassium, and serum sodium. Urinary β2-microglobulin (β2-MG) and cystatin C (CysC) were also measured.

Cardiac function: Left ventricular ejection fraction (LVEF), cardiac output, left ventricular end-diastolic diameter (LVEDD), and 6-minute walk test (6MWT) were compared between the two groups before and after treatment. Echocardiography was performed on both groups before and after treatment, and LVEF and LVEDD were recorded. A Philips EPIQ 7C color Doppler ultrasound diagnostic instrument was used.

Oxidative stress response: Superoxide dismutase (SOD), malondialdehyde (MDA), and nitric oxide (NO) levels were compared between the two groups before and after treatment. Adverse cardiovascular events (MACE). The main focus was on the occurrence of adverse cardiovascular events (MACE) within 6 months after treatment. These included acute myocardial infarction, refractory angina, arrhythmia, new-onset heart failure, readmission, and cardiac death [4].

Statistical analysis

Comparisons between groups were performed using Student's t-test. Continuous data were presented as means ± standard deviation (SD). Categorical variables were compared using Fisher's exact test in univariate analysis. A *P*-value <0.05 was considered statistically significant. Overall survival was estimated using the Kaplan-Meier method, and between-group differences were assessed using the log-rank test. All statistical analyses were performed using GraphPad Prism 8 software (GraphPad Software).

Results

Comparison of baseline characteristics

There were no statistically significant differences in baseline characteristics between the two groups (all, P>0.05), as detailed in **Table 1**.

Comparison of clinical efficacy

The total effective rate in the experimental group was 93.33%, significantly higher than that in the control group (76.67%), with a statistically significant difference (χ^2=6.536, P= 0.011). See **Table 2**.

Comparison of blood lipid indicators

Before treatment, there was no statistically significant difference in blood lipid indicators between the two groups (P>0.05). After treatment, the blood lipid indicators (TG, LDL-C and HDL-C) in the experimental group were all better than those in the control group (t= 3.933, P=0.001; t=3.425, P=0.004; t=3.587, P=0.003). See **Table 3**.

Comparison of cardiac function

Before treatment, there was no statistically significant difference in any cardiac function indicators between the two groups (all P>0.05). After treatment, the experimental group showed better results than the control group in

Table 1. Comparison of basic information of the two groups of patients ($\bar{x}\pm s$) (n, %)

Data and indicators		Experimental Group (n=60)	Control group (n=60)	t/χ^2	*P*
Age ($\bar{x}\pm s$)		65.87±7.33	64.98±7.79	0.387	0.724
Gender (n)	men and women	33/27	31/29	0.134	0.714
Body mass index ($\bar{x}\pm s$, kg/m^2)		22.58±1.63	22.25±1.44	0.513	0.639
blood pressure ($\bar{x}\pm s$, mmHg)	Systolic blood pressure	146.28±8.13	147.08±8.39	0.455	0.683
	Diastolic blood pressure	97.62±7.53	97.24±7.46	0.426	0.704
Heart rate ($\bar{x}\pm s$, Times/min)		92.14±8.55	91.88±8.36	0.176	0.865
Heart function classification (n)	Level I	19	21	0.153	0.927
	Level III	25	24		
	Level IV	16	15		
Causes of Heart Failure (n)	Coronary heart disease	28	26	0.161	0.923
	Arrhythmias	22	24		
	Myocarditis	10	10		
Concomitant diabetes		18	16	0.164	0.685
Combined hypertension		14	16	0.178	0.673
Blood lipid index	Triglycerides TG ($\bar{x}\pm s$, mmol/L)	2.83±0.65	2.63±0.58	0.447	0.678
	Low-density lipoprotein cholesterol LDL-C ($\bar{x}\pm s$, mmol/L)	4.47±0.51	4.58±0.67	0.332	0.784
	High-density lipoprotein cholesterol HDL-C ($\bar{x}\pm s$, mmol/L)	0.73±0.14	0.63±0.11	0.951	0.396
Heart function index	Left ventricular ejection fraction LVEF (%)	34.52±4.87	34.11±5.06	0.138	0.872
	Left ventricular end-diastolic diameter LVEDD ($\bar{x}\pm s$, mm)	67.83±5.52	68.04±5.69	0.179	0.802
Renal function index	Creatinine Cr ($\bar{x}\pm s$, μmol/L)	95.88±7.32	95.51±6.47	0.026	0.957
	Urobilinogen BUN ($\bar{x}\pm s$, mmol/L)	11.37±2.33	11.62±2.24	0.428	0.694
	β2-MG ($\bar{x}\pm s$, mg/L)	14.83±2.15	14.32±2.41	0.633	0.582

TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; LVEF, Left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; Cr, creatinine; BUN, urobilinogen; β2-MG, β2-microglobulin.

Table 2. Comparison of clinical efficacy between two groups of patients (n, %)

Group	n	Effective	Efficient	Invalid	Total efficiency
Experimental Group	60	40 (66.67)	16 (26.67)	4 (6.67)	56 (93.33)
Control group	60	26 (43.33)	20 (33.33)	14 (23.33)	46 (76.67)
χ^2					6.536
P					0.011

Table 3. Comparison of blood lipid indicators between the two groups of patients ($\bar{x}\pm s$)

Group	N	TG (mmol/L)		LDL-C (mmol/L)		HDL-C (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental Group	60	2.83±0.65	1.21±0.36	4.47±0.51	1.25±0.27	0.73±0.14	1.73±0.41
Control group	60	2.63±0.58	1.73±0.45	4.58±0.67	1.59±0.32	0.63±0.11	1.43±0.33
t		0.447	3.933	0.332	3.425	0.951	3.587
P		0.678	0.001	0.784	0.004	0.396	0.003

TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

terms of cardiac function indicators (LVEF, cardiac output, LVEDD, left atrial diameter, and 6MWT) (t=1.526, P=0.024; t=4.366, P=0.000; t=3.336, P=0.004; t=3.874, P=0.001; t=4.876, P=0.000). See **Table 4**.

Comparison of renal function between two groups of patients

Before treatment, there were no statistically significant differences in any renal function

indicators between the two groups (all P>0.05). After treatment, all renal function indicators (BUN, Cr, serum potassium, serum sodium, urine β2-MG and urine CysC) in the experimental group were superior to those in the control group (t=5.176, P=0.000; t=3.982, P=0.001; t=2.908, P=0.013; t=2.458, P=0.023; t=4.875, P=0.000; t=4.045, P=0.001). See **Table 5**.

Comparison of oxidative stress response

Before treatment, there were no statistically significant differences in any oxidative stress response indicators between the two groups (all P>0.05). After treatment, all oxidative stress response indicators (SOD, MDA and NO) in the experimental group were superior to those in the control group. SOD and NO were significantly upregulated, while MDA was significantly downregulated (t=3.725, P=0.005; t=5.787, P=0.000; t=5.295, P=0.000). See **Table 6**.

Comparison of MACE

Six major adverse cardiovascular events occurred in the experimental group, while 16 occurred in the control group. The difference between the two groups was statistically significant (χ^2=5.566, P=0.018). See **Table 7**.

Univariate analysis of the incidence of MACE in the two groups revealed that body mass index, use of sacubitril/valsartan, TG, LDL-C, HDL-C, LVEF, LVEDD, Cr, BUN, β2-MG, were independent influencing factors for the occurrence of MACE in CRS patients. See **Table 8**.

Discussion

CRS refers to a clinical syndrome in which acute or chronic functional impairment of either the heart or kidney leads to secondary acute or chronic functional impairment of the other organ through pathophysiological connection [5]. The risk of death from CRS is higher than that from simple heart failure or kidney failure. The pathogenesis of CRS is relatively complex [6, 7]. Currently, the most widely accepted pathogenesis of CRS mainly includes excessive excitation of the sympathetic nervous system (SNS), excessive activation of the renin-angiotensin-aldosterone system (RAAS), hemodynamic disturbances, inflammatory response, oxidative stress, anemia, and abnormal molecular signaling pathways [8]. In patients with heart failure, weakened myocardial contractility and reduced cardiac output lead to a decrease in effective circulating blood volume and insufficient renal perfusion. This in turn leads to renal ischemia and hypoxia and reflexively activates the RAAS to enhance vasoconstriction and sodium and water reabsorption, protecting the perfusion of vital organs [9]. However, long-term excessive activation of the RAAS leads to continuous secretion of renin, angiotensin, and aldosterone, which easily causes sodium and water retention, strong systemic vasoconstriction, and decreased glomerular filtration rate. At the same time, this can lead to increased release of inflammatory factors, oxidative stress and activation of neurohormones, ultimately causing structural and functional damage to the heart and kidneys, mainly manifested as irreversible myocardial remodeling and renal fibrosis [10]. Therefore, the main treatment principle for CRS is to improve cardiac and renal function and prevent complications.

Sacubatril and valsartan are dual inhibitors of the RAAS, mainly composed of two drug components. Sacubitril can block the activity of endorphinase, reduce the degradation capacity of vascular peptides, promote sodium excretion and vasodilation; while valsartan can effectively inhibit the RAAS, reduce myocardial oxygen consumption and inhibit myocardial contraction, thereby effectively protecting cardiac function. The combined use of the two has a dual-target regulatory effect [11]. Ivabradine is an I(f) channel inhibitor that can selectively block the I_f current of the F-channel, slow down the depolarization rate of the sinoatrial node during diastole, reduce heart rate, thereby reducing myocardial oxygen consumption, increasing coronary blood flow during diastole, improving myocardial ischemia and enhancing cardiac function. Ivabradine has no effect on other channels of the cardiovascular system and has no adverse effects on blood pressure, atrioventricular conduction time, ventricular repolarization and myocardial contractility [12]. Previous reports have indicated that the combined use of sacubitril/valsartan and ivabradine has significant efficacy in patients with heart failure. For example, Lee et al. [13] found that compared with sequential use of sacubitril/valsartan and ivabradine, simultaneous use of these two drugs can better achieve left ventricular remodeling, improve hemodynamic stability, and reduce future cardiovascular mor-

Table 4. Comparison of cardiac function between two groups of patients ($\bar{x}\pm s$)

Group	n	LVEF (%)		Cardiac output (L/min)		LVEDD (mm)		Left atrial diameter (mm)		6-min walking test 6MWT (m)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental Group	60	34.52±4.87	38.93±6.25	3.17±0.15	5.04±0.25	67.83±5.52	48.53±4.14	44.35±4.25	33.04±3.35	225.42±12.39	383.56±14.29
Control group	60	34.11±5.06	36.22±5.46	3.11±0.13	4.22±0.12	68.04±5.69	55.87±5.03	44.49±3.87	37.65±3.04	227.12±11.89	317.88±13.26
t		0.138	1.526	0.437	4.366	0.179	3.336	0.552	3.874	0.433	4.876
P		0.872	0.024	0.688	0.000	0.802	0.004	0.436	0.001	0.647	0.000

LVEF, Left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

Table 5. Comparison of renal function between two groups of patients ($\bar{x}\pm s$)

Group	n	BUN (mmol/L)		Cr (μmol/L)		Serum potassium (mmol/L)		Serum sodium (mmol/L)		Urine β2-MG (mg/L)		Urine CysC (mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental Group	60	11.37±2.33	5.23±0.28	95.88±7.32	74.87±5.14	3.54±0.82	4.13±0.93	131.82±7.52	142.36±6.58	14.83±2.15	4.38±1.62	4.72±1.32	1.84±0.59
Control group	60	11.62±2.24	8.07±0.31	95.51±6.47	81.34±6.88	3.72±0.91	3.83±0.78	133.52±8.13	138.55±6.86	14.32±2.41	7.58±2.06	4.53±1.08	2.73±0.71
t		0.428	5.176	0.026	3.982	0.412	2.908	0.718	2.458	0.633	4.875	0.453	4.045
P		0.694	0.000	0.957	0.001	0.792	0.013	0.512	0.023	0.582	0.000	0.682	0.001

BUN, urobilinogen; Cr, creatinine; β2-MG, β2-microglobulin; CysC, cystatin C.

Table 6. Comparison of oxidative stress response between two groups of patients ($\bar{x}$±s)

Group	n	Superoxide dismutase SOD (U/mL)		Malondialdehyde MDA (mmol/L)		Nitric oxide NO (μmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental Group	60	34.59±3.77	62.89±6.32	211.83±15.82	129.63±12.36	25.72±3.14	46.73±4.54
Control group	60	35.13±3.52	48.13±5.62	208.56±17.59	163.47±15.22	26.78±2.67	35.28±3.89
t		0.269	3.725	0.856	5.787	0.214	5.295
P		0.638	0.005	0.413	0.000	0.655	0.000

SOD, Superoxide dismutase; MDA, malondialdehyde; NO, nitric oxide.

Table 7. Comparison of MACE occurrence in two groups of patients (n, %)

Group	n	Refractory angina	Arrhythmias	New onset heart failure	Readmission	Cardiac death	Overall incidence
Experimental Group	60	2 (3.33)	0	1 (1.67)	3 (3.33)	0	6 (10.00)
Control group	60	4 (6.67)	3 (5.00)	2 (3.33)	6 (10.00)	1 (1.67)	16 (26.67)
χ^2							5.566
P							0.018

MACE, major adverse cardiovascular events.

Table 8. Univariate analysis of factors related to the occurrence of adverse cardiovascular events MACE ($\bar{x}$±s, n)

Data and indicators classification		MACE group (22 cases)	Non-MACE group (98 cases)	χ^2	*P*
Age of the data (years)		65.07±7.85	65.64±8.39	0.736	0.518
Gender (male/female)		12/10	46/52	0.416	0.519
Body mass index	Overweight or obese	17	52	4.310	0.038
	normal	5	46		
Whether to use sacubitril/valsartan	Yes	7	58	5.420	0.020
	No	15	40		
Improved TG levels	Yes	8	62	5.350	0.021
	No	14	36		
Improvement of LDL-C levels	Yes	3	66	21.213	0.000
	No	19	32		
Improved HDL-C levels	Yes	5	64	13.333	0.000
	No	17	34		
Whether LVEF level improves	Yes	6	66	12.021	0.000
	No	16	32		
Whether LVEDD levels have improved	Yes	5	70	18.182	0.000
	No	17	28		
Whether the Cr level improves	Yes	7	72	13.862	0.000
	No	15	26		
Is the BUN level improving	Yes	10	82	14.673	0.000
	No	12	16		
Whether β2-MG levels improve	Yes	4	78	31.307	0.000
	No	18	20		

LVEF, Left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; BUN, urobilinogen; β2-MG, β2-microglobulin; MACE, major adverse cardiovascular events.

tality and readmission rates. To explore the efficacy of sacubitril/valsartan combined with ivabradine in the treatment of CRS, this study retrospectively analyzed the clinical data of 120 patients with CRS, and found that the combined use of the drugs had better clinical efficacy than sacubitril/valsartan alone, as detailed below.

The results of this study showed that the lipid profiles (TG, LDL-C and HDL-C) of the experimental group were better than those of the control group after treatment. This result indicates that the addition of ivabradine to sacubitril/valsartan can improve the lipid metabolism level of patients. The reason may be that ivabradine achieves this effect by reducing heart rate, reducing sympathetic nerve excitability, and improving insulin resistance, thereby further improving the lipid profile [14]. Of course, this hypothesis needs more evidence to support it.

In this study, we focused on observing the cardiac and renal functions of the two groups of patients after treatment. The results showed that all cardiac function indicators of the two groups of patients improved significantly after treatment. The LVEF, cardiac output, and 6MWT of the experimental group were higher than those of the control group, while the LVEDD and left atrial diameter were lower than those of the control group. In addition, all renal function indicators of the two groups of patients also improved significantly. The serum potassium and serum sodium levels of the experimental group were higher than those of the control group, while the BUN, Cr, urine β2-MG and urine CysC were lower than those of the control group. This indicates that sacubitril/valsartan combined with ivabradine can effectively improve cardiac and renal function in CRS patients. From the perspective of drug mechanism of action, sacubitril/valsartan is a combination drug containing the angiotensin receptor antagonist valsartan and the neprilysin inhibitor sacubitril. This drug exerts its therapeutic effect through two different mechanisms: valsartan inhibits angiotensin II receptors, helping to dilate blood vessels, lower blood pressure, and reduce cardiac workload; while sacubitril inhibits the breakdown of neuropeptides by neprilysin, increasing the level of natriuretic peptides in the body, helping to promote diuresis and antidiuresis, and reducing edema symptoms in patients with heart failure [15, 16]. Ivabradine improves cardiac systolic function and stabilizes hemodynamics by reducing myocardial oxygen consumption and enhancing coronary blood flow, thereby alleviating myocardial ischemia. This process helps to reduce systemic fluid retention, reduce venous congestion, and increase glomerular filtration rate, thereby improving renal function [17]. Therefore, the combined use of the two drugs synergistically enhances cardiac and renal function through a dual mechanism of “optimizing neuroendocrine regulation” and “improving cardiac mechanical efficiency”.

Inflammatory responses are involved in the entire process of cardiovascular and renal disease development [18]. Studies have shown that activation of the RAAS, increased excitability of the SNS, and inflammatory responses can lead to oxidative stress damage in patients with heart and/or kidney dysfunction; the heart and kidneys contain a large number of mitochondria, and an imbalance between NO and reactive oxygen species can cause vascular endothelial dysfunction and mitochondrial DNA damage, which in turn leads to the progression of CRS [19]. In this study, after treatment, the experimental group showed better results than the control group in all oxidative stress response indicators. SOD and NO were significantly upregulated, while MDA was significantly downregulated. The possible mechanism is that sacubitril/valsartan alleviates oxidative stress damage by blocking angiotensin II and inhibiting the aldosterone system [20]. Basic research has shown that sacubitril/valsartan can protect cardiomyocytes in a rat model of heart failure through the endoplasmic reticulum stress pathway of cardiomyocytes [21]. The literature also reports that sacubitril/valsartan can reduce the degree of oxidative stress in patients with congestive heart failure by inhibiting the excitability of the SNS [22]. Ivabradine can reduce heart rate, prolong diastole, and increase coronary blood flow, thereby enhancing the body’s antioxidant capacity, reducing the release of oxygen free radicals, and exerting an antioxidant stress effect; ivabradine also has multiple effects such as being anti-inflammatory, improving endothelial function, and inhibiting ventricular remodeling [23]. MACE events are an important indicator for evaluating the clinical efficacy of cardiorenal syndrome [24]. In this study, 3 cases of MACE occurred in

the experimental group and 8 cases occurred in the control group. Overall, the results were good. However, the effect in the experimental group was more significant. This indicates that the combined use of the two drugs significantly improved the patients' cardiorenal function and further reduced the occurrence of MACE events, demonstrating the safety of the combined use. This is consistent with the results of Lee's study [13].

In conclusion, the results of this study indicate that sacubitril/valsartan combined with ivabradine can improve clinical outcomes in the treatment of CRS. It is believed that sacubitril/valsartan combined with ivabradine may exert a beneficial cardiorenal protective effect through multiple pathways, such as synergistic inhibition of the RAAS and SNS, lowering blood pressure, improving vascular endothelial function, and reducing oxidative stress. This can further promote the improvement of patients' clinical symptoms and signs and improve the overall treatment effect. However, due to the limited sample size and short patient follow-up period in this study, the depth of the research needs to be enhanced, and more objective evidence needs to be provided.

Acknowledgements

This study was supported by the 2024 Jishou University Graduate Research Innovation Project (No. JDY2024090).

Disclosure of conflict of interest

None.

Address correspondence to: Wen Xiong, Department of Nephrology, First Affiliated Hospital of Jishou University, No. 26, Century Avenue, Jishou 416000, Hunan, China. Tel: +86-0743-8669306; E-mail: daxiongbb2022@163.com

References

[1] Nie R, Zhou X, Fu J, Hu S, Zhang Q, Jiang W, Yan Y, Cao X, Yuan D, Long Y, Hong H and Tang S. GPR17 modulates anxiety-like behaviors via basolateral amygdala to ventral hippocampal CA1 glutamatergic projection. Acta Pharm Sin B 2024; 14: 4789-4805.

[2] Makary CA, Azar A, Gudis D, Crawford A, Hannikainen P, Kim J, Joe S, Kimple AJ, Lam K, Lee JT, Luong AU, Marcus S, McArdle E, Mullings W, Peppers BP, Lewandrowski C, Lin SY, Ramadan HH, Rose AS, Ryan L, Toskala E and Baroody FM. Evaluation and treatment of rhinosinusitis with primary antibody deficiency in children: evidence-based review with recommendations. Int Forum Allergy Rhinol 2024; 14: 1776-1801.

[3] Rozenfeld A, Goldman A, Stern T, Banai S and Shacham Y. Using urine output trending for the management of acute cardiorenal syndrome. Isr Med Assoc J 2024; 26: 643-649.

[4] Toprak B, Weimann J, Lehmacher J, Haller PM, Hartikainen TS, Schock A, Karakas M, Renne T, Zeller T, Twerenbold R, Sorensen NA, Westermann D and Neumann JT. Prognostic utility of a multi-biomarker panel in patients with suspected myocardial infarction. Clin Res Cardiol 2024; 113: 1682-1691.

[5] Kumar U, Wettersten N and Garimella PS. Cardiorenal syndrome: pathophysiology. Cardiol Clin 2019; 37: 251-265.

[6] Mohammedsaeed W and Alghamdi ZJ. Biomarker for cardiorenal syndrome risk in patients with liver cirrhosis and type 2 diabetes in Saudi Arabia. Saudi Med J 2024; 45: 675-684.

[7] Ronco C and Di Lullo L. Cardiorenal syndrome in Western countries: epidemiology, diagnosis and management approaches. Kidney Dis (Basel) 2017; 2: 151-163.

[8] Buryskova Salajova K, Malik J and Valerianova A. Cardiorenal syndromes and their role in water and sodium homeostasis. Physiol Res 2024; 73: 173-187.

[9] Reddy A, Thappa P, Jangra K, Dhandapani S and Sihag BK. Neurogenic myocardial dysfunction post craniopharyngioma resection: a diagnostic dilemma. Paediatr Anaesth 2024; 34: 178-181.

[10] Bai W, Zhu T, Zuo J, Li Y, Huang X and Li G. Delivery of SAV-siRNA via exosomes from adipose-derived stem cells for the treatment of myocardial infarction. Tissue Eng Regen Med 2023; 20: 1063-1077.

[11] Jadhav UM, Ray S, Unni TG, Sawhney JPS, Mehta A, Guha S, Karnik RD, Desai BN, Khan A, Patel K, Prajapati JS, Shah HJ, Reddy RK, Kumar S, Dutta SK, Chakraborty S, Ahmed A, Prasad RV, Chaudhary G, Kumar A, Manjappa M, Shetty S, Raja P and Shanmugam VB. Expert opinion on the role of sacubitril/valsartan in the management of hypertension in India. Cardiol Ther 2024; 13: 663-677.

[12] Kamali H, Ozturk E, Ciftci M, Kafali HC, Sahin GT, Haydin S, Hatemi AC, Tanidir IC, Guzeltas A and Ergul Y. Use of ivabradine in children with junctional ectopic tachycardia after pediatric cardiac surgery; two-centre experience. J Arrhythm 2024; 40: 1473-1480.

[13] Lee YH, Lin PL, Chiou WR, Huang JL, Lin WY, Liao CT, Chung FP, Liang HW, Hsu CY and Chang HY. Combination of ivabradine and sacubitril/valsartan in patients with heart failure and reduced ejection fraction. ESC Heart Fail 2021; 8: 1204-1215.

[14] Chuppa S, Liang M, Liu P, Liu Y, Casati MC, Cowley AW, Patullo L and Kriegel AJ. MicroRNA-21 regulates peroxisome proliferator-activated receptor alpha, a molecular mechanism of cardiac pathology in cardiorenal syndrome type 4. Kidney Int 2018; 93: 375-389.

[15] Wang S, Wang Y, Deng Y, Zhang J, Jiang X, Yu J, Gan J, Zeng W and Guo M. Sacubitril/valsartan: research progress of multi-channel therapy for cardiorenal syndrome. Front Pharmacol 2023; 14: 1167260.

[16] Cheng S, Zhou T, Yu L, Chen Y, Zhang Z, Wang J and Yu Y. The effect of sacubitril/valsartan treatment on cardiac and renal functions of a patient with cardiorenal syndrome type 4 and stage 5 CKD after more than three years of follow-up. Front Med (Lausanne) 2022; 9: 817833.

[17] Asbeutah AAA and Goldberger ZD. Novel therapies for the treatment of cardiovascular disease. Med Clin North Am 2024; 108: 953-964.

[18] Xu Z, Luan J, Wan F, Zhang M, Ding F, Yang L and Dai S. Vitamin D promotes autophagy to inhibit LPS-induced lung injury via targeting cathepsin D. Naunyn Schmiedebergs Arch Pharmacol 2025; 398: 5531-5541.

[19] Hammadi SH, Hassan MA, Allam EA, Elsharkawy AM and Shams SS. Effect of sacubitril/valsartan on cognitive impairment in colchicine-induced Alzheimer's model in rats. Fundam Clin Pharmacol 2023; 37: 275-286.

[20] Dogan Z, Ergun DD, Durmus S, Sahin H, Senturk GE, Gelisgen R, Senyigit A and Uzun H. Empagliflozin and sacubitril/valsartan reverse methotrexate cardiotoxicity by repressing oxidative stress and hypoxia in heart embryonic H9c2 cardiomyocytes - the role of morphology of mitochondria observed on electron microscopy. Eur Rev Med Pharmacol Sci 2023; 27: 3979-3992.

[21] Telesca M, De Angelis A, Donniacuo M, Bellocchio G, Riemma MA, Mele E, Canonico F, Cianflone E, Torella D, D'Amario D, Patti G, Liantonio A, Imbrici P, De Luca A, Castaldo G, Rossi F, Cappetta D, Urbanek K and Berrino L. Effects of sacubitril-valsartan on aging-related cardiac dysfunction. Eur J Pharmacol 2024; 978: 176794.

[22] Mohamad HE, Askar ME, Shaheen MA, Baraka NM and Mahmoud YK. Sacubitril/valsartan alleviates sunitinib-induced cardiac fibrosis and oxidative stress via improving TXNIP/TRX system and downregulation of NF-kB/Wnt/beta-catenin/SOX9 signaling. Int Immunopharmacol 2024; 132: 111963.

[23] Pascual Izco M, Ramirez-Carracedo R, Hernandez Navarro I, Osorio Ruiz A, Castejon Navarro B, Cuadrado Berrocal I, Largo Aramburu C, Alonso Salinas GL, Diez J, Saura Redondo M, Zamorano JL, Zaragoza C and Sanmartin M. Ivabradine in acute heart failure: effects on heart rate and hemodynamic parameters in a randomized and controlled swine trial. Cardiol J 2020; 27: 62-71.

[24] Rajaeinejad M, Parhizkar-Roudsari P, Khoshfetrat M, Kazemi-Galougahi MH, Mosaed R, Arjmand R, Mohsenizadeh SA and Arjmand B. Management of fluoropyrimidine-induced cardiac adverse outcomes following cancer treatment. Cardiovasc Toxicol 2024; 24: 184-198.