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# Study on the Comorbid Mechanism and Treatment of Coronary Heart Disease and Depression under the Framework of Bicardiac Medicine

**Xiaolong Gao[1], Junru Zhang[2,*]**

*[1]Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi, 712000, China*
*[2]Shaanxi Traditional Chinese Medicine Hospital, Xi'an, Shaanxi, 710000, China*
**Corresponding author*

***Abstract:*** *In recent years, coronary heart disease and depression are gradually becoming two diseases that endanger human health and impose a huge burden on medical care in various countries. At present, depression has become one of the risk factors of coronary heart disease, and coronary heart disease can increase the incidence of depression, both of which can be seen in the same patient. With the society entering a new era, the traditional medical model has gradually changed to the bio-psycho-social medical model, and it is particularly important to explore the co-disease mechanism of coronary heart disease and depression based on the framework of bicardiac medicine. it has important clinical significance for disease prevention, early intervention and late treatment.*

***Keywords:*** *Coronary Heart Disease, Depression, Psycho-Cardiology, Comorbidity Mechanisms, Treament*

## 1. Introduction

With the continuous deepening and expansion of reform and opening up, China's comprehensive national strength has been significantly enhanced, and the people's quality of life is also improving day by day. While pursuing material wealth, they gradually put their own health in the first place. At present, cardiovascular disease (Cardiovasculardisease, CVD) has become one of the most harmful diseases to human health, especially coronary heart disease (Coronaryheartdisease, CHD). Coronary heart disease is a kind of heart disease represented by chest tightness and chest pain caused by coronary artery stenosis, cardiomyocyte ischemia and hypoxia. Depression (Depression) is a mental illness characterized by depression, slow thinking and reduced will activity. In recent years, the incidence of the disease has increased year by year. In the past, a large number of epidemiological studies have shown that depression can not only increase the risk of coronary heart disease [1-2], but also be a predictor of poor prognosis (especially increased morbidity and mortality) of the disease [3]. Secondly, it is also found that patients with coronary heart disease are prone to depression [4]. Wynn et al. [5] first noticed a high prevalence of depression in patients with coronary heart disease in 1967, and about 40% of patients developed depression after myocardial infarction. Later, Cay et al. [6] found that after acute myocardial infarction (AMI), about 2/3 of patients showed symptoms of mild depression. Suzuk et al. [7] found that more than 25% of patients who received implanted defibrillators developed depressive symptoms. Although the prevalence of depression is different in patients with different types of coronary heart disease, it is sufficient to show that the occurrence and development of coronary heart disease is often accompanied by depression. Both coronary heart disease and depression are killers harmful to human health, so it is not only necessary to study these two diseases alone, but also to explore the nature of their co-diseases and find the internal relationship, so as to better guide the clinic. Up to now, the co-disease mechanism of coronary heart disease and depression has not been fully elucidated. This paper summarizes the epidemiology, possible co-disease mechanism and integrated traditional Chinese and western medicine treatment of coronary heart disease and depression under the framework of bicardiac medicine.

## 2. Epidemiology of Coronary Heart Disease and Depression

### *2.1. Patients with Coronary Heart Disease Are Prone to Depression*

Depression is more common in patients with coronary heart disease. Colquhoun et al. [8] have

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confirmed that about 15% of patients with coronary heart disease suffer from depression, which is almost three times that of the general population. A number of studies at home and abroad have also proved the above point of view, although there are differences between the data, which may be caused by diagnostic criteria or different races, but this fact is undeniable. Many patients with coronary heart disease lack a correct understanding of the disease, often worry about the prognosis because of one-sided, scattered language and even words, often manifested as gloomy, wishful thinking, fatigue and insomnia. Due to the long course of the disease, as time goes by, it begins to worry about the heavy medical expenses and whether it will become a burden to the family in the future. over time, these emotions surround the heart again and again, making patients have strong mood swings, anxiety, and eventually develop into depression. In the elderly, these negative emotions are more likely to occur, resulting in a significant increase in the risk of depression.

### *2.2. Patients with Depression Are More Likely to Develop Coronary Heart Disease*

Depression increases the risk of a variety of serious diseases, including coronary heart disease, stroke, cancer, renal dysfunction and diabetes [9]. Huang et al. [10] have shown that among patients diagnosed with mood disorders, the prevalence of coronary heart disease is increasing in all age groups. In a 10-year follow-up study of 388 patients with clinical depression and 404 community-matched controls, patients with depression were 2/3 more likely to develop serious physical diseases, including coronary heart disease, than those in the control group [11]. In addition, studies by Shah et al. [12] after adjusting for many personal factors, including income, education, alcohol consumption, body mass index and sedentary lifestyle, still revealed a significant correlation between severe depressive disorder and increased risk of coronary heart disease and mortality. It can be seen that depression increases the cardiovascular morbidity and mortality of patients, and the more serious the depression is, the greater the effect is [13].

The above studies have proved that there is a two-way correlation between coronary heart disease and depression, so it is particularly important to explore the hidden mechanism behind it.

## 3. Comorbid Mechanism of Coronary Heart Disease and Depression

Although epidemiology shows that there is a close relationship between coronary heart disease and depression, the pathophysiological mechanism behind this co-disease phenomenon is relatively complex, and so far, the mechanism of its co-disease has not been fully elucidated. In recent years, people have gradually recognized some possible molecular mechanisms, including inflammatory response, platelet activation, endothelial dysfunction, hypothalamus-pituitary-adrenal axis imbalance, genetic factors and others. The above mechanisms are described as follows:

### *3.1. Inflammatory Reaction*

As we all know, the markers of inflammation include C-reactive protein (C-reactive protein), interleukin-6 (Interleukin-6, IL-6) and tumor necrosis factor-α (TNF--α) and so on. Recent studies have confirmed that the increase of CRP is one of the risk factors of coronary heart disease. Other studies have proved that inflammation plays a very important role in the process of atherosclerosis. on the one hand, inflammation can destroy the stability of atherosclerotic plaque, make the plaque rupture and form thrombus in the later stage [14]. On the other hand, it directly affects myocardial contractility and promotes cell apoptosis [15]. Thus it can be seen that inflammation is very important in the pathogenesis of coronary heart disease. In addition to coronary heart disease, inflammatory reaction is also common in patients with depression. A Meta analysis of depression and inflammatory factors showed that the markers of somatic inflammation in patients with depression were increased and positively correlated with depression [16]. It has been reported that the level of CPR in patients with depression is 41% higher than that in normal people, and the level of IL-IL-6 in patients with depression is 54% higher than that in normal people [17]. In a random sample of 6126 people aged between 45 and 69 from seven towns in the Czech Republic, patients with subdepressive symptoms (CES Depression D score ≥ 1) had higher levels of plasma CRP than healthy controls [18]; in a sample of the same size in Finland, the levels of CRP in patients with severe depression measured with the Baker Depression questionnaire were higher than those in men and women ($P < 0.001$) and women ($P < 0.001$) [19]. Generally speaking, inflammation plays an important role in the pathogenesis of cardiovascular disease and / or depression, and it is likely to be the answer to bridge the two and explain their co-disease. With the further research, this mechanism may be further elucidated.

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### *3.2. Platelet Activation*

Platelets play an irreplaceable role in hemostasis, coagulation and protection of vascular walls, so when the function of platelets is abnormal, it will have serious consequences to the body. Abnormal platelet function can be induced by vascular endothelial injury or pathophysiological stimulation caused by a variety of risk factors, resulting in platelet activation, including platelet adhesion, aggregation and release. Transient calcium influx occurs when platelets are stimulated, followed by the excretion of platelet storage particles (including platelet factor 4, β-thromboglobulin, adenosine diphosphate, calcium ion and 5-hydroxytryptamine), which will promote leukocyte aggregation and enhance its adhesion to the blood vessel wall, leading to the gradual formation of thrombus, aggravating the progression of atherosclerosis, and then affecting the occurrence and development of coronary heart disease. Then, over the past decade, studies have reported that multiple steps in platelet activation and coagulation cascades are associated with depression [20]. Some studies have confirmed that the activation of platelet fibrinogen receptor integrin α II b-β 3 complex in patients with severe depression is significantly higher than that in healthy controls [21-22]. In addition, the expression of P-selectin, a marker of platelet activation, increased significantly in patients with depression after stimulation [23]. In another study, the level of platelet activation in patients with severe depression was significantly higher than that in the control group [24]. Serotonin reuptake (Selectiveserotoninreuptakeinhibitors, SSR), a commonly used antidepressant, has antiplatelet properties. After giving citalopram, fluoxetine and other drugs in clinic, it can be found that the markers of platelet activation are reduced. A domestic study confirmed that platelet volume and activity increased in patients with depression complicated with coronary heart disease [25]. It can be seen that platelet activation may be one of the co-disease mechanisms of coronary heart disease and depression.

### *3.3. Endothelial Dysfunction*

Normal endothelial cells can regulate vascular tension, maintain vascular structure, secrete anticoagulant, antiplatelet substances and fibrinolytic proteins, and have anti-inflammatory effects, which can prevent neutrophils, monocytes and other inflammatory cells from adhering to the blood vessel wall [26]. When endothelial dysfunction can lead to vasospasm, irregular contraction, myocardial ischemia may occur, which in turn leads to thrombosis and aggravates the progress of atherosclerosis. In patients with coronary heart disease, the concentration of plasma endothelin-1 was positively correlated with the score of Baker Depression scale (BeckDepressionInventory, BDI) [27]. With each increase in BDI score, the probability that the level of endothelin-1 reached or exceeded the predicted threshold of increased risk of death after acute coronary syndrome events increased by 14%. A meta-analysis found that there was a negative correlation between depression and endothelial function [28]. Further studies speculated that endothelial dysfunction in patients with depression may be related to NO production. Greaney [29] and other studies confirmed that vascular endothelial oxidative stress in patients with depression increased, and vascular endothelial dysfunction was caused by affecting NO synthesis. It can be predicted that endothelial dysfunction may be closely related to their comorbidities.

### *3.4. Hypothalamus-Pituitary-Adrenal Cortex Axis (HPA) Dysfunction*

Adrenocortical axis dysfunction and coronary heart disease are closely related to depression. When HPA is activated, the hypothalamus synthesizes and releases corticotropin-releasing hormone (Corticotropin-releasinghormone, CRH) and arginine vasopressin, which promotes the synthesis and secretion of corticotropin (Adrenocorticotrophichormone, ACTH). ACTH acts on the fasciculate zone of the adrenocortical layer to promote the synthesis and release of cortisol [14]. When the HPA axis is dysfunctional, excessive production of cortisol can increase blood pressure, enhance myocardial contractility, increase cardiac output, induce inflammation, and then lead to vascular injury and plaque accumulation, leading to the occurrence of coronary heart disease. HPA axis dysfunction has also been widely studied in depression. The concentration of cortisol in plasma, urine and cerebrospinal fluid increased in many patients with depression [30]. The concentration of plasma cortisol decreased after the clinical application of selective serotonin reuptake inhibitors. A Mata analysis of 1124 subjects showed that SSRI antidepressants could effectively reduce the level of inflammatory factors in patients with coronary heart disease complicated with depression, inhibit the further development of coronary heart disease, improve the state of depression, and significantly improve the efficacy [31]. This suggests that the HPA axis may be the mediating mechanism between coronary heart disease and depression.

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### *3.5. Genetic Factor*

Coronary heart disease and depression are complex diseases with the interaction of multiple factors. in the past, people studied the genetic pathogenesis of coronary heart disease and depression respectively, and less to explore whether there is a genetic mechanism of co-disease. So far, the genetic mechanism of the two co-diseases is not clear, it is possible that life factors and genetic factors lead to changes in the structure and function of genes. Phillips-Bute et al. [32] found that depressive patients with L-type alleles carrying the promoter sequence (5-HTTLPR) polymorphism of 5-HT transporter gene were more likely to have cardiovascular events than those with S / S type carriers. Welper et al. [33] suggested that 5-HTTLPR gene polymorphism was associated with HPA dysfunction in patients with severe depression. Support the hypothesis that 5-HTTLPR gene polymorphism and the role of HPA are important components of the pathogenesis of depression, so 5-HTTLPR gene polymorphism may be a genetic mechanism of their co-disease. In addition, some studies [34] confirmed that there is a significant correlation between inflammatory transmitters, especially IL-6, and patients with coronary heart disease with depression (PP01), which may be related to inflammatory genes. A prospective study (nasty 268) confirmed that the FKBP5 genotype is associated with depression in patients with coronary heart disease, which may lead to a common genetic risk of coronary heart disease and depression [35]. In a word, the genetic mechanism may be one of the mechanisms of their co-disease, which needs to be further explored.

### *3.6. Other Mechanisms*

Excessive reactive oxygen species (ROS) and reactive nitrogen (RON) produced by oxidative stress can cause damage to tissues and cells, induce smooth muscle differentiation into proliferative phenotype, make artery remodeling, lumen stenosis, and promote the further development of atherosclerosis. A systematic review and meta-analysis found that oxidative stress markers in MDD increased, among which 8murOH2-deoxyguanosine (8-OHdG) and F2-isoprostaglandin were the most obvious [36]. In the treatment of depressive symptoms with oxidative stress with omega-3 polyunsaturated fatty acids (n-3PUFA), it was found that the markers of oxidative stress decreased significantly, which proved the role of oxidative stress in depression. A prospective cohort study demonstrated that subclinical hypothyroidism was associated with an increased risk of CHD events and CHD death in patients with high TSH levels, especially those with 10mIU/L or higher levels of TSH [37]. Autonomic nerve dysfunction refers to the hyperfunction of sympathetic nerve and the weakening of vagus nerve function, and the sign of autonomic nerve disorder is the decrease of heart rate variability (Heartratevariability, HRV). It has been proved that HRV can be used not only as a non-invasive means to evaluate the function of autonomic nervous system, but also as a relatively independent index to judge the prognosis of many kinds of cardiovascular diseases and the occurrence of sudden death [38]. In addition, it has been noted that the level of HRV in patients with depression is significantly lower than that in healthy controls [39], but it may be due to the decrease of HRV level caused by antidepressant treatment rather than depression itself, so it is still controversial.

## 4. Treatment of Coronary Heart Disease with Depression

### *4.1. Psychological Intervention*

In the process of coronary heart disease complicated with depression, it is affected not only by social factors, but also by biological factors. Due to a variety of psychological factors of patients, the underlying emotion is glued to their own disease, which makes the current symptoms do not match with the disease itself, and is difficult to be detected by clinicians, so psychological intervention arises at the historic moment. The so-called psychological intervention refers to the use of psychological methods and techniques to reduce the mental pressure of patients to improve clinical efficacy, and then improve the prognosis and life of patients. Some studies have proved that psychological intervention can significantly reduce the degree of depression in patients with coronary heart disease complicated with depression, so as to reduce the excitability of sympathetic nerve, improve patients' clinical symptoms and improve their quality of life [40]. Thus it can be seen that psychological intervention is an important part of the treatment of both common diseases, clinical should vary from person to person, choose the most suitable methods and means to guide and reduce the emotional and psychological factors of patients.

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### *4.2. Western Medicine Treatment*

Western medicine plays an irreplaceable role in improving clinical symptoms and controlling the acute attack of the disease, and it is particularly critical to use antidepressants that vary from person to person under appropriate conditions. At present, antidepressants can be divided into monoamine oxidase inhibitors (phenylethylhydrazine, bromofaramine, isazolium, phenylcyclopropylamine), tricycles (imipramine, amitriptyline, clomipramine, doxepin), tetracycles (mianserine, maprotiline), selective serotonin reuptake inhibitors (sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram and esitalopram), SNRI and so on. Sertraline and citalopram are the preferred drugs for coronary heart disease with depression, mirtazapine and venlafaxine can be used as second-line drugs. If there are risk factors such as obesity, you can choose SSRI. If oral SSRI causes bleeding, especially in the gastrointestinal tract, consider combining proton pump inhibitors (PPI) or replacing mirtazapine or bupropion with a lower probability of bleeding. Because tricyclic antidepressants have many side effects on cardiovascular diseases, patients with coronary heart disease, especially acute coronary syndrome, should not be used.

### *4.3. Traditional Chinese Medicine Treatment*

Traditional Chinese medicine is a treasure precipitated by the Chinese nation for thousands of years. It is characterized by holistic view and dialectical argumentation, combined with many contents such as yin and yang, five elements, Zang-fu organs, etiology and pathogenesis theory, and has been continuously perfected and carried forward by doctors of all ages. Finally, traditional medicine in line with the new era has been formed, which plays an irreplaceable role in the occurrence and development of mankind. After thousands of years of continuous renewal and development, traditional Chinese medicine has a more comprehensive understanding of coronary heart disease and depression, and put forward a series of complete theoretical basis.

Coronary heart disease is called "chest arthralgia" in traditional Chinese medicine, which is characterized by chest tightness, even chest pain, wheezing and not lying down. the causes include cold evil invasion, poor diet, poor emotion, old age and body deficiency, and so on. The main pathogenesis is heart obstruction, the disease is located in the heart, involving the liver, spleen, kidney and so on. In the synopsis of the Golden Chamber, the synopsis of chest arthralgia and heartache and short qi and pulse syndrome said: the husband's pulse should be too weak, Yang micro-yin string, that is, chest arthralgia and pain, so it is extremely empty to blame it; today, Yang deficiency is known in Shangjiao, so those with chest arthralgia and heartache are also due to its yin string. Zhang Zhongjing highly summarized the etiology and pathogenesis of chest arthralgia, that is, Yang Weiyin string. Yang micro refers to deficiency of yang qi in upper jiao and weakness of heart yang, while yin string refers to qi stagnation, blood stasis, cold evil and turbid phlegm in excess of cold in lower jiao yin. The pathological changes are deficiency and excess, including deficiency and excess, while deficiency refers to qi deficiency, blood deficiency, yin deficiency and yang deficiency, while standard excess refers to qi stagnation, blood stasis, cold coagulation and phlegm turbidity caused by upper coke disease. Heart pulse loss caused by deficiency of qi and blood, yin and yang deficiency, dishonor leads to pain; qi stagnation, blood stasis, cold coagulation, phlegm turbidity and other solid and evil obstruction of heart pulse lead to pain, which is the disease. In traditional Chinese medicine, depression belongs to the category of "depression syndrome", with depression and restlessness as the main syndrome. its etiology includes emotional imbalance and physical factors, while the pathogenesis is that poor emotion leads to stagnation of liver qi and discomfort of heart qi, which gradually leads to disharmony among the five internal organs, resulting in loss of liver and catharsis, loss of healthy movement of the spleen, loss of nourishment of the heart, imbalance of qi and blood in the viscera, yin and yang of the viscera. The disease is located in the liver, which can involve the heart, spleen and kidney.

To sum up, coronary heart disease and depression have something in common in etiology and pathogenesis, and they are closely related to the heart and liver. As the saying goes in the Secret Book of Suwen Linglan: the mind is the official of the monarch, and the gods are out of the way. The man of the liver, the official of the general, is out of his mind. "Lingshu evil guest" said: "the heart is the master of the five internal organs, and the spirit is also given up." all these show that the normal exertion of the functions of all Zang-fu organs depends on the activities of the heart. The heart is located above the human body, the main blood pulse, the heart qi promotes the blood to run in the pulse in order to play the function of nourishing the whole body, if the liver is lost and the qi is not smooth, it can lead to weakness of the body fluid and blood, transfusion barrier, blood stasis is easy to cause blood stasis; the body fluid stops for drink, drink coagulation for phlegm, and Jin blood homology, phlegm as the source, blood stasis as the basis, the two influence each other, blocking the heart pulse for chest arthralgia. The Internal

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Classic of the Yellow Emperor said: "the heart is the master of the five internal organs, the heart is sad, and the heart moves, and the heart shakes all the internal organs. "The heart is the root of life, and the change of the spirit" all points out the physiological function of the heart and hidden spirit. "The theory of the six sections of the hidden image" said: "the heart is the foundation of life, and the change of God" all points out the physiological function of the heart. Xin Zang Shen means that the heart has the functions of commanding the physiological activities of the whole body, such as viscera, body, official orifices, and in charge of human consciousness, thinking, emotion and other spiritual activities. "Huang Di Nei Jing. Lingshu said, "the liver stores blood, and blood gives up the soul." Traditional Chinese medicine believes that the soul is an activity that comes into being with and accompanied by God, and it is part of the spiritual activity. As the "Tibetan elephant category of the classics" said, "the soul is the word, such as a dream in a trance, a state of change and parade." On the other hand, the liver is just dirty, the happy bar reaches and hates depression, and the main catharsis is adjustable, which makes people feel comfortable, neither excited nor depressed. If the liver is lost and catharsis, qi is not smooth, and then there is qi depression, which can induce blood stasis, turbid phlegm, dampness and other pathological products, glue for disease, hair for depression. Gu Ning [41] believes that the pathogenesis of the two diseases is based on deficiency and excess, that is, pathological pathogens such as deficiency of qi and blood, deficiency of yin and yang, phlegm, blood stasis and qi stagnation; Zhang Junping [42] believes that coronary heart disease complicated with depression is collateral deficiency or damage, and then the mind is not nourished; Li Cheng et al [43] believes that blood stasis block is one of the important pathogenesis of coronary heart disease, and puts forward that stasis and toxin depression is the core pathogenesis of coronary heart disease. Doctors of later generations cut in from different angles, combined with four diagnoses, and flexibly selected the methods of tonifying qi and invigorating the spleen, soothing the liver and relieving depression, tonifying the kidney and solid yuan, promoting blood circulation and removing blood stasis, clearing phlegm and reducing turbidity, calming the heart and mind, clearing purging and stagnant heat, and so on. Gao Denan [44] modified Xuefu Zhuyu decoction was used to treat patients with coronary heart disease complicated with mild depression. after taking Xuefuzhuyu decoction for 8 weeks, the score of Hamilton Depression scale (HAMD) was significantly lower than that in the control group, and the clinical symptoms were significantly improved. Zhu Wenxiu et al [45] self-made Shugan Yangxin decoction granule for the treatment of 30 patients with coronary heart disease complicated with depression, which can significantly improve the patients' depression, angina pectoris and other clinical symptoms. The level of hypersensitive C-reactive protein in blood after treatment was significantly lower than that before treatment. Xuan Zhihong et al [46] 42 patients with coronary heart disease with depression were treated with Shugan Jieyu decoction. After 4 weeks of treatment, the clinical symptoms and depression of the patients were significantly improved.

## 5. Conclusions

According to the current information, it is speculated that inflammatory reaction and HPA axis dysfunction are closely related to their co-disease, so they are likely to be the bridge between coronary heart disease and depression; in addition, there is evidence to directly or indirectly support the role of other mechanisms, including platelet activation, endothelial dysfunction, heredity and other mechanisms, but due to various factors, further research is needed. The discovery and elucidation of any mechanism have certain clinical significance, and it can provide a way of targeted treatment or early intervention. In the treatment of coronary heart disease with depression, no matter western medicine or traditional Chinese medicine, it has its own characteristics and can be used in clinic at the same time. As western medicine takes effect quickly in the process of acute attack of the disease, it is often the first to use such drugs, so it is necessary to master the indications and contraindications of all kinds of drugs, due to people, reasonable choice of relevant drug treatment. Traditional Chinese medicine treatment requires syndrome differentiation and treatment, comprehensive judgment of the condition of patients, as appropriate, the use of traditional Chinese medicine, acupuncture, acupoint application, exercise therapy and so on, the combination of the two drugs often has a good effect. Whether western medicine or traditional Chinese medicine treatment, patients should be advised to develop good habits, healthy diet, moderate exercise, in order to strengthen their own physical quality. Although there is a certain understanding of coronary heart disease complicated with depression, there are still many problems to be solved. First of all, although some possible co-disease mechanisms of coronary heart disease with depression have been proposed, the study of each mechanism remains to be further studied; secondly, it is not clear whether the two co-diseases are caused by one mechanism or the joint action of multiple mechanisms. finally, whether there are undiscovered mechanisms that affect the co-disease of the two need to be further explored in the future. In addition, about the treatment of the two, whether there is a new generation of antidepressant drugs or device treatment in western medicine is still an unknown, which needs to be

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found in further experiments; there are few literatures about traditional Chinese medicine in the treatment of coronary heart disease with depression, and the clinical trials involved are mainly based on small sample studies, which limits the TCM syndrome differentiation and treatment of the two diseases. Therefore, in the future, through the meticulous design of the plan, clinical observation of patients in accordance with the clinical, so as to develop a unified syndrome classification and prescription, so as to give full play to the characteristics of traditional Chinese medicine. Finally, we can be sure that there is a very close relationship between coronary heart disease and depression, and they influence each other. Whether it is the mechanism of co-disease or treatment, in the final analysis, it is an interdisciplinary understanding, which is also in line with the current concept of "two-heart medicine". Therefore, in addition to coronary heart disease with depression, there are many diseases that not only need to treat patients' physical pain, but also need to pay attention to mental health, physical and mental treatment, so as to improve the level of clinical diagnosis and treatment.

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