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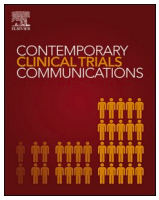

A clinical randomized trial: Effects of early application of sacubitril/valsartan on ventricular remodeling and prognosis in acute myocardial infarction patients

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ABSTRACT

Objectives: To explore the effects of early application of sacubitril/valsartan on ventricular remodeling and prognosis in patients with acute myocardial infarction (AMI).

Methods: Total of 295 patients with AMI admitted to the hospital were enrolled between August 2019 and August 2021. According to different treatment methods, they were divided into observation group (sacubitril/valsartan sodium tables combined with standard treatment, 132 patients) and control group (benazepril hydrochloride tablets combined with standard treatment, 163 patients). The levels of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), creatinine (Cr) and serum K^+ before and at 6 months after treatment, standard deviation of all normal-to-normal intervals (SDNN), standard deviation of the average all normal-to-normal intervals (SDANN), root mean square of differences between adjacent normal-to-normal intervals/root mean square differences of successive R-R (RMSSD), left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF) and left ventricular end-systolic volume (LVESV) in the two groups were compared. The adverse reactions during treatment and major adverse cardiac events (MACE) during 6 months of follow-up in both groups were statistically analyzed.

Results: The levels of NT-proBNP, Cr and K^+, LVEDV and LVESV in observation group were significantly lower than those in control group ($P < 0.05$), while LVEF, SDNN, SDANN and RMSSD were significantly higher than those in control group ($P < 0.05$). The incidence of MACE in observation group was lower than that in control group during 6 months of follow-up (7.58 % *vs* 27.61 %, $P < 0.05$), but there was no significant difference in the incidence of adverse reactions (9.85 % *vs* 12.88 %, $P > 0.05$).

Conclusion: Early application of sacubitril/valsartan sodium can effectively delay ventricular remodeling, improve cardiac function and heart rate variability indexes, reduce NT-proBNP level and improve prognosis in AMI patients.

Acute coronary syndrome (AMI) is a cardiovascular disease caused by continuous myocardial ischemia and hypoxia due to the sharp decrease of coronary blood supply or the obvious increase of myocardial oxygen consumption. Emergency percutaneous coronary intervention (PCI) is the main way to treat AMI, which can quickly restore myocardial blood supply and relieve myocardial ischemic necrosis [1,2]. In some patients, myocardial remodeling caused by left ventricular myocardial repair and functional compensation 24–72h after AMI aggravated the degree of myocardial injury, which could lead to the decrease of left ventricular ejection fraction (LVEF), ventricular dysfunction and malignant arrhythmia, which seriously affected the prognosis of patients [3,4]. Therefore, the selection of effective treatment methods to actively intervene the degree of ventricular remodeling in patients with AMI is conducive to improve the prognosis of patients. Sacubitril valsartan is an angiotensin receptor/neprilysin inhibitor (ARNI). Sacubitril valsartan sodium tablet has a good inhibitory effect on angiotensin receptor and

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enkephalin enzyme, which can effectively reduce the pre - and post-cardiac load and diuretic sodium drainage, which is beneficial to improve ventricular remodeling in patients with AMI [5–7]. In this study, sacubitril valsartan sodium tablets were applied in the clinical treatment of AMI patients. Plasma N-terminal pro-brain peptide (NT-proBNP), echocardiographic left ventricular parameters and cardiac adverse events were used to evaluate the effect of early medication on ventricular remodeling and prognosis, so as to provide a reference for the development of clinical treatment plan for patients with AMI.

1. Data and methods

1.1. General information

A total of 295 AMI patients admitted to our hospital from August 2019 to August 2021 were selected. Inclusion criteria: ① Meet the diagnostic criteria of AMI [8]. Killip I ~ II; ② First onset and admission within 12 h after onset; ③ Successful coronary angiography and PCI; ④ Informed consent of patients and their families. Exclusion criteria: ① Death within 24 h after admission; ② Complicated with severe organ dysfunction; ③ History of cardiac surgery, myocardial infarction or heart failure; ④ Old myocardial infarction; ⑤ Coagulation dysfunction; ⑥ Allergic to the drugs used in this study; ⑦ Complicated with malignant tumor or mental illness. According to different treatment plans, 295 patients with AMI were divided into observation group (132 patients) and control group (163 patients). This study approved by the Ethics Committee of Tianshui First People's Hospital.

1.2. Treatment methods

In the observation group, patients with early AMI were given sacubitril valsartan sodium tablets and standard secondary prevention therapy for coronary heart disease. Sacubitril valsartan sodium tablets (Nosintal, Beijing Novartis Pharmaceutical Co., LTD., Sinophil approval number J20190002, 100 mg*14 tablets), 25mg/time, twice a day, the dose is doubled every 2 weeks, the maximum dose is not more than 200 mg, twice a day. Benazepril hydrochloride tablets (benazepril hydrochloride tablets, Shanghai Xinya Pharmaceutical Minhang Co., LTD., Sinophurt H20044840, 10 mg*14 tablets) combined with standard treatment in the control group was the same as that in the observation group. Both groups were treated for 4 weeks.

1.3. Outcome definitions and measurements

The primary and secondary results were followed up for 6 months. The evaluation of main outcome will be obtained from heart rate variability, echocardiographic parameters and major adverse cardiac events (MACE). Secondary results included blood biochemical indexes and common adverse reactions. See Table 1 for details.

1.3.1. Clinical data collection

Clinical characteristics such as age, sex, body mass index (BMI), underlying diseases (hypertension, diabetes and hyperlipidemia), smoking history, Killip grade, number of diseased vessels and lesion location were collected.

1.3.2. Blood biochemical indexes

Plasma levels of N-terminal pro-brain peptide (NT-proBNP) were measured before and after 6 months of treatment by E602 electrochemiluminescence instrument (Roche) and matching kit. Roche C701 automatic biochemical analyzer was used to detect creatinine (Cr) level. The blood K^+ level was detected by ion selective electrode method.

1.3.3. Heart rate variability and echocardiographic left ventricular parameters

Heart rate variaability (HRV) indexes of the two groups before and after 6 months of treatment were detected by 24-h holter electrocardiogram. standard deviation of N-N interval(SDNN), standard deviation of N-N interval mean(SDANN), root mean square of all sinus beats were included difference between adjacent N-N intervals(RMSSD).

Philips EPIQ7 Doppler color echocardiography was used to detect the left ventricular end-diastolic volume (LVEDV) and left ventricular ejection before and after 6 months of treatment fraction (LVEF), left ventricular end-systolic volume (LVESV) and other left ventricular parameters.

Table 1
Main results and secondary results.

Results	Project	
Main Results	Heart rate variability	SDNN
		SDANN
		RMSSD
	Echocardiographic parameters	LVEDV
		LVEF
		LVESV
	MACE	Cardiovascular death
		Recurrent angina pectoris
		Recurrent myocardial infarction
		Ischemic stroke
		Heart failure readmissions
Secondary Results	Blood biochemical indexes	NT-proBNP
		Cr
		K^+
	Common adverse reactions	Neuroangioedema, Renal insufficiency
		Abnormal blood K^+
		Dry cough

1.3.4. Common adverse reactions and major adverse cardiac events

The occurrence of neuroangioedema, renal insufficiency, abnormal blood K+ and other common adverse reactions during treatment were recorded in the two groups. After treatment, patients in the two groups were followed up for 6 months through outpatient review and telephone and wechat follow-up. The occurrence of major adverse cardiac events, including angina pectoris, recurrent myocardial infarction, ischemic stroke, and readmission for heart failure, were recorded.

1.4. Statistical treatment

Statistical software SPSS 22.0 was used for data analysis. Measurement data were expressed as ($\bar{x} \pm s$), differences between groups were expressed as two-sample independent *t*-test, and differences between groups were expressed as count data rate, χ^2 and Fisher exact test were used for data analysis. A two-sided $P < 0.05$ was considered statistically significant.

2. Results

2.1. Comparison of clinical characteristics of AMI patients between the two groups

There were no significant differences in gender, age, BMI, underlying diseases, smoking history, Killip grade, number of diseased vessels and lesion location between the observation group and the control group ($P > 0.05$). As shown in Table 2.

2.2. Comparison of NT-proBNP, Cr and K^+ levels between the two groups before and after treatment

There were no significant differences in NT-proBNP, Cr and K^+ levels between the two groups before treatment ($P > 0.05$). At 6 months after treatment, the levels of NT-proBNP, Cr and K^+ in the two groups were significantly lower than those before treatment, and the levels of NT-

Table 2
Comparison of clinical characteristics between the two groups of AMI patients [cases(%), $\bar{x} \pm s$].

Indexes		Observation group (n = 132)	Control group (n = 163)	χ^2/t	*P*
Gender (cases)	Male	85 (64.39)	101 (61.96)	0.185	0.667
Age (year)	Female	61.51 ± 3.85	61.83 ± 3.07	0.794	0.428
BMI (kg/m^2)	≤24	92 (69.70)	125 (76.69)	1.832	0.176
	>24	40 (30.30)	38 (23.31)		
Complicated with underlying diseases (case)	Hypertension	37 (28.03)	45 (37.61)	0.007	0.936
	Diabetes	22 (16.67)	31 (19.02)	0.274	0.601
	Hyperlipidemia disease	19 (14.39)	25 (15.34)	0.051	0.821
Smoking history (case)	Yes	76 (57.58)	89 (54.60)	0.262	0.609
	No	56 (42.42)	74 (45.40)		
Killip scale (case)	Grade I	23 (17.42)	41 (25.15)	2.565	0.109
	Grade II	109 (82.58)	122 (74.85)		
Number of diseased vessels (case)	Single	66 (50.00)	89 (54.60)	0.634	0.728
	Double branches	47 (35.61)	52 (31.90)		
	Three branches	19 (14.39)	22 (13.50)		
Site of lesion (case)	Front wall	40 (30.30)	53 (32.52)	1.838	0.607
	The high lateral wall	31 (23.48)	45 (27.61)		
	The inferior wall	35 (26.52)	33 (20.25)		
	The right ventricle	26 (19.70)	32 (19.63)		

proBNP, Cr and K^+ in the observation group were significantly lower than those in the control group ($P < 0.05$). As shown in Table 3.

2.3. Comparison of left ventricular parameters between the two groups before and after treatment

There were no significant differences in LVEDV, LVESV and LVEF between the two groups before treatment ($P > 0.05$). At 6 months after treatment, LVEDV and LVESV in the two groups were significantly lower than before treatment, LVEF was significantly higher than before treatment, and LVEDV and LVESV in the observation group were significantly lower than those in the control group, and LVEF was significantly higher than that in the control group ($P < 0.05$). As shown in Table 4.

2.4. Comparison of HRV index levels in AMI patients between the two groups

There were no significant differences in SDNN, SDANN and RMSSD between the two groups before treatment ($P > 0.05$). At 6 months after treatment, the SDNN, SDANN and RMSSD of the two groups were significantly higher than those before treatment, and the SDNN, SDANN and RMSSD of the observation group were significantly higher than those of the control group ($P < 0.05$). As shown in Table 5.

2.5. Comparison of the incidence of major adverse cardiac events in AMI patients between the two groups during follow-up

During the follow-up period, no cardiovascular death occurred in both groups. The incidence of recurrent angina pectoris, recurrent myocardial infarction, ischemic stroke and heart failure readmission in the observation group was lower than that in the control group ($P < 0.05$). The incidence of major adverse cardiac events in the observation group was 7.58 %, which was lower than 27.61 % in the control group ($P < 0.05$). As shown in Table 6.

2.6. Comparison of the incidence of common adverse reactions in AMI patients between the two groups during treatment

Mild increase of blood K^+ occurred in 2 patients, 7 patients of renal insufficiency, 2 patients of neuroangioedema and 2 patients of dry cough in the observation group, while mild increase of blood K^+ occurred in 5 patients, 10 patients of renal insufficiency, 3 patients of neuroangioedema and 3 patients of dry cough in the control group. The incidence of common adverse reactions during treatment in the observation group was 9.85 %, which was not significantly different from 12.88 % in the control group ($\chi^2 = 0.659$, $P = 0.417$).

3. Discussions

The results of this study showed that at 6 months after treatment, the levels of NT-proBNP, Cr and K+ in the observation group were significantly lower than those in the control group, EDV and ESV in the observation group were significantly lower than those in the control group, LVEF was significantly higher than those in the control group, SDNN, SDANN and RMSSD were significantly higher than those in the control group. During the follow-up period, the incidence of MACE events such as angina pectoris, recurrent myocardial infarction, ischemic stroke and readmission for heart failure in the observation group was significantly lower than that in the control group, but there was no significant difference in the incidence of common adverse reactions between the two groups, indicating that compared with benazepril hydrochloride, Sacubitril valsartan sodium can more effectively

Table 3
Comparison of NT-proBNP, Cr and K^+ levels between the two groups before and after treatment ($\bar{x} \pm s$).

Group	N	NT-ProBNP (pg/mL)		Cr (μmol/L)		K^+ (mmol/L)	
		Before the treatment	6 months after treatment	Before the treatment	6 months after treatment	Before the treatment	6 months after treatment
Observation group	132	862.89 ± 36.44	532.64 ± 36.74*	79.93 ± 11.02	56.96 ± 4.94*	4.26 ± 0.52	3.96 ± 0.37*
Control group	163	870.70 ± 40.86	504.13 ± 34.83*	81.83 ± 11.47	68.11 ± 5.09*	4.25 ± 0.57	4.12 ± 0.49*
t		1.712	3.821	1.439	18.955	0.156	3.102
P		0.087	< 0.001	0.151	< 0.001	0.876	0.002

Note: Compared with the same group before treatment,*$P < 0.05$。.

Table 4
Comparison of left ventricular parameters between the two groups before and after treatment ($\overline{x} \pm s$).

Group	N	LVEDV (mL)		LVESV (mL)		LVEF (%)	
		Before the treatment	6 months after treatment	Before the treatment	6 months after treatment	Before the treatment	6 months after treatment
Observation group	132	47.37 ± 4.74	41.69 ± 3.73*	57.67 ± 5.97	51.37 ± 5.31*	38.86 ± 5.35	48.54 ± 5.48*
Control group	163	47.49 ± 4.44	44.68 ± 4.18*	57.70 ± 5.83	54.73 ± 5.28*	38.12 ± 5.09	43.29 ± 5.05*
t		0.224	6.408	0.043	5.421	1.213	8.546
P		0.823	< 0.001	0.965	< 0.001	0.225	< 0.001

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

Table 5
Comparison of left ventricular parameters between the two groups before and after treatment ($\overline{x} \pm s$).

Group	N	SDNN (ms)		SDANN (ms)		RMSSD (ms)	
		Before the treatment	6 months after treatment	Before the treatment	6 months after treatment	Before the treatment	6 months after treatment
Observation group	132	77.11 ± 9.93	97.63 ± 14.90*	69.13 ± 8.51	81.70 ± 13.81*	25.98 ± 4.69	34.85 ± 6.73*
Control group	163	78.92 ± 11.39	91.50 ± 14.13*	67.47 ± 8.81	76.75 ± 12.02*	25.89 ± 4.72	29.99 ± 5.94*
t		1.436	3.615	1.634	3.289	0.163	6.582
P		0.152	< 0.001	0.103	0.001	0.870	< 0.001

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

Table 6
Comparison of the incidence of major adverse cardiac events between the two groups of AMI patients during follow-up [cases(%)].

Group	N	Cardiovascular death	Recurrent angina pectoris	Recurrent myocardial infarction	Ischemic stroke	Heart failure readmissions	Total MACE incidence
Observation group	132	0 (0.00)	6 (4.55)	1 (0.76)	2 (1.52)	1 (0.76)	10 (7.58)
Control group	163	0 (0.00)	18 (11.04)	9 (5.52)	10 (6.13)	8 (4.91)	45 (27.61)
χ^2							19.295
P							< 0.001

improve the levels of myocardial remodeling serology and echocardiographic left ventricular parameters in patients with AMI, and improve the level of heart rate variability. Sacubitril valsartan sodium tablets can be used as a reliable drug for early clinical treatment of AMI patients. AMI is an acute irreversible myocardial necrotizing disease caused by severe and persistent myocardial hypoperfusion caused by a variety of reasons. It is a common clinical cardiovascular critical illness, which needs early treatment with active thrombolysis, PCI or surgical coronary artery bypass grafting [9,10]. A large number of studies have found that although early emergency interventional treatment for AMI patients can significantly reduce their mortality, some patients still have poor prognosis due to cardiovascular events such as ventricular remodeling and heart failure [11,12]. Ventricular remodeling is a compensatory change of the heart to reduce the tension of the ventricular wall and temporarily guarantee the pumping function of the heart. With the progress of the disease, it can cause heart failure due to the cumulative effect and even cause death of the patient [13,14]. Sympa-adrenergic medulla system and renin-angiotensin-aldosterone system inhibitors are the main drugs in the current clinical treatment of heart failure, which can alleviate the clinical symptoms and reduce the mortality of AMI patients, but the application effect is still poor in some patients [15]. Sacubitril valsartan sodium can inhibit the renin-angiotensin-aldosterone system and enkephalin system, which can relax blood vessels, inhibit sympathetic nerve activity, diuretic sodium drainage and reverse left ventricular remodeling [16].

Usually, after 6 months of treatment with sarkopride/valsartan, the overall longitudinal strain of the left ventricle and the strain of the left atrium reservoir in patients with heart failure with decreased ejection fraction are improved, suggesting that the treatment effect is good and the prognosis is good [17]. Docherty KF et al. [18] found that compared with angiotensin converting enzyme inhibitor enalapril, the angiotensin receptor-brain natriuretic peptide inhibitor (ARNI) sacubitril valsartan has been shown to reduce the risk of cardiovascular death or hospitalization for heart failure and improve symptoms in patients with chronic heart failure with reduced ejection fraction. Ledwidge et al. [19] reviewed the application of sacubitril VALSATAN in the treatment of patients with early heart failure, and proposed that SACUBITRIL VALSATAN sodium was related to the increase of left atrial volume index and the improvement of cardiovascular risk markers. Tocci G [20] and Peng S [21] et al. believe that sacubitril valsartan sodium has a good effect on the echocardiographic left ventricular parameters and heart rate variability in patients with myocardial infarction, and can improve pathological cardiac remodeling induced by oxidative stress and pressure load through a variety of ways. These results are basically consistent with the results of this study, which confirmed that early application of sacubitril valsartan sodium can effectively improve ventricular remodeling and long-term prognosis in patients with AMI. However, during the follow-up period of this study, no cases of cardiovascular death were observed, which may be related to the failure to include a large sample size in multiple centers and the short follow-up time.

After reviewing relevant literature, it is found that some research results are still different from the results of this study. Bhagat AAy [22] and De Vecchis R [23] et al. pointed out that sacubitril valsartan sodium can effectively reduce arterial blood pressure, but does not show significant improvement on cardiac function in hemodynamically unstable heart failure patients. Pfeffer MA et al. [24] proposed that sacubitril valsartan sodium had no significant improvement on the incidence of cardiovascular death or heart failure in patients with acute myocardial infarction compared with ramipril. Zhao J [25] et al. believed that

sacubitril valsartan sodium had no significant effect on the improvement of heart rate variability in patients with acute decompensated heart failure compared with enalapril treatment. The reasons for the differences between the results of this study and those reported above were analyzed. In addition to the regional differences and demographic differences caused by the included samples themselves, there may be a certain correlation with the time and dose of sacubitril valsartan sodium application, which needs to be discussed and analyzed in detail in subsequent studies.

The deficiency of this study is that there is no comparative analysis on the curative effect and prognosis of early application of sacubitril valsartan sodium tablets in AMI patients with different degrees of cardiac function, and this study is a single-center study with short follow-up time and small sample size, which needs multi-center and large-sample research to further confirm its effect and provide evidence-based medical evidence for clinical diagnosis and treatment.

In conclusion, early application of sacubitril valsartan sodium tablets in the treatment of AMI patients can effectively delay ventricular remodeling, improve cardiac function and heart rate variability indicators, reduce the level of NT-proBNP, improve prognosis, and have good safety.

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Declaration of competing interest

The authors declare no conflict of interest, financial or otherwise.

Data availability

Data will be made available on request.

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