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Review Article

Angiotensin Receptors and Neprilysin Inhibitors on Myocardial Remodeling in Patients with Acute Myocardial Infarction after Percutaneous Coronary Intervention

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Received date: June 08, 2024; Accepted date: June 18, 2024; Published date: July 25, 2024

Citation: Yuan Cao MD, , Li Ya Wang MD Bing Bing Zheng MD, Yan Min Xu MD PhD, (2024), Angiotensin Receptors and Neprilysin Inhibitors on Myocardial Remodeling in Patients with Acute Myocardial Infarction after Percutaneous Coronary Intervention, *Clinical Research and Clinical Trials*, 10(3); **DOI:10.31579/2693-4779/211**

Abstract:

Heart failure (HF) is a leading cause of late morbidity and mortality after acute myocardial infarction worldwide. Myocardial remodeling is an important mechanism in the development of chronic heart failure. Development of the HF phenotype in these patients arise from a complex, progressive, molecular and cellular transformation called "ventricular remodeling". In this paper, the research progress of myocardial remodeling is summarized. Left ventricular remodeling is characterized by a progressive increase in both end-diastolic (LVEDV) and end-systolic volumes (LVESV). Cardium remodeling is due to an increased activity of cardiac fibroblasts in response to different soluble fibrogenic mediators. ARNI can inhibit the biological activity of brain natriuretic peptide enzyme, prevent the deactivation of natriuretic peptide and increase its concentration. The inhibition of brain natriuretic peptidase and the increase of natriuretic peptide level by ARNI is an important means to treat heart failure and fight against ventricular remodeling, and the inhibition of RAAS system over activation is also of great significance to delay myocardial remodeling. much of the observed clinical benefit of sacubitril/valsartan therapy in patients with HFrEF, HFpEF and in the post-myocardial infarction setting is likely related to significant reverse cardiac remodeling.

Keywords: angiotensin receptors; neprilysin inhibitors; myocardial remodeling; acute myocardial infarction; heart failure

1.Introduction

Heart failure (HF) is a leading cause of late morbidity and mortality after acute myocardial infarction worldwide. Nearly half of the patients with heart failure are associated with coronary heart disease [1]. The treatment of chronic heart failure has changed from emphasis on improving symptoms and quality of life to focus on prevention and delay of myocardial remodeling, reducing mortality and readmission rate [2]. Myocardial remodeling is an important mechanism in the development of chronic heart failure[3].Development of the HF phenotype in these patients arise from a complex, progressive, molecular and cellular transformation called "ventricular remodeling" First described by Tenant and Wiggers[4], ventricular remodeling includes dilation of the ventricle, the formation of scar and geometrical charges in the overall left ventricle(LV) shape (i e, ellipsoid to more spherical) and is driven, in part by neurohormonal pathways. In this paper, according to the treatment guidelines and large-scale research results, the research progress of myocardial remodeling is summarized as follows.

2. Early and late Cellular Changes of mechanisms in adverse cardiac remodeling

Remodeling begins with a acute infarct, leading to myocardial injury and death. But involves a progressive group of changes that occur in both infarcted and non-infarcted myocardia. Early changes can be seen within hours to days of an acute myocardial infarction. Myocardial necrosis result in an influx of inflammatory cells, including macrophages and other antigen-presenting cells. These processes occur early, about 3-4 hour, in the development of an acute myocardial infarction. the influx of these inflammatory cells leads to be the destruction of the collagen scaffolding that helps to maintain ventricular shape [5]. Leading to regional thinning and dilation of the myocardium in the infarcted areas. During this period, fibroblasts are also directed to the site of myocardial injury and begin to deposit a collagen matrix that contributes to scar formation in the immediate post-infarct period [6,7]. Over the following weeks to months, the viable myocardium undergoes a series of changes. Principally, given increased load on the non-infarcted myocardium, myocytes undergo eccentric hypertrophy,

further leading to LV cavity dilation. these processes are initially compensatory and aimed at preserving cardiac output in response to infarcted myocardium and the resulting non-compliant scar formation. Over time, these changes increase LV size, which causes increasing wall stress and further dilation. this process led to increase in LV end-systolic and end-diastolic volumes, increase preload dependent myocardial oxygen demand, and may ultimately promote increased areas at risk for ischemia [8]. Progressive dilation leads to further hemodynamic consequence, including the formation of possibly both ischemic and functional mitral regurgitation, which have been previously reviewed, as LV preload increases without the subsequently ability to generate sufficient myocardial contractility due to the thinning of the myocardial wall, end-systolic volumes rise and result in a depression of LV ejection fraction (EF). These processes are central to the development of ischemia-driven dilated cardiomyopathy [9].

3. Ventricular remodeling is characterized of heart failure

Left ventricular remodeling is characterized by a progressive increase in both end-diastolic (LVEDV) and end-systolic volumes (LVESV). The increase in LVESV can precede the increase in LVEDV, as a consequence of an impaired systolic function that causes a reduction in stroke volume [10]. The imaging modalities used to noninvasively assess ventricular volumes and function are echocardiography, radionuclide ventriculography, and cardiac magnetic resonance (CMR). A reduction in left ventricular ejection fraction (LVEF) is often observed during post infarct remodeling, predicting heart failure and increased mortality [11].

Ventricular remodeling accompanies different heart diseases, such as dilatative non ischemic cardiomyopathy and cardiac hypertrophy in chronic hypertension and implies a change in myocardial anatomical structure. Post infarct remodeling is a specific type of left ventricular remodeling that is a consequence of an increase in both preload and afterload causing an enlargement of ventricular chamber and a hypertrophy of normal myocardium. The increase in preload is sustained by the phenomenon of infarct expansion, which is an enlargement of infarct scar. This causes a regional increase in the ventricular volume subtended by the expanded infarcted myocardial wall. In infarcted myocardium, ventricular contraction is not symmetrical, because the necrotic segments have lost their contractility, as a result, the force generated by the normal remote myocardium during contraction is not counterbalanced by an equal and opposite force, and the infarcted ventricular wall is thus stretched by an increased wall tension that is not homogeneously distributed in the left ventricle. Infarcted wall usually has longer contraction times than the healthy remote myocardium. This wall motion defect has been recognized as a risk factor for the development of remodeling, and it can be assessed with echocardiography or cine CMR. To maintain a normal, stoke volume with a reduced number of normally working myocardial segments, the healthy myocardium has to produce a greater pressure [12]. The increase in afterload on healthy myocardium causes a hypertrophy of cardiomyocytes. In post infarct ventricular remodeling, hypertrophic cardiomyocytes are longer than normal cardiac cells. post infarct ventricular remodeling was characterized by a lengthening of cardiomyocytes especially in the area surrounding the infarct scar, but also in remote myocardium. This type of ventricular hypertrophy has been termed eccentric and contributes to the worsening of ventricular dilatation during remodeling.Cardiac hypertrophy that occurs during post infarct remodeling is accompanied by an increase in extracellular matrix, which is mainly constituted by collagen[13].

Ventricular remodeling is a predictor of heart failure, an increase of at least 20% of left ventricular end-diastolic ventricular volume (LVEDV) from the first post infarction imaging. as the first imaging study with cardiac magnetic resonance is usually performed a few days after myocardial infarction, early ventricular remodeling, which is the phase of remodeling that occurs in the first hours after myocardial infarction, could not be recognized, leading to an underestimation of the final ventricular dilatation. Also, a kind of compensatory adaptive response of the body, which changes the original shape and function of the heart due to various damage factors. After myocardial injury, the ventricular load increased. At this time, the heart function is still within the physiological range, or there is an imperceptible reduction, and the clinical manifestations and activities are not obvious. This stage is in the subclinical stage of cardiac insufficiency. With the continuous deposition of intercellular glia, the wall of the ventricles is becoming thicker and the function of the heart is decreasing. The ventricles can't shoot out the normal amount of blood to meet the normal needs of the body, and the clinical manifestations of cardiac dysfunction are gradually emerging. The patients showed decreased exercise tolerance, panting after exercise and even limited lying down, sitting upright and breathing. In the process of myocardial remodeling, the ventricular structure and function gradually changed, the ventricular ejection capacity decreased, and the ventricular ejection capacity further decreased after the relative closure of valves caused by the enlargement of cardiac cavity [14]. Especially in the case of mitral valve closure, when the whole heart is enlarged, the mitral valve is seriously and relatively incomplete, and the serious regurgitation of the mitral valve further reduces the ejection efficiency, which cannot meet the normal perfusion of the body. The symptoms of decreased peripheral perfusion were more obvious in patients with end-stage heart failure. At this time, the patient's condition is critical and the death rate is high.

4. Cardiac remodeling and different fibrogenic mediator

Cardium remodeling is due to an increased activity of cardiac fibroblasts in response to different soluble fibrogenic mediators [15], such as transforming growth factor-α(TGF-α) and systemic and local activation of renin-angiotensin aldosterone system (RAAS). The mediators of the RAAS that promote ventricular remodeling are angiotensin II and aldosterone. Remodeling is a pathologic process that involves the entire ventricle, leading to a change in its global structure. There are two types of causes of remodeling: mechanical and biochemical [16]. While mechanical causes, as previously described, are an increase in both preload and afterload, biochemical causes are linked to the production of soluble mediators capable of promoting ventricular remodeling.This causes a regional increase in the ventricular volume subtended by the expanded infarcted myocardial wall. In infarcted myocardium, ventricular contraction is not symmetrical, because the necrotic segments have lost their contractility as a result, the force generated by the normal remote myocardium during contraction is not counterbalanced by an equal and opposite force, and the infarcted ventricular wall is thus stretched by an increased wall tension that is not homogeneously distributed in the left ventricle. Infarcted wall usually has longer contraction times than the healthy remote myocardium. This wall motion defect has been recognized as a risk factor for the development of remodeling, and it can be assessed with echocardiography or cine CMR To maintain a normal stoke volume with a reduced number of normally working myocardial segments, the healthy myocardium has to produce a greater pressure [17]. The increase in workload (afterload) on healthy myocardium causes a hypertrophy of cardiomyocytes in post infarct ventricular remodeling, hypertrophic cardiomyocytes are longer than normal cardiac cells. post infarct ventricular remodeling was characterized by a lengthening of cardiomyocytes especially in the area surrounding the infarct scar, but also in remote myocardium. This type of ventricular hypertrophy has been termed eccentric and contributes to the worsening of ventricular dilatation during remodeling.Cardiac hypertrophy that occurs during post infarct remodeling is accompanied by an increase in extracellular matrix, which is mainly constituted by collagen,. This phenomenon is due to an increased activity of cardiac fibroblasts in response to different soluble fibro genic mediators, such as transforming growth factor-α(TGF-α) and systemic and local activation of renin-angiotensin aldosterone system (RAAS). The mediators of the RAAS that promote ventricular remodeling are angiotensin II and aldosterone [18].

5. Traditional drug therapy and myocardiac remodeling

As an important part of RAAS system, aldosterone has a high degree of involvement in the pathological process of myocardial remodeling. A large amount of aldosterone can be produced in patients with cardiac insufficiency

through the overactivation of RAAS system, and the amount of aldosterone production is directly proportional to the severity of cardiac insufficiency. RASS system is overactivated, which increases the excretion of potassium ions. At the same time, it interferes with the vegetative nerves and sympathetic nerves. At the same time, aldosterone can also play a role in promoting myocardial remodeling and the development of cardiac dysfunction independent of the role of angiotension II [19]. However, aldosterone is in a low level for a long time after treatment. If the drug dose is not adjusted, the concentration of aldosterone in the body will gradually increase, that is, "escape phenomenon" [20]. Therefore, it is necessary to give aldosterone receptor antagonists in time in the course of heart failure. Aldosterone receptor antagonists can be taken together with ACEI / ARB and β receptor blockers. At present, spironolactone is commonly used as an aldosterone receptor antagonist. The drug can definitely reduce the end-point event of cardiac insufficiency [21], but the specificity of the drug for the treatment target is low in the process of action, and adverse reactions such as hyperkalemia and male breast development may occur in the process of treatment. Eplidone, which was approved in 2002, has a high specificity for aldosterone receptor and can reduce the incidence of related adverse reactions [22].

Ivabradine can selectively inhibit the 4-phase automatic depolarization rate of sinoatrial node P cells, and reduce the heart rate by reducing the self-regulation of sinoatrial node. After the heart rate decreased, the diastolic period of heart beat was prolonged simultaneously, and the coronary blood supply of diastolic period was improved. Some research results show that the treatment of ivabradine reduces the incidence of acute cardiac dysfunction in the population with heart rate > 70 times / min [23]. Swedberg et al. [24] followed up for nearly 2 years, and the incidence of acute cardiac dysfunction in patients taking ivabradine was reduced by 18%. The guidelines advocate the use of β - blockers in patients with chronic heart failure with sinus tachycardia that cannot be controlled. However, there is no effective evidence or guideline for ivabradine to be used in the treatment of myocardial remodeling in patients with myocardial infarction. It may be because β - blocker is the most important role in the treatment of myocardial infarction.

Levosimendan can act on troponin, increase its sensitivity to calcium, and promote the process of myofilament sliding initiation. Compared with the original positive inotropic drugs, the drug did not aggravate myocardial injury and affect myocardial electrical activity. It is more suitable for the patients with acute myocardial infarction and cardiac insufficiency. It can reduce the occurrence of mechanical complications such as heart rupture when achieving the purpose of cardiotonic treatment. At the same time of enhancing myocardial contractility, the drug can also relax the vein via Na^+-K^+ pump to reduce the amount of returned blood. The research results of Follath et al. [25] suggest that zuoximendan can significantly improve the performance of heart failure and ejection fraction in patients with severe cardiac insufficiency. At the same time, a number of research results also show that zuoximendan has a good effect in improving the clinical symptoms and short-term prognosis of patients with chronic cardiac insufficiency [26,27]. The European heart failure guidelines recommend levosimendan for the treatment of acute heart failure [28]. Levosimendan cannot be affected by β - blocker to produce positive inotropic effect, so it can be used together with β - blocker. However, it should be noted that although the drug has a positive effect on the short-term treatment of heart failure, it does not benefit the long-term use of AMI patients. The drug is a short-term intravenous preparation, so it should not be discussed separately.

The incidence of thromboembolism in patients with chronic cardiac insufficiency is not high. Most of the patients are not given anticoagulant or antiplatelet therapy. However, most of the patients with chronic cardiac insufficiency have a "cause" and other basic heart diseases, especially in patients with acute myocardial infarction, anticoagulation and antiplatelet therapy are essential. Shaffer et al. [29] showed that there was no significant difference between warfarin and aspirin in the incidence of end-point events in these patients. In clinical work, statins can reduce the incidence of coronary heart disease, but it is not clear whether statins can improve the prognosis of patients with heart failure. A number of research results show that statins have no significant benefits for patients with cardiac dysfunction and myocardial remodeling [30,31], and the guidelines for heart failure in China do not recommend statins for the treatment of heart failure [32]. For patients with acute myocardial infarction, the improvement of myocardial blood supply is also the key point of treatment for myocardial remodeling and heart failure. Therefore, although anticoagulation, antiplatelet and lipid-lowering therapy have no direct effect on myocardial remodeling, the above drugs have special significance for the improvement of myocardial blood supply and prevention of restenosis to a large extent. However, the risk of bleeding and liver function damage during the treatment should also be closely monitored and weighed.

6. ARNI drugs therapy and ventricular remodeling

After being absorbed into human body and metabolized, sacubitril can inhibit the hydrolase that decomposes brain natriuretic peptide. When the biological activity of brain natriuretic peptide hydrolase is inhibited, it can indirectly increase the concentration of ciclosinic acid in the body, so as to have biological effects such as vasodilation, diuresis and sodium excretion, and ultimately reduce the burden on the heart and delay ventricular reconstruction. At the same time, the level of ANG-II and ET-1 can also be decomposed by brain natriuretic peptide hydrolase, which can increase the level of ang-16. Therefore, under the above-mentioned dual effects, it is of no obvious clinical significance to use only sacubitril, so it needs to be used together with ACEI / ARB drugs. As a compound preparation, sacubitrial/valsartan can inhibit the hydrolysis of brain natriuretic peptide and the biological activity of angiotension-II, antagonize the over activation of neuroendocrine system, and finally achieve the effect of vasodilation, inhibition of ventricular remodeling and reduction of heart burden [33]. ACEI and these effects play a key role in the process of myocardial remodeling. The increase of ventricular pressure can stimulate the production and release of natriuretic peptide, promote the excretion of water and sodium, reduce the myocardial pressure and slow down the process of myocardial remodeling.Although natriuretic peptide can improve cardiac function, its degradation rate is faster and its biological activity lasts for a short time[34]. Its inactivation process is closely related to the action of brain natriuretic peptidase. Brain natriuretic peptide enzyme exists in many cells, especially in the brush border of renal tubules, where natriuretic peptide is mainly inactivated. ARNI can inhibit the biological activity of brain natriuretic peptide enzyme, prevent the deactivation of natriuretic peptide and increase its concentration. McMurray and other reports showed that compared with the placebo group from the SOLVD study [35], the relative risk of cardiac end-point events in patients treated with ARNI was reduced by 43%, of which the cardiovascular mortality rate was reduced by 34%, the admission rate of heart failure was reduced by 49%, and the all-cause mortality rate was reduced by 28%. The treatment effect was clear. Because of myocardial necrosis and non-renewable, the patients with acute myocardial infarction are prone to ventricular remodeling, which seriously affects their quality of life. The inhibition of brain natriuretic peptidase and the increase of natriuretic peptide level by ARNI is an important means to treat heart failure and fight against ventricular remodeling, and the inhibition of RAAS system over activation is also of great significance to delay myocardial remodeling [36]. The synergistic effect of the two mechanisms can significantly improve the therapeutic effect. In this study, three-dimensional echocardiographic images were used to study the left ventricular lumen without geometry assumption, so the geometry and volume of the heart measured by this method are highly consistent with the real situation [37]. RT-3DE showed that ejection fraction and other related values were true and easy to operate. There was a high degree of consistency between the results of RT-3DE and MRI, and there was a high degree of consistency between the results of RT-3DE and Doppler. RT-3DE can detect left ventricular remodeling in patients with acute myocardial infarction with high accuracy. At present, the related researches at home and abroad mostly use LVEDV, LVESV, LEDVi, LVEF, LVM, LVMI and other indicators to evaluate the degree of myocardial remodeling. According to de Castro et al. [10], the indexes of LVEDV, LVESV and LVM in patients with acute myocardial infarction increased significantly, while LVEF and LVRI

decreased significantly. Therefore, the experience of myocardial remodeling in patients with acute myocardial infarction can be roughly described as follows: firstly, the compliance of myocardial necrosis with loss of blood supply is decreased, and at the same time, it is affected by intracardiac pressure. At present, there are few related experiments on the treatment of acute myocardial infarction patients with sacubitril/valsartan instead of ACEI / ARB [38].

7.New experimental rsearch with ARNI in myocardial remodeling

Brain natriuretic peptide system is also widely involved in the process of hormone regulation in patients with cardiac insufficiency. It can not only promote diuresis and vasodilation, but also inhibit the activity of RAAS and SNS system. Therefore, under the above-mentioned dual effects, it is of no obvious clinical significance to use only sacubitril, so it needs to be used together with ACEI / ARB drugs. As a compound preparation, sacubitril/valsartan can inhibit the hydrolysis of brain natriuretic peptide and the biological activity of angiotension-II, antagonize the over activation of neuroendocrine system, and finally achieve the effect of vasodilation, inhibition of ventricular remodeling and reduction of heart burden The purpose of XU et al[39] is to explore the improvement of myocardial remodeling in patients with acute myocardial infarction after short-term treatment and long-term treatment by combining with traditional ACEI drugs .85 patients with acute ST segment elevation myocardial infarction were enrolled who were treated with PCI, the patients were randomly divided into two groups: the experimental group (ARNI 25mg-100mg;BID) and the protocol group (benalapril,5-10mg; QD). Gender, height, weight, body surface area, NT Pro- BNP were collected respectively, interventricular septal thickness, septal motion amplitude, left ventricular end diastolic diameter, left ventricular end systolic diameter, posterior wall thickness, posterior wall motion amplitude, LVEF, left ventricular weight, left ventricular weight index and were collected respectively using Color Doppler echocardiography after myocardial infarction 1 month and 3 months respectively. There were 34 males and 14 females and the control group (Benalapril). There were 27 males and 10 females. Average ages are 68.6±12.6 years old. After 1 month of treatment, there was a significant difference in the end systolic diameter between the two groups. There was no statistical significance in other clinical data. three months after treatment with sacubitril/valsartan or benalapril, there were statistical differences in the indexes related to myocardial remodeling between the two groups. Three months after treatment, the indexes of myocardial remodeling in the experimental group were better than those in the benalapril group. For acute myocardial infarction patients with LVEF ≤ 50%, the treatment of ARNI is more effective than that of traditional drugs. For the patients with low left ventricular ejection fraction (LVEF ≤ 50%), most of them are anterior myocardial infarction, with large infarct area and serious myocardial damage, The cardiac function and structure were obviously abnormal. In the treatment, ARNI is better than traditional medicine. For the patients with higher left ventricular ejection fraction (LVEF > 50%), most of them are inferior myocardial infarction. The left ventricular function and structure of the patients are not seriously damaged and there is no evidence of cardiac dysfunction. After the treatment of two drugs, there was no obvious abnormality in the indexes of myocardial remodeling in this group. The indexes with statistical differences, such as the amplitude of interventricular septal motion, the end diastolic diameter of left ventricle, the end systolic diameter of left ventricle, the amplitude of posterior wall motion and LVEF, were analyzed by logistic regression. The results of multivariate logistic analysis showed that the index of left ventricular end systolic diameter was statistically significant OR=0.006 (95% CI: 0.733-0.981), Left ventricular end diastolic diameter was dependently risk of remodeling.

At present, the related researches mostly use LVEDV, LVESV, LEDVI, LVEF, LVM, LVMI and other indicators to evaluate the degree of myocardial remodeling. the indexes of LVEDV, LVESV and LVM in patients with acute myocardial infarction increased significantly, while LVEF and LVMI decreased significantly. Therefore, the experience of myocardial remodeling in patients with acute myocardial infarction can be roughly described as follows: firstly, the compliance of myocardial necrosis with loss of blood supply is decreased, and at the same time, it is affected by intracardiac pressure. At present, there are few related experiments on the treatment of acute myocardial infarction patients with sacubitril/valsartan instead of ACEI / ARB. In this study, we compared the changes of echocardiography related indexes between ACEI and sacubitril/valsartan in patients with acute myocardial infarction after 1 month and 3 months. sacubitril/valsartan has therapeutic effect on myocardial remodeling in patients with acute myocardial infarction and can improve the prognosis of cardiac function in such patients, but the treatment time is relatively short (1 month). The therapeutic effect is not significantly different from that of traditional ACEI and only has advantages on the improvement of left ventricular end systolic diameter. However, after a long time (3 months) treatment, the therapeutic effect of sacubitril/valsartan is better than that of ACEI in the treatment of myocardial remodeling in patients with acute myocardial infarction. There were significant improvement effects on the parameters such as interventricular septal motion amplitude, left ventricular end diastolic diameter, left ventricular end systolic diameter, posterior wall motion amplitude, LVEF. It may be related to the increase of brain natriuretic peptide level. In the subgroup analysis of this study, most of the patients with acute myocardial infarction whose LVEF is less than 50% are anterior wall myocardial infarction, with large infarct area and serious myocardial damage. The cardiac function and structure were obviously abnormal. After treated with sacubitril/valsartan is better than traditional medicine. Most of the patients with LVEF greater than 50% were inferior myocardial infarction. The left ventricular function and structure of the patients were not seriously damaged, and there was no evidence of cardiac insufficiency. After the treatment of two drugs, there was no obvious abnormality in the indexes of myocardial remodeling in two group.

This study [40] was to investigate the effect and mechanism of the inhibitor of Ang II receptor enkephalinase on the susceptibility to ventricular arrhythmia in rats after myocardial infarction.32 adult male Sprague Dawley rats were divided into three groups: control group, myocardial infarction group and ARNI + myocardial infarction group. Ligation of the anterior descending branch of the left coronary artery in rats resulted in myocardial infarction. After operation, the rats were given 68mg / kg / day of ARNI. At 4 weeks after myocardial infarction, all groups were evaluated for ventricular arrhythmia by electrical program stimulation and cardiac function by echocardiography. The indexes of sympathetic and cardiac remodeling were detected to further explore the mechanism. Results show the sensitivity of ARNI group was lower than that of myocardial infarction group, which was consistent with the decrease of sympathetic remodeling, the improvement of myocardial fibrosis and the expression of Cx43. ARNI can effectively reduce the ventricular arrhythmia in rats with ischemic cardiomyopathy, which is related to the reduction of sympathetic remodeling and myocardial fibrosis.

To evaluate the effect of ARNI on left ventricular remodeling and to determine the predictors of ARNI response or intolerance. 52 patients with heart failure were included in the study prospectively. Ultrasound evaluation was performed before the start of ARNI and 3 months after the optimal dose adjustment. under the treatment of Arni, some ultrasound results were significantly improved: LVEF from 32.6 ± 5 to 36 ± 6; LVED from 117 ± 40 to 108 ± 46ml, LVES from 59 ± 12 to 64 ± 13; LVEDi from 60 ± 4 to 57 ± 5; RVSP from 39 ± 10 to 32 ± 8. ARNI can significantly improve left ventricular remodeling, but has no significant effect on left ventricular diastolic or right ventricular systolic ultrasound parameters. ARNI responders showed lighter left ventricular remodeling and lower mitral regurgitation [41]. In the real world, there is insufficient evidence for the safety and effectiveness of ARNI, and the patients in the real world are often more vulnerable and more seriously ill. 452 patients were analyzed. thoes patients had higher baseline serum creatinine and B-type natriuretic peptide levels than those with Paradigm heart failure. After 12 months, 41.6% of the patients received less than half of the standard dose. Overall, the readmission rates of all-cause death, cardiovascular death and heart failure within 12 months were 3.0%, 1.1% and 6.9%, respectively. Compared with the baseline, the renal function of the patients did not change at 12 months, left ventricular ejection fraction improved (30.8% - 36.8%), BNP decreased

(777.0 - 655.8pg/ml,), uric acid decreased (7.5 - 7.1mg/dl,). ARNI is safe and effective in the real world, and left ventricular remodeling can be seen at 12 months [42]. Jorsal A[43] analyzed a single center RCT study, 182 patients were implanted with CRT, all patients received clinical evaluation and blood sampling before and 6 months after operation. At baseline and six months later, the proportion of patients with indications for ARNI and / or ivabradine in line with current guidelines was assessed. 182 patients with CRT indications, 146 (80%) also had indications to optimize drug treatment by adding ARNI and / or ivabradine at baseline. Of the 179 patients who survived for 6 months, 136 (76%) still had symptoms after the device was implanted; 51 (38%) had indications for optimal drug treatment: 37 (27%) of ARNI, 7 (5%) of ivabradine and 7 (5%) of two drugs. Seven (18%) patients had no indication of drug treatment at baseline, and the indication of drug optimization appeared six months after CRT implantation. in this study, 38% of patients with symptoms after 6 months of CRT implantation are eligible for treatment with ARNI and / or ivabradine. Patients with CRT may benefit from systematic follow-up, including optimal drug treatment. Kansas City questionnaire (KCCQ) was used to assess the health status of 3918 hfref patients in 140 centers of Champ HF study in the United States. multiple linear regression showed that the average improvement of kccq-os in patients treated with ARNI was greater in the median of 57 days. In the routine clinical practice, ARNI treatment is related to the early improvement of health status. Within 57 days, 20% of patients have experienced a very large improvement of health status [44]. The optimization of drug treatment with ARNI in patients with ICD or CRT may reduce the risk of adequate and inadequate device intervention, improve the rate of biventricular pacing in resyn Zchronous system, and improve the quality of life and prognosis [*45]*. Paragon-HF [*46]* study is a randomized, double-blind, active controlled multicenter study involving 4822 HFPEF patients, aged > 50 years, LVEF ≥ 45%, cardiac function NYHA II-IV. The inclusion criteria included an increased NT proBNP level and echocardiographic confirmed cardiac structural changes. The patients were randomly divided into two groups. According to the treatment plan shown in the figure below, one group was given valsartan, and the other group was given ARNI. The primary end points of the study were cardiovascular death and hospitalization for heart failure (including first and second hospitalization). The secondary end points included improvement of NYHA cardiac function grade, change of KCCQ clinical score, time of first deterioration of renal function and time of all-cause death. The median follow-up time for the paragon-hf study was 35 months, and the results showed a 13% reduction in the incidence of primary end points compared with valsartan with a very small difference but no significant statistical difference. The decrease in the rate of primary end point events was mainly due to the decrease in hospitalization rate of heart failure. The results showed that the incidence of the main end point events in HFPEF patients treated with ARNI was 13% lower than that in valsartan group.

Conclusions

Above, much of the observed clinical benefit of sacubitril/valsartan therapy in patients with HFrEF, HFpEF and in the post-myocardial infarction setting is likely related to significant reverse cardiac remodeling.

Acknowledgments

We thank Preepal Parpark for his support in language editing

Funding

This work was supported by Clinic Research Fund of Second Hospital of Tianjin Medical University, (CHICTR2300076092/ 2023LC05)

Authors contributions

Yanmin Xu designed the research, Yuan Cao, Liya Wang and Bingbing Zheng conducted the systematic review,data extraction and data conversion. all the authors made critical revisions to important intellectual content in the manuscript.

Conflicts of interest

None

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DOI:10.31579/2693-4779/211