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Effect of Sacubitril-Valsartan Combined with Zhenyuan Capsule in the Treatment of Chronic Heart Failure Comorbid Anxiety and Depression and Its Effect on Inflammatory Factors

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ABSTRACT

Objective: To investigate the effect of sacubitril-valsartan combined with Zhenyuan capsule in the treatment of chronic heart failure comorbid anxiety and depression and its effect on the level of inflammatory factors. Methods: A total of 106 patients with chronic heart failure comorbid anxiety and depression from February 2020 to March 2022 were continuously enrolled and divided into control group (36 cases), observation group A (36 cases) and observation group B (34 cases) according to treatment methods. All groups were given conventional treatment. On the basis of routine treatment, the control group, observation group A and observation group B were given valsartan, sacubitril-valsartan and sacubitril-valsartan plus Zhenyuan Capsules for the treatment of consecutive 8 weeks. The patients in the 3 groups were evaluated by the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) before and after treatment, and the clinical efficacy of heart failure was evaluated, and the detection of left ventricular ejection fraction (LVEF), left ventricular end systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), N terminal brain natriuretic peptide (NT-proBNP), tumor necrosis factor alpha (TNF alpha), interleukin 6 (IL-6), c-reactive protein (CRP) was conducted. Results: The clinical efficacy rate and total effective rate of heart failure in observation group A and observation group B were significantly higher than those in the control group ($P < 0.05$), and the observation group B was higher than the observation group A ($P < 0.05$); SAS and SDS scores in observation group A and observation group B were significantly lower than the control group ($P < 0.05$), and observation group B was lower than observation group A ($P < 0.05$); The LVEF in the

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three groups was all increased compared with those before treatment, and the levels of LVESD, LVEDD, NT-proBNP, TNF-*α*, IL-6, and hs-CRP were all decreased compared with those before treatment; The changes of above indexes in observation group A and observation group B were more significant than those in control group ($P < 0.05$). Except for the LVEDD index, the observation group B had significant changes compared with the observation group A ($P < 0.05$). Conclusion: Sacubitril valsartan can improve cardiac function, reduce inflammatory response, and improve anxiety and depression in patients with chronic heart failure, and the treatment effect of combination with Zhenyuan Capsule is more significant.

1. INTRODUCTION

Chronic heart failure (CHF) is caused by a variety of causes and/or abnormal changes in the heart structure. At present, with the aging of the population and the improvement of cardiovascular disease treatment technology, the incidence of heart failure is increasing day by day [1, 2] with long-term recurrent attacks; Patients suffer from both physical and psychological pressure and are prone to anxiety and depression. Negative emotions such as anxiety and depression not only significantly reduce the quality of life and treatment confidence of CHF patients, but also increase the mortality [3]. Therefore, the psychosomatic diagnosis and treatment model has received more and more attention in the treatment of CHF patients. The application of psychoactive drugs such as anti-anxiety and depression failed to improve the prognosis of cardiovascular disease [4, 5]. This study was to investigate the effect of sacubitril-valsartan combined with Zhenyuan Capsules on chronic heart failure comorbid anxiety and depression on the basis of conventional anti-heart failure treatment and the effect on serum inflammatory factor levels.

2. MATERIALS AND METHODS

2.1. Research Objects

A total of 106 patients with CHF comorbid anxiety and depression who were diagnosed and treated from February 2020 to March 2022 were consecutively included as the research objects.

2.2. Inclusion Criteria

1) Meet the Framingham diagnostic criteria for heart failure; meet the "China Heart Failure Diagnosis and Treatment Guidelines 2018" and the New York Heart Association (NYHA) cardiac function classification; 2) The total score of Self-Rating Anxiety Scale (SAS) > 50 points, and the total score of Self-Rating Depression Scale (SDS) > 53 points; 3) Age 18 - 80 years old; 4) The patients and their families gave informed consent and voluntarily signed the informed consent form.

2.3. Exclusion Criteria

1) Those with disturbance of consciousness, epilepsy, severe aphasia, and obvious sensorimotor impairment; 2) Previous history of mental illness and family history of mental illness; 3) Illiteracy or cognitive impairment; 4) Those who have recently used antipsychotics, antidepressants and alcohol dependence; 5) Combined with other types of serious organic and systemic diseases, such as acute abdomen, electrolyte disturbance, sleep apnea syndrome, organic brain disease, anemia disease, inflammatory disease, thyroid disease, respiratory system disease, Malignant tumors, fractures, blood and rheumatic diseases.

2.4. General Information

A total of 106 patients who met the inclusion criteria were divided into 3 groups according to the random number table method; There were 36 cases in the control group, 36 cases in the observation group A, and 34 cases in the observation group B. There were no significant differences in general data such as

age, gender, primary disease, comorbidities and cardiac function classification among the three groups ($P > 0.05$), as shown in Table 1.

2.5. Treatment Methods

The control group received conventional anti-heart failure therapy mainly including β-receptor blockers, aldosterone antagonists, vasodilators, diuretics, digitalis, etc. On this basis, valsartan sodium tablets were taken orally 80 mg/time, once a day, and increased to 80 mg/time, twice a day two weeks later. On the basis of conventional anti-heart failure therapy, observation group A was given sakobactri valsartan sodium tablets 50 mg/time, twice /day, and increased to 100 mg/time, twice/day two weeks later. Observation group B was added zhenyuan capsule 500 mg/time, 3 times/day on the basis of observation group A. All groups were treated for 8 weeks.

2.6. Observation Indicators and Evaluation Criteria

2.6.1. Observation Indicators

1) The changes of left ventricular ejection fraction (LVEF), left ventricular end systolic diameter (LVESD) and left ventricular end diastolic diameter (LVEDD) were measured by color Doppler echocardiography before and after treatment. 2) The following indicators were performed before and after treatment: Fasting venous blood was collected from patients, and after pretreatment to separate serum, the levels of tumor necrosis factor (TNF-α), C-reactive protein (CRP), and interleukin (IL)-6 were detected. 3) The serum N-terminal pro-brain natriuretic peptide (NT-proBNP) of the two groups of patients was detected before and after treatment, respectively.

Table 1. General information of three groups.

	Control group (n = 36)	Observation group A (n = 36)	Observation group B (n = 34)
Age (years)	66.2 ± 8.26	67.5 ± 7.60	6.8 ± 7.80
Gender (Male/female)	20/16	19/17	18/14
The primary disease			
Coronary heart disease (CHD)	16	17	16
Hypertensive heart disease (FPG, mmol/L)	12	11	10
Valvular heart disease (eGFR, mI7min)	4	5	4
Dilated cardiomyopathy	3	3	4
Arrhythmia cardiomyopathy	1	1	0
Comorbidities			
Hypertension	19	20	17
Diabetes	11	13	10
Dyslipidemia	21	24	19
Hyperuricemia	17	14	15
Cardiac function grading (NYHA)			
II	13	9	10
III	18	20	19
IV	5	7	5

Note: Comparison between groups, $P > 0.05$.

2.6.2. Evaluation of Anxiety and Depression

Before and after treatment, the researchers explained the contents of each item in the SAS and SDS scales to the patients, and instructed the patients to choose the corresponding answers according to their self-cognition. There are 20 items in total, and each item has an original score of 1 to 4 points (ie, a 4-level score). The main statistical indicator of the evaluation standard is the total score. The scores of each item are added to obtain a rough score, and then the standard score is calculated according to the formula (Total crude score × 1.25, whichever is the integer part); And evaluate the changes of depression and anxiety state of patients before and after treatment.

2.6.3. Evaluation Criteria for Clinical Efficacy of Heart Failure

The curative effects of the three groups of patients were divided into markedly effective, improved and ineffective. The effective rate and total effective rate of each group were observed; Remarkable effect: After treatment, the symptoms and signs of the patients basically disappeared, and the cardiac function grade decreased by more than 2 grades; Improvements: After treatment, the patient's symptoms and signs were significantly relieved, and the cardiac function grade was reduced by 1 grade; Ineffectiveness: After treatment, the patient's symptoms and signs were not relieved, and there was no change in cardiac function classification (marked number of cases/total number of cases × 100% = markedly effective rate; total number of cases - invalid number of cases)/total number of cases × 100% = total effective rate.

2.7. Statistical Methods

Statistical analysis was performed using SPSS 24.0 statistical software. Measurement data were expressed as (X mean ± s). Lsd-t test was used for inter-group comparison, and analysis of variance was used for multi-group data comparison. The count data were expressed as percentage (%), and comparison was performed by X2 test. $P < 0.05$ was considered as statistically significant difference.

3. RESULTS

3.1. Evaluation of Clinical Efficacy of Heart Failure

After treatment, the significant efficiency of the control group, observation group A and observation group B were 13.89%, 30.56% and 47.06%, respectively. The observation group A and B were significantly higher than the control group ($P < 0.05$), and the observation group B was significantly higher than the observation group A ($P < 0.05$). The total effective rate of control group, observation group A and observation group B was 69.44%, 83.33% and 94.12%, respectively. The total effective rate of observation group A and B was significantly higher than that of control group ($P < 0.05$), and observation group B was significantly higher than that of observation group A ($P < 0.05$). See Table 2.

3.2. Anxiety and Depression Score

Before treatment, there was no significant difference in SAS and SDS scores among 3 groups ($P > 0.05$). After treatment, observation group A and B were significantly lower than before treatment ($P < 0.05$), while control group had no significant change ($P > 0.05$); observation group B was significantly lower than observation group A ($P < 0.05$). See Table 3.

3.3. Comparison of Plasma NT-Pro BNP and Cardiac Function Indexes in Three Groups of Patients

Before treatment, there was no statistical significance in serum NT-probNP and cardiac function indexes (LVEF, LVESD, LVEDD) in 3 groups ($P > 0.05$); After treatment, there were statistically significant differences in the levels of four indexes in the 3 groups ($P < 0.05$); There were significant differences in serum NT proBNP, LVEF and LVESD between group A and group B ($P < 0.05$); There was no significant difference between LVEDD observation group B and observation group A ($P > 0.05$). See Table 4.

Table 2. Comparison of the clinical efficacy in the three patient groups [case (%)].

Group	Excellence	Effective	Ineffectiveness	Always effectively
control group (n = 36)	5 (13.89)	20 (55.56)	11 (30.56)	25 (69.44)
Observation group A (n = 36)	11 (30.56)①	19 (52.78)	6 (16.67)	30 (83.33)①
Observation group B (n = 34)	16 (47.06)①②	16 (47.06)	2 (5.88)	32 (94.12)①②

Note: ①Compared with the control group, P < 0.05; ②Compared with the observation group A, P < 0.05.

Table 3. Comparison of SAS and SDS scores between the three groups before and after treatment ($\bar{x}$ ± s).

group	SAS score		SDS score	
	Before the treatment	After treatment	Before the treatment	After treatment
The control group (n = 36)	65.1 ± 5.36	62.47 ± 5.44①	62.1 ± 8.51	59.10 ± 9.57①
Observation group A (n = 36)	66.4 ± 6.12	53.07 ± 5.59②③	61.8 ± 9.44	52.70 ± 6.84②③
Observation group B (n = 34)	66.1 ± 5.60	45.20 ± 4.40②③④	62.7 ± 7.04	45.7 ± 5.39②③④

Note: ①Compared with before treatment, P > 0.05; ②Compared with before treatment, P < 0.05; ③Compared with control group, P < 0.05; ④Compared with observation group A, P < 0.05.

Table 4. Comparison of NT-proBNP and cardiac function indexes in three groups of patients ($\bar{x}$ ± s).

(a)

	NT-proBNP (pg/L)		LVEF (%)	
	before treatment	After treatment	before treatment	After treatment
Control group (n = 36)	5285.30 ± 1112.10	1602.68 ± 192.46①	37.90 ± 3.40	43.68 ± 6.42①
Observe Group A (n = 36)	5052.24 ± 1096.26	1114.55 ± 168.68①②	38.26 ± 3.15	50.05 ± 6.10①②
Observe Group B (n = 34)	5106.16 ± 989.66	761.71 ± 141.44①②③	39.25 ± 3.07	56.94 ± 5.86①②③

Note: ①Compared with before treatment, P < 0.05; ②Compared with control group, P < 0.05; ③Compared with observation group A, P < 0.05.

(b)

Group	LVESD (mm)		LVEDD (mm)	
	before treatment	After treatment	before treatment	After treatment
Control group (n = 36)	48.56 ± 3.36	39.05 ± 2.9①	59.92 ± 4.76	54.27 ± 3.56①
Observe Group A (n = 36)	47.65 ± 4.59	40.58 ± 3.46①②	60.12 ± 5.10	49.90 ± 3.21①②
Observe Group B (n = 34)	48.35 ± 3.90	37.61 ± 3.85①②③	60.01 ± 4.85	48.63 ± 3.42①②④

Note: ①Compared with before treatment, P < 0.05; ②Compared with control group, P < 0.05; ③Compared with observation group A, P < 0.05; ④Compared with observation group A, P > 0.05.

3.4. Comparison of Serum Inflammation Indexes

There was no significant difference in the serum inflammatory indexes (CRP, TNF-*a*, IL-6) of the three patients before treatment ($P > 0.05$); After treatment, the serum inflammatory indexes of the three groups were significantly decreased (all $P < 0.05$), and the indexes of observation group B decreased more obviously, and the difference was statistically significant compared with observation group A (all $P < 0.05$). See **Table 5**.

4. DISCUSSION

The correlation between cardiovascular disease and psychological disease has been paid more and more attention by researchers; A large number of evidence-based medical evidence has proved the close relationship between their clinical manifestations and morbidity risk. With the aging of the population and the improvement of cardiovascular disease treatment technology, the incidence of heart failure is increasing [1, 2]; The research shows that the incidence of anxiety and depression in patients with CHF are 31.7% - 71% and 32.5% - 64.5% respectively, which is significantly higher than that in patients with non CHF cardiovascular disease (20.0% vs. 16.9%) [6-8]. Anxiety and depression also aggravate the development of heart failure. The two are causal, coexist and affect each other, which seriously endangers the life safety of CHF patients in my country [9-12]. In terms of treatment, anti-anxiety and depression western medicine is mainly used on the basis of anti-heart failure. Although it can improve patients' anxiety and depression symptoms in the short term, it has not been shown to improve the prognosis of patients with cardiovascular disease [4, 5], and there is poor patient compliance and some anti-anxiety and depression drugs have strong side effects, which may aggravate the underlying heart disease, thus limiting clinical application [13]. Therefore, the use of syndrome differentiation and treatment of Traditional Chinese medicine and relying on the diagnosis and treatment means of modern medicine will become the best strategy for diagnosis and treatment of double-heart disease [14].

New anti-heart failure drug-sacubitril-valsartan is the first angiotensin receptor enkephalinase inhibitor (ARNI), which is chemically combined by sacubitril and valsartan in an equimolar ratio; It has been listed as a class I recommended drug by the guidelines for heart failure in Europe, America and my country [15-17]; ARNI has 2 targets, of which valsartan belongs to the ARB class of drugs, which can inhibit the RASS system, and the in vivo effect of sacubitril Liver enzyme metabolic activity product LBQ657 is a potent inhibitor of enkephalinase [18], which can reduce the degradation of endogenous natriuretic peptides by enkephalinase and increase the concentration of natriuretic peptides; Under the dual effect of valsartan, it can regulate RASS, inhibit sympathetic nerve activity, dilate blood vessels, induce natriuresis, maintain blood pressure, inhibit myocardial fibrosis, and improve ventricular remodeling [19]. A study on the bioequivalence of Sacubitril valsartan and valsartan showed that: Valsartan in 50 mg (24/26mg), 100 mg (49/51mg) and 200 mg (97/103mg) of Sacubitril valsartan is equivalent to 40 mg, 80 mg and 160 mg of valsartan, respectively [20]. In this study, the observation of group A after treatment with Sacubitril Valsartan equivalent to the dose of valsartan in the control group showed that the clinical efficacy, total effective rate and LVEF value of observation group A were significantly higher than those of the control group ($P < 0.05$), and LVESD, LVEDd and NT proBNP were significantly lower than those of the control group ($P < 0.05$); the main reason was that sakubactri in valsartan could inhibit enkephalin enzyme. Inflammatory factors such as CRP, TNF-*a*, and IL-6 are involved in cell apoptosis and damage repair, thereby accelerating myocardial injury and aggravating the disease. Therefore, inflammatory factors also play an important role in the process of heart failure [21]. In addition, studies have shown that the levels of plasma inflammatory factors in CHF patients with anxiety and depression are significantly increased [22]. In this study, it was found that serum inflammatory indexes (CRP, TNF-*a*, IL-6), SAS and SDS scores of patients in observation group A were significantly lower than those in control group ($P < 0.05$) after treatment, indicating that Sacubitril valsartan has anti-anxiety and depression effect as well as anti-heart failure effect; and the mechanism may be inferred as follows: First, it can inhibit enkephalin enzyme, reduce the excitability of sympathetic nerve, reduce the secretion of peripheral catecholamine, restore the normal function

Table 5. Comparison of inflammatory cytokine levels before and after treatment in three groups ($\bar{x}$ ± s).

Group	CRP/(mg/L)		IL-6/(ng/L)		TNF-a/(ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 36)	28.38 ± 3.01	21.30 ± 2.10[①]	27.46 ± 3.12	21.28 ± 2.30[①]	36.19 ± 5.26 31.13 ± 3.15[①]	31.13 ± 3.15[①]
Observation group A (n = 36)	29.21 ± 2.86	16.94 ± 1.73[①②]	26.83 ± 3.07	15.04 ± 1.88[①②]	35.27 ± 6.30 23.90 ± 2. 69[①②]	23.90 ± 2.69[①②]
Observation group B (n = 34)	29.21 ± 2.96	12.94 ± 1.33[①②③]	27.20 ± 3.16	11.64 ± 1.58[①②③]	36.12 ± 5.12 18.90 ± 2.19[①②③]	18.90 ± 2.19[①②③]

Note: [①]Compared with before treatment, $P < 0.05$; [②]Compared with control group, $P < 0.05$; [③]Compared with observation group A, $P < 0.05$.

of autonomic nerve in patients with heart failure; thus correcting the secretion disorder of neurotransmitters such as norepinephrine and 5-hydroxytryptamine in the central nervous system; The second is the effect of effective anti-inflammatory factors; The third is the significant anti-heart failure effect, in the improvement of heart failure symptoms at the same time anxiety and depression symptoms can be alleviated. As a traditional Chinese medicine capsule preparation, Zhenyuan Capsule is mainly composed of total saponins of ginseng fruit, extracted from Araliaceae ginseng, which can enhance myocardial contractility, increase cardiac stroke volume, and significantly improve cardiac function; In addition, it can regulate the endocrine system and improve the autonomic state, which can effectively improve the negative emotions such as anxiety and depression in patients [23]. From the perspective of traditional Chinese medicine, Zhenyuan Capsule can greatly replenish vitality, solidify body fluid, and soothe the nerves. Replenishing the heart-energy can make blood flow smoothly, eliminate evil influence without harming the vital qi; strong heart-energy can promote the passage of the heart and pulse, improve the mind and calm the nerves, calm thinking, and finally play a role in the treatment of various symptoms of depression [24]. This study showed that observation group B was significantly better than the control group and observation group A in clinical improvement effect of cardiac function, anxiety and depression score, lowering serum inflammatory factors, NT-proBNP level and cardiac structure and function indexes except LVEDD, which further verified the anti-heart failure and anti-anxiety effects of Zhenyuan Capsules; In observation group B, the symptoms of heart failure were only slightly improved, but failed to meet the standard of improvement; Both cases were senile multivalvular disease complicated with diabetes mellitus; This kind of disease was also found in the invalid cases in observation group B and control group; The phenomenon suggests that the three different treatment methods in this study have relatively poor effects on heart failure in patients with senile multivalvular disease complicated with diabetes, and there was no significant difference between the two LVEDD observation groups, which may be related to the insufficient observation time.

Under the synergistic effect of sacubitril-valsartan and Zhenyuan capsule, the activation of the renin-angiotensin-aldosterone system (RAAS) system caused by excessive stimulation of sympathetic nerves stimulated by anxiety and depression is corrected, and reduces the harm of water and sodium retention caused by aldosterone to the heart; and weakens the pathophysiological process of heart failure; thus more conducive to the recovery of the patient's heart function.

In conclusion, on the basis of routine treatment, the combined use of Sacubitril Valsartan and Zhe-

nyuan capsule in the treatment of anxiety and depression of CHF comorbidity can effectively reduce the level of serum inflammatory factors and significantly improve the cardiac function, anxiety and depression of patients.

5. CONCLUSION

Sacubitril Valsartan can improve cardiac function, reduce inflammatory reaction, improve anxiety and depression in patients with chronic heart failure. The treatment effect combined with Zhenyuan capsule is more significant. Salkubatroxartan combined with Zhenyuan capsule has a good effect in the treatment of anxiety and depression in patients with chronic heart failure, which is worth popularizing.

6. LIMITATIONS OF THE STUDY

Due to the small amount of samples and the insufficient observation time, there are some limitations in this study. Its clinical efficacy and long-term prognosis still need further observation and research.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

REFERENCES

1. Rosamond, W., Flegal, K., Friday, G., Furie, K., Go, A., Greenlund, K., *et al.* (2007) Heart Disease and Stroke Statistics—2007 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, **115**, e69-e171. https://doi.org/10.1161/CIRCULATIONAHA.106.179918
2. Li, G., Zhu, Y., Han, N., Cao, C.L. and Li, Z.Z. (2015) Effects of Linggui Zhugan Decoction on Cardiac Function in Patients with Chronic Heart Failure. *Journal of Clinical Psychosomatic Diseases*, **21**, 27-28.
3. Lise, T.G., Lars, E.L., Imre, J., Dalen, H. and Bjerkeset, O. (2014) Symptoms of Anxiety and Depression and Risk of Heart Failure: The HUNT Study. *European Journal of Heart Failure*, **16**, 861-870. https://doi.org/10.1002/ejhf.133
4. Sinnamon, A.J.T., Tong, J.K.C., Bailey, E.A., Brown, C., Colbert, L., Murray, S., *et al.* (2018) Prospective Implementation of a Standardized Screening Protocol for Deep Venous Thrombosis in Abdominal Surgical Oncology Patients. *Journal of Surgical Oncology*, **118**, 568-573. https://doi.org/10.1002/jso.25151
5. Brouwers, C., Christensen, S.B., Damen, N.L., Denollet, J., Torp-Pedersen, C., Gislason, G.H., *et al.* (2016) Antidepressant Use and Risk for Mortality in 121, 252 Heart Failure Patients with or without a Diagnosis of Clinical Depression. *International Journal of Cardiology*, **203**, 867-873. https://doi.org/10.1016/j.ijcard.2015.11.032
6. Rutledge, T., Reis, V.A., Linke, S.E., Greenberg, B.H. and Mills, P.J. (2006) Depression in Heart Failure a Meta-Analytic Review of Prevalence, Intervention Effects, and Associations with Clinical Outcomes. *Journal of the American College of Cardiology*, **48**, 1527-1537. https://doi.org/10.1016/j.jacc.2006.06.055
7. Zhang, J., Liu, P., Lyu, R., *et al.* (2008) A Preliminary Study Comparing Different Scales to Evaluate Anxiety/depression in Patients with Heart Failure and Non-Heart Failure. *Chinese Journal of Circulation*, **23**, 120-122.
8. Chen, L., Liu, J., Zhang, J., *et al.* (2017) Research on Cognitive Emotion Regulation, Quality of Life and Anxiety

and Depression in Patients with Chronic Heart Failure. *China Circulation Journal*, **32**, 956-959.

9. Shi, X., Kang, Y., Chen, C., *et al.* (2017) Study on the Comorbidity of Anxiety and Depression and Its Related Factors in Hospitalized Patients with Heart Failure. *Journal of Sichuan University* (*Medical Edition*), **48**, 435-440.
10. Zhang, Y. and Lu, J. (2014) Effects of Anti-Anxiety and Depression Therapy on the Quality of Life of Patients with Chronic Heart Failure Complicated with Anxiety and Depression. *Chinese Medicine Guidelines*, **12**, 62-63.
11. Goldberg, D.P., Wittchen, H.U. and Zimmermann, P., *et al.* (2014) Anxious and Non-Anxious Forms of Major Depression: Familial, Personality and Symptom Characteristics. *Psychological Medicine*, **44**, 1223-1234. https://doi.org/10.1017/S0033291713001827
12. Xie, S., Zhou, T., Zhu, P., *et al.* (2017) Study on the Influencing Factors of Quality of Life in Patients with Chronic Heart Failure. *Journal of Practical Cardiovascular and Cerebrovascular Diseases*, **25**, 32-35.
13. Yang, Y. (2012) Adverse Reactions and Rational Application of Antidepressants. *Evaluation of Rational Drug Use*, **29**, 357-359.
14. Double Heart Group of Cardiovascular Disease Professional Committee of China Association of Integrative Medicine (2017) Expert Consensus on Diagnosis and Treatment of Double Heart Disease with Integrated Traditional Chinese and Western Medicine. *China General Medicine*, **20**, 1659-1662.
15. Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G.F., Coats, A.J.S., *et al.* (2016) 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Revista Espanola de Cardiologia*, **69**, 1167.
16. Yancy, C.W., Jessup, M., Bozkurt, B., Butler, J., Casey Jr., D.E., Colvin, M.M., *et al.* (2016) 2016 ACC/AHA/HFsA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of the American College of Cardiology*, **68**, 1476-1488. https://doi.org/10.1016/j.jacc.2016.05.011
17. Heart Failure Group of Cardiology Branch of Chinese Medical Association, Heart Failure Professional Committee of Chinese Medical Doctor Association and Editorial Committee of Chinese Journal of Cardiovascular Disease (2018) Guidelines for Diagnosis and Treatment of Heart Failure in China 2018. *Chinese Journal of Cardiovascular Diseases*, **46**, 760-789.
18. Gan, L., Langenickel, T., Petruck, J., Kode, K., Rajman, I., Chandra, P., *et al.* (2016) Effects of Age and Sex on the Pharmacokinetics of LCZ696, an Angiotensin Receptor Neprilysin Inhibitor. *The Journal of Clinical Pharmacology*, **56**, 78-86. https://doi.org/10.1002/jcph.571
19. Dong, X., Wang, H., Lai, L., *et al.* (2018) Clinical Study of Sacubitril-Valsartan Combined with Bisoprolol in the Treatment of Chronic Heart Failure. *Modern Medicine and Clinic*, **33**, 2791-2794.
20. Gu, J., Noe, A., Chandra, P., Al-Fayoumi, S., Ligueros-Saylan, M., Sarangapani, R., *et al.* (2010) Phamacokinetics and Pharmacodynamics of LCZ696, A Novel Dual-Acting Angiotensin Receptor-Neprilysin Inhibitor (ARNi). *The Journal of Clinical Pharmacology*, **50**, 401-414. https://doi.org/10.1177/0091270009343932
21. Wang, W. and Zhang, Z. (2019) Effects of Simvastatin Combined with Resistance Training on Cardiac Function, Silent Information Regulator 2-Related Enzyme 3 and Nuclear Transcription Factor-κB Signaling Pathway in Peripheral Blood Mononuclear Cells in Patients with Chronic Heart Failure. *Chronic Disease Prevention and Control in China*, **27**, 97-101.
22. Xia, D., Cao, J., Song, Y., *et al.* (2006) Effects of Depression on Plasma Cytokine Levels and Prognosis in Patients with Chronic Heart Failure. *Chinese Behavioral Medicine Science*, **15**, 1081-1083.
23. Duan, X., Wang, X., Xu, J., *et al.* (2014) Observation on the Efficacy of Zhenyuan Capsule in the Treatment of 42 Cases of Chronic Heart Failure with Coronary Heart Disease. *China Science and Technology of Traditional Chinese Medicine*, **21**, 192-193.

24. Carney, R.M., Freedland, K.E., Steinmeyer, B.C., Rubin, E.H. and Rich, M.W. (2018) Residual Symptoms after Treatment for Depression in Patients with Coronary Heart Disease. *Psychosomatic Medicine*, **80**, 385-392. https://doi.org/10.1097/PSY.0000000000000570