

# Effects of Astragalus injection and Salvia Miltiorrhiza injection on serum inflammatory markers in patients with stable coronary heart disease: a randomized controlled trial study

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## Study protocol

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# Abstract

**Background:** Coronary heart disease (CHD) is a clinical syndrome caused by coronary atherosclerosis (AS) or functional changes of coronary arteries. Our previous experimental study found that the main component of Astragalus, Astragaloside IV, and the main component of Salvia Miltiorrhiza, Tanshinone IIA, can effectively improve myocardial ischemic injury.

**Methods:** This study was a prospective, randomized, blinded, parallel design trial. A total of 160 eligible patients were randomized to a treatment group (in three groups) or the placebo control group in a 1:1:1:1 ratio using a central randomization system. Patients will receive appropriate treatment for 7 days within 24 hours after enrollment and follow-up for 28 days. Main evaluation indicators: cell count, serum high-sensitivity C-reactive protein (hs-CRP) level, monocyte chemoattractant protein 1 (MCP-1), Interleukin-6(IL-6), IL-1 $\beta$ , IL-8, IL-18, IL-10, Tumor necrosis factor(TNF- $\alpha$ ), Oxidized low density lipoprotein(OX-LDL), exosome levels, and angina grade and Traditional Chinese Medicine (TCM) symptom changes scale. Secondary evaluation indicators: B-type natriuretic peptide (BNP) level, troponin (cTn), muscle enzyme isoenzyme (CK-MB), heart-type fatty acid binding protein (H-FABP), liver function, renal function, blood coagulation and the like. Adverse events will be monitored throughout the trial.

**Discussion:** This is a randomized controlled trial of Chinese herbal extracts for the treatment of coronary heart disease. The results of this trial will provide valuable clinical evidence for the recommendations for disease management and identify its underlying mechanisms.

## Background

Coronary heart disease (CHD) is a clinical syndrome caused by coronary atherosclerosis (AS) or functional changes in the coronary arteries. This condition results in narrowing of the vascular lumen and insufficient blood supply to the coronary arteries, thereby increasing the load on the heart and leads to acute and temporary ischemia as well as hypoxia of the myocardium. Coronary atherosclerosis is a serious disease that endangers human health. In recent years, studies have found that AS is not only a simple lipid deposit, but also an inflammatory disease. Local or systemic inflammatory response plays an important role in the development of AS and the related complications(1). Therefore, anti-inflammatory therapies have been proposed as ideal means of treating atherosclerosis. In fact, many studies have shown that statins, angiotensin-converting enzyme inhibitors, antiplatelet agents, calcium channel blockers and other drugs have certain anti-inflammatory properties that can be exploited to manage the condition(2).

Inflammatory factors, endogenous peptides mainly produced by immune cells with strong biological effects, are known to be indicators of inflammatory responses. Specifically, they mediate a variety of immune responses, which are closely related to occurrence and development of coronary heart disease(3). Studies have shown that serum high-sensitivity C-reactive protein (hs-CRP) is one of the markers of inflammation, helping to indicate increased risk of vascular events, and also aid prognosis,

risk stratification. Consequently, this marker is a potential target for the treatment of AS and its complications(4). Numerous reports have demonstrated a close relationship between serum high-sensitivity C-reactive protein hs-CRP level, monocyte chemoattractant protein 1 (MCP-1), Interleukin-6(IL-6), Interleukin-8(IL-8), and tumor necrosis factor(TNF- $\alpha$ ) with pathogenesis of coronary heart disease(5, 6). Since inflammatory factors are involved in the occurrence and development of CHD, exploring the relationship between various inflammatory factors and coronary heart disease can provide a deeper understanding of the pathogenesis of this disease. In addition, quantification of various inflammatory factors can also help to dynamically understand a patient's condition, while assessing the effects of treatment can guide clinical practice(7).

Coronary heart disease is categorized as "chest pain" and "heartache" in Traditional Chinese Medicine (TCM), which plays an important role in its diagnosis and treatment. In particular, the "Yiqihuoxue" is the most widely used method for managing the condition(8). Among the components therein, Astragalus and Salvia are the most commonly used compatibility drugs. In our previous studies, we have focused on investigating the roles of TCM in CHD(9-12). Particularly, it is evident that Astragalus membranaceus, the main component of Astragalus membranaceus, and Tanshinone IIA, the main component of *Salvia Miltiorrhiza*, can effectively improve myocardial ischemic injury(13). Functionally, the mechanism of action of these components is related to the inhibition of cell inflammatory reaction and apoptosis in myocardial ischemic injury(14).

Based on the above understanding, we hypothesize, from a clinical perspective, that individual Astragalus, and *Salvia Miltiorrhiza* injections or a combination of the two have certain anti-inflammatory properties, and could play a role in the treatment of coronary heart disease. We therefore aim to explore the effects of *Salvia Miltiorrhiza* this treatment on stable coronary heart disease and provide the basis for its clinical application.

## Methods/design

### Study design and settings

Our study will be set up using randomly, blinded and single-center experiments. We will recruit 160 patients who meet the eligibility criteria at the Guangdong Provincial Hospital of Traditional Chinese Medicine. Subsequently, the participants will be divided into four equal groups (three groups with treatment: treatment group A: will receive conventional drugs plus Astragalus injection treatment; group B: will receive conventional drugs plus *Salvia Miltiorrhiza* injection; group C: will receive conventional drugs plus *Salvia Miltiorrhiza* and Astragalus injections), the control group will receive conventional drugs plus 0.9% NaCl injection. The study design is as illustrated in Figure.1.

### Objectives

This study intends to explore the effects of Astragalus, Salvia and Miltiorrhiza injections as well as a synergistic treatment (of the 2 components) on stable coronary heart disease from the anti-inflammatory

advantage, and provide the basis for its clinical application.

## **Research standard**

All patients enrolled in the study should meet the following diagnostic and inclusion criteria. In addition, the patients will sign an informed consent form prior to the study.

## **Diagnostic criteria**

The criteria for diagnosis of Coronary heart disease will be as follows: (1) coronary angiography or coronary CT examination confirmed at least one major branch lumen diameter stenosis of more than 50%, clinical with or without angina, heart failure, arrhythmia, sudden or death recovery. (2) there is a clear evidence of ST-segment elevation or non-ST-segment elevation myocardial infarction. (3) defined by the history of percutaneous coronary intervention (PCI) or / and coronary artery bypass grafting (CABG).

Clinical diagnostic criteria for chronic stable angina will be as described(15): Chronic stable angina is a condition in which a patient's degree, frequency, nature, and predisposing factors of angina pectoris have not changed significantly within one month. The criteria will be as follows; (1) Pain area: The typical part is the posterior sternum or left front chest, which can be radiated to the neck, pharynx, jaw, upper abdomen, shoulder and back, left arm and left finger. (2) nature of pain: patients that often show symptoms of tightness, squeezing, pressure, burning, chest, chest tightness or suffocation, heavy feeling, subjective feelings vary widely, and some manifest as fatigue, shortness of breath. (3) Duration: a paroxysmal episode lasting for a few minutes, generally no more than 10 minutes. (4) Predisposing factors and mitigation methods: patients whose seizures are related to labor or emotional excitement, can be relieved after stopping to rest, sublingual nitroglycerin can quickly relieve symptoms within 2-5 minutes.

## **Inclusion criteria**

The inclusion criteria will be as follows; (1) patients meet the Stable coronary atherosclerotic heart disease (SCAD) diagnostic criteria; (2) their medical history is more than three months, frequency of angina pectoris is  $\geq 3$  times in the past one week, and the severity of angina pectoris is grade II/III; (3) patient's age is 18-75 years old; (4) SCAD patients treated with any combination of cardiac-related drugs for more than three months prior to enrollment, including atorvastatin, aspirin, angiotensin-II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors(ACEI), and beta-receptor blockers; and (5) Patients sign the informed consent form.

## **Exclusion criteria**

The exclusion criteria are as follows:

(1) Patients with acute coronary syndrome (ACS) who are asymptomatic or have stable symptoms after stabilization; (2) Patients requiring revascularization, including myocardial infarction, left ventricular dysfunction, multivessel disease, and/or large-scale myocardial ischemia (ischemic area over 10%), left main disease; (3) Patients with Chronic refractory angina pectoris; (4) patients with chronic kidney

disease and severe heart, lung, liver and other important organ dysfunction; Serious primary diseases such as hematopoietic system and endocrine system, malignant tumor, gastrointestinal bleeding, gastric ulcer and bleeding tendency are not expected complete the tester; (5) Patients with severe and uncontrolled hypertension (SBP  $\geq$  180 mmHg or DBP  $\geq$  110 mmHg); (6) Those with severe arrhythmia (ventricular dichotomy, ventricular tachycardia, ventricular fibrillation, third degree atrioventricular block, arrest, severe sinus bradycardia, sick sinus syndrome, reentrant supraventricular tachycardia. Arrhythmia causing hemodynamic changes) (7) Patients who participate in other clinical trials or are taking other proprietary Chinese medicines within one month; (8) Pregnancy or preparation for pregnancy, and lactating women; and (9) people with mental, psychological, and other problems that cannot be matched with the completion of the research.

### **Loss to follow up**

Patients who are enrolling but have not completed clinical observations, including those withdrawing by themselves, losing their follow-up, poor compliance, or being withdrawn by a physician. If there is valid data in the case of shedding, the result of the last major efficacy index will be converted to the final result for statistical analysis.

### **Suspension criteria**

The trial will be suspended in case; (1) Serious adverse reactions occurred during the testing; (2) The trial finds that the clinical trial program has major errors, or the program is good, but serious deviations occur during implementation, and it is difficult to evaluate the efficacy of the drug.

### **Sample size**

This study will use a parallel design of randomized controlled trials, and hs-CRP as the main effect index, conventional western medicine treatment can reduce hs-CRP by 32%, according to clinical conditions, it is estimated that Chinese medicine can reduce hs-CRP by 52%. The set  $\alpha=0.025$ ,  $\beta=0.2$ , superiority limit value  $\delta=20\%$ , and the sample size of each group will be calculated as 30 cases(16, 17); Considering the loss of follow-up, 40 patients with stable coronary heart disease and 160 with four combinations will be selected.

### **Randomization**

Random numbers will be generated using Statistics Analysis System (SAS) 9.2 software according to the principle of randomization. In order to implement random hiding, the random sequence will be kept by a trial manager. Using the remote random concealment method, it is determined that the basic information of qualified research subjects will be transferred by phone to the person who keeps the random numbers, from which the treatment allocation plan for each patient is obtained. Randomization of groups will be done according to a pre-made random scheme.

### **Blinding**

Due to the special color problem of traditional Chinese medicine injection, we anticipate that it will be difficult to achieve double blinding during study. However, in order to avoid bias during the process, the following specific measures are proposed: (1) The researchers strictly adhere to the principle of randomization; (2) The doctors who participate in evaluation of the outcome are non-researchers, to ensure that evaluation of the efficacy of the test is blind; (3) Blood tests, data analysis and statisticians to be covered up until the final analysis is completed. They only obtained the CRF form and related data for analysis, and did not understand the patient and drug use.

## **Intervention**

### **Trial treatment methods**

According to the principle of randomization, the group to be screened will be divided into the following four groups; three groups of treatment comprising: Group A: that receives conventional drug treatment plus Astragalus injection treatment (size 20ml /support, packaging 10/container); Group B: which will receive conventional medicine plus *Salvia Miltiorrhiza* injection (specification 20ml/support, packaging 10/container); Group C: which will receive conventional medicine plus an injection of *Salvia Miltiorrhiza* combined with Astragalus; Both *Salvia Miltiorrhiza* and Astragalus injections will be prepared with 250ml of 5% glucose . The control group received an injection containing 250ml conventional drug plus 5% glucose. For diabetic patients, an injection of 250ml 5% glucose will be changed to 250ml 0.9% sodium chloride. All patients will receive intravenous drip once a day for 60 minutes for a treatment period of seven Days.

The conventional drugs used in the stable coronary heart disease test will be as described in the ESC Guidelines for the diagnosis and treatment of SCAD (18). The standard is given as aspirin, clopidogrel, low molecular weight heparin, statins, nitrates, beta-blockers, ACEI and other drugs.

### **Pharmaceutical and combination methods**

For allocation and combination of the drugs in this test, we will prepare *Salvia Miltiorrhiza* injection and Astragalus injection using 250ml of 5% glucose. If the patient is diabetic, we will change 250ml of 5% glucose injection into 250ml of 0.9% sodium chloride. 2. No other injections will be used simultaneously during intravenous infusion.

### **Matters needing attention**

During the study, patients will receive the test drug within 24 hours of enrollment. Conventional treatment of stable coronary heart disease (such as anti-poly drug, lipid-lowering drug, antihypertensive drug) will be carried out at the same time. Injection of Astragalus and *Salvia Miltiorrhiza* injection should not be used as a substitute.

## **Content and data capture points**

The contents and key points of the data to be collected during the study include the screening period (1 day), 24 hours before recruitment, a treatment period of 1-7 days followed by daily recording of data and follow up on the 28<sup>th</sup> day after treatment.

## **Outcome measures**

### **Primary outcome measures**

Cell counts, Serum detection by enzyme-linked immunosorbent assay, including serum hs-CRP level, MCP-1, IL-6, TNF- $\alpha$ , IL-1 $\beta$ , IL-8, IL-18, OX-LDL, IL-10, improvement of angina (19) and TCM symptom change scale (20), are outlined in Tables 1 and 2.

## **Table 1**

### **Angina pectoris subscale**

Angina pectoris	Score	Symptom grading score	
Number of episodes	0 2 4 6 points	0 points: None. 2 points: 1-6 times a week.	
	□__ times/week□	4 points: 1-3 times a day. 6 points: More than 4 episodes per day.	
Duration	0 2 4 6 points	0 points: None. 2 points: Each time the pain lasts ≤ 5min. 4 points: Each pain lasts longer than 5 minutes and less than 10 minutes. 6 points: Each pain lasts for ≥10min.	
Degree of pain	0 2 4 6 points	0 points: None. 2 points: Relief after a break does not affect daily life. 4 points: Drug treatment is required during the attack, and normal activities can be continued after the remission. 6 points: Frequent seizures affect daily activities (such as dressing, eating, walking, and large symptoms can be induced).	
Nitroglycerin dosage	0 2 4 6 points	0 points: None. 2 points: 1-4 tablets per week. 4 points: 5-9 tablets per week. 6 points: 10 or more servings per week.	
	□__ times/week□		
Total angina		Angina pectoris	<ul style="list-style-type: none"> <li>“ Mild (≤8)</li> <li>“ Moderate(9-16)</li> <li>“ Severe (≥17)</li> </ul>

**Table 2 Coronary heart disease Chinese medicine main symptom scale**

symptom	Symptom grading score
<b>Chest pain</b>	<ul style="list-style-type: none"> <li>“ 0 points: None.</li> <li>“ 3 points: Remission after rest will not affect daily life.</li> <li>“ 6 points: medication is required at the time of onset, and normal life can be continued after remission.</li> <li>“ 9 points: Frequent seizures affect daily activities (such as dressing, eating, walking, and large symptoms can be induced).</li> </ul>
<b>Chest tightness</b>	<ul style="list-style-type: none"> <li>“ 0 points: None.</li> <li>“ 3 points: I feel a chest tightness and can relieve myself.</li> <li>“ 6 points: Chest tightness attacks are more frequent, but do not “ affect normal life and work.</li> <li>“ 9 points: Chest tightness continues to be incomprehensible, affecting life and work.</li> </ul>
<b>Shortness of breath</b>	<ul style="list-style-type: none"> <li>“ 0 points: None.</li> <li>“ 2 points: short after the event.</li> <li>“ 4 points: A little move is short.</li> <li>“ 6 points: I usually feel short of breath.</li> </ul>
<b>Weak</b>	<ul style="list-style-type: none"> <li>“ 0 points: None.</li> <li>“ 2 points: Severe activity is weak.</li> <li>“ 4 points: Moderate activity is weak.</li> <li>“ 6 points: Mild activity is weak.</li> </ul>
<b>Heart palpitations</b>	<ul style="list-style-type: none"> <li>“ 0 points: None.</li> <li>“ 1 point: Occasionally, you can relieve yourself.</li> <li>“ 2 points: Frequent attacks, but can persist at work.</li> <li>“ 3 points: The heart is constantly puzzled, affecting life and work.</li> </ul>

### Secondary outcome measures

The following measurements will also be taken; blood lipid levels, B-type natriuretic peptide (BNP), troponin (cTn), muscle enzyme isoenzyme (CK-MB), heart-type fatty acid binding protein (H-FABP); and electrocardiogram.

### Safety outcomes

These are vital signs including blood, urine, and fecal routines, liver, and renal functions as well as coagulation. These indicators will be closely monitored during this process.

### **Observation records of adverse events**

Any adverse events that occur during the course of the trial, including laboratory abnormalities, must be carefully interrogated and tracked. We will therefore judge these events by their nature, severity, and drug relevance and strictly record their outcomes in the case report form.

### **Research process record points**

The subject content and data at each time point, according to the patient's hospitalization period, will be recorded as shown in Figure. 2. Specifically, the screening period (0 days) will be 24 hours before recruitment followed by a daily data tracking and recording from day 1 to day 7 , and a follow up on day 28 after treatment is administered.

### **Statistical analysis**

Statistical analysis will be performed using SPSS 19.0 statistical software. Measured data will be described using means and standard deviation of the mean, while count data will be by the number of cases in percentages. First, a baseline analysis of the demographic characteristics in the four groups of selected cases will be conducted to investigate the balance and comparability across groups. Then, the effectiveness and safety indices will be compared across the four groups. The comparison of iso-quantitative data between the experimental and the control group will be performed using a student *t*-test of two-sample comparison for group design, while the comparison of the two classification indicators such as gender will be performed using the Cochran-Mantel-Haenszel  $c^2$  test or the Fisher's exact probability method. The missing supplementary data will be adjusted using imputation methods. To validate ineffectiveness among the groups, we will perform a rank sum test of the two-sample comparison in the groups. All statistical tests will be two-sided with  $p \leq 0.05$  to be used for statistical significance.

### **Data management**

In this study, the Case Report Form (CRF) will be filled out in time by the person in charge of the research. In addition, the patients will carefully fill in their relevant information and this will be regularly checked by clinical researchers to avoid missing data, . The revisions provided by the clinical researcher will be implemented and corrected by the researcher in a timely manner. The researchers center will also confirm and sign the complete CRF form, in which no modifications are expected to be added after the trial. The entire research process will be conducted in a confidential manner, with none of the information disclosed to other parties. Only the lead researcher will have access to all data.

### **Quality control**

## Construction of research institutions and Monitoring

During clinical research, multi-department construction and composition are required, and each department should firmly cooperate to ensure the completion of quality research. In the current study, the main departments will include the following: (1) A competent department, composed of clinicians, pharmaceutical researchers and quality supervision experts, which will be mainly responsible for the problems in clinical research, ensuring provision of solutions in a timely manner; (2) Data Monitoring and Ethics Committee (DMEC) comprising experts in the field to monitor the overall conduct of the trial as well as relevant data, and ensure that the rights of patients are adhered to; and (3) Safety management: here, researchers from each center will be responsible for timely observations of the patient's vital signs and laboratory indicators, and generate timely adjustments and feedback.

## Supervision and inspection

Effective supervision and inspection must be carried out throughout the clinical trial study. In this study, each researcher will conduct an examination once a week, including completion of a patient's CRF form, verifying a complete informed consent, accurate patient's inclusion criteria, laboratory indicators and related scale collection and preservation. During the test, patients with any adverse reactions and records of withdrawal will be identified. Researchers center will ensure authenticity and integrity of all data.

**Table 3 Ethics committee names and approval registration number**

Ethics committees' name	Approval registration number
Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine	BF2018-182-01

The hospital has approved qualification for drug clinical trials from the China Food and Drug Administration (CFDA), and the investigator had a Good Clinical Practice (GCP) certificate.

## Ethical issues

### Ethics statement

In clinical trials, researchers will comply with the Helsinki Declaration and ethical principles. The investigator will fully respect the subject's choices, and will not force the subject to participate in the trial. The subject has the right to voluntarily participate, provide and sign a written informed consent form, and may withdraw at any time. During recruitment, each subject will be assigned a random number to ensure

blind implementation during the trial. In addition, researchers must protect the privacy, and confidentiality of the subject.

### **Ethical approval**

This subject has been approved by the Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine on February 1, 2019. A clinical research plan and the relevant documents of the informed consent form are approved by the Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine. The Approval registration number is BF2018-182-01 (Table 3).

### **Informed consent form**

The informed consent form will be fully explained to the subject or guardian by the researcher. Those agreeing to participate will sign the ICF, and both the researcher and subject will keep the signed ICF individually. Project managers will be allowed access to the ICF kept by researchers for monitoring and inspection.

## **Discussion**

Coronary heart disease is a clinical syndrome caused by coronary atherosclerosis or coronary functional changes. The condition results in narrowing of the lumen in the blood vessels, insufficient blood supply to the coronary arteries, leading to cardiac load, and causing acute, transient ischemia as well as hypoxia of the myocardium(21). Atherosclerosis is one of the main causes of coronary heart and cerebrovascular diseases, which contributes to a high global morbidity and mortality. Despite management options such as medical thrombolysis, and interventional or surgical bypass surgery, coronary artery recanalization directly results in myocardial ischemic injury. Myocardial ischemic injury has become a major clinical problem, and has attracted wide research attention globally(22). However, there is still no definitive and effective clinical method for prevention and treatment of this condition. It is, therefore, imperative to develop effective drugs for preventing and treating myocardial ischemic injury.

Recent studies have shown that chronic inflammation of the intima may play an important role in the pathogenesis of coronary atherosclerotic heart disease(16, 23). There is a low degree of chronic inflammatory disease in atherosclerosis. In fact, the vascular injury-response hypothesis suggests that endothelial dysfunction alters the anti-inflammatory properties of the endothelium. Inflammation, therefore, plays a major role in the development of atherothrombotic thrombosis and triggers cardiovascular events. For instance, since the 1990s, clinical research studies have linked cardiovascular events to chronic inflammation(24). Furthermore, the role of inflammation in development of atherosclerosis and sensitivity to predicting cardiovascular events has been identified. Current reports confirm that the inflammatory process is involved in initiation of atherosclerotic, progression and secondary lesions(25).

Traditional Chinese medicine has been vastly implicated in the prevention and treatment of coronary heart disease. In fact, since the development of integrated Chinese and Western medicine, coupled with the gradual deepening of research, TCM has acquired its own advantages in clinical practice enabling achievement of good efficacy. The basic pathogenesis of coronary heart disease is deficiency and blood stasis(22). A treatment therapy for this condition has involved the use of *Salvia Miltiorrhiza* injection, a traditional Chinese medicine, whose main components are *Salvia Miltiorrhiza* and antibalm. According to the relevant studies in modern medicine, *Salvia Miltiorrhiza* can enhance cardiac function, improve the strength of myocardial contraction, increase blood supply to the myocardium, expand the blood vessels outside the heart, and generate very good anti-inflammatory effects(14). In addition, *Salvia Miltiorrhiza* injection has been found to promote blood circulation and remove blood stasis. Studies have further reported that static dripping of *Salvia Miltiorrhiza* injection can significantly reduce inflammatory factors in patients with acute coronary syndrome(16). while in patients with acute myocardial infarction, its intravenous injection can reduce the level of hsCRP and relieve chest tightness and pain(17). Similarly, Astragalus injection has been reported to increase myocardial contractility, with good protective effects on myocardial cells. Consequently, it has been found to effectively improve the cardiovascular function of patients. The drug can also strengthen the phagocytic function of macrophages, improve conversion rate of T cells, promote synthesis of interferon, and improve activity of interleukin. Furthermore, it affects immune regulation, antiviral replication, inhibits allergens and bacteriostasis. Reports have shown that ulinastatin combined with Astragalus injection generates good clinical effects on inflammatory reactions after PCI, which can reduce the expression levels of inflammatory factors in patients and reduce the myocardial injury caused by ischemia and reperfusion, which has important clinical application value(23).

In our previous studies, we found that the main components of Astragalus, Astragaloside IV, and *Salvia Miltiorrhiza*, Tanshinone IIA, can effectively improve myocardial ischemic injury(13, 26). Functionally, the mechanism of action of these drugs targeted cellular inflammation in myocardial ischemic injury and inhibited death. However, from a clinical point of view, it remains unclear whether individual Astragalus, *Salvia Miltiorrhiza* injections or a combination of the two, results in significantly different anti-inflammatory properties, during treatment of coronary heart disease. This study will explore the effects of Astragalus Injection, *Salvia Miltiorrhiza* Injection and their synergistic treatment on stable coronary heart disease from the anti-inflammatory advantage, and provide the basis and basis for its clinical application.

### **Trial status**

Participant recruitment is currently underway. The version number / date 2.0/20190601.

The start date of the recruitment of this project is June 01, 2019, and the approximate date of recruitment is June 1, 2020, for a period of one year.

## **Abbreviations**

CHD: Coronary heart disease; AS: Atherosclerosis; hs-CRP: high-sensitivity C-Reactive Protein; MCP-1: Monocyte Chemoattractant Protein 1; IL-6: Interleukin-6; IL-1 $\beta$ : Interleukin-1 $\beta$ ; IL-8: Interleukin-8; IL-18: Interleukin-18; IL-10: Interleukin-10; TNF- $\alpha$ : Tumor necrosis factor; OX-LDL: Oxidized low density lipoprotein; TCM: Traditional Chinese Medicine; BNP: B-type natriuretic peptide; cTn: troponin; CK-MB: muscle enzyme isoenzyme; H-FABP: Heart-type fatty acid binding protein; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; SCAD: Stable Coronary Atherosclerotic Heart Disease; ASA: Aspirin Enteric Capsules; ACEIs: Angiotensin converting enzyme inhibitor; ARBs: Angiotensin-II receptor blockers;  $\beta$ RB:  $\beta$ -receptor blocker; ACS: acute coronary syndrome; CRF: Case Report Form; CRA: clinical research associate; PI: principal investigator; SAS: Statistics Analysis System; GCP: Good Clinical Practice; SFDA: State Food and Drug Administration; ICF: Informed Consent Form.

## **Declarations**

### **Funds**

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### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

### **Availability of data and materials**

Not applicable.

### **Authors' contributions**

DW and QL designed the study. ZL, YL and XY drafted the manuscript. QL finalized the manuscript. Critical comments and typesetting correction on the final version are made by ZZ. All authors read, revised and approved the final manuscript.

### **Ethics approval and consent to participate**

This trial complies with the principles of Declaration of Helsinki and the regulations of quality management of clinical trials in China. The research activities in this trial have been approved by the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine, the committee's reference number is BF2018-182-01(Table 3). All study participants will sign written informed consent forms before participating in the trial.

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## Figures

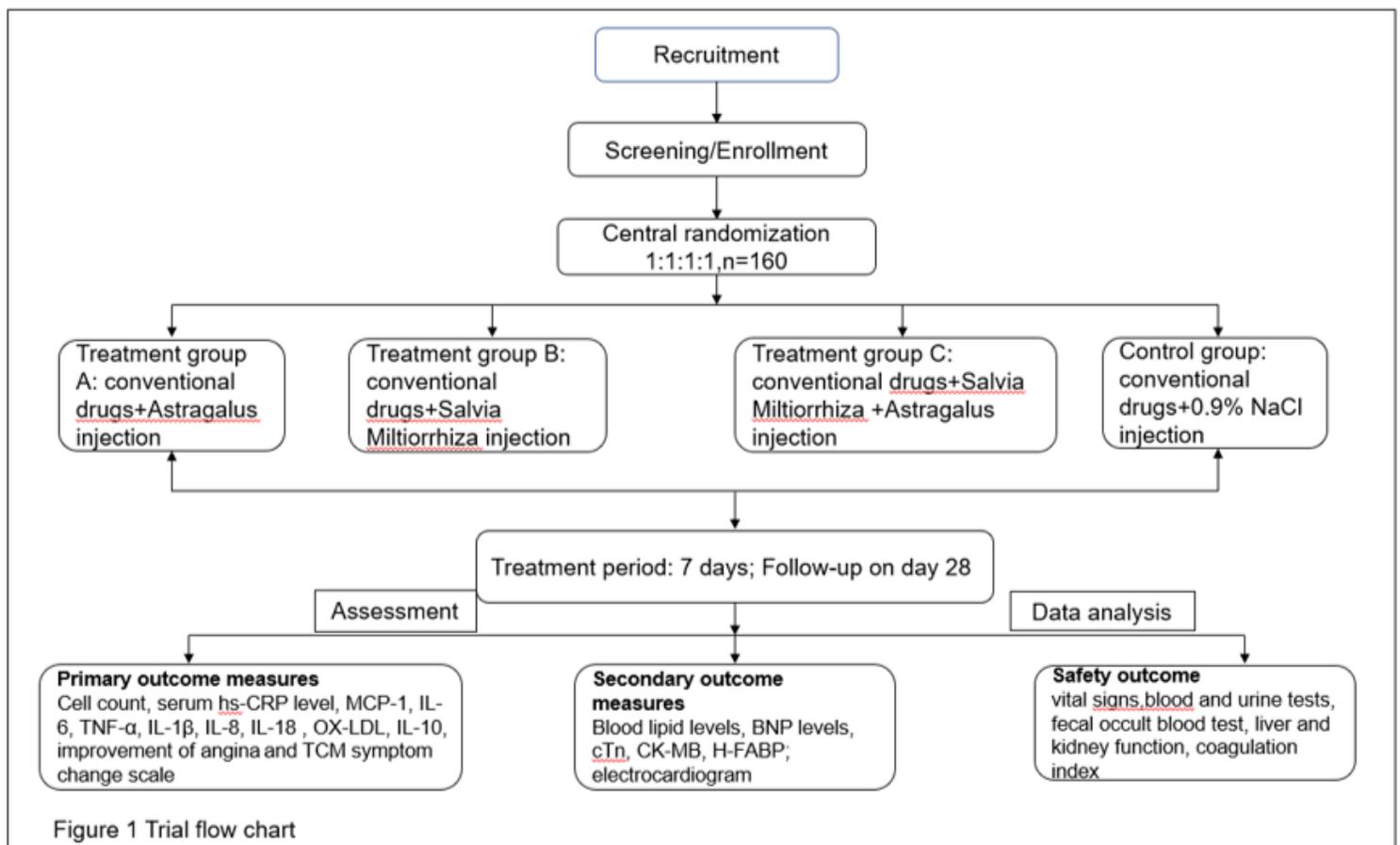


Figure 1

Trial flow chart

Visit	Screening	Intervention (7 days)							Follow up
	V1	V2	V3	V4	V5	V6	V7	V8	V9
Unit: day	0	1	2	3	4	5	6	7	28
Informed consent form	√								
Screening the subject	√								
Demographic information	√								
Inclusion/exclusion criteria	√								
Get random number	√								
History of SCAD	√								
Concomitant diseases	√								
Complication	√								
Vital signs	√								
Meet the SCAD diagnostic criteria	√								
the frequency of angina pectoris	√								
the severity of angina pectoris	√								
Age 18-75 years old	√								
Cell count, serum hs-CRP level, MCP-1, IL-6, TNF- $\alpha$ , IL-1 $\beta$ , IL-8, IL-18, OX-LDL, IL-10,		√						√	√
improvement of angina		√						√	√
TCM symptom change scale		√						√	√
Blood lipid levels, BNP levels, cTn, CK-MB, H-FABP		√						√	√
electrocardiogram		√						√	√
Laboratory tests		√						√	√
Safety outcomes		√						√	√
Length of stay in hospitalization	√	√	√	√	√	√	√	√	√
Cost of stay in hospitalization	√	√	√	√	√	√	√	√	√
28-day survival follow-up									√
Efficacy and safety evaluation		√	√	√	√	√	√	√	√

Figure. 2Content and points of data capture

## Figure 2

Content and points of data capture

## Supplementary Files

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