Medicine Character ： Z20025697

Clinical trial scheme of Xinnaoning Capsule

A randomized, double-blind, parallel-controlled, multi-center clinical trial was conducted to evaluate the efficacy and safety of Xinnaoning capsule in the treatment of chronic stable angina pectoris (Qi stagnation and blood stasis syndrome).

Unit in charge of clinical trials: Xiyuan Hospital, Chinese Academy of Traditional Chinese Medicine
Bidder: Guizhou Jingcheng Pharmaceutical Co., Ltd.
Statistical Unit: Beijing Huaxia Zhongchuang Medical Research Institute
Contract Research Organization: Beijing Duheng for Drug Evaluation and Research Co., Ltd. (DDER)
Version number: V1.1
Version date: January26, 2018

Confidentiality statement

This clinical trial scheme is a confidential document, which is only for the use of Xinnaoning capsule clinical trial researchers and the ethical committee of the experimental unit, and should not be disseminated or leaked. The reader agrees that the contents of this document shall not be disseminated and published without the written approval of the applicant, Guizhou Jingcheng Pharmaceutical Co., Ltd. The applicant requests that this document be submitted to the authorized representative of the National Drug Review and Clinical Trial Institutions in case of confidentiality.

Clinical trial scheme of Xinnaoning Capsule- Multiparty statement

1. Bidders

We have participated in discussions to revise this clinical trial program and will conscientiously fulfill the bidder's responsibilities in accordance with the "Quality Management Standards for Drug Clinical Trials". Responsible for initiating, applying, organizing, funding and investigating the clinical trial, especially providing insurance for subjects who suffer from test-related damage or death in the clinical trial, undertaking financial compensation for treatment, and providing legal guarantees to researchers.

Bidder: Guizhou Jingcheng Pharmaceutical Co., Ltd.

Address: No. 158 Gaoxin Road, Wudang District, Guiyang City Zip code：550002

Project Leader：Minghuan Luo Telephone：13891950813

2. Clinical trial institute

I will conscientiously fulfill the responsibilities of researchers in accordance with the "Standards for Quality Management of Drug Clinical Trials".

I have received the Researcher's Manual. I know the testing process of the experimental drug. I have been informed that the updated Researcher's Manual will be received in time.

I have read this program, and this experiment will be conducted in accordance with the moral, ethical and scientific principles stipulated in the Helsinki Declaration and the Chinese GCP. I agree to carry out this clinical trial in accordance with the design and provisions of this program.

I will be responsible for making clinically relevant medical decisions to ensure that patients receive timely and appropriate treatment when adverse reactions occur during the trial. I know the requirements for correct reporting of serious adverse events, and I will record and report these events as required.

I guarantee that the data will be true, accurate, complete and timely in the case report form. I will accept the inspectors or inspectors dispatched by the applicants and the inspections, inspections and inspections of the drug regulatory authorities to ensure the quality of clinical trials.

I agree that the test results will be used for drug registration and publication. I will provide a curriculum vitae to the Ethics Committee and possibly to the Pharmaceutical Administration for review before the start of the experiment.

Test Responsible Unit: Xiyuan Hospital, Chinese Academy of Traditional Chinese Medicine

Address: No. 1 Xiyuan Playground, Haidian District, Beijing

Zip code：100091

Major Researcher：Fengqin Xu Telephone：010-62835113

3. Contract Research Organization

I will conscientiously perform the duties of the inspector in accordance with the provisions of the GCP.

I have read this plan, and I will conscientiously perform the duties of supervisor in accordance with the "Standards for Quality Management of Drug Clinical Trials". I will ensure that the rights and interests of subjects in clinical trials are guaranteed, and the data recorded and reported in trials are true, accurate and complete. To ensure that the trials follow the approved program, the "Quality Management Standards for Drug Clinical Trials" and relevant regulations.

Contract Research Organization: Beijing Duheng for Drug Evaluation and Research Co., Ltd. (DDER)
Address: Building No.2603,2,2,Chaoyang North Road No.8,Chaoyang District,Beijing 100024,P.R.China
Zip code:100024
Project Leader:Chunsheng Qiao Telephone: 010-58462584

4. Data management and statistical analysis

I will conscientiously perform the duties of statisticians in accordance with the "Standards for Quality Management of Drug Clinical Trials".
Statistical Unit: Beijing Huaxia Zhongchuang Medical Science and Technology Research Institute Address: No. 401 Building, 28 Guangqu Road, Chaoyang District, Beijing.
Zip code: 100022
Statistician: Wangjun Liu Telephone: 010-58409120

Catalog

Abbreviation

Abbreviation	English full name	Chinese
AE	Adverse Event	不良事件
ALP	Alkaline Phosphatase	碱性磷酸酶
ALT	Alanine Aminotransferase	丙氨酸氨基转移酶/谷丙转氨酶
AST	Asparate Aminotransferase	门冬氨酸氨基转移酶/谷草转氨酶
BUN	Blood Urea Nitrogen	尿素氮
CFDA	China Food and Drug Administration	国家食品药品监督管理总局
HCY	Homocysteine	血同型半胱氨酸
Cr	Creatinine	肌酐
CRF	Case Report Form	病例报告表
CRO	Contract Research Organization	合同研究组织
FAS	Full Analysis Set	全分析集
GCP	Good Clinical Practice	药物临床试验质量管理规范
GGT/γ-GT	γ-Glutamyl Transpeptadase	谷氨酰转肽酶
ITT	Intention to Treat	意向性治疗
PPS	PerProtocol Set	符合方案集
QA	Quality Assurance	质量保证
QC	Quality Control	质量控制
SAE	Serious Adverse Event	严重不良事件
SOP	Standard Operating Procedures	标准操作程序
SS	Safety Analysis Set	安全性数据集

Clinical trial scheme of Xinnaoning capsule • Abstract

Title	To evaluate the efficacy and safety of Xinnaoning Capsule in treating chronic stable angina pectoris (Qi stagnation and blood stasis syndrome) with placebo as control: a randomized, double-blind, parallel controlled, multi-center clinical study
Purpose	To evaluate the efficacy and safety of Xinnaoning Capsule in the treatment of chronic stable angina pectoris (Qi stagnation and blood stasis syndrome)
Experimen-tal design	A randomized, double-blind, placebo-controlled, multi-center, efficacy test design is used.
Subject population	Subjects with chronic stable angina pectoris (qi stagnation and blood stasis syndrome)
Inclusion Criteria	1. Refer to the Guidelines for Diagnosis and Treatment of Chronic Stable Angina issued by the Chinese Medical Association in 2007, 2012ACP/ACCF/AHA/AATS/PCNA/STS (Guidelines for Diagnosis and Management of Stable Ischemic Heart Disease: American Heart Foundation/American Heart Association/American Medical Association/American Thoracic Surgery Association/American Association for Cardiovascular Preventive Nursing/American Association for Cardiovascular Angiography and Intervention/American Thoracic Association The Diagnosis of Stable Ischemic Heart Disease: Guidelines for Clinical Practice, Guidelines for the Management of Stable Coronary Artery Diseases in 2013 ESC, which can diagnose coronary heart disease in accordance with any of the following: (1) Has a clear history of old myocardial infarction, or PCI history, or bypass history; (2) Coronary angiography (results indicate at least one coronary artery stenosis with stenosis (>50%) or coronary CTA suggests stenosis with stenosis (>50%). 2. Those who met the diagnostic criteria of chronic stable angina pectoris: those who had a history of angina pectoris more than 1 month and had no significant changes in the degree, frequency, nature and inducing factors of angina pectoris; 3. The severity of angina pectoris of the Canadian Cardiovascular Society (CCS) was classified as Grade I to Grade III, and angina pectoris occurred more than twice a week. 4. The syndrome differentiation of TCM is Qi stagnation and blood stasis syndrome. 5. Age ranges from 30 to 79 years old.

	6. Sign the informed consent.
Exclusion Criteria	1. Severe cardiopulmonary insufficiency (grade III, IV, severe abnormal pulmonary function); 2. Poor control of hypertension (systolic blood pressure (> 160 mmHg) or diastolic blood pressure (> 100 mmHg) after treatment; 3. Complicated with liver and kidney function damage, ALT, AST (> 1.5 times of the upper limit of normal value), or Cr (> the upper limit of normal value), combined with hematopoietic system and other serious primary diseases; 4. Acute myocardial infarction within 3 months after interventional therapy; 5. Cardiac pacemaker; 6. Pregnancy, lactation or pregnancy planning; 7. Anaphylactic constitution or allergic to known ingredients of research drugs; 8. Chest pain caused by other causes (moderate anemia, hyperthyroidism, etc.) 9. Those who participated in other clinical drug trials within one month; 10. According to the judgement of the researchers, it is not advisable to participate in clinical researchers. 11. Other factors affecting ST-T changes in ECG, such as myocardial hypertrophy, left bundle branch block, etc.
Sample size	According to the statistical requirements, the sample size was estimated. The main effect index was the curative effect of angina pectoris symptoms treated for 12 weeks. According to the literature, the total effective rate of basic treatment plus placebo was 67.5%, and the total effective rate of basic treatment plus experimental drugs was predicted to be 84.3%. set α=0.05, 1-β=0.2, according to the experimental group: control group = 1:1 set up group, $$n = \frac{P_1\times(100-P_1)+P_2\times(100-P_2)}{(P_2-P_1)^2}\times f(a, b)$$ The minimum sample size to meet the statistical requirements was

	98.4 cases in each group, and the dropping rate was not more than 20%, 120 cases in each group, a total of 240 cases.
Effectiven-ess evaluating indicator	1. Main outcome measures: The curative effect of angina pectoris; 2. Secondary indicators: curative effect of TCM syndromes, grading changes of severity of angina pectoris, changes of attack times per week, nitroglycerin dosage, score of Seattle Angina Scale and incidence of cardiovascular events, blood HCY (blood homocysteine).
Safety evaluating indicator	1. Possible adverse reaction symptoms. 2. General physical examination items, such as body temperature, pulse, breathing, blood pressure, etc. 3. Laboratory examination: blood routine, urine routine + microscopy, stool routine + Occult blood, liver and kidney function (ALT, AST, ALP, GGT, TBIL, BUN, Cr), blood lipid (HDL-C, LDL-C, TG, CH), blood coagulation.
Dosage regimen	The induction period was 2 weeks and the treatment period was 12 weeks. Introducing period: 2 weeks, time window (+2 days). Introducing drug regimen: Both groups were given Xinnaoning capsule Simulator 3 capsules per time, 3 times per day, orally, after meals. Course of treatment: 12 weeks, time window (+4 days). Test group: Xinnaoning capsule, 3 capsules per time, 3 times per day Control group: Xinnaoning capsule Simulator 3 tablets per time, 3 times per day, oral, after meals.
Combined medication	1. In addition to experimental medication, nitroglycerin tablets can be used to alleviate symptoms when angina attacks. For drugs already used to treat coronary heart disease before inclusion, such as antiplatelet drugs, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB), statins, calcium antagonists, beta-blockers and long-acting nitrates, the original varieties and dosages can be continued without adjustment. During the study period, it is forbidden to add any other Chinese and Western medicines which have therapeutic effects on angina pectoris of coronary heart disease. 2. For the original and emerging diseases requiring drug treatment, the drug combination should be recorded in the medical record and CRF in

	detail, including the generic name of the drug, dosage and method of administration, the starting time of drug use and the reasons for its use.
Course of treatment	The induction period was 2 weeks and the medication period was 12 weeks.
Experimen-tal progress	The preliminary plan is to complete all clinical trials within 18 months from the arrival of the drug in the hospital.

Clinical trial scheme of Xinnaoning Capsule • main body

1. Test background

Coronary heart disease (CHD) is the most harmful cardiovascular disease worldwide. It is also the first cause of hospitalization and death of adult heart disease in China. Its morbidity and mortality are still on the rise. Active treatment and prevention of CHD is an important subject in medical research.

Coronary heart disease angina pectoris is a kind of heart disease caused by myocardial ischemia and anoxia caused by coronary atherosclerosis. It belongs to the category of "chest obstruction" and "heartache" in traditional Chinese medicine. The occurrence of angina pectoris is mostly related to cold pathogenic invasion, improper diet, emotional disorder, old body deficiency and other factors. The pathogenesis of "Chest Bi" is deficiency and reality, which is actually cold coagulation, Qi stagnation, blood stasis, phlegm obstruction, obstruction of chest Yang and heart vein; deficiency is deficiency of heart, spleen, liver and kidney, heart and vein dystrophy. One of its common pathogenesis is stagnation of Qi and blood stasis, blockage of blood vessels, so it should be treated by activating blood circulation and removing blood stasis, dredging channels and collaterals, as well as tranquilizing Qi and tranquilizing spirit, in order to achieve the goal of blood stasis to remove new life and nourish the blood vessels of viscera and viscera.

Xinnaoning Capsule (Z20025697), produced by Guizhou Jingcheng Pharmaceutical Co., Ltd., is mainly composed of Ginkgo biloba leaves, Salvia miltiorrhiza, Ginger fruit, Euonymus microphylla and Allium macrophylla. It has the functions of activating blood circulation, promoting Qi circulation, dredging collaterals and relieving pain. Chest stuffiness, dizziness, vertigo, symptoms: chest tightness, tingling, palpitation restlessness, dizziness and dizziness, as well as coronary heart disease, cerebral arteriosclerosis see the above symptoms. Xinnaoning Capsule has not had any adverse reactions for many years after it was put on the market.

Pharmacological research

Xinnaoning Capsule, in which Ginkgo biloba leaf is the monarch medicine, Ginkgo biloba leaf promotes blood circulation and removes blood stasis, relieves pain, is used for coronary heart disease, angina pectoris and blood stasis syndrome caused by hyperlipidemia. Salvia miltiorrhiza and Ginger fruit are the main medicines. Among them, Salvia miltiorrhiza has good effect on promoting blood circulation and removing blood stasis, cooling blood and tranquilizing mind, and has good effect on all diseases caused by blood stasis, especially on heart and brain blood stasis

syndrome. In addition, Salvia miltiorrhiza can cool blood and calm the nerves. It has good effect on palpitation and insomnia in the above diseases. Ginger has the function of dispelling cold in warmth, regulating qi and relieving pain. The combination of the two medicines can not only promote blood circulation, but also regulate qi. Qixing can promote blood circulation and remove blood stasis. Populus microphylla and Allium macrophylla were used as adjuvants. Effectiveness of Euonymus microphylla is promoting qi and blood circulation, dredging collaterals and relieving pain. It is used for chest pain, heart pain and coronary heart disease caused by qi stagnation and blood stasis. The effect of Xiebai can regulate qi, broaden chest, promote Yang and disperse. It is used to treat thoracic paralysis and heartache. "Compendium of Materia Medica" says that it can "treat Shaoyin disease, syncope, diarrhea, and chest pain. These two medicines have the functions of regulating qi, promoting blood circulation and strengthening the functions of activating blood circulation, regulating qi and stasis of other medicines. The above medicines are mainly used to promote blood circulation, supplemented by regulating qi. Regulating Qi helps to promote blood circulation. Promoting blood circulation helps to promote qi circulation, blood stasis, meridians and collaterals, and all kinds of symptoms go by themselves to treat chest pain, stroke, stroke, dizziness and other diseases caused by qi stagnation and blood stasis, blockage of blood vessels.

Modern pharmacology shows that flavonoids and terpene lactones are effective components of Ginkgo biloba leaves. Experiments show that flavonoids and terpene lactones are beneficial to blood vessel and brain metabolism and inhibit platelet activating factor. Ginkgolides and ginkgolides can significantly improve the oxygen tolerance of brain cells and enhance local brain flow. Ginkgolides have a strong neuroprotective effect. Salvia miltiorrhiza can inhibit platelet aggregation, dilate coronary artery, increase the opening of collateral circulation, improve myocardial hypoxia, and also have good scavenging effect of oxygen free radicals. The experiment of Gingeria officinalis L. showed that Gingeria officinalis L. oil could reduce the area of myocardial infarction and the level of serum lactate dehydrogenase after myocardial infarction. It has protective effect on myocardial ischemia. It can also slow down the systolic and diastolic blood pressure, slow down the heart rate and reduce the cardiac output. Allium sibiricum can inhibit platelet aggregation and reduce serum lipid peroxide and blood lipid. Euonymus microphylla can dilate coronary artery, improve myocardial ischemia and reduce oxygen consumption.

Previous clinical trials

1. To observe the clinical effect of Xinnaoning Capsule on angina pectoris of coronary heart disease of qi stagnation and blood stasis type.

From February 2011 to October 2011, Xinnaoning was observed in 309 Hospital

of PLA. Methods: 182 patients with angina pectoris of qi stagnation and blood stasis type were randomly divided into treatment group (102 cases) and control group (80 cases). The control group was treated with routine treatment group (isosorbide mononitrate tablets, aspirin enteric-coated tablets, 100 mg each time, once a day). The treatment group was treated with routine treatment in the control group. Xinnaoning capsule was taken three times a day for 8 weeks. The results are as follows:

Table1 Comparison of improvement effect of angina pectoris between two groups n (%)

Group	n	Markedly effective	effective	invalid	total effective rate
Test	102	34（33.3）	52（51）	16（15.7）	86（84.3）
Control	80	26（32.5）	28（35）	24（32.5）	56（67.5）

There were significant differences between groups.，P＜0.05

Table2 Comparison of the curative effect of TCM syndromes improvement between two groups before and after treatment

Symptom	Group	n	ME	effetive	invalid	TER（%）
Chest pain	T	102	36	56	12	92（92.2）
	C	80	19	44	17	63（78.7）
Chest tightness	T	102	42	50	10	92（90.2）
	C	80	20	42	18	62（77.5）
palpitation	T	102	34	54	14	88（86.2）
	C	80	18	43	19	61（76.3）
pant	T	102	32	49	21	81（79.4）
	C	80	20	35	25	55（68.7）
dizzy	T	102	36	54	12	90（88.2）
	C	80	15	23	42	38（47.5）
headache	T	102	32	47	22	79（77.4）
	C	80	7	27	46	34（42）

Note: Chest pain, palpitation and other symptoms of the two groups were significantly improved after treatment. The treatment group had significant effect on improving chest tightness, chest pain, dizziness, headache and other clinical symptoms, compared with the control group, P＜0.01.T=test group,C=control roup,ME= Markedly effective,TER= total effective rate

Table3 Comparison of ECG changes before and after treatment in two groups

Group	n	ME	effective	invalid	TER（%）
T	102	39	38	25	76（74.5）
C	80	31	27	22	58 （72.5）

Note: After treatment, ECG in both groups improved, but there was no significant difference between the two groups.

The clinical results showed that the total effective rate of angina pectoris in the treatment group was better than that in the control group, especially in improving the symptoms of chest pain, chest tightness, dizziness and headache. There were no significant changes in blood pressure and heart rate before and after treatment, and no obvious adverse reactions during treatment, suggesting that the drug is safe. It is an effective and safe drug for the treatment of coronary heart disease and angina pectoris.

2. Evaluation of Xinnaoning Capsule in the Treatment of Angina Pectoris after Coronary Stent Implantation

From June 2012 to June 2014, the cardiovascular disease center of Xiyuan Hospital, Chinese Academy of Traditional Chinese Medicine was studied. Methods: 160 patients with recurrent angina pectoris after coronary artery stent implantation were randomly divided into treatment group (80 cases) and control group (80 cases). The course of treatment was 8 weeks. Control group: aspirin enteric-coated tablets 100mg, once a day, isosorbide mononitrate tablets 20mg, twice a day, atorvastatin calcium tablets 20mg, once a day. Treatment group: On the basis of the control group, Xinnaoning capsule was added, three capsules each time, three times a day. The results are as follows:

Table 4 Comparison of curative effect of angina pectoris between two groups (%)

Group	ME	effective	invalid	TER
T	28（35.00）	41（51.25）	11（13.75）	69（86.25）
C	19（23.75）	30（37.50）	31（38.75）	49（61.25）

Note: Compared with the control group, P＜0.05

Table 5 Comparison of curative effect of TCM syndromes between two groups (%)

Group	Chest pain			
	ME	effective	invalid	TER
Test（n=80）	26（32.50）	45（56.25）	9 （11.25）	71（88.75）
Control（n=80）	19 （23.75）	32（40.00）	29（36.25）	51（63.75）

Group	Chest tightness			
	ME	effective	invalid	TER
Test（n=80）	26（32.50）	46（57.50）	8 （10.00）	72（90.00）
Control（n=80）	28（22.50）	35（43.75）	27（33.75）	53（66.25）

Group	pant			
	ME	effective	invalid	TER
Test（n=80）	24（32.50）	48（60.00）	8 （10.00）	72（90.00）
Control（n=80）	18（22.50）	34（42.50）	28（35.00）	52（65.00）

Group	palpitation			
	ME	effective	invalid	TER
Test（n=80）	22（27.50）	48（60.00）	10 （12.50）	70（87.50）
Control（n=80）	17（21.25）	34（42.50）	29（36.25）	51（63.75）

Note: Compared with the control group，p＜0.05

Table 6 Comparison of ECG changes after treatment between two groups (%)

Test	（n=80）	18（22.50）	39（48.75）	23（28.75）	57（71.25）
Cntrol	（n=80）	16（20.00）	35（47.50）	29（36.25）	51（63.75）

Note: Compared with the control group，P＜0.05

Studies have confirmed that Xinnaoning Capsule has a good clinical effect on angina pectoris patients after coronary artery stent implantation by improving myocardial microcirculation, promoting the opening of collateral circulation, inhibiting platelet aggregation, lowering blood lipid and stabilizing platelet. There were no significant changes in ECG, blood pressure and heart rate before and after treatment, and no obvious adverse reactions during treatment, suggesting that the drug is safe.

For many years after Xinnaoning capsule was put on the market, no adverse reactions were recorded in the literature. This experiment completes the clinical trial of Xinnaoning Capsule in treating chronic stable angina pectoris (Qi stagnation and blood stasis syndrome), and objectively evaluates its clinical efficacy and safety.

2. Experimental purpose

To evaluate the efficacy and safety of Xinnaoning Capsule in the treatment of chronic stable angina pectoris (Qi stagnation and blood stasis syndrome)

3. Experimental design

3.1 Integral test design

The design adopted a placebo parallel control, randomized, double-blind, multi-center clinical research design method.

(1) Multi-center: This multi-center clinical study is expected to be carried out in Beijing, Shanghai, Shanxi and Tianjin.

(2) Random: block random method. SAS 9.1.3 statistical software was used to generate random number grouping table according to the number of cases allocated and random proportion of participating units.

(3) Double blindness: the appearance of the control drug is the same as that of

the test drug; the researchers who did not participate in the clinical research compiled the blindness of the research drug according to the randomized distribution table generated; according to the standardized operation steps of the double blindness clinical research, the test drug and the corresponding simulator were repackaged and distributed (including emergency letters).

(4) Control: placebo control. The purpose of this clinical trial is to evaluate the efficacy of Xinnaoning Capsule in the treatment of stable angina pectoris, which can reflect its "absolute" efficacy and safety, so the placebo control is used in this trial. For well-executed clinical trials, placebo-controlled trials can reliably prove the efficacy of research drugs, unlike non-inferiority design trials, which need to introduce the hypothesis of external efficacy sensitivity and test sensitivity; secondly, placebo-controlled clinical trials can clearly study the absolute efficacy of drugs; thirdly, they can better differentiate between non-inferiority design trials. Good events are caused by drugs or by some potential diseases or other factors; fourthly, they are more efficient and require a smaller number of subjects than any other parallel controlled study; fifthly, they can reduce the degree of disease improvement expected by the subjects and clinical researchers, and increase the ability to detect and study the true efficacy of drugs.

All subjects in this study received basic treatment routinely. Placebo use did not affect the normal treatment of subjects, which met the ethical requirements.

In the experiment, remedial measures such as nitroglycerin (uniformly provided by the applicant) will be given after the attack of angina pectoris. Diary cards and exercise manual of coronary heart disease will be issued during the clinical trial. Researchers should strengthen the observation of the number of attacks of angina pectoris and the dosage of nitroglycerin. The rights and interests of the subjects will be guaranteed and meet the ethical requirements.

Usage: When angina pectoris patients attack, take one tablet under the tongue, and repeat one tablet every 5 minutes until the pain relieves. If the pain persisted after a total of 3 tablets in 5 minutes, the subjects were immediately treated.

(5) Sample size: 120 cases in the experimental group and 120 cases in the control group.

3.2 Sample size

According to the statistical requirements, the sample size was estimated. The main effect index was the curative effect of angina pectoris symptoms treated for 12 weeks. According to the literature, the total effective rate of basic treatment plus placebo was 67.5%, and the

total effective rate of basic treatment plus experimental drugs was predicted to be 84.3%. Set α=0.05, 1-β=0.2, According to the experimental group: control group = 1:1 set up group,

$$n = -\frac{P_1\times(100-P_1)+P_2\times(100-P_2)}{(P_2-P_1)^2}\times f(a, b)$$

The minimum sample size to meet the statistical requirements was 98.4 cases in each group, and the dropping rate was not more than 20%, 120 cases in each group, a total of 240 cases.

4. Subject selection and withdrawal

4.1 Diagnostic criteria of Western Medicine

4.1.1 Diagnostic criteria for coronary heart disease

Referring to the Guidelines for the Diagnosis and Treatment of Chronic Stable Angina issued by the Chinese Medical Association in 2007, the Diagnosis of Stable Ischemic Heart Disease by 2012ACP/ACCF/AHA/AATS/PCNA/STS: Clinical Practice Guidelines, and the Guidelines for the Management of Stable Coronary Artery Diseases issued by 2013 ESC, we can diagnose coronary heart disease by conforming to any of the following:

(1) There is a clear history of old myocardial infarction, PCI or bypass.
(2) Coronary angiography (results indicate that at least one coronary artery is stenosed and the lumen is stenosed more than 50%) or coronary CTA indicates that the lumen is stenosed more than 50%.

4.1.2 Diagnostic criteria for angina pectoris

Referring to the Guidelines for the Diagnosis and Treatment of Chronic Stable Angina Pectoris issued by the Editorial Board of the Chinese Journal of Cardiovascular Diseases in 2007, the Society of Cardiovascular Diseases of the Chinese Medical Association:

When physical activity or mental stress occurs, coronary artery blood flow can not meet the needs of myocardial metabolism, leading to angina attack induced by myocardial ischemia. Resting or taking nitroglycerin can alleviate it. Chronic stable angina pectoris refers to the degree, frequency, nature and inducing factors of angina

pectoris attacks in 1 to 3 months without significant changes in subjects.

Referring to the International Heart Association and WHO Joint Thematic Group on Standardization of Clinical Nomenclature, "Criteria for Nomenclature and Diagnosis of Ischemic Heart Disease" [2].

Tired angina pectoris: Tired angina pectoris is characterized by a brief onset of chest pain induced by exercise or other conditions that increase myocardial oxygen demand. After rest or sublingual administration of nitroglycerin, the pain often disappears rapidly. There are three types of fatigue angina pectoris:

First-onset fatigue angina pectoris: the course of the disease is less than one month. Stable fatigue angina pectoris: the course of the disease is stable for more than one month.

Deteriorating fatigue angina pectoris: The number, severity and duration of fatigue induced by the same degree of fatigue suddenly increased.

Spontaneous angina pectoris: The characteristic of spontaneous angina pectoris is that there is no significant relationship between chest pain attack and the increase of myocardial oxygen demand. Compared with fatigue angina pectoris, the pain generally lasts longer and is more severe, and is not alleviated by nitroglycerin. There was no change of enzymes in this type. There were some temporary S-T segment depression or T wave changes in ECG. Spontaneous angina pectoris can occur alone or in combination with fatigue angina pectoris.

The frequency, duration and degree of pain in subjects with spontaneous angina pectoris may have different clinical manifestations. Sometimes the subjects may have sustained chest pain attacks, similar to myocardial infarction, but without characteristic changes of electrocardiogram and enzymes. Temporary S-T elevation occurs in some subjects with spontaneous angina pectoris, often referred to as variant angina pectoris. However, this name cannot be used when the ECG pattern is recorded in the early stage of myocardial infarction.

Initial fatigue angina pectoris, worsening fatigue angina pectoris and spontaneous angina pectoris are collectively referred to as "unstable angina pectoris".

4.1.3 Classification criteria for angina pectoris

Reference to Canadian Cardiovascular Society (CCS) Angina Severity Classification [4] Standard。

Ⅰ：General physical activity does not cause angina pectoris, such as walking and going upstairs, but tension, rapid or sustained exertion can cause the onset of angina pectoris.

Ⅱ：Daily physical activity is slightly restricted. Walking fast or upstairs, climbing high, walking after meals or upstairs, walking in cold or wind, and emotional excitement can cause angina or only occur within a few hours after waking up. It is limited to walk more than 200 meters or climb stairs above one floor at normal speed.

Ⅲ：Daily physical activity is obviously limited, and angina pectoris can occur when walking 100-200 m at normal speed or climbing a staircase.

Ⅳ：Angina symptoms can occur when you are slightly active or at rest.

This table is cited from the guidelines for the management of chronic stable angina pectoris (ACC/AHA/ACP-ASIM, American College of Cardiology/American Heart Association/American College of Internal Medicine and American Medical Association).

4.2. Differentiation Standard of Traditional Chinese Medicine

According to the prescription composition and function of Xinnaoning Capsule, and referring to the Guiding Principles for Clinical Research of Coronary Heart Disease and Angina Pectoris Treated with Chinese Medicine and Natural Medicine in 2011, the syndrome differentiation and diagnosis criteria of Angina Pectoris with Qi stagnation and blood stasis syndrome were drawn up:

Diagnostic criteria of chest arthralgia in traditional Chinese medicine

①Chest pain, even chest pain thoroughly back chest pain, even chest pain thoroughly back；

②The lighter ones only feel chest tightness, suffocation and breathlessness.；

Qi stagnation and blood stasis syndrome：

Main symptoms: chest pain, chest tightness

Secondary symptoms: chest swelling, palpitation, shortness of breath, purple lips, fatigue, dizziness, dark purple veins at the bottom of the tongue, irritability.

Tongue image: dark tongue. Pulse: astringent.

One of the main symptoms, two of the secondary symptoms and supporters of tongue and vein can be diagnosed.

4. 3. Angina Pectoris Integral Scoring Method

（**Angina Pectoris**）		
1. Frequency：	0	0
	weekly	2
	1-3times per day or CCS Ⅱ	4
	≥4times per day or CCSⅢ	6
2. Duration：	0	0
	Every pain lasting≤5min。	1
	Every pain lasting＞5，and＜10min。	2
	Every pain lasting≥10min	
3. Degree of pain：	nothing	0
	The pain is not serious and does not affect daily life.	1
	The pain is severe and needs nitroglycerin.	2
	Severe seizures affect daily activities (such as dressing, defecation, etc.).	3
4.Nitroglycerin dosage	nothing	0
	1-4tablets per week	1
	5-9tablets per week。	2
	≥10tablets per week	3

4. 4. TCM Syndrome Integral Scoring Method

Main symptom	Chest pain	0：nothing 2：The seizure is relieved by rest and does not affect daily life. 4：Medication should be taken during seizures and normal activities can continue after remission. 6：Frequent seizures affect daily activities (such as clothing, eating, walking, fecal symptoms)
	Chest tightness	0：nothing 2：Occasionally chest tightness can be alleviated by oneself 4：Chest tightness attacks are frequent, but do not affect life and work 6：Chest tightness continues to puzzle, affecting life and work

Secondary symptom	palpitation	0：nothing 1：Occasional palpitation can be alleviated by itself 2：Frequent episodes, but able to work persistently 3：Palpitations persist, affecting life and work
	pant	0：nothing 1：Short breath after general activities 2：Short breath after a little exercise 3：Normally inactive and short of breath
	Chest and side fullness	0：nothing 1: Occasional distension and discomfort, short time, self-relief 2: Depressed for a long time, occasionally need to take medicine. 3: Recurrent seizures can only be alleviated by taking medicine.
	Mental exhaustion and fitigue	0：nothing 1: Mentally depressed, weak in strength teaching, can adhere to daily work and activities. 2: Mental weakness, physical weakness, reluctant to stick to work 3: Mental energy is so weak that it is difficult to stick to daily work.
	Purple lips	0：no 1：yes
	dizziness	0：no 1:yes
	Sublingual venation	0：Lavender 1：Dark purple with bruises
	Impatient and irritable	0：no 1：yes
Tongue manifestation		Dark others _____
Pulse condition		uneven/ string-like pulse others_____

Note: Tongue and pulse are only described and not scored.

4. 5 Seattle Angina Questionnaire,SAQ。

4.6 Participant selection criteria

1) Referring to the Guidelines for the Diagnosis and Treatment of Chronic Stable Angina [6], issued by the Chinese Medical Association in 2007, the diagnosis of stable ischemic heart disease in 2012ACP/ACCF/AHA/AATS/PCNA/STS: Guidelines for Clinical Practice, and Guidelines for the Management of Stable Coronary Artery Disease in 2013 ESC, the diagnosis of coronary heart disease can be made in accordance with any of the following:

(1) Has a clear history of old myocardial infarction, or PCI history, or bypass history;

(2) Coronary angiography (results indicate that at least one coronary artery is stenosed and the lumen is stenosed more than 50%) or coronary CTA suggests that the lumen is stenosed more than 50%.

2) Those who met the diagnostic criteria of chronic stable angina pectoris: those who had a history of angina pectoris more than 1 month and had no significant changes in the degree, frequency, nature and inducing factors of angina pectoris;

3) The severity of angina pectoris of the Canadian Cardiovascular Society (CCS) was classified as Grade I-III, and the number of episodes per week was more than two.

4) The syndrome differentiation of TCM is Qi stagnation and blood stasis syndrome.

5) Age between 30 and 79 years old;

6) Sign the informed consent.

4.7 Subject exclusion criteria

1) Severe cardiopulmonary insufficiency (grade III, IV, severe abnormal pulmonary function);

2) Poor control of hypertension (systolic blood pressure (> 160 mmHg) or diastolic blood pressure (> 100 mmHg) after treatment;

3) Severe primary diseases such as ALT, AST (> 1.5 times the upper limit of normal value) or Cr (> upper limit of normal value), hematopoietic system and so on.

4) Acute myocardial infarction within 3 months after interventional therapy;

5) Other factors affecting ST-T changes in ECG, such as myocardial hypertrophy, left bundle branch block, etc.

6) Cardiac pacemaker;

7) Chest pain caused by other causes (moderate anemia, hyperthyroidism, etc.);

8) Pregnancy, lactation or pregnancy planning;

9) allergic constitution or allergic to known ingredients of research drugs;

10) Those who participated in other clinical drug trials within one month;

11) Researchers consider it inappropriate to participate in clinical research.

4.8 Exfoliation excluded cases

4.8.1 The withdrawal of the researcher's decision

Subject withdrawal from the study refers to the decision to withdraw the case from the study according to the judgement of the researcher when the selected subjects are unsuitable for further study in the course of the study.

① In the study, patients with aggravated or aggravated conditions, such as increased number of angina attacks, prolonged duration of each attack or aggravated pain, must take emergency treatment measures such as adjusting treatment drugs, hospitalization or surgery；

② In the study, some complications, complications or special physiological changes occurred in the subjects, and it was not appropriate to continue the study；

③Prohibited drugs prescribed by the scheme were used in the study。

④ In the study, if angina symptoms worsened in the subjects, those who were judged by the researchers to need to take other angina medicines or increase the dosage of drugs were withdrawn as invalid cases。

4.8.2 Subjects withdraw spontaneously

According to the informed consent, the subjects have the right to withdraw from the study halfway, or they have not explicitly proposed to withdraw from the study, but no longer accept medication and testing and lost interviews, which also belongs to "withdrawal" (or "fall off"). The reasons for their withdrawal should be understood and recorded as far as possible. Such as: poor self-efficacy; intolerable to some adverse reactions; unable to continue to accept clinical research; economic factors; or missing interviews without explaining the reasons.

Whatever the reason, the case records should be kept for the withdrawal cases, and the final test results should be transferred to the final results. The efficacy and adverse reactions of the withdrawal cases should be analyzed by a full data set. All withdrawal cases should be filled in the case report form, the conclusion form and the reasons for withdrawal. In general, there are six kinds, namely, adverse events

(including adverse drug reactions and allergic reactions), lack of efficacy (deterioration or complications), violation of research programs, loss of interviews (including withdrawal of the subjects themselves), suspension of the applicant and others.

4.8.3 Criteria for excluding cases

① Misdiagnosis and wrong acceptance；

② No post-medication record；

③ No medication at all。

4.9 Conditions for discontinuation of research

Research discontinuation means that clinical studies have not been completed as planned and all studies have been stopped halfway. The main purpose of the suspension of research is to protect the rights and interests of subjects, ensure the quality of research and avoid unnecessary economic losses.

(1) Serious safety problems occur in the study, and the study should be discontinued in time.

(2) The study found that the effect of drug treatment is too poor, even ineffective, and has no clinical value. The study should be discontinued, on the one hand, to avoid delaying the effective treatment of subjects, while avoiding unnecessary economic losses.

(3) It is difficult to evaluate the drug effect because of the major mistakes in the clinical research program. Or a well-designed program has significant deviations in its implementation, and it is difficult to evaluate the drug effect if it continues.

(4) The applicant requests suspension (e.g. financial reasons, management reasons, etc.).

(5) Drug administration departments should withdraw research, etc.

5. Dosage regimen

5.1 Administration method

The course of treatment was 14 weeks, including 2 weeks of introduction and 12 weeks of double blind treatment.

Introducing period: 2 weeks, time window (+2 days).

Introducing drug regimen: Both groups were given Xinnaoning capsule Simulator 3 capsules per time, 3 times per day, orally, after meals.

Course of treatment: 12 weeks, time window (+4 days).

Drug regimen for treatment period:

Test group: Xinnaoning capsule 3 capsules per time, 3 times per day, oral, after meals.

Control group: Xinnaoning capsule Simulator 3 tablets per time, 3 times per day, oral, after meals.

Basic treatment: During the introduction and treatment period, the experimental group and the control group could use antiplatelet drugs, angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB), statins lipid-lowering drugs, calcium antagonists, beta-blockers, long-acting nitrates and other drugs without changing the original dosage. Nitroglycerin 0.5 mg can be administered sublingually, and the times and dosage of medication can be recorded in detail.

Sports regulations: 3-5 times a week, each lasting 30-40 minutes, 6.5-7.5 kilometers a week. See Annex 1 for details.

5.2 Pharmaceutical Information for Testing Drugs

(1) Introducing drugs: Xinnaoning capsule simulator, the production unit is Guizhou Jingcheng Pharmaceutical Co., Ltd. Specification: 0.45g for each tablet, 12 tablets for each board, batch number: 20171113 valid until August 2019.

(2) The experimental group drug: Xinnaoning Capsule, the production unit is Guizhou Jingcheng Pharmaceutical Co., Ltd. Specification: 0.45g for each tablet, 12 tablets for each board, drug batch number 20170916. It is valid until August 2019.

(3) Control group drug: Xinnaoning capsule simulator, the production unit is Guizhou Jingcheng Pharmaceutical Co., Ltd. Specification: 0.45g for each tablet, 12 tablets for each board, drug batch number: 20171113. It is valid until August 2019.

5.3 Pharmaceutical Packaging for Testing Drugs

There are corresponding drug numbers and labels attached to the test drugs. The test drugs and the control drugs are packed in the same package. Each large package contains three boxes. The package contains Xinnaoning capsule or Xinnaoning capsule placebo. Each package contains 28 + 4 days of dosage. The drug was packed independently during the introduction period, and the dosage of 14 + 2 days was included in the package. The contents of the label include batch approval number, drug number, drug name, function, taking method, storage condition, drug supplier, etc., and the words "for clinical research only".

5.4 Case allocation method

Randomization method was adopted, which was carried out according to the center. With the help of SAS 9.1.3 statistical software, the random arrangement (i.e. random coding table) of the treatment (test drug and control drug) received by 240 subjects was generated. According to the randomly determined drug number allocated by each hospital, each center allocates continuously coded drugs connected with each other. Random numbers are sealed in opaque envelopes and centralized managed by test centers.

Each center screens patients, and qualified persons are selected. Drug administrators distribute drugs one by one according to the order of each subject's visiting and drug number from small to large. Subjects were asked to take the remnant drugs back when prescribed visiting points were prescribed. Drug administrators should fill in the "test drug distribution and recovery record form" in time.

5.5 Dose selection and administration time

In this experiment, all subjects were given a uniform fixed dose, which remained unchanged during the experiment, i.e. during the experiment, the dosage should not be adjusted or the mode of administration should not be changed. If the adverse events necessarily changed or other reasons caused changes, detailed records and treatment according to excluded cases were made.

5.6 Blind method

A double blind design was used in this study.

(1) Generation of processing codes

Randomization method was used. They are carried out according to the center. With the help of SAS 9.1.3 statistical software, the random arrangement (i.e. random coding table) of the treatment (test drug and control drug) received by 240 subjects

was generated.

(2) Drug preparation

Firstly, random sampling of the drugs prepared by the applicant (test drugs and control drugs) is conducted to provide the corresponding drug inspection report. Secondly, the bidders will package the drugs according to the requirements of drug packaging.

(3) Preparing for Emergency Letters

1) Emergency letters, drug numbers and blindness regulations of Xinnaoning Capsule in the clinical study of chronic stable angina pectoris are printed on the sealed opaque envelope. If it is disassembled, it is necessary to specify the disassembler, the date of disassembly, the reason and so on, and record it in the case report form.

2) The envelope contains the information of the patient's medication and the address of the unit and the address that should be reported immediately. After the preparation of the emergency letter, it will be sent to the centers along with the drugs, which will be recovered after the study.

(4) Packaging and numbering of drugs according to processing codes
Personnel unrelated to clinical observation, surveillance and statistical analysis of this clinical study will attach the corresponding drug number to the conspicuous position of the external packaging of the drug according to the established processing code.

(5) Processing Blind Records of Coding and Drug Packing

The whole drug coding process is written into a document form by the blind person, that is, a blind record, which is kept as one of the documents of the clinical research. Its contents include: preparation of bidders'medicines, packaging, usage, storage requirements, methods of drug distribution, generation of random processing codes, packaging of medicines according to each subject, emergency letters, inspection reports of test drugs and control drugs, preservation of blind bases, provisions for eliminating blindness and distribution of the number of medicines in each center, etc.

(6) Distribution of packaged drugs

Emergency letters with separate packages of research drugs and corresponding drug numbers are sent to the research centers according to random central numbers.

(7) Blind bottom preservation

All the blind bases formed by coding, together with the initial values of random numbers and the length of blocks, are sealed and handed over to the drug clinical research institutes and bidders of Xiyuan Hospital, Chinese Academy of Medical

Sciences, respectively, for proper preservation. During the research period, the blind bases are not to be dismantled. The study will be considered invalid if any non-prescribed blind bottom leak occurs and affects the objectivity of the results of the study.

(8) Blind Audit and Disclosure Provisions

Blind auditing refers to checking and evaluating the data of the database after the last medical record report form is input into the database until the first blindness is uncovered.

When all the case reports are entered in two copies and checked correctly, the data manager writes out the database inspection report, which includes the completion of the study (including the list of dropped subjects), selection/exclusion criteria, integrity check, logical consistency check, outlier data check, time window check, combined drug use check, adverse event check and so on.

At the blind auditing meeting, the main researchers, bidders, supervisors, data managers and biostatistics professionals will examine the subjects'signing of informed consent, the situation of maintaining the blindness in the research process and the emergency situation of eliminating the blindness in the research process, and make decisions on the issues raised in the database inspection report, and write the blind auditing report. The database will be locked at the same time.

After data locking, the first blindness was uncovered by the staff who kept the blind bottom. This blindness uncovering only listed the group code of each subject (such as the experimental group or the control group). It was input to the computer by the statistic analyst and linked to the data file for statistical analysis. When the statistical analysis is finished, the statistical analysis report is written. At the summary meeting, the second blindness was uncovered. This blindness uncovering marked the actual corresponding groups of A and control group (such as experimental group or control group).

(9) Regulations on Emergency Disclosure of Blindness

When an emergency (such as a serious adverse event) occurs or the patient needs to know what kind of treatment the patient receives, the researcher immediately notifies the main researcher, urgently opens the emergency letter, and promptly notifies the head of the base and the inspector of the unit. Once the emergency letter is opened, the numbered subjects will withdraw from the study. Researchers should record the causes in the case report form, and record the time, place and cause of emergency blindness on the emergency letter. At least two people should sign it. At the end of the study, the case report forms were retrieved together for blind review after the study.

(10) Failure of double-blind study stipulates that the rate of blind bottom leak or emergency letter open exceeds 20%.

5.7 Drug Distribution and Preservation

Drug administrators (centers, according to their own management system, set up a special person responsible for the preservation, distribution, recovery, recording and return or recovery of experimental drugs) distribute drugs according to the order of the selected time and the number of drugs from small to large, and then withdraw the surplus experimental drugs after stopping the drugs, and fill in the Test Drug Use Record Form in time, which includes: The date of drug release, the name of the subject, the quantity of drug delivery, the date of drug recovery, the quantity of drug recovery, the signature of the dispenser and the signature of the drug collector, etc. After the completion of all trials, the drug administrator is responsible for returning the remaining drugs to the applicant or destroying them according to the procedure (filling in the "Test Drug Return/Destruction Certificate") and submitting them to the clinical trial unit for archiving.

During the test period, a management system should be established for the trial period of the test drugs, and special cabinets should be set up to keep the test drugs and store them in places where ventilation, drying and temperature are suitable. The drug administrator shall carry out unified management.

5.8 Drug counting and drug compliance judgment of subjects

During each follow-up visit, the observer should check the remaining empty boxes of the subjects, ask whether they take the drugs on time and in quantity, whether they are missing, missing or undertaking, and record them in the case report form in time for judging the compliance of clinical medication.

In the course of clinical trials, the compliance of subjects is mainly prescribed medication. The subjects should be strictly prescribed medication to avoid self-imposed other treatment methods.

Compliance of test medication=(dosage-not-dosage)/dosage x l00%

5.9 Regulations on combined use of drugs

1. In addition to experimental medication, nitroglycerin tablets can be used to alleviate symptoms when angina attacks. For drugs already used to treat coronary heart disease before inclusion, such as antiplatelet drugs, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB), statins, calcium antagonists, beta-blockers and long-acting nitrates, the original varieties and dosages can be continued without adjustment. During the study period, it is forbidden to add any other Chinese and Western medicines which have therapeutic effects on angina pectoris of coronary heart disease.

2. For the original and emerging diseases requiring drug treatment, the drug combination should be recorded in the medical record and CRF in detail, including the generic name of the drug, dosage and method of administration, the starting time of drug use and the reasons for its use.

6. Observation items

6.1 General record items

Drug number, center code, subject name, start date, etc.

6.2 Observation index

6.2.1 General observation indicators

1) Demographic characteristics: gender, age, height, weight, etc.
2) Medical history, course of disease, treatment history, allergic history, complications and medication, etc.
3) Other screening indicators: urinary pregnancy test (women of childbearing age).

6.2.2 Effectiveness indicators

Main effective indicators: the efficacy of angina symptoms.
Secondary effectiveness indicators:
(1) Curative effect of TCM syndromes;
(2) Grading changes of severity of angina pectoris;
(3) Changes in the number of angina attacks per week;
(4) Nitroglycerin dosage;
(5)Seattle Angina Scale score;
(6)Blood HCY: The changes of blood HCY before and after treatment were compared between the two groups.
（7）Incidence of cardiovascular events (sudden cardiac death, acute myocardial infarction, heart failure, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, malignant arrhythmia, cardiogenic cerebrovascular accident, angina pectoris requiring hospitalization, etc.).

6.2.3 Safety indicators

(1) adverse event

(2) vital signs: (blood pressure, body temperature, breathing and heart rate after 10 minutes'rest);

(3) Routine safety laboratory examinations: blood routine (RBC, WBC, HGB, PLT), urine routine (ERY, LEU, PRO), stool routine (containing occult blood), liver function (ALT, AST, ALP, TBIL, GGT), renal function (BUN, Cr), coagulation (PT, APTT, FIB, TT)

6.2.4 Other observational indicators

(1) Fasting blood glucose: The changes of fasting blood glucose before and after treatment were compared between the two groups.

(2) Four items of blood lipid: The changes of four items of blood lipid before and after treatment were compared between the two groups.

6.3 Observation window

12 weeks ±4 days.

6.4 Test procedure

6.4.1 Visit 1-Import Period (-14±2 days)

- Obtain written informed consent
- Verification of selection/exclusion criteria for the import period
- Access to demographic information
- Obtain medical history, including concomitant medication
- Conduct a comprehensive physical examination
- Record concomitant medication
- Issuance of medication and diary cards during the introduction period
- ECG examination
- Record nitroglycerin dosage

6.4.2 Visit 2 - before treatment (0 days)

- Verification of selection/exclusion criteria
- TCM Symptom Score
- General information, main related symptoms and signs
- Record concomitant medication
- Subsequently, the experimental drugs were distributed in groups, and the remaining drugs were recovered and recorded.
- Physicochemical examination: blood routine, urine routine, stool routine + Occult blood, electrocardiogram, liver function (ALT, AST, ALP, GGT, TBIL), renal function (BUN, Cr), four items of coagulation, blood HCY, fasting blood sugar and blood lipid
- Major related symptoms and signs

- Seattle Angina Questionnaire
- Grading changes of severity of angina pectoris;
- Record nitroglycerin dosage
- Record adverse events

6.4.3 Visit 3 (4 weeks ± 4 days)

- Fill in the syndrome integral form
- Major related symptoms and signs
- Seattle Angina Questionnaire
- Grading changes of severity of angina pectoris;
- Record concomitant medication
- Record adverse events
- Recovery of surplus drugs and distribution of experimental drugs
- Record nitroglycerin dosage
- Evaluation of curative effect

6.4.4 Visit 4 (8 weeks ±4 days)）

- Fill in the syndrome integral form
- Major related symptoms and signs
- Seattle Angina Questionnaire
- Grading changes of severity of angina pectoris;
- Confirmation of the subjects'return of unused research drugs
- Record concomitant medication
- Record adverse events
- Record the dosage of nitroglycerin
- Evaluation of curative effect

6.4.4 Visit 5 (12 weeks ± 4 days)

- Fill in the syndrome integral form
- Major related symptoms and signs
- Seattle Angina Questionnaire
- Grading changes of severity of angina pectoris;
- To confirm that the subjects returned untreated research drugs;
- Record concomitant medication
- Record adverse events
- ECG examination
- Physicochemical examination: blood routine, urine routine, stool routine + Occult blood, electrocardiogram, liver function (ALT, AST, ALP, GGT, TBIL), renal function (BUN, Cr), four items of coagulation, blood HCY, fasting blood sugar and blood lipid
- Record the dosage of nitroglycerin
- Evaluation of curative effect

7. Observation of adverse events

7.1 Recording of adverse events

In the research case history and case report form, "adverse event record form" is set up, which requires researchers to fill in the occurrence time, severity, duration, measures taken and outcome of adverse events truthfully. The relationship between adverse events and experimental drugs was also judged.

7.1.1 Definition of Adverse Event (AE)

It refers to adverse medical events that occur during a clinical trial when a subject receives a drug, but it does not necessarily have a causal relationship with the treatment. Specifically, it includes the following: suspicious adverse drug reactions, such as central nervous system, digestive system, hematopoietic system, rash, pruritus and other toxic and side effects; all reactions due to drug overdose, abuse, withdrawal, allergy or toxicity; apparently unrelated diseases, including the aggravation of pre-existing diseases; abnormal biochemical indicators of liver and kidney function. Abnormalities found by physical examination or physical examination and requiring clinical treatment or further examination (unlike repeated validation tests), etc. Abnormalities found in laboratory tests require clinical treatment or further investigation (unlike repetitive validation tests). If these abnormalities are related to reported events (e.g. elevated transaminase levels in jaundiced subjects), they should be described in the notes to the clinical event report and not included as a separate adverse event.

7.1.2 Judgment of Causality between Adverse Events and Testing Drugs

In the event of adverse events, the researcher decides the diagnosis and treatment measures based on the condition of the patient and whether to discontinue the observation. In case of serious adverse events, the unit undertaking clinical research should take necessary measures immediately to protect the safety of the subjects. If the duration of the trial is more than 4 weeks, the subjects will quit because of the aggravation of the illness (increased number of attacks, prolonged duration of attacks, increased degree of pain, increased dosage of nitroglycerin or increased level of attacks). Such cases need to be included in PPS statistics as non-curative cases. Researchers should record the relevant information in detail on the medical records of scientific research.

Criteria for grading the severity of adverse events

Mild: Usually temporary and does not affect normal daily activities.

Moderate: quite uncomfortable, can affect normal daily activities.

Severity: unable to carry out normal daily activities.

Judgment of causality with drugs:

1) Causal judgment indicators of adverse reactions:

Item 1: Whether there is a reasonable relationship between the time of starting medication and the time of suspicious occurrence;

Item 2: Does the suspicious adverse reactions conform to the known types of adverse reactions of the drug?

Item 3: Whether the suspected adverse reactions can be explained by the patient's pathological condition, combination of medication, therapy or previous therapy;

Item 4: Does the suspicious adverse reaction decrease or disappear after withdrawal or dose reduction?

Item 5: Does the same reaction reappear after the suspicious drug is used again?

Causality criteria: according to the above five judgment indicators to determine the order.

Causal Judgment of Adverse Reactions

Result	Judgement index				
	item1	item 2	item 3	item 4	item 5
Definitely related	+	+	—	+	+
Vey kikely related	+	+	—	+	?
Probably related	+	+	±	±	?
May be irrelevant	+	—	±	±	?
Impossibly related	+	—	+	—	—

Explanation：＋yes、－no、±not sure、？unknown。

2) Based on the above table, the relationship between the following five levels of adverse events and drugs was determined.

①Definitely related；②Vey kikely related；③Probably related；④May be irrelevant；⑤Impossibly related。

The total number of cases with 1+2+3 was used as the molecule to calculate the incidence of adverse reactions, and all the selected cases for adverse reactions

evaluation were used as denominators.

7.1.3 Recording and reporting of adverse events

Researchers should explain to the subjects that they should truthfully reflect the changes of their condition after medication, but avoid induced questions. While observing the curative effect, we should pay close attention to adverse events or unexpected side effects (including symptoms, signs, laboratory tests), analyze the causes, make judgments, and follow up observation and record.

For adverse events during the trial, the researchers should record the occurrence time, symptoms, degree, duration, treatment measures and outcome in the case report form, judge the correlation between the adverse events and the test drugs, sign and date them.

7.1.4 Treatment of subjects with adverse events

When adverse events occur, researchers can decide on the measures to be taken according to their condition. Generally, the following methods are adopted:

(1) observation without discontinuing the drug test;

(2) observation and discontinuation of the drug test without remedial treatment;

(3) discontinuation of the drug test with remedial treatment.

All adverse events should be tracked and investigated, and the treatment process and results should be recorded in detail until the subjects are properly resolved or the condition is stable. Those with abnormal laboratory indicators should be tracked back to normal or pre-medication level. According to the severity of adverse events, follow-up methods can be used to select hospitalization, outpatient service, home visits, telephone and other forms.

7.2 Dealing with Serious Adverse Events

7.2.1 Definition of Serious Adverse Event

Serious adverse events refer to the following adverse events occurring at any dose of the test drug or at any time during the observation period, including the need for hospitalization, prolonged hospitalization time, disability, impairment of working ability, life-threatening or death-threatening events.

7.2.2 Treatment and Report of Serious Adverse Events

If serious adverse events occur in the trial, the unit undertaking the clinical trial shall take necessary measures immediately to protect the safety of the subjects, and report to the local provincial drug supervision and administration department, the State Food and Drug Administration, the applicant and the ethical committee of the

unit responsible for the clinical trial within 24 hours, and notify the experimental units. The applicant will ensure that the reporting procedure meets all legal and regulatory requirements.

Table 7.2.2 Contacts for reporting serious adverse events

Organization	Contacts	Telephone	Fax
Ethics Committee of Xiyuan Hospital, Chinese Academy of Traditional Chinese Medicine	Mingjie Zi	010—62835646	010-62835646
Guizhou Jingcheng Pharmaceutical Co., Ltd.	Minghu an Luo	13891950813	010-58462594
Beijing Duheng for Drug Evaluation and Research Co., Ltd. (DDER)	Chunshe ng Qiao	010-58462584	010-65735819
CFDA Drug and Cosmetics Registration and Administration Department, Drug Research and Supervision Department	-----	010-88863120	010-88363228

7.2.3 Recording of serious adverse events

Researchers must fill in the "Serious Adverse Events Report Form", record the occurrence time, duration, measures taken and outcome of serious adverse events, and sign and date the report.

7.3 Disassembly and Processing of Emergency Letters

Emergency letters are called emergency blindness cracking only when the subject has serious adverse events and needs to identify the types of drugs used immediately. Once blindness is broken, the subject will be discontinued and treated as an exfoliated case. At the same time, the results will be notified to the unit responsible for the test, the bidder and the inspector. Researchers should record the reasons for breaking the blindness, date it and sign it in the case report form.

7.4 Follow-up of unremitted adverse events

All adverse events that have not been completely alleviated at the end of the course of treatment should be tracked and observed to be properly resolved or stable.

8. Evaluation of clinical trials

8.1 Evaluation of clinical effectiveness

Referring to the Guiding Principles of Clinical Research Technology of Traditional Chinese Medicine and Natural Medicine for Coronary Heart Disease and Angina Pectoris.

8.1.1 Criteria for evaluation of main therapeutic indicators

The curative effect of angina pectoris symptoms: According to the method of

angina symptom integral, the scores of angina pectoris symptoms before and after the two groups were compared:

- Significant effect: n (> 70%);
- Effective: n (>30%) and (< 70%);
- Invalid: n < 0, n < 30%;
- Aggravation: n < 0.效：n≥70%；

8.1.2 Evaluation criteria of secondary efficacy indicators

1) The curative effect of TCM syndrome scoring:
Relevant statistical methods were used to analyze the score reduction value and 50% score reduction rate of the two groups.

2) Grading changes of severity of angina pectoris: Comparing the severity grading of CCS angina pectoris between the two groups before and after treatment, and evaluating the therapeutic effect of drugs on chronic stable angina pectoris.

3) The change of angina pectoris attack times per week: The change of angina pectoris attack times per week before and after treatment was compared between the two groups.

4) Nitroglycerin consumption: The corresponding statistical methods were used to analyze the consumption of nitroglycerin before and after treatment in the two groups.

5)SAQ: Compare the changes of each dimension of the Seattle Angina Scale before and after the treatment of the two groups, and evaluate the effects of drugs on the body function and quality of life of the subjects.

6) Change of HCY: Compare the changes of HCY before and after treatment in the two groups, and evaluate the effect of drugs on reducing the incidence of heart disease.

7) Incidence of cardiovascular events (sudden cardiac death, acute myocardial infarction, heart failure, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, malignant arrhythmia, cardiogenic cerebrovascular accident, angina pectoris requiring hospitalization, etc.).心血管事件发生率(心源性猝死、急性心肌梗死、心力衰竭、经皮冠状 动脉腔内血管成形术、冠状动脉搭桥术、恶性心律失常、心源性脑血管意外、需要住院治疗的心绞痛等)。

8.2 Clinical safety evaluation

1. Possible adverse reaction symptoms.

2. General physical examination items, such as body temperature, pulse, breathing, blood pressure, etc.

3. Laboratory examination: blood routine, urine routine, stool routine + Occult blood, electrocardiogram, liver function (ALT, AST, ALP, GGT, TBIL), renal function (BUN, Cr), coagulation, fasting blood sugar, blood lipid.

9. data management

(1) Fill-in and transfer of case report form (CRF)

The completed case report forms are reviewed by clinical researchers and monitors, and then submitted to the data statistical units for data entry and management. All processes need to be documented.

(2) Data input and modification

Data entry and management reasons are the responsibility of data managers in statistical units. Two data managers independently enter and proofread two copies. Questions on the case report form. Data managers will fill in the Question Answer Form (DRO) and send inquiries to researchers through clinical monitors. Researchers should answer and return the questions as soon as possible. Data managers modify the data according to the researchers'answers, confirm and input them, and then issue DRO again if necessary.

(3) Locking of database

After blindly checking and confirming the correctness of the database, the main researchers, bidders and statisticians lock the database. If the problem is found after database locking, it can be corrected in the process of statistical analysis after confirmation, and recorded and explained.

(4) blindness elimination

After all the research data are checked and locked, the first blindness detection is carried out, and then the statistical analysis is carried out according to the statistical plan, the statistical analysis report is written, and finally the second blindness detection is carried out.

10. statistical analysis

10.1 Analytical Data Set

(1) Full Analysis Set (FAS): refers to the ideal set of subjects as close as possible to the principle of intentional analysis. The data set is derived from all randomized participants by eliminating the participants with the least and reasonable method.

(2) PPS: It is a subset of the total analysis set. These subjects are more compliant with the scheme. Compliance includes the following considerations, such as the treatment they received, the absence of major efficacy indicators, and the absence of major violations of the research scheme.

(3) Safety Data Set (SS): When evaluating safety and tolerance, the set of subjects used to aggregate is called Safety Data Set. Subjects who received at least one treatment after randomization were included in the safety analysis set.

10.2 Statistical analysis method

10.2.1 Statistical description

(1) whether it conforms to normal distribution: modifying statistical methods or transforming data when it does not conform;

(2) Whether there is outlier value or not: make statistical and professional analysis to decide whether to choose or not;

(3) Processing the missing value of the main therapeutic index data: When the main therapeutic effect data of individual subjects are missing, the way to fill the missing data is determined from the statistical and professional point of view. For missing cases, the data were transferred from the previous measurements; for missing data, the measurements were made only once, and the mean of all the data was used to fill in the missing data.

(4) The proportion of exfoliated cases: generally not more than 20%, otherwise it should be analyzed and explained;

(5) Descriptive statistical analysis: calculating mean, standard deviation, confidence interval, maximum, minimum, median, frequency (constituent ratio), etc.

10.2.2 Statistical expression

(1) The report is mainly expressed in tables, which are self-evident, i.e. with headings, annotations and examples.

(2) The results of repeated measurements can be expressed in tables or statistical charts to increase readability.

(3) Bilateral tests are used in statistical tests. Those whose P is less than or equal to 0.05 will be considered as having statistical significance.

10.2.3 Statistical analysis content

(1) CDAS3.0 statistical software will be used for statistical analysis.

(2) The main therapeutic data set was FAS analysis population, and the therapeutic PPS population was also analyzed.

(3) Except for the superiority test of the main therapeutic indicators, all other statistical tests are carried out by bilateral test, and the difference of P value less than or equal to 0.05 will be considered statistically significant.

(4) The measurements of each visit in different treatment groups will be described by means of standard deviation. Compared with the baseline values at the time of admission, paired t-test was used to compare the differences between before and after admission. Variance analysis was used to compare the changes before and after treatment in each group.

(5) Frequency (constituent ratio) was used to describe the counting data of each visit in different treatment groups. 2 test or non-parametric test were used to test the changes before and after treatment in each group.

(6) Comparability analysis: Comparing demographic data and other basic value indicators to measure the comparability between the two groups.

(7) Compliance analysis: Compare the two groups of patients whether to use the research drugs on time and in quantity, not using the drugs prohibited in the program.

(8) Abscission analysis: _2 test will be used to compare the total abscission rate and the abscission rate due to adverse events in each group.

(9) Equilibrium analysis of basic values: using variance analysis or 2 test to compare demographic data and other basic value indicators to measure the two groups of equilibrium.

(10) Effectiveness analysis: PPS and FAS were used to analyze the main indicators and global indicators, and CMH test considering the central effect was used to analyze the efficacy of the two groups. The main effect indicators were selected to treat 12 weeks of angina symptoms, and the placebo was used as the control for statistical test.

(11) Analysis of factors affecting efficacy: If there are significant correlative factors affecting efficacy, these factors should be considered as covariance analysis or logistic regression analysis when comparing the efficacy of the two groups. Detailed list of combined medication is required.

(12) Safety analysis: 2 test was used to compare the incidence of adverse events in the two groups, and list the adverse events in the study; analysis of the normal/abnormal changes of laboratory results before and after the study and the relationship between abnormal changes and research drugs.

11. Quality Control and Guarantee of Clinical Trials

11.1 Records of clinical trials

Researchers should fill in all cases according to the design requirements of the "case report form" one by one. Research medical records and case report forms shall be used as original records and shall not be changed. When making any corrections,

the original record shall not be blackened. Only a horizontal line can be drawn at the amendment and the reasons can be explained by adding a description. The physician participating in the clinical trial shall sign and date it.

Laboratory data in clinical trials should be recorded, and original reports (or copies) should be glued to the medical records of the study. Data that are significantly higher or beyond clinical acceptability should be verified and explained by the physician participating in the clinical trial.

All medical records and case reports should be filled in with black or blue-black signature pens. Ball pens, pens or pencils are prohibited.

11.2 Management of experimental drug use

All drugs should be kept in the scientific pharmacy of the hospital and designated special persons to be responsible for the preservation, distribution, recovery and return of the drugs. For the cases of withdrawal and missing visits, the experimental drugs should be recovered. At the same time, we should establish the Record of Use of Drugs in Clinical Trials, which includes the date of issuance of drugs, the names of subjects, the number of drugs issued, the date of recovery, the number of drugs recovered, the signature of the dispenser and the signature of the drug collector.

11.3 Training Researchers

Before the start of clinical trials, the personnel participating in clinical trials should be trained in a unified way so that researchers can fully understand the specific connotations of the clinical trial program and its indicators; the quantification criteria of symptoms and signs are basically the same; the description of conscious symptoms should be objective, and should not be induced or prompted; and the prescribed objective indicators should be carried out according to the time points and methods prescribed by the program. Check; Familiar with the recording methods of case history and CRF; pay attention to observe adverse reactions or unexpected side effects, and follow up observation.

11.4 Measures to Improve Observation Consistency

1) Qualification examination of researchers participating in clinical trials: They must have the professional expertise, qualification and ability of clinical trials. After qualification examination, they are determined and the personnel requirements are relatively fixed.

2) Researchers should verify significant deviations or data beyond acceptable limits and make necessary explanations by the researcher.

3) Each test item must indicate the unit of measurement used.

4) Each clinical research unit should appoint a special person to regularly check the progress of clinical trials and carefully verify the data and records.

5) If necessary, the bidding unit will organize a mid-term clinical meeting to check the previous work, analyze the problems found in the clinical trial process and put forward the rectification.

11.5 Laboratory Quality Control Requirements

Standard operating procedures and quality control procedures should be established in laboratories. When the main indicators may be subjectively affected, a consistency test is needed.

Each testing unit shall provide "normal range of laboratory inspection" for its own unit. If there is any change in the test, additional explanation should be provided in time. Effective measures should be taken to correct the differences in the results of laboratory tests or the range of normal reference values.

11.6 Surveillance of clinical trials

Qualified inspectors appointed by the applicants will regularly visit the test centers during the trial period to ensure that the rights and interests of the subjects in the clinical trials are guaranteed, that the data recorded and reported in the trials are accurate and complete, and that the trials follow the approved programs, drug clinical trial management norms and relevant regulations.

The inspector is required to have direct access to source documents (original documents, data and records). Direct contact includes allowing examination, analysis, and verification of important records and reports for any evaluation of clinical trials.

Researchers should be able to contact the Ombudsman by telephone at any time for discussion.

12. Ethical principles

Before the clinical trial is officially started, it must be discussed, revised and signed by the researcher and the applicant (i.e. this scheme), which can be submitted to the Ethics Committee for approval before the trial can be started. If problems arise in the actual implementation of clinical trials and need to be revised, please submit to the applicants that, after consultation and discussion by the multi-center coordinating committee, the responsible unit of clinical trials should revise the scheme and submit it it in writing to the applicants and the experimental units for signature and approval, and then to the Ethics Committee for approval; if it is found that the drug used in the trial is involved, it should be carried out after approval by the ethics committee.

Important new material must be revised in writing and sent to the Ethics Committee for approval, and the subject's consent will be obtained again.

Before the start of a clinical trial, researchers must provide the subjects with detailed information about the nature of the trial, the purpose of the trial, the potential benefits and risks, alternative therapies available, and the rights and obligations of the subjects in line with the Helsinki Declaration, so that the subjects can fully understand and consent and sign the informed consent. Bed test. Every subject should leave detailed contact address, telephone, identity certificate and other information. At the same time, the doctor should leave his own contact telephone to the subject so that the subject can find the doctor whenever the condition changes. This is also conducive to the doctor to keep abreast of the change of the condition, reminding the subject to return to the doctor in time to avoid missing the visit.

13. Data preservation

Researchers must keep the original data of each subject, including all medical records and visiting records (including demographic and medical information, laboratory data, electrocardiogram, other examination or evaluation results), and a signed consent form.

Case report forms are written in carbon-free duplicate triple format. After data entry is completed, the applicants, clinical trial units and responsible units of clinical trials are filed separately.

All test data must be kept for 5 years after the end of the test. If required by existing regulations or agreements with bidders, such information should be kept for a longer period of time. The applicant or his agent will notify the researcher in writing of the deadline when the information no longer needs to be kept. If the research unit adjusts the location of the documents, the researcher shall notify the applicant or his agent in writing.

14. Modification of the scheme

After approval by the ethics committee, if there are significant changes in the implementation process, the main researchers in charge of clinical trials will write the "revised instructions" and sign them. At the same time, they need to report to the Ethics Committee for approval before they can be implemented. If no principled modification is made, the principal investigators, statisticians and bidders of the responsible unit of clinical trial shall discuss and decide together, and notify other participating units.

15. Organization and Management of Tests

15.1 Progress and Arrangement of Test Work

This pilot project will submit an application for ethical review in November 2017.

It is planned to start clinical trials in January 2018.

All cases are scheduled to be enrolled in November 2018.

All cases are scheduled to be completed in January 2019.

It is planned that all CRF checks and collections will be completed in February 2019, and data entry and data answering will be completed.

The statistical report is scheduled to be completed in April 2019.

The final report is scheduled to be completed in May 2019.

All clinical trials are planned to be completed within 18 months after the trial costs and drugs are in place.

Signature Page for Participating Center Researchers

1. I have obtained and reviewed the researcher's Manual of Xinnaoning Capsule Project.

2. I have read the test plan and consider it ethical.

3. I agree to carry out this test in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information obtained or related to this scheme.

5. I agree that all electronic signatures will be equally handwritten and legally binding.

Title：	A randomized, double-blind, parallel-controlled, multi-center clinical trial was conducted to evaluate the efficacy and safety of Xinnaoning capsule in the treatment of chronic stable angina pectoris (Qi stagnation and blood stasis syndrome).
Version number：	V1.1
Version date：	January 18, 2018

Organization：	
Signature of main researcher：	Date：

Clinical trial of Xinnaoning Capsule

Bidder's signature page

1. I am responsible for initiating, applying, organizing, funding and monitoring this clinical trial.

2. Our company is responsible for the financial compensation for the treatment of subjects who suffer from damage or death related to the clinical trial, and provides legal and economic guarantees to the researchers.

3. I agree to carry out this test in accordance with all applicable regulations and guidelines.

4. I agree that all electronic signatures will be equally handwritten and legally binding.

Title：	A randomized, double-blind, parallel-controlled, multi-center clinical trial was conducted to evaluate the efficacy and safety of Xinnaoning capsule in the treatment of chronic stable angina pectoris (Qi stagnation and blood stasis syndrome).
Version number：	V1.1
Version date：	January 18, 2018

Bidder: Guizhou Jingcheng Pharmaceutical Co., Ltd.	
Signature of Project Leader:	Date：

Clinical trial of Xinnaoning capsule

Statistician's signature page

1. I promise that the statistical data of this experiment are true and accurate.

2. I agree to carry out this test in accordance with all applicable

regulations and guidelines.

3. I agree to maintain the confidentiality of all information obtained or related to this test.

4. I agree that all electronic signatures will be equally handwritten and legally binding.

Title：	A randomized, double-blind, parallel-controlled, multi-center clinical trial was conducted to evaluate the efficacy and safety of Xinnaoning capsule in the treatment of chronic stable angina pectoris (Qi stagnation and blood stasis syndrome).
Version number：	V1.1
Version date：	January 18, 2018

Statistical Unit: Beijing Huaxia Zhongchuang Medical Science and Technology Research Institute	
Statistician's signature:	Date：

Clinical trial of Xinnaoning capsule

Inspector's signature page

1. I promise to ensure that the rights and interests of subjects in clinical trials are guaranteed.

2. I undertake to perform the duties of the Ombudsman in accordance with this scheme and all applicable regulations and guidelines.

3. I promise that the test records and reports are true, accurate and complete.

4. I agree to maintain the confidentiality of all information obtained or related to this test.

5. I agree that all electronic signatures will be equally handwritten and legally binding.

Title：	A randomized, double-blind, parallel-controlled, multi-center clinical trial was conducted to evaluate the efficacy and safety of Xinnaoning capsule in the treatment of chronic stable angina pectoris (Qi stagnation and blood stasis syndrome).
Version number：	V1.1
Version date：	January 18, 2018

Contract Research Organization：Beijing Duheng for Drug Evaluation and Research Co., Ltd. (DDER)	
Signature:	Date：

Enclosure 1 Coronary Heart Disease Subject Sports Manual Coronary Heart Disease Subject Sports Manual

The formulation of exercise methods for subjects with coronary heart disease is based on the patient's condition, age, sports history and hobbies. Clinicians will tell patients what activities should be carried out, how to master the amount of exercise and matters needing attention. The following will introduce the specific content of exercise methods for coronary heart disease subjects.

1. When can coronary heart disease subjects exercise?

1) Normal blood pressure and pulse can be used for exercise.

2) Exercise after noon is better: Angina pectoris, myocardial infarction and sudden death often occur from 5 am to 11 noon due to high tension of coronary artery in the morning and morning. The most suitable time for subjects with coronary heart disease is 7-9 pm. If some people are used to exercise in the morning, they should drink a large glass of water on an empty stomach before exercise.

3) Controlling the amount of motion;

4) No competitive sports activities;

5) Step by step and persevere;

6) inappropriate activities before and after meals: in principle, no exercise within 2 hours after meals, no meals or strong tea within 1 hour after exercise;

7) Don't take a bath immediately after exercise.

8) Prepare and relax before exercise;

9) Be in a good mood;

10) Avoid direct sunlight and windward exercise;

2. When can coronary heart disease subjects not exercise?

1) In quiet conditions, angina attacks often occur, and all kinds of coronary heart disease can not be controlled by treatment.

2) mild activity, i.e. palpitation, shortness of breath, wheezing or accompanied by cardiac insufficiency;

3) those who have serious arrhythmia, tachycardia, bradycardia, atrioventricular block and can not be controlled by medication;

4) Acute infection subjects;

5) accompanied by severe hypertension;

6) Patients with diabetes mellitus and uncontrolled condition after treatment;

7) Severe stenosis of three coronary arteries ranged from 80% to 90%.

8) Myocardial infarction with pericarditis and myocarditis;

9) Those with obvious myocardial ischemia, thrombophlebitis or recent history of embolism.

3. Notices for exercise of subjects with coronary heart disease:

1) Avoid training in bad weather, training before noon or afternoon in winter and early morning or evening in summer.

2) When walking, avoid windward, upper and lower steps and explosive force;

3) Avoid excessive exertion of upper limbs, especially lifting weights;

4) Avoid emotional excitement, tension and anger. In such cases, stop exercising and learn to relax.

5) When you feel tired, chest pain, dizziness, shortness of breath, whatever you are doing, you should stop and rest immediately.

6) Do not exceed the target heart rate prescribed by the doctor.

7) insist on taking medicine according to doctor's advice. Do not randomly add or subtract prescribed medicines by doctors; if some acute diseases occur, such as colds, diarrhea, etc., stop training.

4. Motion Method

1) Type of exercise: Walking, jogging, cycling or fitness bike, swimming and other sports are more suitable for coronary heart disease subjects. Because these sports belong to low to moderate intensity sports, mainly endurance sports. The energy metabolism of these exercises is mainly in the form of aerobic metabolism, so it is called "aerobic exercise" in medicine. Long-term exercise can improve the body's oxygen carrying capacity and cardiopulmonary function.

2) Volume of exercise: It is mainly composed of intensity, duration and frequency of exercise, which can be coordinated with each other.

① The intensity of exercise is an important index to ensure that the effect of exercise is achieved without causing danger.

Exercise intensity can be divided into three levels (low intensity, medium intensity and high intensity). It is measured by the amount of oxygen consumption during exercise. The greater the oxygen consumption, the greater the intensity of exercise. However, because it is difficult to measure oxygen consumption in clinical practice, heart rate is often used as the most practical index to measure exercise

intensity in actual exercise. The subjects only needed to count their own pulse for 15 seconds, multiplied by 4, to get a heart rate per minute. But this method is only suitable for subjects without arrhythmia. The highest heart rate at low and moderate intensity exercise was 100 beats per minute and 100-120 beats per minute respectively.

Generally speaking, subjects with coronary heart disease can exercise at low to moderate intensity.

② Number of exercises: exercise 3 to 5 times a week to achieve the purpose of calcination.

③ Exercise time: 30-40 minutes each time, including 5-10 minutes of preparation exercise; 15-20 minutes of formal exercise, during which the expected heart rate can be achieved; 5-10 minutes of finishing exercise.

3) Generally speaking, the slight increase of systolic blood pressure (systolic blood pressure does not exceed 20 mmHg) and the increase of heart rate (the ratio of heart rate to activity does not exceed 20 beats/min or the maximum heart rate does not exceed 120 beats/min) after exercise are normal reactions. But if there are shortness of breath, angina pectoris, arrhythmia, dizziness, nausea, paleness and long-term fatigue, insomnia and other discomforts after the activity, it is suggested that this exercise should be reduced or suspended in the next exercise.