ORIGINAL RESEARCH

Early Application of Sacubitril Valsartan Sodium After Acute Myocardial Infarction and its Influence on Ventricular Remodeling and TGF-β1/Smad3 Signaling Pathway

Linqing Wang, MM; Yajing Zhang, MM; Jieqian Xue, BM; Yingxiao Da, MM; Yanzhou Gao, MM; Yunjing Sun, MM; Song Zhou, MM

ABSTRACT

Objective • The objective of this study was to investigate the early application of sacubitril valsartan sodium (LCZ696) following acute myocardial infarction (AMI) and its impact on ventricular remodeling and the TGF-β1/Smad3 signaling pathway in patients.

Methods • The clinical data of 73 patients with AMI admitted to the hospital from June 2021 to September 2022 were retrospectively analyzed, and the patients were grouped according to the treatment methods, including 36 cases in the control group (conventional drug treatment) and 37 cases in the observation group (conventional drug + LCZ696 treatment). The clinical efficacy, cardiac function parameters [left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), stroke volume (SV)], cardiac function biochemical indicators [N-terminal pro-B-type natriuretic peptide (NT-proBNP), galectin 3 (Gal-3), amino-terminal peptide of type III procollagen (PIIINP)], ventricular remodeling indicators [left ventricular posterior wall end-diastolic thickness (PWD), posterior wall end-systolic thickness (PWS), ventricular septal end-systolic thickness (IVSS)], ventricular hydrodynamic parameters [left ventricular flow rate in peak ejection (FRPE), flow reversal rate (FRR), flow reversal interval (FRI)], TGF-β 1/Smad3 signaling pathway-related indicators (TGF-β1, Smad3), quality of life score (SF-36 Quality of Life Scale) and occurrence of adverse reactions were compared between the two groups.

Results • The main findings of the study are as follows: The observation group was significantly better than the control group in many aspects such as overall clinical effectiveness, cardiac function parameters, biochemical indicators, ventricular structure and function, TGF-β1/Smad3 signaling pathway, and quality of life. Specifically, the observation group showed more significant positive effects in terms of improvement of cardiac function, adjustment of biochemical status, and adjustment of ventricular structure and fluid dynamics parameters. These results provide strong support for the application of new therapeutic approaches in the management of cardiovascular disease. After treatment, the total clinical effective rate in the observation group (89.19%) was significantly higher than that in the control group (69.44%) ($P < .05$). LVEF and SV in the two groups were significantly increased ($P < .05$), while LVEDD was significantly decreased ($P < .05$), and there were statistically significant differences in parameters between the two groups ($P < .05$). The levels of NT-proBNP, Gal-3 and PIIINP in both groups were significantly reduced ($P < .05$), and the levels in the observation group were significantly lower than those in the control group ($P < .05$). The PWD, PWS and IVSS in both groups significantly declined ($P < .05$), and the indicators in the observation group were significantly lower than those in the control group ($P < .05$). The FRPE and FRR in the two groups were significantly enhanced ($P < .05$), while the FRI was significantly reduced ($P < .05$), and the differences in the above parameters between the two groups were statistically significant ($P < .05$). The levels of TGF-β1 and Smad3 in the two groups were significantly declined ($P < .05$), and the levels in the observation group were significantly lower than those in the control group ($P < .05$). During the period from before treatment to 6 months of treatment, the quality of life score in the two groups showed a significant downward trend ($P < .05$), and the score in the observation group after 3 months to 6 months of treatment was significantly lower than that in the control group ($P < .05$). During treatment, there was no statistical significance in the total incidence rate of adverse reactions between the two groups ($P > .05$).

Conclusion • Early application of LCZ696 after AMI has a significant efficacy, and it can effectively improve the ventricular remodeling, regulate the expression levels of TGF-β1 and Smad3, inhibit the TGF-β1/Smad3 signaling pathway, promote the improvements of cardiac function and quality of life, and it has good safety and is worthy of clinical promotion and application. The study's key findings have important clinical implications for understanding and managing acute myocardial infarction (AMI). The observation group showed significant improvements in overall clinical efficacy, cardiac function, biochemical status, ventricular structure and function, etc., providing strong evidence for comprehensive treatment of AMI patients. This treatment method is expected to become an important part of the care and treatment strategy for AMI patients, help reduce cardiovascular risk, improve quality of life, and provide new research directions for future AMI treatment. (*Altern Ther Health Med.* [E-pub ahead of print.])

Linqing Wang, MM, Attending doctor; **Yingxiao Da,** MM, Attending doctor; **Yanzhou Gao,** MM, Associate chief physician; **Yunjing Sun,** MM, Associate chief physician; **Song Zhou,** MM, Chief physician; Cardiology Department No.2 Ward, Xingtai Third Hospital, Xingtai, China. **Yajing Zhang,** MM, Attending doctor; Cardiology Department No.4 Ward, Xingtai Third Hospital, Xingtai, China. **Jieqian Xue,** BM, Attending doctor; Department of Emergency, Xingtai Third Hospital, Xingtai, China.

Corresponding author: Song Zhou, MM
E-mail: 15127978088@163.com

INTRODUCTION

Acute myocardial infarction (AMI) is an acute coronary syndrome, which is characterized by a sharp reduction or interruption of coronary blood supply, leading to myocardial necrosis due to sustained and severe acute ischemia. It has complex causes and is the most serious form of coronary heart disease. One of the manifestations poses a huge threat to the patient's life safety.[1] Many studies have shown that some patients develop LV systolic dysfunction after AMI. These patients are at higher risk for heart failure and a corresponding increased risk of death.[2] Therefore, finding more effective therapeutic drugs to control disease

Table 1. Comparison of the general information of the two groups

Group	n	Gender (n)		Age (years)	Infarct-related arteries (n)				Admission heart rate (beats/min)
		Male	Female		anterior descending branch (geology)	right coronary artery	cyclotron (particle physics)	Left main	
Control group	36	21	15	67.15±4.31	20	13	3	1	76.17±15.32
Observation group	37	20	17	67.74±4.89	23	7	6	1	76.82±14.85
t/χ^2		0.136		0.546	2.512				0.184
P value		.712		.587	.473				.854

progression and improve patient prognosis has been the focus of clinical research. Sacubitril valsartan (Sacubitril/Valsartan, LCZ696) is a new dual inhibitor officially introduced to China in 2017. Its main components are sacubitril and valsartan, and has achieved good results in the treatment of AMI.[3] The main adverse prognosis of AMI is ventricular remodeling and myocardial cell fibrosis, the extent of which directly affects the patient's readmission rate and even the patient's morbidity and mortality.[4] The transforming growth factor-β1 (TGF-β1)/Smad pathway has been found to be involved in the process of myocardial fibrosis, which may lead to changes in cardiac structure and function, but most relevant studies have focused on animal experiments.[5] Based on this, this study aimed to investigate the early application of LCZ696 after AMI and its effect on patients' ventricular remodeling and TGF-β1/Smad3 signaling pathway to provide more favorable evidence to reduce cardiac injury, as described below.

MATERIALS AND METHODS

General information

The clinical data of 73 AMI patients admitted to Xingtai Third Hospital from June 2021 to September 2022 were retrospectively analysed. This study has been approved by the Ethics Committee of Xingtai Third Hospital(Ethical approval number:202101LL-009)

Inclusion criteria: (1) Meet the diagnostic criteria of AMI and confirm the diagnosis; (2) Clear autonomic consciousness and cardiac function grading ≥ class II; (3) Age > 18 years old.

Exclusion criteria: (1) Combined with other heart diseases, such as hypertrophic or restrictive cardiomyopathy, severe heart valve disease, myocarditis, myocardial amyloidosis, cardiogenic shock, etc.; (2) Previous history of heart failure or angioedema; (3) Severe hepatic and renal insufficiency; (4) Combined with acute and chronic infections, coagulation abnormalities, malignant tumors, etc.; (5) Accompanied with immune, blood, respiratory, and other systemic diseases; (6) Allergic to the drugs under study; (7) Lack of clinical information. The enrolled patients were divided into the control group (n=36) and the observation group (n=37) according to the different treatment methods, and the differences in the general information of the two groups were not statistically significant ($P > .05$), with good comparability (Table 1).

Treatment method

The control group received conventional drug treatment, including diuretics, antihypertensive drugs, beta-blockers, nitrate vasodilators, and vasoactive drugs. The observation group used LCZ696 (Beijing Novartis Pharmaceuticals Co., Ltd., National Drug License No. HJ20170363, specification and model: 50 mg × 28 tablets) on the basis of conventional drug treatment. If the patient is not taking antihypertensive drugs, the initial dose is 50 mg/time, twice a day, orally administered 30 minutes after meals, and gradually increased to the target maintenance dose of 200 mg/time after 2 weeks based on the patient's tolerance; if the patient is already taking antihypertensive drugs, The drug should be taken 36 hours after stopping the drug. The initial dose is adjusted to 100 mg/time, twice a day. It is also gradually increased to the target maintenance dose of 200 mg/time based on the patient's tolerance. Treatment lasts for 6 months.

Observation indexes

(1) Clinical efficacy: clinical symptoms significantly improved, cardiac function improved by 1~2 grades is considered effective; clinical symptoms improved, cardiac function improved by 1 grade is considered effective; no change or aggravation of clinical symptoms and cardiac function is considered ineffective. (2) Cardiac function parameters: before and after treatment, a color Doppler ultrasound diagnostic instrument was used to detect patients' left ventricular ejection fraction (LVEF), left ventricular end-diastolic internal diameter (LVEDD), and output per beat (SV). (3) Biochemical indexes of cardiac function: 5 ml of fasting venous blood was collected from patients before and after treatment, and serum was centrifuged (3000 r/min, 10 min) to detect the levels of N-terminal B-type natriuretic peptide precursor (NT-proBNP), galactose agglutinin 3 (Gal-3), and pre-collagen type III aminoterminal peptide (PIIINP), of which NT-proBNP was detected by electrochemiluminescence immunoassay, Gal-3 by enzyme analysis, and P-IIINP by enzyme analysis. (4) Ventricular remodeling indexes: color Doppler ultrasound diagnostic instrument was used to detect patients' left ventricular posterior wall end-diastolic thickness (PWD), posterior wall end-systolic thickness (PWS), and interventricular septal end-systolic thickness (IVSS) before and after treatment. (5) Ventricular hydrodynamic parameters: changes in left ventricular peak ejection flow rate (FRPE), ejection-filling flow reversal flow rate (FRR), and ejection-filling flow reversal interval (FRI) were detected before and after treatment using ultrasound blood flow vector imaging. (6) TGF-β1/Smad3 signaling pathway-related indexes: patients' fasting venous blood was collected before and after treatment and centrifuged to take the serum, and the levels of TGF-β1 and Smad3 were detected, both by enzyme-linked immunosorbent assay. (7) Quality of life: assessed by SF-36 Quality of Life Survey Scale before treatment, after 3 months of treatment, and after 6 months of treatment, which has 8 dimensions, with 0-100 points for each dimension, and the

higher the score indicates the better the quality of life of the patients. Each dimension in the SF-36 quality of life survey scale ranges from 0 to 100, with higher scores indicating better quality of life in the corresponding dimension. This range of scores helps assess different aspects of a patient's health and quality of life. (8) Occurrence of adverse reactions: the occurrence of adverse reactions in the two groups during the treatment period was recorded.

Statistical analysis

The data were statistically analyzed using Statistic Package for Social Science (SPSS) 22.0 software (IBM, Armonk, NY, USA). Clinical efficacy and the incidence of adverse reactions were expressed in the form of n (%) using the chi-square test; cardiac function parameters, cardiac function biochemical indexes, ventricular remodeling indexes, ventricular hydrodynamics parameters, indicators related to the TGF-β1/Smad3 signaling pathway and the quality of life scores were all expressed in the form of (±s), and the comparison between groups was made using the independent *t* test, and within-group comparisons were performed using the paired *t*-test or the continuity-corrected test. Differences were considered statistically significant at $P < .05$.

RESULTS

Comparison of clinical efficacy between the two groups

According to the data in Table 2, there were 36 patients in the control group, of which 10 (27.78%) were effective, 15 (41.67%) were effective, and 11 (30.56%) were ineffective. The total effective rate was 69.44 %. In comparison, there were 37 patients in the observation group, of which 16 (43.24%) were effective, 17 (45.95%) were effective, and 4 (10.81%) were ineffective. The total effective rate reached 89.19%. Statistical analysis showed that there was a significant difference between the two groups, with a t/χ^2 value of 4.357 and $P = .037$. This shows that the overall clinical efficacy rate of the observation group is significantly higher than that of the control group, and the difference is statistically significant. See Table 2.

Comparison of cardiac function parameters between the two groups

The cardiac parameters, including left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and stroke volume (SV), were assessed in both groups before and after treatment. In the control group (n=36), the pre-treatment LVEF was 51.49±5.49%, which increased to 55.41±4.85% after treatment ($P < .001$). The LVEDD decreased from 58.98±3.40 mm to 51.15±2.38 mm ($P < .001$), and SV increased from 41.56±3.49 mL to 48.57±4.84 mL ($P < .001$). Similarly, in the observation group (n=37), the pre-treatment LVEF was 51.03±5.17%, significantly increasing to 59.04±4.61% post-treatment ($P < .001$). The LVEDD decreased from 58.45±3.59 mm to 54.53±2.71 mm ($P < .001$), and SV increased from 41.04±3.83 mL to 53.39±5.21 mL ($P < .001$). Statistical analysis revealed significant differences in the post-treatment values of LVEF, LVEDD, and SV between the two groups ($P < .05$), indicating a more favorable cardiac response to treatment in the observation group compared to the control group. See Table 3.

Comparison of cardiac function biochemical indexes between the two groups

After treatment, the levels of NT-proBNP, Gal-3 and PIIINP were significantly reduced in both groups ($P < .05$), and the levels of each index in the observation group were significantly lower than those in the control group ($P < .05$). See Table 4.

Comparison of ventricular remodeling indexes between the two groups

After treatment, the values of PWD, PWS and IVSS were significantly reduced in both groups ($P < .05$), and the values

Table 2. Comparison of clinical efficacy between liver-expanding and spleen-strengthening soup group and conventional treatment group (n, %)

Group	n	Effective	Effective	Ineffective	Total effective rate
Control group	36	10(27.78)	15(41.67)	11(30.56)	25(69.44)
Observation group	37	16(43.24)	17(45.95)	4(10.81)	33(89.19)
t/χ^2					4.357
P value					0.037

Table 3. Comparison of cardiac function parameters between the two groups (±s)

Group	n	LVEF (%)		LVEDD(mm)		SV(mL)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	36	51.49±5.49	55.41±4.85[a]	58.98±3.40	51.15±2.38[a]	41.56±3.49	48.57±4.84[a]
Observation group	37	51.03±5.17	59.04±4.61[a]	58.45±3.59	54.53±2.71[a]	41.04±3.83	53.39±5.21[a]
t		0.369	3.278	0.647	5.656	0.606	4.092
P value		.714	.002	.519	<.001	.547	<.001

[a]$P < .05$, comparison with the same group before treatment

Table 4. Comparison of cardiac function biochemical indexes between the two groups (±s)

Group	n	NT-proBNP (pg/mL)		Gal-3(ng/mL)		PIIINP(ng/mL)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	36	4765.42±891.86	794.45±95.87[a]	10.94±2.37	8.21±1.36[a]	58.25±10.93	32.37±5.75[a]
Observation group	37	4812.65±903.29	621.66±51.35[a]	11.01±2.16	6.89±1.18[a]	57.68±11.14	28.69±7.02[a]
t		0.225	9.635	0.132	4.433	0.221	2.446
P value		.823	<.001	.895	<.001	.826	.017

[a]$P < .05$, comparison with the same group before treatment

Table 5. Comparison of ventricular remodeling indexes between the two groups (±s, mm)

Group	n	PWD		PWS		IVSS	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	36	15.51±2.72	12.84±2.09[a]	14.49±2.70	12.52±1.92[a]	13.53±2.21	12.39±1.98[a]
Observation group	37	15.06±2.64	11.06±1.87[a]	14.97±2.95	10.14±1.76[a]	13.17±2.36	10.31±1.83[a]
t		0.717	3.837	0.725	5.523	0.672	4.663
P value		.478	<.001	.471	<.001	.504	<.001

[a]$P < .05$, comparison with the same group before treatment

Table 6. Comparison of ventricular hydrodynamic parameters between the two groups (±s)

Group	n	FRPE (cm^2/s)		FRR(cm^2/s)		FRI(ms)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	36	40.13±8.29	51.92±6.33[a]	28.01±5.17	32.28±5.11[a]	113.21±23.47	91.96±11.37[a]
Observation group	37	40.75±8.61	55.24±5.46[a]	27.34±4.69	36.15±6.84[a]	115.14±24.28	82.52±10.44[a]
t		0.313	2.402	0.580	2.733	0.345	3.697
P value		.755	.019	.564	.008	.731	<.001

[a]$P < .05$, comparison with the same group before treatment

Table 7. Comparison of TGF-β1/Smad3 signaling pathway-related indexes between the two groups (±s)

Group	n	TGF-β1 (ng/L)		Smad3(ng/ml)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	36	538.51±85.72	501.14±63.69[a]	9.82±1.17	9.09±1.24[a]
Observation group	37	532.06±81.64	472.36±59.57[a]	9.67±1.05	8.14±1.16[a]
t		0.329	3.838	0.577	3.381
P value		.743	<.001	.566	.001

[a]$P < .05$ comparison with the same group before treatment

Table 8. Comparison of Quality of Life Scores between Two Groups (± s, points)

Group	n	Before treatment	After 3 months of treatment	After 6months of treatment	*F*	*P* value
Control group	36	66.32±5.11	71.75±7.07	79.55±8.68	18.829	<.001
Observation group	37	65.76±5.27	76.57±8.73	86.42±7.05	26.317	<.001
t		0.461	2.588	3.717		
P value		0.646	0.012	<.001		

Table 9. Comparison of the incidence rate of adverse reactions between the two groups (n, %)

Group	n	Gastrointestinal reactions	Angioedema	Hypotension	Potassium abnormalities	Total Occurrence
Control group	36	1(2.78)	1(2.78)	1(2.78)	0(0.00)	3(8.33)
Observation group	37	1(2.70)	1(2.70)	1(2.70)	1(2.70)	4(10.81)
χ^2						0.129
P value						.719

of each index in the observation group were significantly lower than those in the control group ($P < .05$). See Table 5.

Comparison of ventricular hydrodynamic parameters between the two groups

After treatment, FRPE and FRR values were significantly higher ($P < .05$), and FRI values were significantly lower ($P < .05$) in both groups, and the differences in each parameter between the two groups were statistically significant ($P < .05$). See Table 6.

Comparison of TGF-β1/Smad3 signaling pathway-related indexes between the two groups

After treatment, the levels of TGF-β1 and Smad3 were significantly reduced in both groups ($P < .05$), and the levels in the observation group were significantly lower than those in the control group ($P < .05$). See Table 7.

Comparison of quality of life scores between the two groups

Before treatment ~ after 6 months of treatment, the quality of life scores of the two groups showed a significant downward trend ($P < .05$). The scores of the observation group were significantly lower than those of the control group in the same period after 3 months of treatment ~ after 6 months of treatment ($P < .05$). See Table 8. Quality of life scores showed clear trends over time in both groups. The initial score showed the baseline level at the beginning of treatment, and as treatment progressed, the quality of life score of the observation group showed an upward trend, while the score of the control group was relatively low. This shows that under LCZ696 treatment, the patient's quality of life improved during the treatment period, while the improvement in the control group was smaller. These trends reflect the positive impact of LCZ696 on patients' overall quality of life.

Comparison of the incidence of adverse reactions between the two groups

The occurrence of adverse reactions in both groups was evaluated, focusing on gastrointestinal reactions, angioedema, hypotension, and potassium abnormalities. In the control group (n=36), one patient (2.78%) experienced gastrointestinal reactions, one patient (2.78%) had angioedema, one patient (2.78%) exhibited hypotension, and there were no cases of potassium abnormalities, resulting in a total occurrence of adverse reactions in 8.33% of patients. In the observation group (n=37), one patient (2.70%) had gastrointestinal reactions, one patient (2.70%) experienced angioedema, one patient (2.70%) showed hypotension, and one patient (2.70%) presented with potassium abnormalities, leading to a total occurrence of adverse reactions in 10.81% of patients. Statistical analysis indicated no significant difference in the occurrence of adverse reactions between the two groups ($P = .719$). Overall, the observed adverse reactions were relatively low and comparable between the control and observation groups. See Table 9.

DISCUSSION

It has been found that ventricular remodeling and myocardial fibrosis can diminish myocardial contractility and contribute to cardiac decompensation, which is an important pathological aspect contributing to the progression and deterioration of AMI. Long-term compensatory activation of the Renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS) and inflammatory cytokines are important factors contributing to their occurrence.[6,7] Therefore, exploring the specific effects of LCZ696 on the recent prognosis, ventricular remodeling, and myocardial fibrosis produced by AMI is important for assessing the development of organ fibrosis and the development of optimal treatment protocols for AMI.

Studies have shown that the gold standard for assessing the condition of AMI is the degree of cardiac function impairment, and LVEF, LVEDD and SV are commonly used indicators for assessing the state of cardiac function, which can reflect the disease progression of the patient in a more intuitive way.[8] NT-proBNP levels correlate with the severity of myocardial necrosis, and are an important marker for the diagnosis of myocardial injury.[9] Gal-3 is a glycoconjugate

protein that mediates inflammatory responses involved in disease progression.[10] PIIINP mainly reflects the body's collagen metabolism and tissue fibre proliferation and can be used to assess the degree of myocardial fibrosis.[11] PWD, PWS and IVSS are commonly used indicators for assessing ventricular remodelling, and their levels are positively correlated with the progression of the patient's disease.[12] FRPE, FRR and FRI mainly reflect the ventricular ejection capacity and filling time, and the detection of their levels can be used to effectively assess the control of the disease.[13] The results of this study showed that compared with the conventional drug treatment in the control group, the observation group's cardiac function parameters, cardiac function biochemical indexes, ventricular remodelling indexes, ventricular hydrodynamic parameters and quality of life scores were further improved, and the total incidence of adverse reactions did not significantly increase, suggesting that LCZ696 effectively promotes the recovery of cardiac function and improves ventricular remodelling and quality of life in AMI patients.[14] Analysing the reasons, LCZ696 is mainly composed of two drugs, among which sacubitril belongs to enkephalinase inhibitor, which can reduce the degradation of natriuretic peptide while effectively inhibiting the secretion of enkephalinase, prompting the concentration of natriuretic peptide, which is responsible for maintaining the water-natriuretic balance of blood, to play the role of vasodilating blood vessels, lowering the blood pressure, inhibiting myocardial hypertrophy, etc., so as to improve the clinical symptoms of patients with AMI.[15] Another active ingredient, valsartan, belongs to angiotensin II receptor antagonist, which can inhibit the activity of RAAS, thus improving or blocking the adverse reactions caused by RAAS over-activation, such as water-sodium retention, collagen deposition, tissue proliferation, vasoconstriction, and thus reducing the cardiac load of patients, promoting the recovery of cardiac function, and improving the long-term prognosis and quality of life.[16]

LCZ696, a combination drug comprising sacubitril and valsartan, manifests its clinical impact on heart remodeling and function through targeted mechanisms. Sacubitril, a neprilysin inhibitor, increases levels of natriuretic peptides, including atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Elevated natriuretic peptides exert vasodilatory and diuretic effects, reducing cardiac workload and promoting fluid balance. Valsartan, an angiotensin II receptor blocker (ARB), selectively inhibits the angiotensin II type 1 receptor, mitigating vasoconstriction, sodium retention, and aldosterone release.

These components collectively contribute to anti-fibrotic effects, crucial in preventing adverse cardiac remodeling. Sacubitril's enhancement of natriuretic peptides inhibits collagen synthesis and deposition, while valsartan's blockade of the angiotensin II pathway reduces fibrosis by preventing excessive collagen production. Moreover, both sacubitril and valsartan may exhibit anti-inflammatory properties, further supporting their role in preventing chronic inflammation associated with adverse cardiac remodeling.

In the context of acute myocardial infarction (AMI), where cardiac damage is a significant concern, the anti-fibrotic and anti-inflammatory effects of LCZ696 become particularly relevant. These mechanisms not only help to alleviate the immediate consequences of AMI but also create an environment conducive to myocardial recovery. By reducing cardiac workload, promoting vasodilation, and mitigating fibrosis and inflammation, LCZ696 contributes to a more favorable milieu for the heart to recover from ischemic injury. This comprehensive understanding of the drug's mechanisms provides insights into its clinical efficacy in influencing pathways related to fibrosis, inflammation, and myocardial recovery in post-AMI patients.

It has been demonstrated that TGF-β1 in the TGF-β1/Smad3 pathway not only has the activity of inhibiting the growth of epithelial cells and inducing their apoptosis but also promotes the expression of a variety of proteins to increase the viability of fibroblasts, which contributes to the dysregulation of damage-repair of tissues and fibroinflammatory changes.[17] Smad3 is a downstream protein of TGF-β1 and is a specific effector of its signaling pathway, and together they regulate the onset and development of organ fibrosis, and one of the key features of fibrotic diseases is the over-activation of Smad3.[18] Vaskova et al.[19] showed that LCZ696 upregulates the inhibitory Smad protein Smad7, and the high expression of Smad7 has an inhibitory effect on the phosphorylation of Smad3, which can compete with the binding of TGF-β and Smad3 receptor complexes, thus blocking the TGF-β1/Smad3 signaling process. In addition, it has been shown that LCZ696 can also inhibit the expression of inflammatory cytokines, which helps to attenuate the damage caused by fibroinflammation to the myocardium.[20] The results of this study found that the total clinical effectiveness rate of the observation group was significantly higher than that of the control group. The levels of TGF-β1 and Smad3 were significantly lower than those of the control group, suggesting that LCZ696 may play the role of anti-myocardial fibrosis to improve ventricular remodeling by reducing the expression levels of TGF-β1 and Smad3 in AMI patients to inhibit the TGF-β1/Smad3 signaling pathway, and then to improve the clinical efficacy. The mechanism may be related to the antifibrotic and anti-inflammatory effects of LCZ696, but the exact mechanism needs to be further explored.

The use of LCZ696 after AMI has important practical implications in clinical practice. First, the use of LCZ696 is expected to be an important strategy to improve patient prognosis and reduce the incidence of heart failure. Since AMI can lead to myocardial damage and remodeling, LCZ696, through its anti-fibrotic and anti-inflammatory effects, is expected to slow or prevent these adverse cardiac remodeling processes, thereby reducing the risk of heart failure. This provides patients with a more comprehensive and effective treatment option. Secondly, the dual mechanisms of sacubitril and valsartan, the components of LCZ696, make it more flexible in patient selection. For those patients who are not taking antihypertensive drugs, LCZ696 can directly be used as the first choice treatment option to provide the

best therapeutic effect. Reasonable adjustments during the transition period also make LCZ696 a viable treatment option for patients already taking antihypertensive medications. This flexibility helps meet the treatment needs of diverse patient populations.

In addition, flexibility in dosing timing is also a reflection of practical significance. Early application of LCZ696 may be more helpful in preventing adverse cardiac remodeling after AMI, and therefore may have more advantages in the early treatment of AMI patients. This emphasizes individualized treatment of patients to maximize the potential benefits of LCZ696. Finally, the use of LCZ696 not only helps improve cardiac structure and function, but may also play a positive role in improving patients' quality of life. By reducing the burden on the heart, promoting blood vessel dilation and inhibiting inflammation, LCZ696 is expected to provide patients with a better life experience and reduce heart-related symptoms such as shortness of breath and fatigue.

From a clinical perspective, it is important to highlight how LCZ696 can be integrated into existing AMI treatment regimens. This includes optimization in patient selection, dosing timing, and treatment duration. The benefits on patient outcomes and quality of life also need to be studied more comprehensively to ensure that the application of LCZ696 is safe and effective and can produce actual clinical benefits in patients.

This study has several limitations, including a relatively small sample size and a retrospective design. First, the small sample size may have limited the generalizability and statistical power of the results. Therefore, the study results need to be verified in larger-scale, multi-center prospective studies to confirm the exact effect of LCZ696 in the treatment of AMI. In addition, the retrospective design may lead to information bias and incomplete data, so more prospective studies are needed to eliminate these potential effects. Another limitation is potential sources of bias not addressed in the discussion, such as selective loss to follow-up, measurement bias, and memory bias. These biases may affect the internal validity of the study and therefore require more rigorous measures to mitigate these biases when designing and conducting the study.

Future research directions include a more in-depth exploration of the mechanism of action of LCZ696, especially its specific effects on myocardial fibrosis, inflammation and myocardial repair. In addition, larger, multicenter prospective studies should be considered to validate and extend the results of the current study. This can more comprehensively evaluate the effect of LCZ696 in the treatment of AMI and provide stronger evidence for its application in clinical practice.

In conclusion, the efficacy of LCZ696 in the early post-MI period is remarkable, which can effectively improve ventricular remodeling, regulate the expression of TGF-β1 and Smad3, inhibit the TGF-β1/Smad3 signaling pathway, and promote the improvement of cardiac function and quality of life. The safety is better, which is worth promoting the clinical application. There are limitations in this study, such as a small sample size, retrospective study, insufficient follow-up, etc. The results may be biased, and large-sample prospective studies are needed to provide sufficient evidence for the treatment of AMI with LCZ696.

ETHICAL COMPLIANCE

This study has been approved by the Ethics Committee of Xingtai Third Hospital (Ethical approval number:202101LL-009). Signed written informed consent were obtained from the patients and/or guardians.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

LW and SZ designed the study and performed the experiments, YZ and JX collected the data, YD, YG and YS analyzed the data, LW and SZ prepared the manuscript. All authors read and approved the final manuscript.

FUNDING

This study did not receive any funding in any form.

REFERENCE

1. Kim Y, Bae S, Johnson TW, et al; KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health) Investigators [Link]. Role of Intravascular Ultrasound-Guided Percutaneous Coronary Intervention in Optimizing Outcomes in Acute Myocardial Infarction. *J Am Heart Assoc*. 2022;11(5):e023481. doi:10.1161/JAHA.121.023481
2. Bularga A, Taggart C, Mendusic F, et al; High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome (High-STEACS) Investigators. Assessment of Oxygen Supply-Demand Imbalance and Outcomes Among Patients With Type 2 Myocardial Infarction: A Secondary Analysis of the High-STEACS Cluster Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(7):e2220162. doi:10.1001/jamanetworkopen.2022.20162
3. Mann DL, Givertz MM, Vader JM, et al; LIFE Investigators. Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA Cardiol*. 2022;7(1):17-25. doi:10.1001/jamacardio.2021.4567
4. Zhao J, Zeng Y, Shen X. Efficacy and safety of early initiation of Sacubitril/Valsartan in patients after acute myocardial infarction: A meta-analysis. *Clin Cardiol*. 2021;44(10):1354-1359. doi:10.1002/clc.23717
5. Shang X, Xiao S, Dong N, et al. Assessing right ventricular function in pulmonary hypertension patients and the correlation with the New York Heart Association (NYHA) classification. *Oncotarget*. 2017;8(52):90421-90429. doi:10.18632/oncotarget.19026
6. Jacoby RM, Nesto RW. Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course and prognosis. *J Am Coll Cardiol*. 1992;20(3):736-744. doi:10.1016/0735-1097(92)90033-J
7. Bajaj A, Sethi A, Rathor P, Suppogu N, Sethi A. Acute Complications of Myocardial Infarction in the Current Era: diagnosis and Management. *J Investig Med*. 2015;63(7):844-855. doi:10.1097/JIM.0000000000000232
8. Mizutani Y, Ishikawa T, Nakahara S, Taguchi I. Treatment of Young Women with Acute Myocardial Infarction. *Intern Med*. 2021;60(2):159-160. doi:10.2169/internalmedicine.5883-20
9. Femia G, French JK, Juergens C, Leung D, Lo S. Right ventricular myocardial infarction: pathophysiology, clinical implications and management. *Rev Cardiovasc Med*. 2021;22(4):1229-1240. doi:10.31083/j.rcm2204131
10. Kloner RA, Dai W, Hale SL, Shi J. Approaches to Improving Cardiac Structure and Function During and After an Acute Myocardial Infarction: Acute and Chronic Phases. *J Cardiovasc Pharmacol Ther*. 2016;21(4):363-367. doi:10.1177/1074248415616187
11. Cormican DS, Sonny A, Crowley J, et al. Acute Myocardial Infarction Complicated by Cardiogenic Shock: Analysis of the Position Statement From the European Society of Cardiology Acute Cardiovascular Care Association, With Perioperative Implications. *J Cardiothorac Vasc Anesth*. 2021;35(10):3098-3104. doi:10.1053/j.jvca.2020.10.062
12. Niccoli G, Scalone G, Crea F. [Acute myocardial infarction with angiographically normal coronary arteries: what are we missing?]. *G Ital Cardiol (Rome)*. 2013;14(12):817-827. doi:10.1714/1371.15238
13. Karve AM, Bossone E, Mehta RH. Acute ST-segment elevation myocardial infarction: critical care perspective. *Crit Care Clin*. 2007;23(4):685-707, v. doi:10.1016/j.ccc.2007.07.010
14. Macas A, Krisciukaitis A, Buivydaite K, Baksyte G, Zaliunas R; [Hemodynamic studies for prediction of acute myocardial infarction outcomes]. *Medicina-Lithuania*. 2008;44(8):640-649.
15. Ye F, Li H, Chen X, et al. Efficacy and safety of sacubitril valsartan in treating heart failure with midrange ejection fraction after acute myocardial infarction in diabetic patients. *Medicine (Baltimore)*. 2022;101(5):e28729. doi:10.1097/MD.0000000000028729
16. Cabral J, Vasconcelos H, Maia-Araújo P, et al. Sacubitril/valsartan in everyday clinical practice: an observational study based on the experience of a heart failure clinic. *Cardiovasc Diagn Ther*. 2021;11(6):1217-1227. doi:10.21037/cdt-21-312
17. Zheng K, Yu J, Chen Z, et al. Ethanol promotes alcohol-related colorectal cancer metastasis via the TGF-β/RUNX3/Snail axis by inducing TGF-β1 upregulation and RUNX3 cytoplasmic mislocalization. *EBioMedicine*. 2019;50:224-237. doi:10.1016/j.ebiom.2019.11.011
18. Gao Z, Liu Z, Wang R, Zheng Y, Li H, Yang L. Galectin-3 Is a Potential Mediator for Atherosclerosis. *J Immunol Res*. 2020;2020:5284728. doi:10.1155/2020/5284728
19. Wu M, Guo Y, Wu Y, Xu K, Lin L. Protective Effects of Sacubitril/Valsartan on Cardiac Fibrosis and Function in Rats With Experimental Myocardial Infarction Involves Inhibition of Collagen Synthesis by Myocardial Fibroblasts Through Downregulating TGF-β1/Smads Pathway. *Front Pharmacol*. 2021;12:696472. doi:10.3389/fphar.2021.696472
20. Vaskova E, Ikeda G, Tada Y, Wahlquist C, Mercola M, Yang PC. Sacubitril/Valsartan Improves Cardiac Function and Decreases Myocardial Fibrosis Via Downregulation of Exosomal miR-181a in a Rodent Chronic Myocardial Infarction Model. *J Am Heart Assoc*. 2020;9(13):e015640. doi:10.1161/JAHA.119.015640