International Journal of General Medicine Dovepress

Open Access Full Text Article

STUDY PROTOCOL

Efficacy and Safety of Jiuxin Pill in the Treatment of Patients with Stable Angina Pectoris: A Protocol for a Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial

Tongzuo Liu[1,2,*], Jingyi Zhang[1,2,*], Zhiqiang Zhao[1], Yingfei Bi[1], Ying Zheng[1], Shuai Wang[1], Xiaohua Dai[3], Jun Li[4], Qian Lin[5], Daimei Ni[6], Chenglong Wang[7], Jianguang Wu[8], Yitao Xue[9], Mingjun Zhu[10], Xianliang Wang[1,*], Jingyuan Mao[1,*]

[1]Cardiovascular Department, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, People's Republic of China; [2]Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; [3]Cardiovascular Department, The First Affiliated Hospital of Anhui University of Chinese Medicine, Anhui, People's Republic of China; [4]Cardiovascular Department, Guang'anmen Hospital of China Academy of Chinese Medicine Science, Beijing, People's Republic of China; [5]Cardiovascular Department, Dongzhimen Hospital of Beijing University of Chinese Medicine, Beijing, People's Republic of China; [6]Cardiovascular Department, Taihe Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Chinese Medicine, Anhui, People's Republic of China; [7]Cardiovascular Department, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing, People's Republic of China; [8]Cardiovascular Department, Affiliated Hospital of Jiangxi University of Chinese Medicine, Jiangxi, People's Republic of China; [9]Cardiovascular Department, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Shandong, People's Republic of China; [10]Cardiovascular Department, The First Affiliated Hospital of He'nan University of Traditional Chinese Medicine, Henan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jingyuan Mao; Xianliang Wang, Cardiovascular Department, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, People's Republic of China, Tel +86-13820498886; +86-13920007825, Email jymao@126.com; xlwang1981@126.com

Background: Stable angina pectoris (SAP), as a common type of coronary heart disease (CHD), is characterized by transient retrosternal squeezing pain or suffocation induced by exercise, mood swings, or other stress. Most patients with stable angina pectoris do not benefit from interventional therapy and medication, so optimizing treatment plans has important clinical significance. Jiuxin pill is a Chinese patent medicine developed by Huatuo Chinese Medicine Co. Ltd. (Bozhou, China) to relieve the symptoms of stable angina pectoris (SAP). However, there is a lack of evidence support from high-quality clinical studies.

Methods: In this randomized, double-blind, placebo-controlled, multicenter clinical trial, 170 patients with SAP were recruited from 11 centers in China. The patients were randomized to either the treatment group (Jiuxin pill, 2 pills, bid) or the control group (Jiuxin pill simulant, 2 pills, bid) without changing the original conventional western medicine. The trial was set up with a run-in period of 7 days, a treatment period of 28 ± 2 days, and a follow-up period of 28 ± 2 days. Total exercise time (TED) in the treadmill test and Seattle Angina Questionnaire (SAQ) scores were set as the main efficacy outcomes, and the 1-minute heart rate recovery (HRR1), metabolic equivalents (METs), maximum ST segment depression, Borg perceived exertion after exercise, the average number of angina attacks per week, usage of nitroglycerin, drug withdrawal and reduction rate, information scoring of four diagnostic methods in traditional Chinese medicine and incidence of major adverse cardiovascular events were set as the secondary efficacy outcomes. Adverse events were monitored throughout the trial.

Discussion: In China, the use of Chinese patent medicine in the treatment of stable angina pectoris is more common. This trial evaluated the efficacy and safety of the Jiuxin pill in the treatment of patients with SAP, and the trial results provide high-quality research evidence for its clinical application.

Trial Registration: This trial has been registered in the China Clinical Trial Registry on 11 June 2022 (Registration No.: ChiCTR2200060780, https://www.chictr.org.cn/showproj.html?proj=172352).

Keywords: traditional Chinese medicine, Jiuxin pill, stable angina pectoris, protocol, randomized controlled trial

Received: 3 July 2024
Accepted: 9 October 2024
Published: 15 October 2024

Background

Stable angina pectoris (SAP), as a common type of coronary heart disease (CHD), is characterized by transient retrosternal squeezing pain or suffocation induced by exercise, mood swings, or other stress.[1] Studies have shown that SAP is associated with an increased risk of cardiovascular endpoint events and all-cause mortality.[2,3] Despite the increasing sophistication of modern medical treatments for SAP, several studies have shown that interventional therapies for patients with SAP cannot provide enough additional clinical benefits to patients, and thus there would remain such clinical problems as recurrent angina pectoris symptoms, daily exercise intolerance or compromised quality of life.[4–7]

Jiuxin pill is a Chinese patent medicine developed by Huatuo Chinese Medicine Co., Ltd. (Bozhou, China). The prescription comes from the Angong Niuhuang pill, a famous classic prescription. Consisting of *Total Ginsenoside of Ginseng Stems and Leaves* (Renshen Jingye Zongzaogan), *Ox Gall Paste Powder* (Niudangaofen), *Artificial Moschus* (rengongshexiang), *Margarita* (Zhenzhu), *Bovis Calculus* (Niuhuang), *Borneolum Syntheticum* (Bingpian), *Bufonis Venenum* (Chansu), *Notoginseng Radix et Rhizoma Paste Powder* (Sanqigaofen), the Jiuxin pill provides the effect of promoting qi and activating blood circulation, resolving phlegm and dredging collaterals. A previous study[8] proved that the Jiuxin pill can reduce the lactic serum dehydrogenase (LDH) and creatine kinase-MB (CK-MB) levels of rats with myocardial ischemia, reduce the myocardial infarction area, and lower the value of the blood viscosity. Li Hongliang et al[9,10] showed that the Jiuxin pill combined with regular western medicine therapy could reduce the plasma endothelin level of patients with CHD and improve the coronary blood flow of patients with ischemic heart disease and myocardial ischemia. However, there is still a lack of evidence from high-quality clinical studies that are rigorously designed. Therefore, this study was designed as a randomized, double-blind, placebo-controlled, multicenter clinical trial to evaluate the efficacy and safety of the Jiuxin pill in the treatment of patients with SAP and to provide high-quality evidence for its clinical application.

Methods/Design

Study Design

This study is designed as a randomized, double-blind, placebo-controlled, multicenter trial. A total of 170 subjects with SAP who fulfill the inclusion and exclusion criteria were enrolled and randomly assigned to either a treatment group (n = 85) or a control group (n = 85) by the proportion of 1:1. The study flow included a 7-day run-in period, a 28 ± 2 days treatment period and a 28±2 day follow-up period, as is shown in Figure 1. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2200060780).

Subjects Recruitment

All subjects were recruited from 11 centers across China, including The First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, First Affiliated Hospital of Anhui University of Chinese Medicine, Taihe Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Chinese Medicine, the Affiliated Hospital to Changchun University of Chinese Medicine, Dongzhimen Hospital of Beijing University of Chinese Medicine, First Affiliated Hospital of Henan University of Chinese Medicine, Affiliated Hospital of Jiangxi University of Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Guang'anmen Hospital of China Academy of Chinese Medical Sciences, Hebei General Hospital, Xiyuan Hospital of China Academy of Chinese Medical Sciences. Qualified subjects will be identified by trained researchers at each center based on inclusion and exclusion criteria. Each subject was informed of the purpose, procedure, benefits, and potential hazards of the study, as well as their rights and responsibilities regarding the study. Any subject may withdraw from the trial at any time without giving any reason, and their medical care and legal rights will not be affected. Subjects were enrolled in this study after understanding relevant information and signing informed consent.

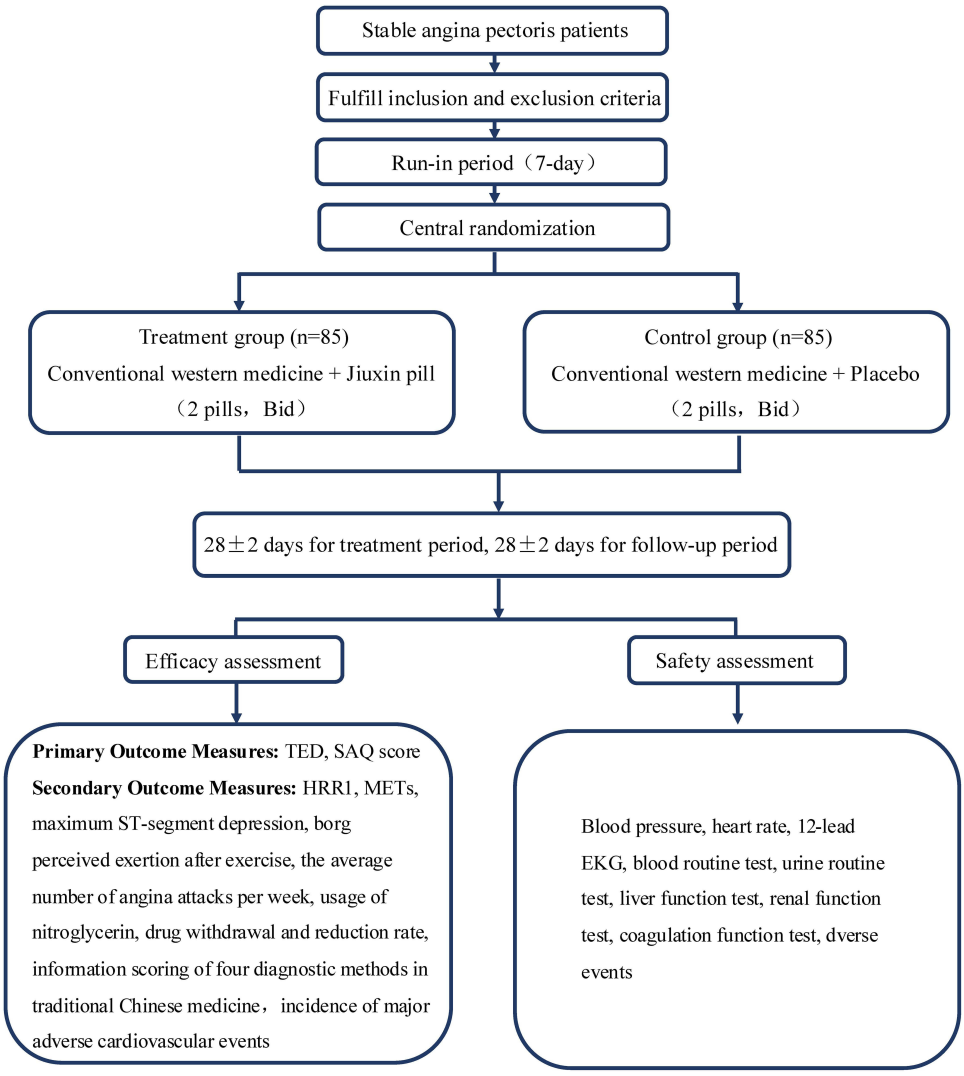

Figure 1 Flow diagram of the study.
Abbreviations: Bid, bis in die; TED, total exercise time; SAQ, Seattle Angina questionnaire; HRR1, 1-minute heart rate recovery; METs, metabolic equivalents; EKG, electrocardiogram.

Participants

Diagnostic Criteria

(1) Diagnostic Criteria for CHD

A diagnosis can be made if any of the criteria are met.

① Coronary angiography revealed a narrowing of more than 50% of the lumen diameter of at least one major branch of the coronary artery;

② After percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG).

(2) Diagnostic Criteria for SAP

① There were no significant changes in the severity, frequency, nature, and predisposing factors of angina attacks in the past 60 days;

② A negative TnT/I result combined with an electrocardiogram (ECG) result ruled out acute coronary syndrome.

Grading of Angina of Effort by the Canadian Cardiovascular Society (CCS)

I. Ordinary activity, such as walking and ascending stairs, does not cause angina; angina with strenuous or rapid or prolonged exertion at work or recreation;
II. Slight limitation of ordinary activity; angina walking or ascending stairs rapidly, walking or ascending stairs after meals, or in the cold, wind or under emotional stress, or only during the first few hours awake, walking more than 200m on level ground or ascending more than one flight of ordinary stairs at a normal pace under normal conditions;
III. Marked limitations in ordinary physical activity; angina when walking 100–200 m on level ground or one flight of stairs under normal conditions and at a normal pace;
IV. Inability to partake in any physical activity without discomfort–angina syndrome may be present at rest.

Inclusion Criteria

(1) Age from 35 to 74 (including boundary value), no gender restriction;
(2) Conform to the western medicine diagnostic criteria for SAP due to CHD;
(3) The history of SAP no less than 2 months;
(4) The average number of angina pectoris attacks per week ≥ 1 in the first month before being selected;
(5) CCS angina pectoris classification grading II–III;
(6) Sign informed consent.

Exclusion Criteria

(1) Patients with myocardial infarction in recent 3 months;
(2) Patients who have received PCI or other cardiac surgery (such as CABG) in the past 1 year;
(3) Patients who plan to undergo coronary revascularization (CABG or PCI) within 2 months;
(4) Patients with unstable angina pectoris, intractable heart failure, cardiogenic shock, severe heart valve disease and other serious cardiovascular diseases;
(5) Patients with poorly controlled hypertension (systolic blood pressure ≥ 160mmHg or diastolic blood pressure ≥ 100mmHg after treatment);
(6) Patients with severe respiratory diseases such as severe pulmonary insufficiency;
(7) Patients with severe liver and kidney diseases such as liver dysfunction (alanine aminotransferase or aspartate aminotransferase levels more than 2 times higher than the normal value), renal dysfunction (creatinine level more than 2 times higher than the normal value);
(8) Patients with malignant tumors, severe anemia, severe renal artery stenosis, and other serious diseases or conditions;
(9) Patients with contraindications to exercise treadmill test;
  (a) Hypertrophic obstructive cardiomyopathy;
  (b) Severe hypertension (systolic blood pressure ≥ 180mmHg and/or diastolic blood pressure ≥ 100mmHg);
  (c) Unexplained hypotension (systolic blood pressure ≤ 85mmHg);
  (d) Tachyarrhythmia (<50 beats/min) or tachyarrhythmia (>100 beats/min);
  (e) Left bundle branch block;
  (f) Ventricular pacing rhythm;
  (g) Preexcitation syndrome;
  (h) CCS-IV angina, acute coronary syndrome, acute heart failure, potentially life-threatening arrhythmias, acute myocarditis, acute pericarditis, endocarditis;
  (i) Stenosis of left main coronary artery;
  (j) Aortic dissection;
  (k) Moderate and severe stenosis of the aortic valve;
  (l) Pulmonary artery embolism or pulmonary infarction or deep venous thrombosis of lower limbs;
  (m) Recent stroke or transient ischemic attack;

(n) Unsolved clinical problems: electrolyte disorder, digitalis poisoning, severe anemia, hyperthyroidism, hypoglycemia, etc.;
(o) Unable to complete the test due to physical or mental reasons.

(10) Patients who have participated in other clinical studies in the past 2 months;
(11) Patients who are allergic to known ingredients of the study drug;
(12) Women with a positive pregnancy test, planned pregnancy or lactation;
(13) Patients who could not participate in the study due to recent infection, trauma, and other reasons considered by the researchers.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Randomization and Blind Method

Randomization

Interactive Web Response System (IWRS), a central randomization management system, was employed for randomized group allocation. Through a dynamic randomization process, the patients were randomly assigned to a treatment group or a control group in a ratio of 1:1. The format of subject screening number in this study was AA+BBB. AA indicates the center number, which is a 2-digit Arabic numeral. BBB represents the screening sequence number of the subject, which is a 3-digit Arabic numeral. The random numbers in the random table are in R+ three Arabic digits format, written from R001 in turn.

Blind Method

The blinding will be maintained amongst the investigators and patients. Before the trial started, the applicant unit (or the contract research organization) and the random blind personnel conducted a unified blind edit of the study drug. The drug blinding was carried out by the randomization staff at the site designated by the sponsor, and the corresponding test drug label was affixed to the drug package according to the randomization table. Before the blinding operation, the test drug and the placebo were placed separately, and the labeling of drugs was carried out in sequence. The labeling of test drugs (including standby drugs) and placebo (including standby drugs) were carried out separately. After label pasting was completed, drugs were mixed in the order of random numbers in the random table to complete the blind operation.

Sample Size Calculation

This trial involves multiple outcomes so there are two sample sizes estimated separately and the larger one was taken. 1) The sample size estimated according to the primary outcome TED is based on results from the study by Thomas Münzel et al.[11] It was assumed that after 2 months of intervention, the TED change from baseline is 53.20 ± 100.75 (s) in the placebo group and 107.0 ± 118.0 (s) in the treatment group. The calculation was performed with PASS 2021 software, module Two-Sample *t*-Tests Allowing Unequal Variance. Considering the shedding risk of ≤20%, patients would be randomly assigned to two groups in the ratio of 1:1 and each group requires at least 85 patients, and a total of 170 cases were needed to produce positive results (one-tailed test, significant level α=0.05, the power (1-β) = 0.80).

Taking the SAQ score as the primary outcome measure, the sample size was estimated based on results from the study by Liang Xiaopeng et al.[12] It was assumed that the change in SAQ score from baseline was 9.87 ± 14.43 in the placebo group and 21.08 ± 14.00 in the treatment group. The calculation was performed with PASS 2021 software, module Two-Sample t-Tests Allowing Unequal Variance. Considering the shedding risk of ≤20%, patients would be randomly assigned to two groups in the ratio of 1:1 and each group requires at least 46 patients, and a total of 92 cases were needed to produce positive results.

In summary, the sample size of this study was 170 cases.

Interventions

Treatment Methods for Each Group

Subjects who preliminarily met the inclusion criteria entered the 7-day run-in period. Based on not changing the original conventional western medicine treatment, they took the placebo of Jiuxin pill orally, 2 pills/time, twice daily. After the end of the run-in period, subjects with stable conditions were randomly divided into the treatment group (based on no changes in the

original conventional Western medicine treatment, oral Jiuxin pill, 2 pills/time, twice daily) or the control group (based on no changes in the original conventional western medicine treatment, oral Jiuxin pill placebo, 2 pills/time, twice daily). The treatment period was 28 ± 2 days, and the follow-up period was 28 ± 2 days. Both the Jiuxin pill and placebo were provided by Huatuo Chinese Medicine Co., Ltd., each weighing 25 mg. The appearance, smell, shape, and specifications of the placebo were the same as the Jiuxin pill, the main ingredient is starch, and no more than 5% of the ingredients of the Jiuxin pill are added.

Western Medicine Treatment

The subjects were treated refer to the *Diagnosis and Treatment Guidelines for Stable Coronary Heart Disease* issued by the Chinese Society of Cardiology of the Chinese Medical Association in 2018[5] for conventional western medicine treatment and did not change their original routine western medicine treatment plan in principle.

Drug Combination

(1) Subjects could continue to use the drugs used before the study for the treatment and try to keep the original drug type, usage and dosage unchanged during the study;
(2) When subjects had angina attacks, they could take sublingual nitroglycerin (Beijing Yimin. Although the methods of modern medical treatment of SAP have been improved, such as the application of therapeutic medicines becoming more and more standardized, interventional therapy and surgical operation are becoming more and more mature, SAP still limits the daily exercise tolerance and affects the quality of life of many patients. Pharmaceutical Co., Ltd. (Beijing, China), 0.5mg), which was dispensed uniformly, and record in detail;
(3) If adverse events occured to subjects during the study, the researchers could use the corresponding drugs for treatment according to relevant guidelines, but the researchers should evaluate whether the drugs used affect the efficacy or safety evaluation of the drugs in the study, and determine whether the subjects should withdraw from the study after taking the corresponding treatment.
(4) Drugs or other treatments taken during the study were used under the guidance of the researchers. Any drug used during the study was recorded and described in detail in the medical records of the study, including the name of the drug, the method of use, the dosage of the drug, the reason for use, etc., for analysis and reporting in summary;
(5) Other traditional Chinese medicine preparations are prohibited during the trial.

Outcomes

Primary outcomes

(1) Treadmill exercise test (Bruce protocol): total exercise time;
(2) Seattle Angina Questionnaire (SAQ) score.

Secondary outcomes

(1) Treadmill exercise test (Bruce protocol): 1-minute heart rate recovery (HRR1), metabolic equivalents (METs), maximum ST segment depression;
(2) Borg perceived exertion after exercise;
(3) The Average number of angina attacks per week;
(4) Usage of nitroglycerin, drug withdrawal and reduction rate;
(5) Information scoring of four diagnostic methods in traditional Chinese medicine;
(6) Incidence of major adverse cardiovascular events.

Safety Assessment

Safety assessment was based on vital signs, 12-lead ECG, laboratory examinations, and adverse events. Vital signs documented before and after treatment will include blood pressure, heart rate, etc. Laboratory examinations to be performed include blood and urine routines, liver and kidney profile, coagulation function (hepatic event and renal event definition/threshold are provided in Table 1). Adverse events, especially the severe adverse events, are to be reported to the research group committee within 24h.

Table 1 Hepatic Event and Renal Event Definition/ Threshold

Hepatic Event Definition/ Threshold	
AE of special interest	ALT or AST > 3×ULN ALP > 2×ULN TBL > 1.5×ULN
Medically significant event (SAE)	ALT or AST > 5×ULN (with or without TBL > 2×ULN) ALP > 5×ULN (with or without TBL > 2×ULN) TBL > 3×ULN Potential Hy's Law cases (defined as ALT/AST > 3×ULN and TBL > 2×ULN without notable increase in ALP to > 2×ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3×ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
Renal event definition/ threshold	
AE of special interest	eGFR decreases by ≥ 25% from baseline [or serum creatinine concentration increase to 2.5 mg/dL (221 μmol/L)]
Medically significant event (SAE)	eGFR decreases by ≥ 40% from baseline [or serum creatinine concentration rises above 3 mg/dL (265μmol/L)]

Abbreviations: AE, adverse events; SAE, serious adverse event; ULN, upper limit of normal; ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; ALP, alkaline phosphatase; TBL, total bilirubin; eGFR, estimated glomerular filtration rate.

Data Collection

The time points for data collection in this study are, respectively, screening period (Day −9~-8), baseline period (0 ± 2 days), treatment period (14 ± 2 days, 28 ± 2 days), and follow-up period (42 ± 2 days, 56 ± 2 days), and the details are shown in Table 2.

Adverse Events

Every AE occurring during the study must be recorded in the CRF, according to the actual circumstances. The following information should be recorded: occurrence time, severity, duration, adopted measure, and outcome of the AE. The researcher should evaluate the correlation between the AE and the drug and decide whether to stop the observation, according to the condition, and follow-up investigations should be conducted on the cases that are discontinued due to adverse reactions.

Serious adverse events (SAEs) are defined as events that can cause hospitalization, loss of ability to work, disability, congenital deformity, or death, according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. In addition to the abovementioned measures, in the incidence of any SAE, the principal investigator will be notified. Additionally, a report will be submitted to the ethics committee and the data and safety monitoring committee (DSMC) within 24 hours.

Data Management

The data management of this trial was performed by Hunan Qinglang Data Technology Co. (Changsha, China). In this trial, electronic data capture (EDC) was used for the collection and management of trial data, and the system kept a complete modification track to ensure the traceability of clinical trial data. The Clinical Data Interchange Standards Consortium (CDISC) standard was adopted as far as possible for the establishment of a database. The data was entered online by the investigator or by personnel authorized by the investigator promptly after the visit. After data entry was completed, any data changes were explained and automatically recorded in the system. The data management personnel will query and manage the trial data according to the data verification plan. Medical coding was performed by medical coders, including concomitant medications and adverse events. A medical review of coding was required before the

Table 2 Measurement Items and Points of Data Capture

Points / Items	Screening Period Day-9~-8	Baseline Period 0 ±2 Days	Treatment period		Follow-Up Period	
			Treatment visit 1 14±2 Days	Treatment Visit 2 28 ±2 Days	Follow-Up visit 1 42±2 Days	Follow-Up Visit 2 56±2 Days
Collect demographic data	√					
Height and weight	√					
Medical history, treatment history and allergic history	√					
Life style	√					
Vital signs	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√
Blood routine test		√		√		
Urine routine test		√		√		
Liver function test		√		√		
Renal function test		√		√		
Coagulation function test		√		√		
Serum pregnancy test		√				
TnT/I		√				
12-lead EKG	√	√		√		
UCG	√					
ETT	√	√		√		
Borg perceived exertion after exercise	√	√		√		
SAQ score		√		√		√
Information scoring of four diagnostic methods in traditional Chinese medicine		√		√		√
Record nitroglycerin usage		√	√	√	√	√
Record number of angina attacks		√	√	√	√	√
Record adverse events		√	√	√	√	√

Abbreviations: TnT/I, troponin-T/I; EKG, electrocardiogram; UCG, ultrasonic cardiogram; ETT, exercise treadmill testing; SAQ, Seattle Angina questionnaire; TCM, traditional Chinese medicine.

database lock. At the end of the trial, the electronic case report form (eCRF) of each subject will be electronically archived and stored at the clinical trial site.

Statistical Analysis

SAS (version 9.4 or above) software will be used for statistical analysis in this trial. Quantitative data were described with mean, standard deviation, median, quartile, minimum, maximum, etc. Differences between groups were compared using a *t*-test, analysis of variance, Wilcoxon rank sum test, or Friedman's M test. Intra-group differences before and after treatment were compared using paired *t*-test or Wilcoxon paired signed rank test, etc. Categorical and grade data were described by frequency and percentage. Differences between groups were compared using the Chi-square test, Fisher's exact test, or CMH test. Intra-group differences before and after administration were compared by the McNemar chi-

square test or binomial distribution test. Unless otherwise specified, all hypothesis tests are two-sided tests, with type I error α=0.05 (two-sided), type II error β=0.2, and power 1-β=0.8. When $P<0.05$, the null hypothesis is rejected, and the difference will be considered statistically significant.

Discussion

According to the statistics of the World Health Organization, about 17.3 million people worldwide die from CHD each year, and the number of cardiovascular deaths has prospected to rise to 23.6 million by 2030.[13] The *China Cardiovascular Health and Disease Report 2020 Summary*[14] points out that cardiovascular disease was the leading cause of death among urban and rural residents in China in 2018, among which the mortality rate of CHD is still on the rise, accounting for the first place of cardiovascular disease. It is projected that there are a total of 330 million patients with cardiovascular diseases in China, including 11.39 million patients with CHD. The burden of cardiovascular disease in China is increasing, which has become a major public health problem. SAP, as a common type of CHD, is characterized by transient substernal squeezing pain or suffocation and is triggered by exercise, mood swings, or other stress. Although the methods of modern medical treatment of SAP have been improved, such as the application of therapeutic medicines becoming more and more standardized, interventional therapy and surgical operation are becoming more and more mature, SAP still limits the daily exercise tolerance and affects the quality of life of many patients. Most patients with stable angina pectoris do not benefit from interventional therapy and medication, so optimizing treatment plans has important clinical significance. In China, Chinese patent medicines are commonly used to treat SAP, which are often used as substitutes for western medicine or often combined with western medicine to treat angina pectoris.[15,16] Much research evidence has been accumulated on the clinical efficacy of traditional Chinese medicine in treating SAP.[17–19] Clinical practice and relevant studies[20–22] have confirmed that Chinese patent medicines have certain advantages in relieving angina pectoris, intervening in restenosis after PCI, improving quality of life, increasing exercise tolerance, and reducing the incidence of cardiovascular events and adverse reactions.

Jiuxin pill is a Chinese patent medicine developed by Huatuo Chinese Medicine Co., Ltd. The prescription comes from Angong Niuhuang pill, a classic famous prescription. The main ingredients are *Total Ginsenoside of Ginseng Stems and Leaves* (Renshen Jingye Zongzaogan), *Ox Gall Paste Powder* (Niudangaofen), *Artificial Moschus* (rengongshexiang), *Margarita* (Zhenzhu), *Bovis Calculus* (Niuhuang), *Borneolum Syntheticum* (Bingpian), *Bufonis Venenum* (Chansu), *Notoginseng Radix et Rhizoma Paste Powder* (Sanqigaofen). It has the effect of promoting qi and activating blood circulation, resolving phlegm, and dredging collaterals. Previous studies[9,10] showed that applying the Jiuxin pill along with the conventional western medicine treatment could reduce the plasma endothelin level of patients with CHD, improve the coronary blood flow of patients with ischemic heart disease and improve myocardial ischemia. However, there is still a lack of evidence support from rigorously designed high-quality clinical studies. Therefore, it is necessary to design a high-quality clinical trial to evaluate the efficacy and safety of Jiuxin pill in the treatment of patients with SAP.

This trial is a randomized, double-blind, placebo-controlled, multicenter clinical trial involving 11 tertiary hospitals nationwide. Before the initiation of the trial, the project team invited relevant experts in clinical medicine, statistics, and medical ethics to conduct relevant consultation and repeated demonstration, optimize the clinical trial protocol, and developed a flow diagram for subject screening and enrollment, standard operation procedure (SOP) for treadmill exercise test and recommendations on traditional Chinese medicine syndrome identification, etc., to ensure the proper progress of the clinical trial. A strict placebo control was selected for this clinical trial. The purpose of using placebo control is to exclude the placebo effect and to maximally reflect the efficacy and safety of the drug. The placebo effect is the effect on the body of a patient's strong belief that he or she will be cured by the drug or method. In clinical trials, placebo-controlled trials can reliably demonstrate the efficacy of the study medicine and determine whether an adverse event is caused by the medicine or an underlying disease. The selection of placebo contributes to the successful implementation of the double-blind method. Jiuxin pill placebo adopts a special manufacturing process. Its appearance, smell, shape, and specifications are the same as Jiuxin pill, the main ingredient is starch, and the added ingredients do not exceed 5% of Jiuxin pill. Jiuxin pill placebo is not harmful to human health and does not produce obvious adverse drug reactions. Its packaging, labeling, and identification are completely consistent with the experimental drug. In addition, we focused on evaluating the improvement of exercise tolerance and quality of life of the patients, combining the traditional four diagnostic methods with modern medical indicators, and evaluating the efficacy of drugs from the perspectives of

traditional Chinese and western medicine, which not only reflected the evaluation of relevant efficacy of western medicine but also reflected the characteristics and advantages of traditional Chinese medicine treatment.

Exercise tolerance represents the maximum exercise that the body can achieve, can reflect the blood and oxygen supply of the myocardium, and is closely related to the prognosis and quality of life of patients with CHD. Relevant studies[23,24] showed that with the decrease in exercise tolerance, exercise capacity and social function of patients with CHD are also restricted in many aspects, which seriously affects the quality of life of patients. According to the requirements of Technical Guidelines for Clinical Study of Traditional Chinese Medicine and Natural Medicine in the Treatment of Angina Pectoris of Coronary Heart Disease,[25] clinical trials with the improvement of SAP as the target indication should generally focus on the evaluation of exercise tolerance of exercise stress test, anti-myocardial ischemia effect, dosage of nitrate drugs, etc. The treadmill exercise test is the most common type of exercise stress test. The gradient and/or slope of the exercise treadmill is adjusted according to certain rules, and the myocardial ischemia and exercise tolerance of patients are evaluated by continuously monitoring the changes in heart rate, blood pressure, ECG, and other indicators during exercise.[26] The Bruce protocol was used in the treadmill exercise test in this experiment, that is, the variable speed and variable slope exercise with the graded increase of exercise load over time. The Bruce protocol is easy to reach the predetermined heart rate level, and for older patients, moderate exercise intensity is easier to complete, and exercise safety is better.[27] In this trial, TED and SAQ scores were used as the primary efficacy evaluation indicators, and HRR1, METs, maximum ST segment depression, Borg perceived exertion after exercise, the average number of angina attacks per week, usage of nitroglycerin, drug withdrawal, and reduction rate, information scoring of four diagnostic methods in traditional Chinese medicine, and the incidence of major adverse cardiovascular events is used as the secondary efficacy evaluation indicators to evaluate the effectiveness of Jiuxin pill in improving the exercise tolerance and quality of life of patients with SAP from subjective and objective perspectives. A 7-day run-in period is set in this trial to eliminate the delayed effect of similar drugs already taken, stabilize the baseline level, and remove the placebo effect, to improve the compliance of subjects. According to the recommendations of the above guidelines and in combination with previous studies, a treatment period of 28 ± 2 days was set up in this trial. However, this trial was designed for a short follow-up period of 28 ± 2 days, and it may be difficult to obtain beneficial evidence for reducing acute cardiovascular events and all-cause mortality in patients with stable angina pectoris.

In conclusion, this trial will evaluate the efficacy and safety of the Jiuxin pill in the treatment of SAP, and provide a high-quality research evidence for the clinical application of the Jiuxin pill.

Abbreviations

SAP, Stable angina pectoris; CHD, Coronary heart disease; TED, Total exercise time; SAQ, Seattle Angina questionnaire; HRR1, 1-minute heart rate recovery; MET, Metabolic equivalent; LDH, Lactic serum dehydrogenase; CK-MB Creatine kinase-MB; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass graft; ECG, Electrocardiogram; TnT/I, Troponin-T/I; CCS, Canadian cardiovascular society; IWRS, Interactive web response system; EDC, Electronic data capture; CDISC, Clinical data interchange standards consortium; eCRF, Electronic case report form; SOP, Standard operation procedure.

Trial Status

Since August 12, 2022, this study has recruited 130 patients. We plan to complete all subject recruitment by June 2025.

Dissemination Policy

Results will be published in peer-reviewed journals and presented at national and international scientific meetings regardless of the magnitude or direction of effect.

Protocol Amendments

The current version is version 1.0, if there are any problems during the implementation of the plan and it becomes necessary to revise it, the revised plan will be submitted to the ethics committee for approval before implementation.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

This trial was conducted by the Declaration of Helsinki and approved by the institutional review board (IRB) of the First Teaching Hospital of Tianjin University of TCM (EC Approval Letter No: TYLL2022[Y] Zi 004) and the Institutional Review Boards of other participating hospitals.

Consent for Publication

Written informed consent must be signed by the subject or his/her legally authorized representative before enrollment. All the patient details will be fully anonymous and confidential.

Acknowledgments

The authors would like to thank the following participating organizations: The First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, First Affiliated Hospital of Anhui University of Chinese Medicine, Taihe Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Chinese Medicine, the Affiliated Hospital to Changchun University of Chinese Medicine, Dongzhimen Hospital of Beijing University of Chinese Medicine, First Affiliated Hospital of Henan University of Chinese Medicine, Affiliated Hospital of Jiangxi University of Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Guang'anmen Hospital of China Academy of Chinese Medical Sciences, Hebei General Hospital, Xiyuan Hospital of China Academy of Chinese Medical Sciences.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Ministry of Education of the People's Republic of China "Program for Innovative Research Team in University" (NO. IRT_16R54), and Traditional Chinese Medicine Innovation Team and Talent Support Program of National Administration of Traditional Chinese Medicine (ZYYCXTD-C-202203).

Disclosure

The authors confirm that they have no conflict of interest. None of the authors in this study received funding from the drug manufacturers involved. The drug manufacturer did not participate in any aspects of the study design, data collection, publication of the paper, etc. of this trial.

References

1. Section of Interventional Cardiology of Chinese Society of Cardiology. Section of atherosclerosis and coronary artery disease of Chinese society of cardiology; specialty committee on prevention and treatment of thrombosis of Chinese college of cardiovascular physicians guideline on the diagnosis and treatment of stable coronary artery disease. *Zhonghua xin xue guan bing za zhi*. 2018;46:680–694. doi:10.3760/cma.j.issn.0253-3758.2018.09.004
2. Jespersen L, Hvelplund A, Abildstrom SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–744. doi:10.1093/eurheartj/ehr331
3. Spertus JA, Jones P, McDonell M, et al. Health status predicts long-term outcome in outpatients with coronary disease. *Circulation*. 2002;106:43–49. doi:10.1161/01.CIR.0000020688.24874.90
4. Tanaka A, Kawarabayashi T, Nishibori Y, et al. No-reflow phenomenon and lesion morphology in patients with acute myocardial infarction. *Circulation*. 2002;105:2148–2152. doi:10.1161/01.CIR.0000015697.59592.07

5. Wiest FC, Bryson CL, Burman M, et al. Suboptimal pharmacotherapeutic management of chronic stable angina in the primary care setting. *Am j Med*. 2004;117:234–241. doi:10.1016/j.amjmed.2004.02.044
6. Kirwan B-A, Lubsen J, Poole-Wilson PA. Treatment of angina pectoris: associations with symptom severity. *Int J Cardiol*. 2005;98:299–306. doi:10.1016/j.ijcard.2003.10.050
7. Borrás X, Garcia-Moll X, Gómez-Doblas JJ, et al. Stable angina in Spain and its impact on quality of life. The AVANCE Registry. *Rev Españ de Cardiol*. 2012;65:734–741. doi:10.1016/j.rec.2012.03.010
8. Zhou WL, Zhong QS, Li LF, et al. Preliminary pharmacodynamics on effects of Kyushin pills on myocardial ischemia and promoting blood circulation to remove stasis. *Central South Pharm*. 2020;18(3):402–406. doi:10.7539/j.issn.1672-2981.2020.03.012
9. Li HL, Li ZG, Wang SX, et al. Effect of Jiuxin pill on plasma endothelin levels in a patient with coronary heart disease. *Modern Health*. 2016;(12):186. doi:10.3969/j.issn.1671-0223(x).2016.12.163
10. Li HL, Zhang XY, Wang SX, et al. Comparison of the effect of Huatuo Jiuxin pill in the treatment of ischemic heart disease. *Health All*. 2017;11(11):139. doi:10.3969/j.issn.1009-6019.2017.04.196
11. Münzel T, Meinertz T, Tebbe U, et al. Efficacy of the long-acting nitro vasodilator pentaerithrityl tetranitrate in patients with chronic stable angina pectoris receiving anti-anginal background therapy with beta-blockers: a 12-week, randomized, double-blind, placebo-controlled trial. *Eur Heart J*. 2014;35:895–903. doi:10.1093/eurheartj/eht384
12. Xiao-Peng L, Cai-Xia G, Jie MA, et al. Treatment of stable angina pectoris of coronary heart disease patients by huoxin wan(Concentrated Pill): A multicenter, randomized, double-blinded, placebo-controlled clinical trial. *Chin J Integ Tradit West Med*. 2018. doi:10.7661/j.cjim.20171220.376
13. World Health Organization. Global status report on noncommunicable diseases 2014. *Women*. 2011;47:2562–2563. doi:10.1056/NEJMc1313604#SA2
14. The Writing Committee of the Report on Cardiovascular Health and Diseases in China, Hu SS. Report on cardiovascular health and diseases burden in China: an updated summary of 2020. *Chin Circul J*. 2021;36(6):25. doi:10.3969/j.issn.1000-3614.2021.06.001
15. Gao ZY, Xu H, Shi DZ, et al. Analysis on outcome of 5284 patients with coronary artery disease: the role of integrative medicine. *J Ethnopharmacol*. 2012;141:578–583. doi:10.1016/j.jep.2011.08.071
16. Chen K, Shi D, Xu H, et al. XS0601 reduces the incidence of restenosis: a prospective study of 335 patients undergoing percutaneous coronary intervention in China. *Chinese Med J*. 2006;119:6–13. doi:10.1097/00029330-200601010-00002
17. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in China. *Evid Bas Complem Alternat Med*. 2012;2012:268542. doi:10.1155/2012/268542
18. Luo J, Shang Q, Han M, et al. Traditional Chinese medicine injection for angina pectoris: an overview of systematic reviews. *Am J Chin Med*. 2014;42:37–59. doi:10.1142/S0192415X14500037
19. Zhang Z, Zhang F, Wang Y, et al. Traditional Chinese medicine for stable angina pectoris via TCM pattern differentiation and TCM mechanism: study protocol of a randomized controlled trial. *Trials*. 2014;15:1–8. doi:10.1186/1745-6215-15-422
20. Standardization Project Group of Clinical Application Guidelines for Chinese Patent Medicine Treatment of Dominant Diseases. Guidelines for clinical application of Chinese patent medicine in the treatment of coronary heart disease (2020). *Chin J Integ Tradit West Med*. 2021;19(9):1409–1435. doi:10.12102/j.issn.1672-1349.2021.09.001
21. Bi YF, Mao JY, Wang XL, et al. Clinical advantages of traditional Chinese medicine in prevention and treatment of coronary heart disease and thinking on curative effect evaluation. *J Traditional Chin Med*. 2015;56(5):437–440.
22. Zhang J, Zhang MZ, Wang L. Systematic review of compound danshen dripping pills for coronary heart disease. *Chin J New Drugs*. 2009;18(6):465–468.
23. Jeng C, Yang MH, Chen PL, Ho C-H. The influence of exercise tolerance on quality of life among patients with heart failure. *Qu Al Life Res*. 2004;13(5):925–932. doi:10.1023/B:QURE.0000025604.15624.82
24. Christensen SB, Dall CH, Prescott E, et al. A high-intensity exercise program improves exercise capacity, self-perceived health, anxiety and depression in heart transplant recipients: a randomized, controlled trial. *J Heart Lung Transplant*. 2012;31:106–107. doi:10.1023/B:QURE.0000025604.15624.82
25. Center for Drug Evaluation, NMPA. Technical guidelines for clinical study of traditional Chinese medicine and natural medicine in treating angina pectoris of coronary heart disease [EB/OL]; 2011.
26. Zhang JH. Application of treadmill exercise test, dynamic electrocardiogram and CTA in diagnosis of coronary heart disease. *Chin J CT MRI*. 2019;17(4):62–64. doi:10.3969/j.issn.1672-5131.2019.04.020
27. Ping YU, Yao T, Peng J, et al. Elderly hypertensive patients of moderate intensity exercise test blood pressure response. *J Geriat Med*. 2023;5(11):1130–1133.