European Journal of Clinical Pharmacology (2024) 80:223–230
https://doi.org/10.1007/s00228-023-03595-0

RESEARCH

Effect of azilsartan on myocardial remodeling after acute myocardial infarction

Jing Wang[1] · Ying Ding[1] · Yi-Ren Yao[1] · Hong-Yang Liu[1] · Yang Gu[1]

Received: 8 June 2023 / Accepted: 15 November 2023 / Published online: 22 November 2023

Abstract

Purpose To investigate the effect of azilsartan on myocardial remodeling after acute myocardial infarction (AMI).

Methods A total of 200 AMI patients under percutaneous coronary intervention (PCI) were selected from the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University from Jan 2021 to Dec 2021. The subjects were randomly divided to take either azilsartan or benazepril. Serum C1q tumor necrosis factor-associated protein 1 (CTRP1) levels were detected in all subjects after admission, and the indices of left ventricular end-diastolic volume (LVEDV), left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF) were measured by using echocardiography. At the follow-up of 6 months and 1 year after PCI, the differences in CTRP1 and echocardiogram indices between the two groups were compared, and the influencing factors of myocardial remodeling after acute myocardial infarction were analyzed.

Results The levels of LVEDV and CTRP1 in all subjects at 6 months and 1 year after PCI were lower than those before discharge, and the LVEDV in the azilsartan group at 6 months and 1 year after PCI was lower than that in the benazepril group. An improvement in myocardial remodeling was obviously observed within 6 months after PCI, but the effect declined over time.

Conclusions Azilsartan can improve myocardial remodeling after acute myocardial infarction. CTRP1 may become an effective target for the prevention and treatment of myocardial remodeling after acute myocardial infarction.

Keywords Azilsartan · Myocardial remodeling after acute myocardial infarction · C1q tumor necrosis factor-associated protein 1

Introduction

Due to the aging of the population, there has been an increase in the overall incidence of heart failure (HF), with current rates estimated at approximately 5 cases per 1000 person-years among adults in Europe [1]. The global impact of this issue is significant, placing a substantial burden on both national economies and medical resources. Currently, coronary heart disease has become the most common cause of heart failure [2]. Acute myocardial infarction is a serious type of coronary heart disease, and even after percutaneous coronary intervention (PCI), the incidence of heart failure after myocardial infarction is still high. Myocardial remodeling often occurs after myocardial infarction, manifested as left ventricular volume enlargement, myocardial thinning, and even ventricular wall aneurysm formation, which is the fundamental pathological mechanism for the occurrence and development of heart failure [3]. Therefore, it is particularly important to prevent and treat complications of myocardial infarction, improve the long-term quality of life of myocardial infarction patients, and inhibit the progression of myocardial remodeling. Azilsartan is a new generation of angiotensin II receptor blockers (ARBs) with a unique oxadiazole ring molecular structure, which improves the affinity of the drug to AT1 receptors and enhances its blocking effect on AT1 receptors. As azilsartan is the 8th ARB approved for hypertension, there are few studies on the effects of azilsartan beyond lowering blood pressure. This study is aimed at exploring the role of azilsartan in improving myocardial remodeling in patients with acute myocardial infarction and providing a reference for clinical treatment and subsequent mechanistic research on myocardial remodeling after myocardial infarction.

✉ Yang Gu
guyang1028@163.com

[1] Department of Cardiology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huai'an, Jiangsu 223300, China

Methods

Subjects and grouping

Two hundred consecutive patients with ST-segment elevation myocardial infarction who were admitted to our hospital from January 2021 to December 2021 were selected. The inclusion criteria were as follows: (1) diagnosis and treatment in accordance with the "2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation" [4] and (2) emergency PCI performed after admission. This study was approved by the Ethics Committee of the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, and all study subjects signed informed consent forms. The exclusion criteria were as follows: contraindication to azilsartan/benazepril, pulmonary embolism, aortic dissection, valvular heart disease, congenital heart disease, myocarditis, malignant tumor, severe infection, severe liver and kidney dysfunction, hyperthyroidism, hypothyroidism, acute cerebrovascular accident, etc. Two interventional cardiologists from the Chest Pain Center performed emergency coronary angiography using the Judkin method on all subjects, recorded the infarction-related artery (IRA) and the time elapsed from symptom onset to the insertion of the guide wire through the IRA (referred to as "Time"), and actively performed reperfusion therapy and drug treatment according to the guidelines.

Using a concealed grouping method, the study subjects were divided into two groups of 100: the azilsartan group and the benazepril group. Patients in the azilsartan group received regular oral administration of azilsartan (40 mg qd) from admission to discharge, while patients in the benazepril group received regular oral administration of benazepril (10 mg qd) from admission to discharge. Both azilsartan and benazepril were titrated to the target dose or the maximum tolerated dose. Other treatments were in accordance with the guidelines.

Collection of clinical data and laboratory tests

The medical history and basic clinical data of the subjects, including age, sex, body mass index (BMI), blood pressure, heart rate, 18-lead electrocardiogram, history of hypertension, diabetes, and family history of coronary heart disease, were collected. Before emergency PCI, all subjects had their serum creatinine levels tested, and 5 ml of venous blood was drawn and placed in an anticoagulant tube, centrifuged at 1500 r/min, stored in a −80 °C freezer, and later tested for serum C1q tumor necrosis factor-related protein 1 (CTRP1) levels using an enzyme-linked immunosorbent assay (ELISA) kit. The fasting blood glucose (FBG) and low-density lipoprotein cholesterol (LDL-C) levels were also tested on the morning of the second day of hospitalization in a resting, seated position. All subjects were evaluated using the GRACE risk score based on age, systolic blood pressure, heart rate, serum creatinine, Killip classification at admission, cardiac arrest at admission, elevated cardiac biomarkers, and ST-segment changes on electrocardiogram. Within 24 h of admission, all subjects underwent echocardiography using the biplane method (modified Simpson) to measure left ventricular end-diastolic volume (LVEDV), left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF).

Drug treatment and follow-up

According to the guidelines, besides receiving azilsartan/benazepril, all study subjects received regular oral drug therapy from admission to discharge, including dual antiplatelet therapy, lipid-lowering drugs, and beta-blockers. Follow-up echocardiography and serum CTRP1 levels were reviewed at 6 months and 1 year after PCI.

Sample size calculation

This study was a parallel randomized controlled trial in which the experimental group received oral azilsartan and the control group received oral benazepril. The primary outcome measure in this study was the incidence of myocardial remodeling after myocardial infarction. Based on previous studies, the estimated incidence of myocardial remodeling 1 year after discharge was 30% in the benazepril group and 10% in the azilsartan group. The sample size for both the azilsartan group and the benazepril group was determined to be $N1 = N2 = 82$ cases using PASS 15 software (2-sided alpha = 0.05, beta = 0.10). Assuming a dropout rate of 10%, at least 194 cases ($N1 = N2 = 82/0.9 = 92$) are needed.

Statistical analysis

Statistical analysis was performed using SPSS 25 software. For normally distributed data, the mean ± standard deviation was used, and the independent sample *t*-test was used for comparison of quantitative data. The comparison of echocardiographic indicators and CTRP1 at different times was performed using a two-factor repeated-measures ANOVA. Count data were expressed as percentages, and the chi-square test was used for comparison. A difference was considered statistically significant at $P < 0.05$.

Table 1 Comparison of clinical and laboratory data between the azilsartan group and benazepril group

Items	Benazepril group ($n=95$)	Azilsartan group ($n=95$)	t/χ^2	P
Age (years old)	63.77 ± 8.34	65.45 ± 9.32	− 1.313	0.191
Gender (male/female)	58/37	53/42	0.542	0.462
Hypertension (*n*, %)	53 (55.8%)	55 (57.9%)	0.086	0.770
Diabetes mellitus (*n*, %)	39 (41.1%)	34 (35.8%)	0.556	0.456
Family history of CHD (*n*, %)	44 (46.3%)	48 (50.5%)	0.337	0.561
BMI (kg/m^2)	23.77 ± 2.07	23.93 ± 2.35	− 0.472	0.638
Scr (μmol/L)	66.29 ± 14.22	64.16 ± 10.61	1.167	0.245
FBG (mmol/L)	6.38 ± 1.06	6.43 ± 1.20	− 0.352	0.725
LDL-C (mmol/L)	3.31 ± 0.88	3.14 ± 0.61	1.497	0.136
Time (h)	6.40 ± 2.49	7.01 ± 2.25	− 1.769	0.079
GRACE score	156.30 ± 23.49	153.77 ± 20.58	0.790	0.431
IRA (LAD/LCX/RCA)	35/27/33	45/23/27	2.170	0.338

LAD left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery

Results

Follow-up results

As of December 2022, the follow-up work after discharge for all subjects had been completed. Among them, 5 patients were unable to continue taking azilsartan/benazepril due to low blood pressure during the follow-up period, and 5 patients dropped out due to sudden death or loss to follow-up, resulting in a total of 10 patients exiting the study. After data completeness was ensured, the final statistical analysis included 95 cases in the benazepril group and 95 cases in the azilsartan group.

Comparison of clinical data and laboratory test results

There were no statistically significant differences in age, sex, medical history (hypertension, diabetes, and family history of coronary heart disease), BMI, creatinine, FBG, LDL-C, time from onset to IRA during PCI, or GRACE score between the two groups ($P>0.05$), as shown in Table 1.

Comparison of follow-up indicators between the two groups

Through statistical analysis, it was shown that there was an interaction effect between different drug interventions and different follow-up time points on the impact of LVEDD, LVEDV, and CTRP1 ($F=4.490$, $P=0.017$; $F=3.288$, $P=0.049$; $F=3.595$, $P=0.034$, as shown in Figs. 1, 2, and 3). Therefore, separate tests were performed on the effects of different drug interventions and different follow-up time points (as shown in Table 2). Before discharge, there was no statistically significant difference in LVEDD, LVEDV, or CTRP1 between the azilsartan group and the benazepril group. However, at 6 months and 1 year after PCI, LVEDD,

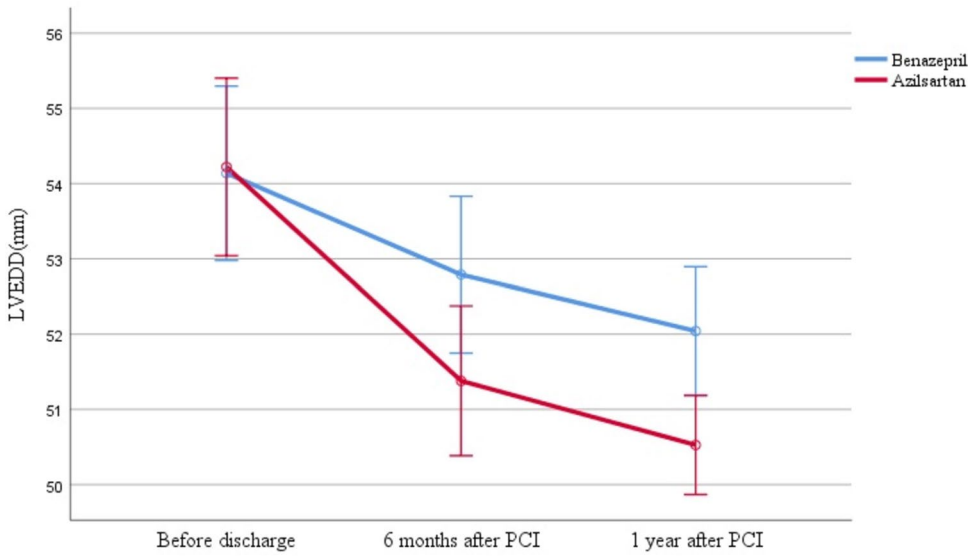

Fig. 1 Effects of different drugs and treatment times on LVEDD

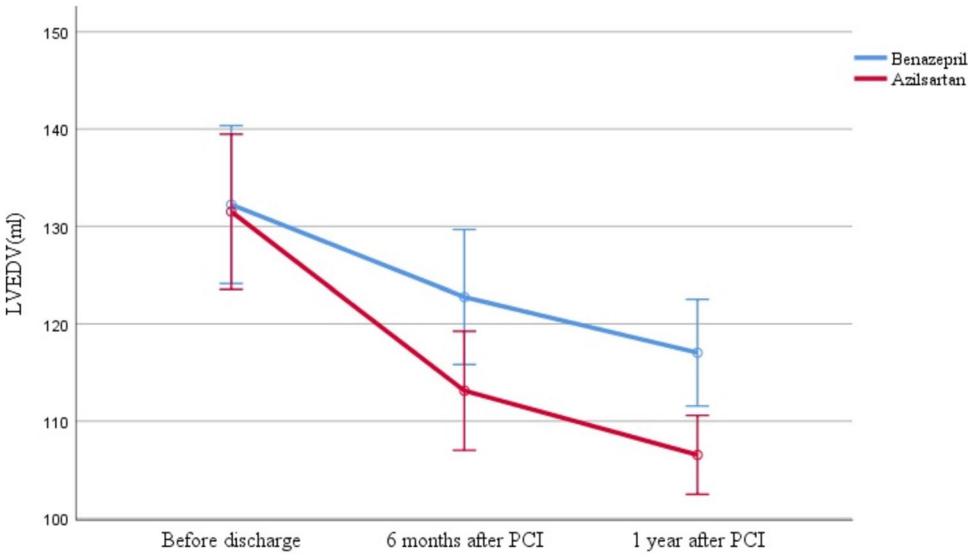

Fig. 2 Effects of different drugs and treatment times on LVEDV

LVEDV, and CTRP1 in the azilsartan group were lower than those in the benazepril group, and the difference was statistically significant. In both groups, LVEDD at 6 months and 1 year after PCI decreased compared to before discharge, and the difference was statistically significant. However, there was no statistically significant difference between 6 months and 1 year after PCI. In both groups, LVEDV and CTRP1 at 6 months and 1 year after PCI were decreased compared to before discharge, and the difference was statistically significant. Unlike LVEDD, LVEDV and CTRP1 in both groups at 1 year after PCI were further decreased compared to 6 months after PCI.

There was no interaction effect between different drug interventions and different follow-up time points on the impact of LVEF ($F = 0.929$, $P = 0.397$). Therefore, the main effect tests were performed on different drug interventions and different follow-up time points. There was no statistically significant difference in LVEF between the azilsartan group and the benazepril group at different follow-up time points. During the follow-up period, the LVEF of both groups increased significantly at 1 year after PCI compared to before discharge, while there was no statistically significant difference between 6 months after PCI and before discharge.

Analysis of factors influencing late myocardial remodeling after acute myocardial infarction

Late myocardial remodeling was defined as LVEDV at 6 months being ≥ 20% higher than the baseline [5]. There were 12 cases of late myocardial remodeling, and compared with the non-remodeling group, there were statistically

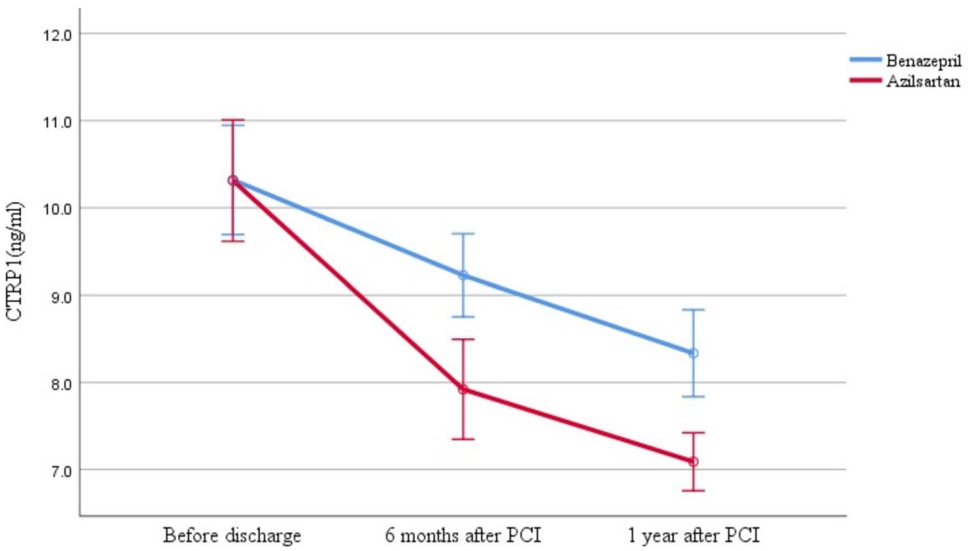

Fig. 3 Effects of different drugs and treatment times on CTRP1

Table 2 Comparison of Follow-up Indicators between the azilsartan group and benazepril group

Items	Time	Benazepril ($n=95$)	Azilsartan ($n=95$)	F	P
LVEDD	Before discharge	54.14 ± 5.69	54.22 ± 5.80	0.010	0.920
	6 months after PCI	52.79 ± 5.11^{b}	51.38 ± 4.89^{ab}	4.006	0.048
	1 year after PCI	52.04 ± 4.18^{b}	50.53 ± 3.23^{ab}	8.914	0.004
		$F_{\text{intra-group}}=15.548$, $P<0.001$	$F_{\text{intra-group}}=33.766$, $P<0.001$	$F_{\text{interaction}}=4.490$, $P=0.017$	
LVEDV	Before discharge	132.23 ± 39.83	131.50 ± 39.11	0.016	0.899
	6 months after PCI	122.75 ± 34.00^{b}	113.13 ± 30.04^{ab}	4.490	0.037
	1 year after PCI	117.04 ± 26.94^{bc}	106.53 ± 19.91^{abc}	10.364	0.002
		$F_{\text{intra-group}}=15.228$, $P<0.001$	$F_{\text{intra-group}}=32.869$, $P<0.001$	$F_{\text{interaction}}=3.288$, $P=0.049$	
LVEF	Before discharge	50.51 ± 6.80		0.043	0.836
	6 months after PCI	51.38 ± 6.30			
	1 year after PCI	52.39 ± 6.49^{b}			
		$F_{\text{time main effect}}=6.598$, $P=0.002$		$F_{\text{interaction}}=0.929$, $P=0.397$	
CTRP1	Before discharge	10.32 ± 3.08	10.31 ± 3.42	0.000	0.985
	6 months after PCI	9.23 ± 2.34^{b}	7.92 ± 2.82^{ab}	14.437	0.000
	1 year after PCI	8.33 ± 2.45^{bc}	7.09 ± 1.64^{abc}	19.399	0.000
		$F_{\text{intra-group}}=14.449$, $P<0.001$	$F_{\text{intra-group}}=47.343$, $P<0.001$	$F_{\text{interaction}}=3.887$, $P=0.026$	

[a]Compared to benazepril group, $P<0.05$

[b]compared to before discharge, $P<0.05$

[c]compared to 6 months after PCI, $P<0.05$

significant differences in the time elapsed from symptom onset to the insertion of the guide wire through the IRA, GRACE score, CTRP1 level before discharge, and the left anterior descending artery as IRA, as shown in Table 3.

Discussion

PCI has made remarkable advances in recent years due to the rapid development and adoption of new technologies and techniques. Thanks to the implementation of a regional collaborative treatment system for chest pain centers, the mortality rate of STEMI patients has been successfully reduced. However, approximately 30 to 45% of STEMI survivors progress to heart failure [6]. The HORIZONS-AMI study [7] showed that even after PCI, the incidence of heart failure in STEMI patients increased nearly twice as much as the baseline level. Although research on the treatment of heart failure has been flourishing, including the appearance of angiotensin receptor neprilysin inhibitors in recent years, the incidence of heart failure after myocardial infarction is

Table 3 Comparison of clinical and laboratory data between the late myocardial remodeling group and non-remodeling group

Items	Non-remodeling group ($n=178$)	Remodeling group ($n=12$)	t/χ^2	P
Age (years)	64.78 ± 8.92	62.08 ± 7.70	1.021	0.308
Gender (male/female)	106/72	5/7	0.836	0.361
Hypertension (n,%)	103 (57.9%)	5 (41.7%)	1.202	0.273
Diabetes mellitus (n, %)	71 (39.9%)	2 (16.7%)	1.675	0.196
Family history of CHD (n, %)	87 (48.9%)	5 (41.7%)	0.234	0.629
BMI (kg/m^2)	23.85 ± 2.22	23.80 ± 2.14	0.080	0.936
Scr (μmol/L)	65.54 ± 12.78	60.58 ± 7.57	1.325	0.187
FBG (mmol/L)	6.43 ± 1.16	6.02 ± 0.61	2.079	0.053
LDL-C (mmol/L)	3.24 ± 0.77	2.98 ± 0.66	1.143	0.254
Time (h)	6.59 ± 2.35	$8.37 \pm 2.29^{*}$	−2.533	0.012
GRACE score	154.11 ± 22.21	$168.79 \pm 14.33^{*}$	−3.292	0.005
Drugs (benazepril/azilsartan)	91/87	4/8	1.423	0.233
CTRP1 (before discharge)	10.19 ± 3.21	$12.17 \pm 3.31^{*}$	−2.059	0.041
IRA (LAD/LCX/RCA)	70/49/59	10/1/1[*]	7.810	0.016

[*]Compared to non-remodeling group, $P<0.05$

still high, and exploring its underlying mechanisms is still a research hotspot in the cardiovascular field.

At the tissue level, myocardial remodeling is characterized by myocardial cell hypertrophy, apoptosis, and increased interstitial collagen, which has important pathological and physiological significance in the progression of heart failure [8, 9] and is one of the major factors affecting the prognosis of STEMI patients. After myocardial infarction, the renin angiotensin system (RAS) in myocardial tissue is activated and mainly plays a pathological and physiological role through angiotensin II (Ang II), which can stimulate AT1 receptors [10] and induce the generation of multiple proinflammatory factors, such as IL-1, IL-6, and monocyte chemoattractant protein-1 (MCP-1), which aggravate pathological damage [11, 12]. In early animal experiments, we found that continuous infusion of Ang II in rats increased the expression of type I collagen, type III collagen, and TGF-β in the heart, significantly increased the cross-sectional area of myocardial cells, and exacerbated myocardial hypertrophy and fibrosis [13, 14]. Azilsartan acts on RAS, selectively blocking the combination of Ang II and AT1 receptors, thereby blocking the pathological processes induced by Ang II. In our study, we found that both azilsartan and benazepril can inhibit myocardial remodeling, as evidenced by the decrease in LVEDV at 6 months and 1 year after PCI compared to before discharge. However, there were significant differences in their effects on improving myocardial remodeling, as the LVEDV of the azilsartan group was lower than that of the benazepril group at 6 months and 1 year after PCI. Furthermore, there is an interactive effect between drug intervention and time. As time goes on, the improvement of drug therapy on myocardial remodeling is most evident within 6 months after PCI, with its impact decreasing thereafter. Moreover, we found that there was no statistically significant difference in LVEF between 6 months after PCI and before discharge, which may be the result of the combined effect of the Frank-Starling compensatory mechanism and myocardial remodeling process. Therefore, compared with LVEDV, measuring LVEF cannot accurately reflect the progress of myocardial remodeling.

It has been suggested that the mechanisms of myocardial remodeling after myocardial infarction include loss of myocardial cells, activation of the neuroendocrine system, inflammation, and fibrosis[15]. However, there are still no unified diagnostic criteria or classifications for myocardial remodeling based on time trends and characteristic changes. It is generally believed that myocardial remodeling after myocardial infarction can be divided into early remodeling and late remodeling. Early remodeling usually occurs within 24 to 72 h after myocardial infarction, and its mechanism is mainly due to myocardial cell necrosis and activation of neurohormones. The individual differences in late remodeling are large and can occur several months or even a year after myocardial infarction, which is related to factors including inflammatory factors [15]. According to the study of Cokkinos DV [5], we defined late myocardial remodeling as LVEDV ≥ 20% higher than baseline at 6 months. The results showed that the factors predicting late myocardial remodeling are a longer time elapsed from symptom onset to the insertion of the guide wire through the IRA, a higher GRACE score, a higher CTRP1 level before discharge, and a left anterior descending artery as the IRA, which is consistent with many other studies [16, 17]. However, there was no statistically significant difference in the occurrence of late myocardial remodeling between the azilsartan group and the benazepril group. However, we found in the study that myocardial remodeling is a dynamic and continually changing pathological process with individual differences. According to this definition standard, a large number of late remodeling patients may be incorrectly labeled as non-remodelers in the early stages after myocardial infarction and may be ignored in clinical treatment until the patient has progressed to heart failure.

There is consensus on the role of inflammation in the occurrence and development of myocardial infarction. In the acute phase of myocardial infarction, damage to myocardial cells and the extracellular matrix quickly activates the complement cascade reaction through various signaling pathways, which plays a key role in the inflammatory response of myocardial infarction [18]. In the late stage of healing in the infarct area, myocardial tissue may still be the fundamental source of the inflammatory response, mainly due to sustained ventricular wall stress (including myocardial stretch and hemodynamic load) leading to the release of various inflammatory factors, including TNF-α, IL-18, IL-6, and IL-1β [19]. The excessive generation and release of these inflammatory factors can significantly promote the process of myocardial remodeling after myocardial infarction [18]. CTRP1 is a cytokine secreted by adipose tissue, and there have been studies investigating the mechanisms by which ARB affects CTRP1. Wu et al. found that the expression of CTRP1 increases in rat heart tissue and cardiomyocytes following Ang II administration [20], while azilsartan inhibits the effects of Ang II. Moreover, research has indicated that azilsartan can reduce the levels of TNF-α and IL-1β in an inflammatory model [21], and the LPS-induced increase in CTRP1 gene expression was found to be mediated by TNF-α and IL-1β [22]. In this study, the serum CTRP1 levels of patients at 6 months and 1 year after PCI were lower than those before discharge, similar to LVEDV, and the trend of CTRP1 decrease was most significant within 6 months after PCI. These results suggest a potential connection between CTRP1 and myocardial remodeling after myocardial infarction, which is related to our previous research [23]. From animal experiments, we also found that CTRP1 worsens heart function after myocardial infarction through the TLR4 receptor on macrophages [17].

Conclusions

In summary, azilsartan may improve myocardial remodeling after myocardial infarction, which may be related to its antagonistic effect on RAS and anti-inflammatory properties. Further experimental evidence is needed to determine the specific mechanism. Targeted anti-inflammatory drugs aimed at inflammatory factors, including CTRP1, may be an effective strategy for preventing and treating myocardial remodeling after myocardial infarction. The limitations of this study include being a single-center study with a small sample size and only exploring the anti-inflammatory effects of azilsartan in myocardial remodeling after myocardial infarction at the molecular level. There is a dearth of statistical analysis on noncriminal arteries, which may have resulted in the omission of important information. Therefore, further extensive clinical studies and genomic-level basic research are needed to validate these preliminary findings.

Author contribution G.Y. contributed to the conception and design of the experiments; W.J., D.Y., and Y.Y.R. carried out the experiments; D.Y., Y.Y.R., and L.H.Y. analyzed the experimental results and revised the manuscript; and W.J. and G.Y. wrote and revised the manuscript.

Funding This study was supported by the China Heart House-Chinese Cardiovascular Association HX fund (2022-CCA-HX-008) and Innovative Key Talents' Project of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University (ZC202203).

Availability of data and material Data are available from the corresponding author upon request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University (KY-2022-137-01).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The manuscript does not contain figures or other images with personal data.

Conflict of interest The authors declare no competing interests.

References

1. McDonagh TA, Metra M, Adamo M et al (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 42(36):3599–3726
2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1789–1858
3. Lindsey ML, Hall ME, Harmancey R et al (2016) Adapting extracellular matrix proteomics for clinical studies on cardiac remodeling post-myocardial infarction. Clin Proteomics 13:19
4. Ibanez B, James S, Agewall S et al (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 39(2):119–177
5. Cokkinos DV, Belogianneas C (2016) Left ventricular remodelling: a problem in search of solutions. Eur Cardiol 11(1):29–35
6. Weir RA, McMurray JJ, Velazquez EJ (2006) Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance. Am J Cardiol 97(10a):13f–25f
7. Kelly DJ, Gershlick T, Witzenbichler B et al (2011) Incidence and predictors of heart failure following percutaneous coronary intervention in ST-segment elevation myocardial infarction: the HORIZONS-AMI trial. Am Heart J 162(4):663–670
8. Konstam MA, Kramer DG, Patel AR et al (2011) Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC Cardiovasc Imaging 4(1):98–108
9. Chen X-Y, He Y, Chen J-Y (2023) Pharmacological effects and mechanisms of Gastrodia elata and its active ingredients in the treatment of cardiovascular diseases. Tradit Med Res 8:49–54
10. Chang Y, Wei W (2015) Angiotensin II in inflammation, immunity and rheumatoid arthritis. Clin Exp Immunol 179(2):137–145
11. Marchesi C, Paradis P, Schiffrin EL (2008) Role of the renin-angiotensin system in vascular inflammation. Trends Pharmacol Sci 29(7):367–374
12. Fung ML (2014) The role of local renin-angiotensin system in arterial chemoreceptors in sleep-breathing disorders. Front Physiol 5:336
13. Gu Y, Ding Y, Zhang X et al (2022) Secreted frizzled-related protein 3 alleviated cardiac remodeling induced by angiotensin II via inhibiting oxidative stress and apoptosis in mice. Eur J Pharmacol 934:175303
14. Gu Y, Zhang S, Chen X et al (2022) LongShengZhi alleviated cardiac remodeling via upregulation microRNA-150-5p with matrix metalloproteinase 14 as the target. J Ethnopharmacol 291:115156
15. Yalta K, Yilmaz MB, Yalta T et al (2020) Late versus early myocardial remodeling after acute myocardial infarction: a comparative review on mechanistic insights and clinical implications. J Cardiovasc Pharmacol Ther 25(1):15–26
16. Zaliaduonyte-Peksiene D, Simonyte S, Lesauskaite V et al (2014) Left ventricular remodelling after acute myocardial infarction: impact of clinical, echocardiographic parameters and polymorphism of angiotensinogen gene. J Renin Angiotensin Aldosterone Syst 15(3):286–293
17. Gu Y, Hu X, Ge PB et al (2021) CTRP1 aggravates cardiac dysfunction post myocardial infarction by modulating TLR4 in macrophages. Front Immunol 12:635267
18. Westman PC, Lipinski MJ, Luger D et al (2016) Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction. J Am Coll Cardiol 67(17):2050–2060
19. Van Linthout S, Tschöpe C (2017) Inflammation - cause or consequence of heart failure or both?. Curr Heart Fail Rep 14(4):251–265
20. Wu L, Gao L, Zhang D et al (2018) C1QTNF1 attenuates angiotensin II-induced cardiac hypertrophy via activation of the AMPKa pathway. Free Radic Biol Med 121:215–230
21. de Araújo AA, Varela H, de Medeiros CA et al (2015) Azilsartan reduced TNF-α and IL-1β levels, increased IL-10 levels and

upregulated VEGF, FGF, KGF, and TGF-α in an oral mucositis model. PLoS ONE 10(2):e0116799
22. Kim KY, Kim HY, Kim JH et al (2006) Tumor necrosis factor-alpha and interleukin-1beta increases CTRP1 expression in adipose tissue. FEBS Lett 580(16):3953–3960
23. Gu Y, Zhang X, Zhang XW et al (2022) Correlation between serum Level of C1q/TNF-related protein 1 and prognosis of patients with acute ST segment elevation myocardial infarction. Mol Cardiol China 22(1):4427–4431