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Effectiveness and safety of Chinese herbal medicine xuanbi antong granules for the treatment of borderline coronary lesions: study protocol for a central-randomized, double-blind, placebo-controlled, multicenter clinical trial

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ABSTRACT

Introduction： As the early stage of coronary heart disease (CHD), borderline coronary lesion (BCL) is defined as a 30% to 70% diameter stenosis. Previous studies have demonstrated that BCL may progress to acute coronary syndrome easily. However, routine medications available for the treatments of BCL have some limitations. Xuanbi Antong Granule (XAG) has been used for the treatment of BCL in China for many years. Previous studies have shown that XAG has effectiveness in improving clinical symptoms and quality of life in patients with CHD. This study aims to evaluate the effectiveness and safety of XAG in patients with BCL.

Methods and analysis： This is a multicenter, central-randomized, double-blinded, placebo-controlled clinical trial. A total of 300 participants will be randomly assigned to the intervention group and the placebo group. Based on routine medications, the intervention group will be treated with XAG and the placebo group will be treated with XAG placebo. All participants will receive a 6-month treatment and then be followed up for another 6 months. The primary outcome indicators are the changes of target plaque characteristics (including target plaque volume, degree of stenosis, CT value and calcification score) measured by dual source computed tomography angiography. The secondary outcome indicators include blood lipid indicators, efficacy of angina symptoms, Seattle Angina Questionnaire, high-sensitivity C-reactive protein and occurrence of major adverse cardiac events. All the data will be recorded in electronic case report forms and analyzed by SPSS 20.0.

Ethics and dissemination： This study has been approved by Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (No.

2017-083-KY-01). Written informed consent will be obtained from all participants. The results of this study will be disseminated to the public through academic conferences and peer-reviewed journals.

Trial registration number： Chinese Clinical Trial Registry (ChiCTR-IOR-17013189); Pre-results.

Key words: Chinese herbal medicine, borderline coronary lesions, randomized controlled trial, protocol.

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Strengths and limitations of this study

Strength 1: This multicenter, central-randomized, double-blinded, placebo-controlled clinical trial is exploring the effectiveness and safety of Xuanbi Antong Granule (XAG) for the treatment of borderline coronary lesions (BCL).

Strength 2: We used a noninvasive test dual source computed tomography angiography (DSCTA) to evaluate the degree of coronary artery stenosis and plaque compositions, which is easy for investigators to operate and more acceptable to participants.

Strength 3: Participants are randomized in a 1:1 ratio using central randomization system (CRS), and the blinding codes will be kept by the manufacturer of CRS, which effectively guarantees the implementation of blinding in clinical trials.

Strength 4: The data from all participating centers will be recorded in electronic case report forms (eCRF) and imported into public clinical trial management platform (www.medresman.org) within six months after the trial completes.

Limitations: Our experiments will be conducted in three regions of China, and whether similar effects are available to other ethnic groups and regions remains uncertain.

Introduction

In China, cardiovascular disease（CVD）remains the leading cause of mortality, which accounts for 44.8% and 41.9% of deaths in rural and urban area, respectively. In Europe, CVD is still the most common cause of deaths, which accounts for 45% of all deaths. Among them, coronary heart disease (CHD) is the most common cause, which accounts for 20% of all death. The incidence of CHD is continuously increasing and the burden of CHD remains heavy, which has become a major public health issue [1, 2]. As the early stage of CHD, borderline coronary lesion (BCL), also called intermediate lesion, is defined as a 30% to 70% diameter stenosis [3]. Although the presence of severe coronary stenosis has been traditionally explained as indication of myocardial ischemia, yet it has been reported that coronary occlusion and myocardial infarction most frequently evolve from mild to moderate stenosis [4]. Some other studies have recently demonstrated that approximately 87% of lesions requiring subsequent percutaneous coronary intervention (PCI) were ≤60% in severity during original PCI, and 6% of patients with intermediate lesions needed PCI in 1 year because of acute coronary syndrome (ACS) [5]. There is evidence that BCL may become unstable and can be the starting point for ACS [6]. Studies have shown that patients with BCL have a higher burden of mixed plaque (MP, 46%) and non-calcified plaques (NCP, 33%), also known as vulnerable plaque [7]. The number of deaths resulting from

BCL continues to rise despite the use of currently recommended antiplatelet therapy, lipid-lowering therapy, revascularization procedures as appropriate, and other evidence-based secondary preventive measures [8]. It has been demonstrated that plaque regression was associated with a lower rate of major adverse cardiac events (MACEs) [9]. Therefore, it is necessary to develop supplementary therapeutic methods that can relay or reverse plaque progression and eventually reduce the occurrence of MACEs in patients with BCL.

Chinese herbal medicine (CHM), a popular type of supplementary and alternative medicine, plays a significant role in treating BCL in China. Within the framework of Traditional Chinese Medicine (TCM) theory, all the related symptoms at a certain stage of a disease are summarized as a syndrome ('Zheng' in TCM), which has been used in China for more than 3000 years [10]. Patients with BCL can be divided into varied syndromes. In the diagnosis of BCL, 'phlegm, blood stasis and heat syndrome' is an important syndrome based on the viewpoint of TCM theory and our previous clinical practice [11]. Therefore, the principle of 'clear up heat, resolve phlegm and promoting blood circulation' is applied in the treatment of BCL. TCM practitioners always attach importance to preventing disease before it arises and controlling the development of existing disease. Therefore, there are some special advantages for TCM in controlling the plaque progression of BCL.

Xuanbi Antong Granule (XAG) is a commonly used CHM based on the TCM theory of 'clear up heat, resolve phlegm and promoting blood circulation' for prevention of BCL in China. Clinical trials have found that XAG is effective in improving clinical symptoms and improving the quality of life in patients after PCI by protecting endothelial cells and regulating platelet function [12]. Experimental studies have found that XAG can significantly improve the heart function of ventricular remodeling rats after myocardial infarction, by down-regulating inflammatory factors of TNF-a [13]. XAG consists of eight herbal medicines (table 1), including salviae miltiorrhizae (Dan Shen), puerariae lobatae radix (Ge Gen), peaoniae radix rubra (Chi Shao), cistanches herba (Rou Cong Rong), pinellia rhizoma (Ban Xia), ginseng radix et rhizoma (Ren Shen), coptis chinensis (Huang Lian), panax notoginseng (San Qi). Among them, salvia miltiorrhiza, panax notoginseng and coptis chinensis are the principal pharmacologically active components. They have various pharmacological effects, including anti-oxidation, anti-atherosclerotic, lipid-lowering, anti-platelet aggregation, protecting vascular endothelial cells, anti-inflammatory and so on [14-17]. However, there is no evidence for XAG in the treatment of BCL. Therefore, we designed a central-randomized, double-blinded, multicenter trial aiming to evaluate effectiveness and safety of XAG for the treatment of BCL.

Table 1 Components and dose of XAG.

Chinese name	English name	Origin	Pharmacological effects	Weight (%)*
Dan Shen	Salvia miltiorrhiza	The dried root or rhizome of Salvia miltiorrhiza Bge	Improve microcirculatory, anti-coagulant, anti-thrombotic, and anti-inflammatory	20.83%

Ge Gen	Puerariae lobatae radix	The dried root of pueraria lobata (wild.) Ohwi	Antihypertensive, slow heart rate, and dilate coronary vessels	20.83%
Chi Shao	Peaoniae radix rubra	The dried root of paeonia lactiflora Pall	Antiplatelet aggregation, anti-erythrocyte aggregation, anti-coagulant, anti-thrombotic and protect myocardial cells	16.67%
Rou Cong Rong	Cistanches herba	The dried scaled fleshy stalk of Cistanche deserticola Y.C.Ma	Protect ischemic myocardium，and antioxidant	13.89%
Ban Xia	Pinellia rhizoma	The dried tubers of Pinellia (Thunb.) Breit	Hypolipidemic，lower blood viscosity, antilipid peroxidation, and anti-thrombotic	8.33%
Ren Shen	Ginseng radix et rhizoma	The dried roots and rhizomes of Panax ginseng C. A. Mey.	Bidirectional regulation of blood pressure, and protect myocardial cells	8.33%
Huang Lian	Coptis chinensis	The dried rhizome of Coptis chinensis Franch	Antiplatelet, antihypertensive, protect myocardial cells, and anti-inflammatory	6.94%
San Qi	Panax notoginseng	The dried root or rhizome of Panax notoginseng F.H.Chen	Anti-atherosclerotic，antioxidant, anti-inflammatory, anti-hyperlipidemic , and anti-coagulation，	4.18%

*The weight of every single herb in each bag of XAG (7.72g).

Methods and Design

Study Design

This is a multicenter, central-randomized, double-blinded, placebo-controlled, parallel-group clinical trial. The protocol, electronic case report form (eCRF) of this study and written informed consent were approved by the Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences on September 20, 2017 (No. 2017-083-KY-01). The study was registered at the Chinese Clinical Trial Registry on October 31, 2017 (ChiCTR-IOR-17013189). This study complies with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. We will rigorously follow the latest Consolidated Standards of Reporting Trials (CONSORT 2017) for CHM recommendations [18], Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and 2013 statement [19] for herbal interventions. Written

informed consent will be acquired from all patients prior to their participation in this study. Totally 300 participants diagnosed BCL will be enrolled in the trial, which consists of a 1-week screening period, a 6-month treatment period, and another 6-month follow-up period. The recruited patients will be randomized and allocated to either the intervention group or the placebo group in a 1:1 ratio using central randomization system (CRS). In addition to routine medications, they will be given 7.72g XAG or placebo in granule form twice a day for 6 months. The study design is briefly illustrated in figure 1.

Patient and public involvement

This trial was designed to evaluate the effectiveness and safety of XAG in patients with BCL. In our previous clinical practice, early intervention of BCL may prevent the occurrence of MACEs and it is considered very important in BCL patients. XAG, a type of Chinese herbal medicine, is easily accepted by patients. Adding XAG to routine medications may increase the effectiveness in preventing the progression of BCL, thus significantly improve patients' quality of life and reduce the occurrence of MACEs. The outcome measures used in this trial were considered as important endpoints in clinical practice. The participants of this trial will be recruited from 3 participating hospitals. However, patients were not directly involved in design, recruitment or conduct of the study. After the trial completes, the results of this study will be disseminated to the public through academic conferences and peer-reviewed journals. Once the manuscript is published, the results will be briefly summarized in a simple language and sent to all trial participants through e-mail and phone. The burden of intervention will not be assessed by trial participants.

Participant Recruitment

Consecutive patients undergoing coronary dual source computed tomography angiography (DSCTA) for a clinical indication will be evaluated for the entry into the study. Inpatients and outpatients at the 3 participating hospitals (table 2) will be screened according to the inclusion and exclusion criteria by two experienced cardiologists separately. Only two cardiologists both agree that the participants will be enrolled in the trial. In addition, recruitment advertisements of the study will be posted on webpages and notice boards in 3 participating hospitals and resident communities. It includes a brief description of the subjects needed, the medicines, medical examinations and the ways to participate in this study. For those people who are ineligible or decline to participate, we will record the basic demographic information and reasons for non-participation. The trial began in December 2017 and will continue until December 2020.

Table 2 The hospitals participating in this study

Code	Participating Hospitals
01	Guang'anmen Hospital, China Academy of Chinese Medical Sciences
02	Yunnan Provincal Hospital of Traditional Chinese Medicine
03	The First Affiliated Hospital of Xinxiang Medical University

Diagnostic Criteria of BCL

The diagnosis of BCL will refer to the criteria published in "ACC/AHA Guidelines for Coronary Angiography", which is defined as 30% to 70% diameter stenosis [3]. The diameter stenosis of the main coronary, including left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA), is between 30% to 70% measured by DSCTA.

Diagnostic criteria of CHD

Two types of CHD will be recruited, including stable angina and unstable angina. The diagnostic criteria will refer to the "Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease" [20] (2012 edition) and the "Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes" [21] (2014 edition).

Diagnostic Criteria of TCM syndrome

Diagnostic criteria of 'phlegm, blood stasis and heat' syndrome in TCM will based on the "Syndrome Elements Diagnostic Criteria of Coronary Heart Disease of Angina" published by Chinese Society of Traditional Chinese Medicine Cardiovascular Disease Branch on March 2018 [22]. Syndrome elements are the smallest diagnostic unit for the diagnosis of TCM syndromes. 'Phlegm, blood stasis and heat' syndrome is the combination of 'phlegm', 'blood stasis' and 'heat' syndrome elements. TCM syndrome of each participant will be estimated by two TCM experts blindly. The consistency will be checked on by kappa test.

Inclusion Criteria:

(1) Provision of written informed consent by participants or surrogates voluntarily;

(2) Patients aged 30 to 75 years at the time of their consent;

(3) Demonstration of at least one obstruction with 30% to 70% diameter narrowing with NCP or MP (target plaque) in at least one main coronary artery (the diameter of the target vessel is≥ 2.5mm) determined by DSCTA.

Exclusion Criteria:

(1) Chest pain caused by severe left main coronary artery lesions, severe valvular heart disease (aortic stenosis), severe psychoneurosis, climacteric syndrome, hyperthyroidism, cervical spondylosis, gallbladder heart syndrome, gastroesophageal reflux disease;

(2) Uncontrolled hypertension with SBP≥160mmHg or DBP≥100mmHg, severe cardiac insufficiency with EF < 35%, severe arrhythmia (Fast Atrial Fibrillation, Atrial Flutter, paroxysmal ventricular tachycardia, atrioventricular block higher that second degree subtype II, complete bundle branch block);

(3) Patients with severe primary diseases like heart, brain, liver, kidney, hemopoietic system related diseases, and patients whose ALT or AST is higher than 1.5 times of the upper limit, patients with abnormal renal function or insulin dependent diabetes mellitus;

(4) Reference vessel diameter of the target vessel < 2.5mm, or there is no NCP or MP in the main coronary artery, or severe tortuosity of the target vessel or any other anatomical reasons that the investigator deems inappropriate for DSCTA procedure;

(5) patients have undergone revascularization including PCI or coronary artery bypass grafting (CABG);
(6) Patients with depression or anxiety;
(7) Stroke or resuscitated sudden death in the past 6 months;
(8) Hyperthyroidism with TSH levels more than 1.5 times upper limit of normal;
(9) Patients with malignant tumor;
(10) Pregnant women or breast feeding women;
(11) Chronic disease requiring treatment with oral, intravenous, or intra-articular corticosteroids (use of topical, inhaled, or nasal corticosteroids is permissible);
(12) Patients with allergic constitution or are allergic to many kinds of TCM herbs and iodine;
(13) Patients with low compliance, who might miss the follow-up;
(14) Participation in other clinical trials in last 1 month.

Removal, Dropout and Termination Criteria

During the course of the study, a participant may be removed if one was not taken medication after inclusion, occurrence of myocardial infarction, revascularization (PCI or CABG) or sudden cardiac death during the treatment period. Participants can voluntarily drop out at any time during the trial. Eligible subjects failing to complete the observation period presented in the trial will be considered as dropout cases regardless of the time and reason. Reasons for dropout will be recorded in eCRFs, and the last data recorded for these participants will be included in the data analysis. The trial can be terminated in the following circumstances: (1) occurrence of serious adverse events (AEs) relevant to the XAG, (2) the test medications has no clinical value during the trial, and/or (3) financial and management reasons.

Randomization and Blinding

Participants are randomized in a 1:1 ratio using CRS for Clinical Research (Web Edition) of block randomization, which is successfully developed and widely applied to multicenter clinical trials [23]. The CRS achieved the functions of subject screening, randomization, emergency exposure, drug delivery and drug supply management. It has the advantage of shortening the clinical trial cycle, improving the efficiency of clinical trials, and saving drug use. The researcher uses the screening module to input some basic information of the subject such as date of birth, sex, and answer tests to identify the subject and then obtain the subject's unique identification number. After the subjects pass the screening period, subjects are randomized into either XAG or placebo group by using a randomization module. In addition, CRS effectively guarantees the implementation of blinding in clinical trials. In order to ensure that the blinding method in randomized controlled clinical trials is effectively guaranteed, the random number and the drug number are separated in the system. The researcher uses the drug designation module to obtain the drug number for the subject. All patients, laboratory and inspection staff and attending physicians will be blinded to treatment assignment until the research is completed. If no subject's emergency occurs during the study period, then unblinding is performed according to normal procedures. The blinding codes will be kept by the manufacturer of CRS (Clinical Evaluation Center of China Academy of Chinese Medical Sciences).

Target Plaque Selection and Analysis by DSCTA

The target plaque to be monitored will be determined in NCP or MP on the main coronary vessel (diameter of the target vessel is ⩾2.5mm such as LAD, CX, and/or RCA), and the diameter stenosis is between 30% to 70%. The distance from the target plaque to the coronary opening will be measured as a reproducible fiduciary index to guarantee the accuracy of the after-treatment measurement. The target plaque will be selected in each subject according to the standard operating procedures (SOP) illustrated in the figure 2, which will be evaluated as representative effect of XAG. Investigators will be required to use the same DSCTA operating system (SOMATOM Definition Flash, Siemens Healthineers, Erlangen, Germany) for both the baseline and after-treatment DSCTA image acquisition. The DSCTA images of target plaque characteristics include plaque volume, CT values, degree of stenosis and calcification scores by using the same workstation (Syngo.via VB10B). The images will be logged, and quantitative analysis of DSCTA will be performed by two independent blinded experienced investigators who are blinded to the patient group allocation in the Radiology Department of Guang'anmen Hospital of China Academy of Chinese Medical Sciences. We will use kappa test to evaluate the consistency of the results of the two investigators.

Interventions

Eligible patients will be allocated to receive XAG or placebo granules for 6 months randomly using CRS, based on routine medications including lipid-lowering, antiplatelet, antihypertensive or antidiabetic therapy [3]. Eligible participants are prohibited from using other TCM therapies for treating BCL. The XAG and placebo granules (7.72g/ bag, one bag at a time, twice a day, 6 months) will be provided by Sichuan New Green Pharmaceutical Technology Development Co. Ltd. (Peng Zhou, China). The placebo has one tenth the dose of XAG. Both XAG and placebo have the same outer packaging, color, shape and flavor. After the treatment, the packaging will be returned to the investigators.

Data collection

Background Information

Background information includes demographic data and general clinical data, which will be recorded during the 1-week screening period. Demographic data consists of gender, age, height, weight and so on. General clinical data consists of medical history, course of disease, treatment history, combined diseases, concomitant medications and so on. The participants' information and privacy will be strictly protected and forbidden to the public.

Safety Outcomes

Safety is assessed by vital signs, laboratory examinations and AEs. Vital signs include body temperature, breathing, blood pressure and heart rate. Laboratory examinations include blood, urine and stool routine, liver and kidney function. AEs will be recorded all the time during the treatment. The development of AEs will also be observed until the adverse reactions disappear.

Primary and Secondary Outcomes

The primary outcome measures of the study are plaque characteristics including target plaque volume, degree of stenosis, CT value, and calcification score measured by DSCTA, which will be measured at baseline and 6 months after randomization. Secondary outcomes include the efficacy of angina symptoms, Seattle Angina Questionnaire (SAQ), which will be recorded at baseline and every month during the treatment period (1 to 6 months after randomization), blood lipid indicators, including cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein, and high-sensitivity C-reactive protein (hs-CRP) which will be recorded at baseline, 3 months, and 6 months after randomization. At the same time, the trial also observes the occurrence of MACEs defined as the composites of deaths from any cardiac causes, myocardial infarction, and revascularization (PCI or CABG) at 9 months and 12 months after randomization. Items to be measured and the time window of data collection are shown in table 3.

Table 3 Schedule of data collection

Items	Screening Period within 1 week	Treatment Period 1-6 month	Follow-up Period 7-12 month
Signed informed consent	√		
Inclusion/exclusion criteria	√		
Demographic data	√		
Medical history, course of disease, treatment history	√		
Combined diseases	√		
Concomitant medications	√	√	
Plaque characteristics	√	√	
Blood lipid indicators	√	√	
Efficacy of angina symptoms	√	√	
SAQ	√	√	
MACEs			√
hs-CRP	√	√	
Vital signs	√	√	
Blood, urine and stool routine	√	√	
Liver and kidney function	√	√	
Adverse events		√	√
eCRF examination			√

√ represents the indicators tested in the specific time period.

Vital signs: temperature, heart rates, breathing and blood pressure.

Sample Size Calculation

The formula used to calculate the sample size is as follows，which is based on superiority clinical trial interval hypothesis test sample size estimation [24]. The sample size was calculated on the basis of expected reduction in plaque volume. Our previous study suggested that the reducing

value for plaque volume after interventional treatment is 1mm^3, and the combined standard deviation is 2.75mm^3. Therefore, the hypothesis of this study is to reduce plaque volume to 1mm^3 in the intervention group. In the following formula, c is the ratio between two sample cases. $n_1 = n_2$, so c=1. σ is the combined standard deviation and δ is the expected effect size, so σ=2.75, δ=1. Given a type I error rate of α = 0.05, a power of 90 % (type II error rate of β = 0.1), so $u_{1-\alpha}$=1.64, $u_{1-\beta}$=1.28. n1=n2≈128，the sample size for one group needs to be 128, resulting n=2×128=256 patients. Considering the maximum possible dropout rate is 15%, a total of 294 patients need to be allocated to reach the required number of patients for the efficacy analysis. For convenience of randomization, we decided to recruit 300 patients.

$$n_1 = \left[\frac{(u_{1-\alpha} + u_{1-\beta})\sigma}{\delta}\right]^2 \frac{(1+\mathrm{c})}{c}\ ,\ n_2 = cn_1$$

$n_1 = n_2 \approx 128$

Adverse Events

AEs are defined as negative or unintended clinical manifestations following the treatment. Patients will be asked to report to the investigators any abnormal reactions occurring at any time during the trial. In addition, investigators will collect information about abnormal reactions monthly. All details of related and unexpected AEs, such as time of occurrence, degree and duration of AEs, suspected causes, and the effective measures and outcomes will be recorded on eCRFs. Any AEs, such as subjective discomfort and laboratory abnormalities, should be taken seriously. Careful analysis and immediate measures are taken to protect the safety of the subjects until the adverse events disappeared. There is also a data safety monitoring board to oversee the trial.

Quality Control of Data

eCRFs will be used for data collection, and data from all participating centers will be imported into public clinical trial management platform (www.medresman.org) within six months after the trial completes. To maintain the quality of the data, we will adopt valid measures to ensure information accuracy, integrity, and authenticity. First, all investigators will receive pre-trial training on patients screening, data filling, medication use, AEs reporting and other matters. Second, a trial inspector will visit each site regularly to check the electronic database and ensure the trial is strictly following the protocol. Third, the Data Coordination Center will be in charge of data validation. Fourth, the researchers should take measures to control the incidence rate of drop-out within 15%.

Planned Analysis

The data from all participating centers will be combined for statistical analysis of the primary and secondary outcomes as well as AEs. Demographic and laboratory characteristics will be calculated at baseline and after-treatment period for all patients. A safety analysis will be performed in all patients. The analysis will be done at Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing. Continuous variables will be reported as the Mean ± SD with 95% confidence intervals [Cis]. Categorical variables will be shown as counts and percentages. The comparability of the characteristics between the two study groups will be assessed by using a two-samples

Student's t test for continuous variables and the $\chi 2$ test or Wilcoxon test for categorical variables. All statistical tests are unilateral test, P <0.05 will be considered as statistically significant. All statistical analyses will be performed using SPSS 20.0.

Ethics and dissemination

The procedures were approved by the Guang'anmen Hospital Ethics Committee on September 20, 2017 (The approved number is 2017-083-KY-01). And this trial has been registered at Chinese Clinical Trial Registry http://www.chictr.org.cn/ (The register number is ChiCTR-IOR-17013189). The data of this trial will be managed by ResMan at http://www.medresman.org/ and posted on Chinese Clinical Trial Registry. The results of this study will be disseminated to the public through academic conferences and peer-reviewed journals.

Discussion

Most of the plaques in BCL are thin-cap fibroatheromas or characterized by a large plaque burden, also called vulnerable plaques [4], which may progress to ACS easily. The main pathogenesis of myocardial infarction is the rupture of vulnerable plaques and thrombosis [25, 26]. Coronary atherosclerotic plaque assessment provides improved discrimination of ischaemia compared with stenosis assessment alone [27]. Coronary artery angiography is considered as the gold standard for diagnosis of coronary artery stenosis [28]. However, it cannot observe the characterisistics of plaque. DSCTA, a noninvasive testing, is widely used in clinical practice, which can not only measure the degree of coronary artery stenosis but also measure plaque compositions. As the primary outcome indicators, target plaque volume, degree of stenosis, CT value and calcification score can not only reflect the size of the plaque but also reflect the stability of the plaque. CT value demonstrates the density of the plaque. The vulnerable lesions demonstrate low-attenuation plaques and NCP with <30 HU (CT value) density identified by multi-slice computed tomography [29, 30]. In this study, we will investigate whether XAG has the effect on relaying or reversing plaque progression by reducing plaque volume and stabilizing plaque via turning NCP and MP into calcified plaque (CP) (figure 3).

Currently, the main treatment methods for BCL include lifestyle changes, medical treatment and coronary revascularization. Among these treatments, revascularization, including PCI and CABG, is recommended for patients with significant anatomic ($\geq$ 50% Left Main or $\geq$ 70% Non-Left Main) coronary artery stenosis to improve survival and symptoms [3]. In the era of drug-eluting stents, some might suggest that stenting all BCL is a suitable therapy. However, there are still some procedural complications related to revascularization, such as in-stent restenosis and stent thrombosis [31]. Moreover, research shows that revascularization is not relevant to improved long-term survival which may not be warranted in patients with BCL [32]. Among routine medications, antiplatelet and lipid-lowering therapy are mostly important in the treatment of BCL. Aspirin and clopidogrel are the most commonly used antiplatelet medications, which can reduce MACEs in patients with BCL. Whereas, studies have found that in patients with CHD, 5% to 45% are aspirin-resistant, 4% to 30% are clopidogrel-resistant and 10% are resistant to both [33]. Previous study has demonstrated that aggressive lipid-lowering therapy using high-dose statins could reduce coronary plaque volume obviously and stabilize plaque to improve long-term

progression [8]. However, long-term statin therapy may cause symptomatic adverse events such as myopathy, defined as muscle pain or weakness with creatine kinase increasing in blood concentrations, and haemorrhagic stroke [34]. In addition, many patients do not receive the conventional treatments, because of the side effects, contraindications, and insufficient relief of symptoms [35]. It is therefore crucial to develop supplementary therapeutic approaches for the treatment of BCL.

Integrative medicine, combined TCM with routine medicine, emerges as an optimal approach for achieving higher efficacy in patients with BCL. As a supplementary and alternative medicine, TCM is attracting our attention. With lifestyle and dietary changes, the number of patients with obesity and abnormal lipid metabolism increase significantly. In TCM studies, the level of low-density lipoprotein cholesterol was obviously increased in BCL patients with 'intermingled phlegm and blood stasis' syndrome [36]. People are getting more and more anxious under increasing pressure, which is related to 'heat' syndrome in TCM theory. 'Phlegm, blood stasis and heat syndrome' is the core pathogenesis in patients with BCL. XAG has the effect of 'clear up heat, resolve phlegm and promoting blood circulation'. As the principal active components, pharmacological studies have shown that salvia miltiorrhiza could perform the function of anti-oxidation, adjusting lipid metabolism, inhibiting thrombosis and expanding the coronary artery [14, 15]. Panax notoginseng is reported to protect vascular endothelial cells against hypoxia and have the anti-atherosclerotic, lipid-lowering, anti-platelet aggregation and anti-thrombosis effects [16]. Previous studies have shown that coptis chinensis can stabilize plaque by anti-inflammatory therapy [17]. However, whether XAG is effective in the patients with BCL still requires confirmation by large-sample, multi-centre and randomised controlled clinical trials. This study is a multicenter, central-randomized, double-blinded, placebo-controlled clinical trial with the objective of determining the effectiveness and safety of XAG for treating BCL.

There are also some limitations in this study. Firstly, DSCTA is easy for investigators to operate and more acceptable to participants, but plaques with diffuse irregular calcification always produce the image artifacts of DSCTA, which might cause deviation in the degree of stenosis of CP. It is recommended that the use of IVUS on the evaluation of plaque characteristics of coronary lesions would enhance the accuracy of the plaque evaluation. Secondly, our experiments will be conducted in three regions of China. Whether similar effects are available to other ethnic groups and regions remains uncertain.

Author Contributions JW is the principal investigator of this study. MYH and GC contributed equally to the article, who conceptualized the study design and wrote the manuscript. JW, KY and JL modified the manuscript. XJX, CL, QYG and HQH participated in the establishment of the eCRF. QZ, FL and XHH participated in the recruitment of patients. YL, ZPZ and YML will participate in the data collection and analysis. All authors read and approved the final manuscript.

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Competing Interest The authors declare that they have no competing interests.

Patient consent Obtained.

Ethics approval This study has been approved by Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (No. 2017-083-KY-01).

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure 1 Study flow chart.

XAG: Xuanbi Antong Granules, SAQ: Seattle Angina Questionnaire, hs-CRP: high-sensitivity, C-reactive protein, MACEs: major adverse cardiac events.

Figure 2 Flow chart of target plaque selection.

Figure 3 Subtypes of coronary plaques determined by DSCTA

A reflects non-calcified plaque (NCP), B reflects mixed plaque (MP), C reflects calcified plaque (CP).

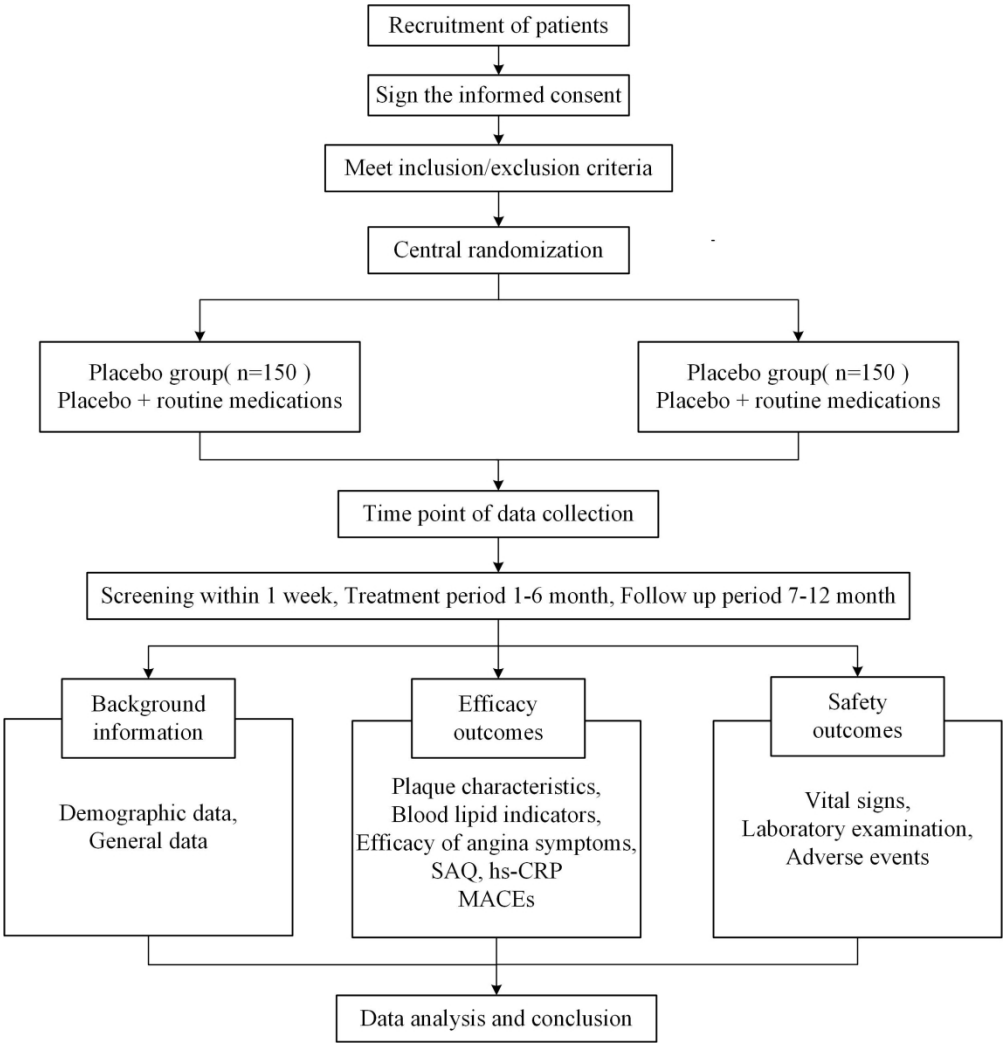

Figure 1 Study flow chart

210x218mm (300 x 300 DPI)

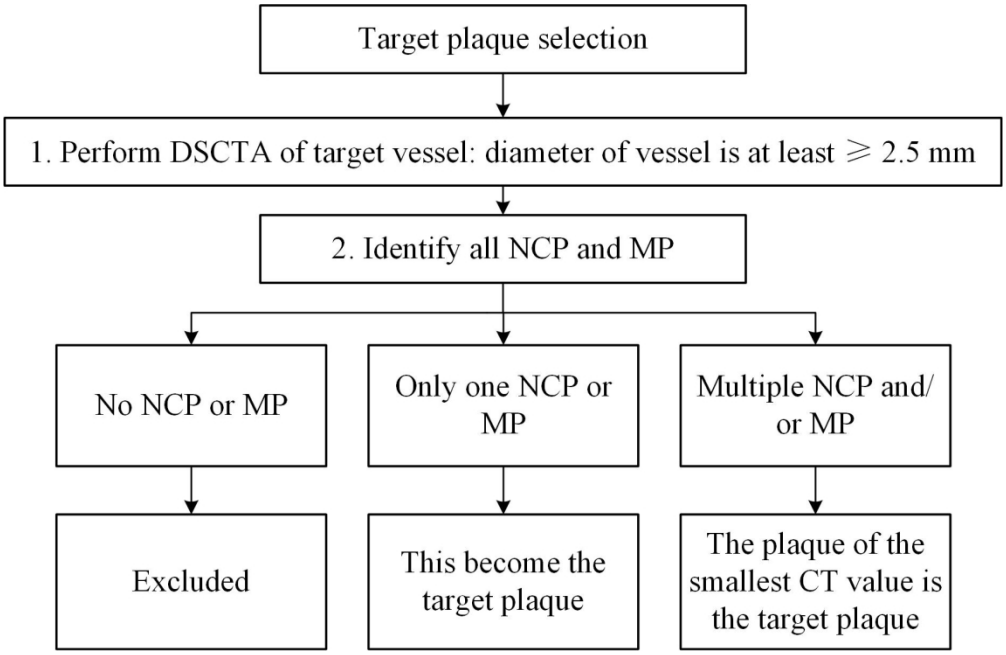

Figure 2 Flow chart of target plaque selection.

158x102mm (300 x 300 DPI)

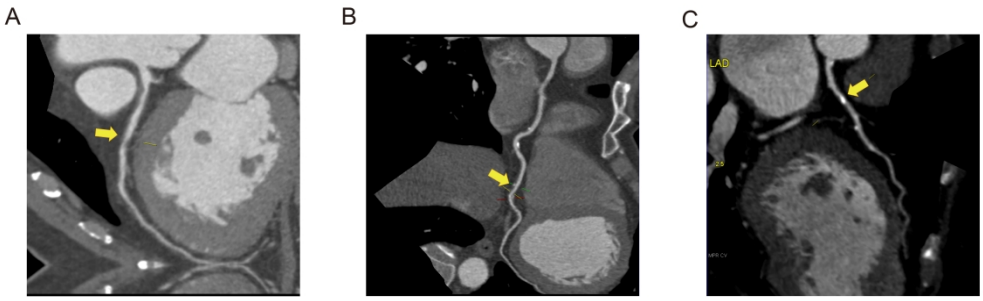

Figure 2 Flow chart of target plaque selection.

537x162mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,12
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4-5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5-7
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	7

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset,	11

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Effectiveness and safety of Chinese herbal medicine xuanbi antong granules for the treatment of borderline coronary lesions: study protocol for a central-randomized, double-blind, placebo-controlled, multicenter clinical trial

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Chinese herbal medicine, borderline coronary lesions, randomized controlled trial, protocol

Effectiveness and safety of Chinese herbal medicine xuanbi antong granules for the treatment of borderline coronary lesions: study protocol for a central-randomized, double-blind, placebo-controlled, multicenter clinical trial

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ABSTRACT

Introduction： As the early stage of coronary heart disease (CHD), borderline coronary lesion (BCL) is defined as a 30% to 70% diameter stenosis. Previous studies have demonstrated that BCL may progress to acute coronary syndrome easily. However, routine medications available for the treatments of BCL have some limitations. Xuanbi Antong Granule (XAG) has been used for the treatment of BCL in China for many years. Previous studies have shown that XAG has effectiveness in improving clinical symptoms and quality of life in patients with CHD. This study aims to evaluate the effectiveness and safety of XAG in patients with BCL.

Methods and analysis： This is a multicenter, central-randomized, double-blinded, placebo-controlled clinical trial. A total of 300 participants will be randomly assigned to the intervention group and the placebo group. Based on routine medications, the intervention group will be treated with XAG and the placebo group will be treated with XAG placebo. All participants will receive a 6-month treatment and then be followed up for another 6 months. The primary outcome indicators are the changes of target plaque characteristics (including target plaque volume, degree of stenosis, CT value and calcification score) measured by dual source computed tomography angiography. The secondary outcome indicators include blood lipid indicators, efficacy of angina symptoms, Seattle Angina Questionnaire, high-sensitivity C-reactive

protein and occurrence of major adverse cardiac events. All the data will be recorded in electronic case report forms and analyzed by SPSS 20.0.

Ethics and dissemination： This study has been approved by Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (No. 2017-083-KY-01). Written informed consent will be obtained from all participants. The results of this study will be disseminated to the public through academic conferences and peer-reviewed journals.

Trial registration number： Chinese Clinical Trial Registry (ChiCTR-IOR-17013189); Pre-results.

Key words: Chinese herbal medicine, borderline coronary lesions, randomized controlled trial, protocol.

Word Count: 4324

Strengths and limitations of this study

Strength 1: This multicenter, central-randomized, double-blinded, placebo-controlled clinical trial is exploring the effectiveness and safety of Xuanbi Antong Granule (XAG) for the treatment of borderline coronary lesions (BCL).

Strength 2: We used a noninvasive test dual source computed tomography angiography (DSCTA) to evaluate the degree of coronary artery stenosis and plaque compositions, which is easy for investigators to operate and more acceptable to participants.

Strength 3: Participants are randomized in a 1:1 ratio using central randomization system (CRS), and the blinding codes will be kept by the manufacturer of CRS, which effectively guarantees the implementation of blinding in clinical trials.

Strength 4: The data from all participating centers will be recorded in electronic case report forms (eCRF) and imported into public clinical trial management platform (www.medresman.org) within six months after the trial completes.

Limitations: Our experiments will be conducted in three regions of China, and whether similar effects are available to other ethnic groups and regions remains uncertain.

Introduction

In China, cardiovascular disease（CVD） remains the leading cause of mortality, which accounts for 44.8% and 41.9% of deaths in rural and urban area, respectively. In Europe, CVD is still the most common cause of deaths, which accounts for 45% of all deaths. Among them, coronary heart disease (CHD) is the most common cause, which accounts for 20% of all death. The incidence of CHD is continuously increasing and the burden of CHD remains heavy, which has become a major public health issue [1, 2]. As the early stage of CHD, borderline coronary lesion (BCL), also called intermediate lesion, is defined as a 30% to 70% diameter stenosis [3]. Although the presence of severe coronary stenosis has been traditionally explained as indication of myocardial ischemia, yet it has been reported that coronary occlusion and myocardial infarction most frequently evolve from mild to moderate stenosis [4]. Some other studies have recently demonstrated that approximately 87% of lesions requiring subsequent percutaneous coronary

intervention (PCI) were ⩽60% in severity during original PCI, and 6% of patients with intermediate lesions needed PCI in 1 year because of acute coronary syndrome (ACS) [5]. There is evidence that BCL may become unstable and can be the starting point for ACS [6]. Studies have shown that patients with BCL have a higher burden of mixed plaque (MP, 46%) and non-calcified plaques (NCP, 33%), also known as vulnerable plaque [7]. The number of deaths resulting from BCL continues to rise despite the use of currently recommended antiplatelet therapy, lipid-lowering therapy, revascularization procedures as appropriate, and other evidence-based secondary preventive measures [8]. It has been demonstrated that plaque regression was associated with a lower rate of major adverse cardiac events (MACEs) [9]. Therefore, it is necessary to develop supplementary therapeutic methods that can relay or reverse plaque progression and eventually reduce the occurrence of MACEs in patients with BCL.

Chinese herbal medicine (CHM), a popular type of supplementary and alternative medicine, plays a significant role in treating BCL in China. Within the framework of Traditional Chinese Medicine (TCM) theory, all the related symptoms at a certain stage of a disease are summarized as a syndrome (‘Zheng’ in TCM), which has been used in China for more than 3000 years [10]. Patients with BCL can be divided into varied syndromes. In the diagnosis of BCL, ‘phlegm, blood stasis and heat syndrome’ is an important syndrome based on the viewpoint of TCM theory and our previous clinical practice [11]. Therefore, the principle of ‘clearing away heat, resolving phlegm, promoting blood circulation and removing blood stasis’ is applied in the treatment of BCL. TCM practitioners always attach importance to preventing disease before it arises and controlling the development of existing disease. Therefore, there are some special advantages for TCM in controlling the plaque progression of BCL.

Xuanbi Antong Granule (XAG) is a commonly used CHM based on the TCM theory of ‘clear up heat, resolve phlegm and promoting blood circulation’ for prevention of BCL in China. Clinical trials have found that XAG is effective in improving clinical symptoms and improving the quality of life in patients after PCI by protecting endothelial cells and regulating platelet function [12]. Experimental studies have found that XAG can significantly improve the heart function of ventricular remodeling rats after myocardial infarction, by down-regulating inflammatory factors of TNF-a [13]. XAG consists of eight herbal medicines (table 1), including salviae miltiorrhizae (Dan Shen), puerariae lobatae radix (Ge Gen), peaoniae radix rubra (Chi Shao), cistanches herba (Rou Cong Rong), pinellia rhizoma (Ban Xia), ginseng radix et rhizoma (Ren Shen), coptis chinensis (Huang Lian), panax notoginseng (San Qi). Among them, salvia miltiorrhiza, panax notoginseng and coptis chinensis are the principal pharmacologically active components. They have various pharmacological effects, including anti-oxidation, anti-atherosclerotic, lipid-lowering, anti-platelet aggregation, protecting vascular endothelial cells, anti-inflammatory and so on [14-17]. However, there is no evidence for XAG in the treatment of BCL. Therefore, we designed a central-randomized, double-blinded, multicenter trial aiming to evaluate effectiveness and safety of XAG for the treatment of BCL.

Table 1 Components and dose of XAG.

Chinese name	English name	Origin	Pharmacological effects	Weight (%)*

Dan Shen	Salvia miltiorrhiza	The dried root or rhizome of Salvia miltiorrhiza Bge	Improve microcirculatory, anti-coagulant, anti-thrombotic, and anti-inflammatory	20.83%
Ge Gen	Puerariae lobatae radix	The dried root of pueraria lobata (wild.) Ohwi	Antihypertensive, slow heart rate, and dilate coronary vessels	20.83%
Chi Shao	Peaoniae radix rubra	The dried root of paeonia lactiflora Pall	Antiplatelet aggregation, anti-erythrocyte aggregation, anti-coagulant, anti-thrombotic and protect myocardial cells	16.67%
Rou Cong Rong	Cistanches herba	The dried scaled fleshy stalk of Cistanche deserticola Y.C.Ma	Protect ischemic myocardium，and antioxidant	13.89%
Ban Xia	Pinellia rhizoma	The dried tubers of Pinellia (Thunb.) Breit	Hypolipidemic，lower blood viscosity, antilipid peroxidation, and anti-thrombotic	8.33%
Ren Shen	Ginseng radix et rhizoma	The dried roots and rhizomes of Panax ginseng C. A. Mey.	Bidirectional regulation of blood pressure, and protect myocardial cells	8.33%
Huang Lian	Coptis chinensis	The dried rhizome of Coptis chinensis Franch	Antiplatelet, antihypertensive, protect myocardial cells, and anti-inflammatory	6.94%
San Qi	Panax notoginseng	The dried root or rhizome of Panax notoginseng F.H.Chen	Anti-atherosclerotic，antioxidant, anti-inflammatory, anti-hyperlipidemic , and anti-coagulation，	4.18%

*The weight of every single herb in each bag of XAG (7.72g).

Methods and Design

Study Design

This is a multicenter, central-randomized, double-blinded, placebo-controlled, parallel-group clinical trial. The protocol, electronic case report form (eCRF) of this study and written informed consent were approved by the Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences on September 20, 2017 (No. 2017-083-KY-01). The study was registered at the Chinese Clinical Trial Registry on October 31, 2017 (ChiCTR-IOR-17013189).

This study complies with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. We will rigorously follow the latest Consolidated Standards of Reporting Trials (CONSORT 2017) for CHM recommendations [18], Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and 2013 statement [19] for herbal interventions. Written informed consent will be acquired from all patients prior to their participation in this study. Totally 300 participants diagnosed BCL will be enrolled in the trial, which consists of a 1-week screening period, a 6-month treatment period, and another 6-month follow-up period. The recruited patients will be randomized and allocated to either the intervention group or the placebo group in a 1:1 ratio using central randomization system (CRS). In addition to routine medications, they will be given 7.72g XAG or placebo in granule form twice a day for 6 months. The study design is briefly illustrated in figure 1.

Patient and public involvement

This trial was designed to evaluate the effectiveness and safety of XAG in patients with BCL. In our previous clinical practice, early intervention of BCL may prevent the occurrence of MACEs and it is considered very important in BCL patients. XAG, a type of Chinese herbal medicine, is easily accepted by patients. Adding XAG to routine medications may increase the effectiveness in preventing the progression of BCL, thus significantly improve patients' quality of life and reduce the occurrence of MACEs. The outcome measures used in this trial were considered as important endpoints in clinical practice. The participants of this trial will be recruited from 3 participating hospitals. However, patients were not directly involved in design, recruitment or conduct of the study. After the trial completes, the results of this study will be disseminated to the public through academic conferences and peer-reviewed journals. Once the manuscript is published, the results will be briefly summarized in a simple language and sent to all trial participants through e-mail and phone. The burden of intervention will not be assessed by trial participants.

Participant Recruitment

Consecutive patients undergoing coronary dual source computed tomography angiography (DSCTA) for a clinical indication will be evaluated for the entry into the study. Inpatients and outpatients at the 3 participating hospitals (table 2) will be screened according to the inclusion and exclusion criteria by two experienced cardiologists separately. Only two cardiologists both agree that the participants will be enrolled in the trial. In addition, recruitment advertisements of the study will be posted on webpages and notice boards in 3 participating hospitals and resident communities. It includes a brief description of the subjects needed, the medicines, medical examinations and the ways to participate in this study. For those people who are ineligible or decline to participate, we will record the basic demographic information and reasons for non-participation. The trial began in December 2017 and will continue until December 2020.

Table 2 The hospitals participating in this study

Code	Participating Hospitals
01	Guang'anmen Hospital, China Academy of Chinese Medical Sciences

02	Yunnan Provincal Hospital of Traditional Chinese Medicine
03	The First Affiliated Hospital of Xinxiang Medical University

Diagnostic Criteria of BCL

The diagnosis of BCL will refer to the criteria published in "ACC/AHA Guidelines for Coronary Angiography", which is defined as 30% to 70% diameter stenosis [3]. The diameter stenosis of the main coronary, including left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA), is between 30% to 70% measured by DSCTA.

Diagnostic criteria of CHD

Two types of CHD will be recruited, including stable angina and unstable angina. The diagnostic criteria will refer to the "Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease" [20] (2012 edition) and the "Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes" [21] (2014 edition).

Diagnostic Criteria of TCM syndrome

Diagnostic criteria of 'phlegm, blood stasis and heat' syndrome in TCM will based on the "Syndrome Elements Diagnostic Criteria of Coronary Heart Disease of Angina" published by Chinese Society of Traditional Chinese Medicine Cardiovascular Disease Branch on March 2018 [22]. Syndrome elements are the smallest diagnostic unit for the diagnosis of TCM syndromes. 'Phlegm, blood stasis and heat' syndrome is the combination of 'phlegm', 'blood stasis' and 'heat' syndrome elements. TCM syndrome of each participant will be estimated by two TCM experts blindly. The consistency will be checked on by kappa test.

Inclusion Criteria:

(1) Provision of written informed consent by participants or surrogates voluntarily;

(2) Patients aged 30 to 75 years at the time of their consent;

(3) Demonstration of at least one obstruction with 30% to 70% diameter narrowing with NCP or MP (target plaque) in at least one main coronary artery (the diameter of the target vessel is $\geqslant$ 2.5mm) determined by DSCTA.

Exclusion Criteria:

(1) Chest pain caused by severe left main coronary artery lesions, severe valvular heart disease (aortic stenosis), severe psychoneurosis, climacteric syndrome, hyperthyroidism, cervical spondylosis, gallbladder heart syndrome, gastroesophageal reflux disease;

(2) Uncontrolled hypertension with SBP $\geqslant$ 160mmHg or DBP $\geqslant$ 100mmHg, severe cardiac insufficiency with EF $<$ 35%, severe arrhythmia (Fast Atrial Fibrillation, Atrial Flutter, paroxysmal ventricular tachycardia, atrioventricular block higher that second degree subtype II, complete bundle branch block);

(3) Patients with severe primary diseases like heart, brain, liver, kidney, hemopoietic system related diseases, and patients whose ALT or AST is higher than 1.5 times of the upper limit, patients with abnormal renal function or insulin dependent diabetes mellitus;
(4) Reference vessel diameter of the target vessel < 2.5mm, or there is no NCP or MP in the main coronary artery, or severe tortuosity of the target vessel or any other anatomical reasons that the investigator deems inappropriate for DSCTA procedure;
(5) Patients have undergone revascularization including PCI or coronary artery bypass grafting (CABG);
(6) Patients with depression or anxiety;
(7) Stroke or resuscitated sudden death in the past 6 months;
(8) Hyperthyroidism with TSH levels more than 1.5 times upper limit of normal;
(9) Patients with malignant tumor;
(10) Pregnant women or breast feeding women;
(11) Chronic disease requiring treatment with oral, intravenous, or intra-articular corticosteroids (use of topical, inhaled, or nasal corticosteroids is permissible);
(12) Patients with allergic constitution or are allergic to many kinds of TCM herbs and iodine;
(13) Patients with low compliance, who might miss the follow-up;
(14) Participation in other clinical trials in last 1 month.

Removal, Dropout and Termination Criteria

During the course of the study, a participant may be removed if one was not taken medication after inclusion, occurrence of myocardial infarction, revascularization (PCI or CABG) or sudden cardiac death during the treatment period. Participants can voluntarily drop out at any time during the trial. Eligible subjects failing to complete the observation period presented in the trial will be considered as dropout cases regardless of the time and reason. Reasons for dropout will be recorded in eCRFs, and the last data recorded for these participants will be included in the data analysis. The trial will be suspended in a specific participant if 1) serious adverse events (AEs) relevant to the XAG occur; 2) the participant decides to join in another clinical research project in terms of cardiovascular diseases; 3) the participant demonstrates hypersensitivity towards XAG, such as abnormal thirsty, stomachache and diarrhea; 4) the participant suffers from acute life-threatening disease. The whole research would be terminated in the following circumstances: 1) masking of the randomization fails; 2) unblinding rate exceeds 20% of the sample size; 3) assessments of all follow-up are completed.

Randomization and Blinding

Participants are randomized in a 1:1 ratio using CRS for Clinical Research (Web Edition) to achieve computerized randomization in blocks of 4, stratified by center. CRS could not only avoid factitious randomization mistake but also promote the real-time track for the progress of the participant enrollment, which is successfully developed and widely applied to multicenter clinical trials [23]. The CRS achieved the functions of subject screening, randomization, emergency exposure, drug delivery and drug supply management. It has the advantage of shortening the clinical trial cycle, improving the efficiency of clinical trials, and saving drug use. The researcher

uses the screening module to input some basic information of the subject such as date of birth, sex, and answer tests to identify the subject and then obtain the subject's unique identification number. After the subjects pass the screening period, subjects are randomized into either XAG or placebo group by using a randomization module. In addition, CRS effectively guarantees the implementation of blinding in clinical trials. In order to ensure that the blinding method in randomized controlled clinical trials is effectively guaranteed, the random number and the drug number are separated in the system. The researcher uses the drug designation module to obtain the drug number for the subject. All patients, laboratory and inspection staff and attending physicians will be blinded to treatment assignment until the research is completed. If no subject's emergency occurs during the study period, then unblinding is performed according to normal procedures. The blinding codes will be kept by the manufacturer of CRS (Clinical Evaluation Center of China Academy of Chinese Medical Sciences). All the participants and investigators in this trial will be asked to complete a questionnaire about which treatment the patents received to evaluate the success of blinding at the last visit.

Target Plaque Selection and Analysis by DSCTA

The target plaque to be monitored will be determined in NCP or MP on the main coronary vessel (diameter of the target vessel is $\geqslant$2.5mm such as LAD, CX, and/or RCA), and the diameter stenosis is between 30% to 70%. The distance from the target plaque to the coronary opening will be measured as a reproducible fiduciary index to guarantee the accuracy of the after-treatment measurement. The target plaque will be selected in each subject according to the standard operating procedures (SOP) illustrated in the figure 2, which will be evaluated as representative effect of XAG. Investigators will be required to use the same DSCTA operating system (SOMATOM Definition Flash, Siemens Healthineers, Erlangen, Germany) for both the baseline and after-treatment DSCTA image acquisition in order to make sure that each center can keep in same standard level in terms of data collection for DSCTA parameters. The DSCTA images of target plaque characteristics include plaque volume, CT values, degree of stenosis and calcification scores by using the same workstation (Syngo.via VB10B). The images will be logged, and quantitative analysis of DSCTA will be performed by two independent blinded experienced investigators who are blinded to the patient group allocation in the Radiology Department of Guang'anmen Hospital of China Academy of Chinese Medical Sciences so that the data assessment for DACTA parameters could be conducted within the same standard for each center. We will use kappa test to evaluate the consistency of the results of the two investigators.

Interventions

Eligible patients will be allocated to receive XAG or placebo granules for 6 months randomly using CRS, based on routine medications including lipid-lowering, antiplatelet, antihypertensive or antidiabetic therapy [3]. Eligible participants are prohibited from using other TCM therapies for treating BCL. The XAG and placebo granules (7.72g/ bag, one bag at a time, twice a day, 6 months) will be provided by Sichuan New Green Pharmaceutical Technology Development Co. Ltd. (Peng Zhou, China). The placebo has one tenth the dose of XAG, to test whether the placebo effects exit. Both XAG and placebo have the same outer packaging, color, shape and flavor, so that neither the participant nor the investigator could recognize which group of intervention the

participants are receiving before unblinding. After the treatment, the packaging will be returned to the investigators.

Data collection

Background Information

Background information includes demographic data and general clinical data, which will be recorded during the 1-week screening period. Demographic data consists of gender, age, height, weight and so on. General clinical data consists of medical history, course of disease, treatment history, combined diseases, concomitant medications and so on. The participants' information and privacy will be strictly protected and forbidden to the public.

Safety Outcomes

Safety is assessed by vital signs, laboratory examinations and AEs. Vital signs include body temperature, breathing, blood pressure and heart rate. Laboratory examinations include blood, urine and stool routine, liver and kidney function. AEs will be recorded all the time during the treatment. The development of AEs will also be observed until the adverse reactions disappear.

Primary and Secondary Outcomes

The primary outcome measures of the study are plaque characteristics including target plaque volume, degree of stenosis, CT value, and calcification score measured by DSCTA, which will be measured at baseline and 6 months after randomization. Secondary outcomes include the efficacy of angina symptoms, Seattle Angina Questionnaire (SAQ), which will be recorded at baseline and every month during the treatment period (1 to 6 months after randomization), blood lipid indicators, including cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein, and high-sensitivity C-reactive protein (hs-CRP) which will be recorded at baseline, 3 months, and 6 months after randomization. At the same time, the trial also observes the occurrence of MACEs defined as the composites of deaths from any cardiac causes, myocardial infarction, and revascularization (PCI or CABG) at 9 months and 12 months after randomization. Items to be measured and the time window of data collection are shown in table 3.

Table 3 Schedule of data collection

Items	Screening Period within 1 week	Treatment Period 1-6 month	Follow-up Period 7-12 month
Signed informed consent	√		
Inclusion/exclusion criteria	√		
Demographic data	√		
Medical history, course of disease, treatment history	√		

Combined diseases	√		
Concomitant medications	√	√	
Plaque characteristics	√	√	
Blood lipid indicators	√	√	
Efficacy of angina symptoms	√	√	
SAQ	√	√	
MACEs			√
hs-CRP	√	√	
Vital signs	√	√	
Blood, urine and stool routine	√	√	
Liver and kidney function	√	√	
Adverse events		√	√
eCRF examination			√

√ represents the indicators tested in the specific time period.
Vital signs: temperature, heart rates, breathing and blood pressure.

Sample Size Calculation

The formula used to calculate the sample size is as follows， which is based on superiority clinical trial interval hypothesis test sample size estimation [24]. The sample size was calculated on the basis of expected reduction in plaque volume. One previous study suggested that the reducing value for plaque volume after interventional treatment is 1mm^3, and the combined standard deviation is 2.75mm^3. Therefore, we assume the reduction in plaque volume as 1 mm^3 in this study. In the following formula, c is the ratio between two sample cases. $n_1 = n_2$, so c=1. σ is the combined standard deviation and δ is the expected effect size, so σ=2.75, δ=1. Given a type I error rate of $\alpha = 0.05$, a power of 90 % (type II error rate of $\beta = 0.1$), so $u_{1-\alpha}$=1.64, $u_{1-\beta}$=1.28. n1=n2$\approx$128， the sample size for one group needs to be 128, resulting n=2$\times$128=256 patients. Considering the maximum possible dropout rate is 15%, a total of 294 patients need to be allocated to reach the required number of patients for the efficacy analysis. For convenience of randomization, we decided to recruit 300 patients.

$$n_1 = \left[\frac{(u_{1-\alpha} + u_{1-\beta})\sigma}{\delta}\right]^2 \frac{(1+c)}{c}, \quad n_2 = cn_1$$

$n_1 = n_2 \approx 128$

Adverse Events

AEs are defined as negative or unintended clinical manifestations following the treatment. Patients will be asked to report to the investigators any abnormal reactions occurring at any time during the trial. In addition, investigators will collect information about abnormal reactions monthly. All details of related and unexpected AEs, such as time of occurrence, degree and duration of AEs, suspected causes, and the effective measures and outcomes will be recorded on eCRFs. Any AEs, such as subjective discomfort and laboratory abnormalities, should be taken seriously. Careful analysis and immediate measures are taken to protect the safety of the subjects until the adverse events disappeared. There is also a data safety monitoring board to oversee the trial.

Quality Control of Data

eCRFs will be used for data collection, and data from all participating centers will be imported into public clinical trial management platform (www.medresman.org) within six months after the trial completes. To maintain the quality of the data, we will adopt valid measures to ensure information accuracy, integrity, and authenticity. First, all investigators will receive pre-trial training on patients screening, data filling, medication use, AEs reporting and other matters. Second, a trial inspector will visit each site regularly to check the electronic database and ensure the trial is strictly following the protocol. Third, the Data Coordination Center will be in charge of data validation. Fourth, the researchers should take measures to control the incidence rate of drop-out within 15%.

Planned Analysis

All the efficacy and safety analyses will be conducted within the full analysis set (FAS) according to the intention-to-treat (ITT) principle. Furthermore, we will also conduct the per-protocol set (PPS) analysis to compare the results from FAS and PPS. The data from all participating centers will be combined for statistical analysis of the primary and secondary outcomes as well as AEs. Demographic and laboratory characteristics will be calculated at baseline and after-treatment period for all patients. The primary endpoint will be analyzed by the absolute change in DSCTA-defined total plaque volume and degree of stenosis within the target segment, CT value, and calcification score measured by DSCTA workstation from baseline to follow-up. A safety analysis will be performed in all patients. The analysis will be done at Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing. Continuous variables will be expressed by mean ± SD; Categorical variables will be shown as counts and percentages. Whether the hypothesis of superiority is available will be judged by comparing the 95% CI of the difference in intergroup efficacy. The comparability of the characteristics between the two study groups will be assessed by using t test for continuous variables with normal distribution, while the nonparametric Mann–Whitney–Wilcoxon test will be used for the comparison of data with non-normal

distribution. Categorical variables will be compared using chi-square statistics, while the Fisher exact test will be used when the theoretical frequency is less than 5 in more than 25% of the cells. In order to control the center and baseline effects, covariance analysis will be applied for the intergroup comparison with continuous variables and Cochran-Mantel-Haenszel (CMH) test for categorical variables. We will also use the Bonferroni test for multiplicity correction of the change in each of 4 parameters (total plaque volume, degree of stenosis, CT value, and calcification score). We will also conduct the subgroup analyses stratified by whether or not the participant is receiving statin therapy at the time of randomization and by subtypes of the target segment of coronary plaque determined by DSCTA. The subtypes include NCP, calcified plaque (CP) and MP, as shown in figure 3. All statistical tests are unilateral test, P <0.05 will be considered as statistically significant. All statistical analyses will be performed using SPSS 20.0.

Ethics and dissemination

The procedures were approved by the Guang'anmen Hospital Ethics Committee on September 20, 2017 (The approved number is 2017-083-KY-01). And this trial has been registered at Chinese Clinical Trial Registry http://www.chictr.org.cn/ (The register number is ChiCTR-IOR-17013189). The data of this trial will be managed by ResMan at http://www.medresman.org/ and posted on Chinese Clinical Trial Registry. The results of this study will be disseminated to the public through academic conferences and peer-reviewed journals.

Discussion

Most of the plaques in BCL are thin-cap fibroatheromas or characterized by a large plaque burden, also called vulnerable plaques [4], which may progress to ACS easily. The main pathogenesis of myocardial infarction is the rupture of vulnerable plaques and thrombosis [25, 26]. Coronary atherosclerotic plaque assessment provides improved discrimination of ischaemia compared with stenosis assessment alone [27]. Coronary artery angiography is considered as the gold standard for diagnosis of coronary artery stenosis [28]. However, it cannot observe the characterisistics of plaque. DSCTA, a noninvasive testing, is widely used in clinical practice, which can not only measure the degree of coronary artery stenosis but also measure plaque compositions. As the primary outcome indicators, target plaque volume, degree of stenosis, CT value and calcification score can not only reflect the size of the plaque but also reflect the stability of the plaque. CT value demonstrates the density of the plaque. The vulnerable lesions demonstrate low-attenuation plaques and NCP with $<$ 30 HU (CT value) density identified by multi-slice computed tomography [29, 30]. In this study, we will investigate whether XAG has the effect on relaying or reversing plaque progression by reducing plaque volume and stabilizing plaque via turning NCP and MP into calcified plaque (figure 3).

Currently, the main treatment methods for BCL include lifestyle changes, medical treatment and coronary revascularization. Among these treatments, revascularization, including PCI and CABG, is recommended for patients with significant anatomic ($\geqslant$ 50% Left Main or $\geqslant$ 70% Non-Left Main) coronary artery stenosis to improve survival and symptoms [3]. In the era of drug-eluting stents, some might suggest that stenting all BCL is a suitable therapy. However, there are still some procedural complications related to revascularization, such as in-stent restenosis and

stent thrombosis [31]. Moreover, research shows that revascularization is not relevant to improved long-term survival which may not be warranted in patients with BCL [32]. Among routine medications, antiplatelet and lipid-lowering therapy are mostly important in the treatment of BCL. Aspirin and clopidogrel are the most commonly used antiplatelet medications, which can reduce MACEs in patients with BCL. Whereas, studies have found that in patients with CHD, 5% to 45% are aspirin-resistant, 4% to 30% are clopidogrel-resistant and 10% are resistant to both [33]. Previous study has demonstrated that aggressive lipid-lowering therapy using high-dose statins could reduce coronary plaque volume obviously and stabilize plaque to improve long-term progression [8]. However, long-term statin therapy may cause symptomatic adverse events such as myopathy, defined as muscle pain or weakness with creatine kinase increasing in blood concentrations, and haemorrhagic stroke [34]. In addition, many patients do not receive the conventional treatments, because of the side effects, contraindications, and insufficient relief of symptoms [35]. It is therefore crucial to develop supplementary therapeutic approaches for the treatment of BCL.

Integrative medicine, combined TCM with routine medicine, emerges as an optimal approach for achieving higher efficacy in patients with BCL. As a supplementary and alternative medicine, TCM is attracting our attention. With lifestyle and dietary changes, the number of patients with obesity and abnormal lipid metabolism increase significantly. In TCM studies, the level of low-density lipoprotein cholesterol was obviously increased in BCL patients with 'intermingled phlegm and blood stasis' syndrome [36]. People are getting more and more anxious under increasing pressure, which is related to 'heat' syndrome in TCM theory. 'Phlegm, blood stasis and heat syndrome' is the core pathogenesis in patients with BCL. XAG has the effect of 'clear up heat, resolve phlegm and promoting blood circulation'. As the principal active components, pharmacological studies have shown that salvia miltiorrhiza could perform the function of anti-oxidation, adjusting lipid metabolism, inhibiting thrombosis and expanding the coronary artery [14, 15]. Panax notoginseng is reported to protect vascular endothelial cells against hypoxia and have the anti-atherosclerotic, lipid-lowering, anti-platelet aggregation and anti-thrombosis effects [16]. Previous studies have shown that coptis chinensis can stabilize plaque by anti-inflammatory therapy [17]. However, whether XAG is effective in the patients with BCL still requires confirmation by large-sample, multi-centre and randomised controlled clinical trials. This study is a multicenter, central-randomized, double-blinded, placebo-controlled clinical trial with the objective of determining the effectiveness and safety of XAG for treating BCL.

There are also some limitations in this study. Firstly, DSCTA is easy for investigators to operate and more acceptable to participants, but plaques with diffuse irregular calcification always produce the image artifacts of DSCTA, which might cause deviation in the degree of stenosis of CP. It is recommended that the use of IVUS on the evaluation of plaque characteristics of coronary lesions would enhance the accuracy of the plaque evaluation. Secondly, our experiments will be conducted in three regions of China. Whether similar effects are available to other ethnic groups and regions remains uncertain.

Author Contributions JW is the principal investigator of this study. MYH and GC contributed equally to the article, who conceptualized the study design and wrote the manuscript. JW, KY and

JL modified the manuscript. XJX, CL, QYG and HQH participated in the establishment of the eCRF. QZ, FL and XHH participated in the recruitment of patients. YQZ and MH designed the method for statistic analysis. YL, ZPZ and YML will participate in the data collection and analysis. All authors read and approved the final manuscript.

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Competing Interest The authors declare that they have no competing interests.

Patient consent Obtained.

Ethics approval This study has been approved by Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (No. 2017-083-KY-01).

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Figure 1 Study flow chart.

XAG: Xuanbi Antong Granules, SAQ: Seattle Angina Questionnaire, hs-CRP: high-sensitivity, C-reactive protein, MACEs: major adverse cardiac events.

Figure 2 Flow chart of target plaque selection.

Figure 3 Subtypes of coronary plaques determined by DSCTA

A reflects non-calcified plaque (NCP), B reflects mixed plaque (MP), C reflects calcified plaque (CP).

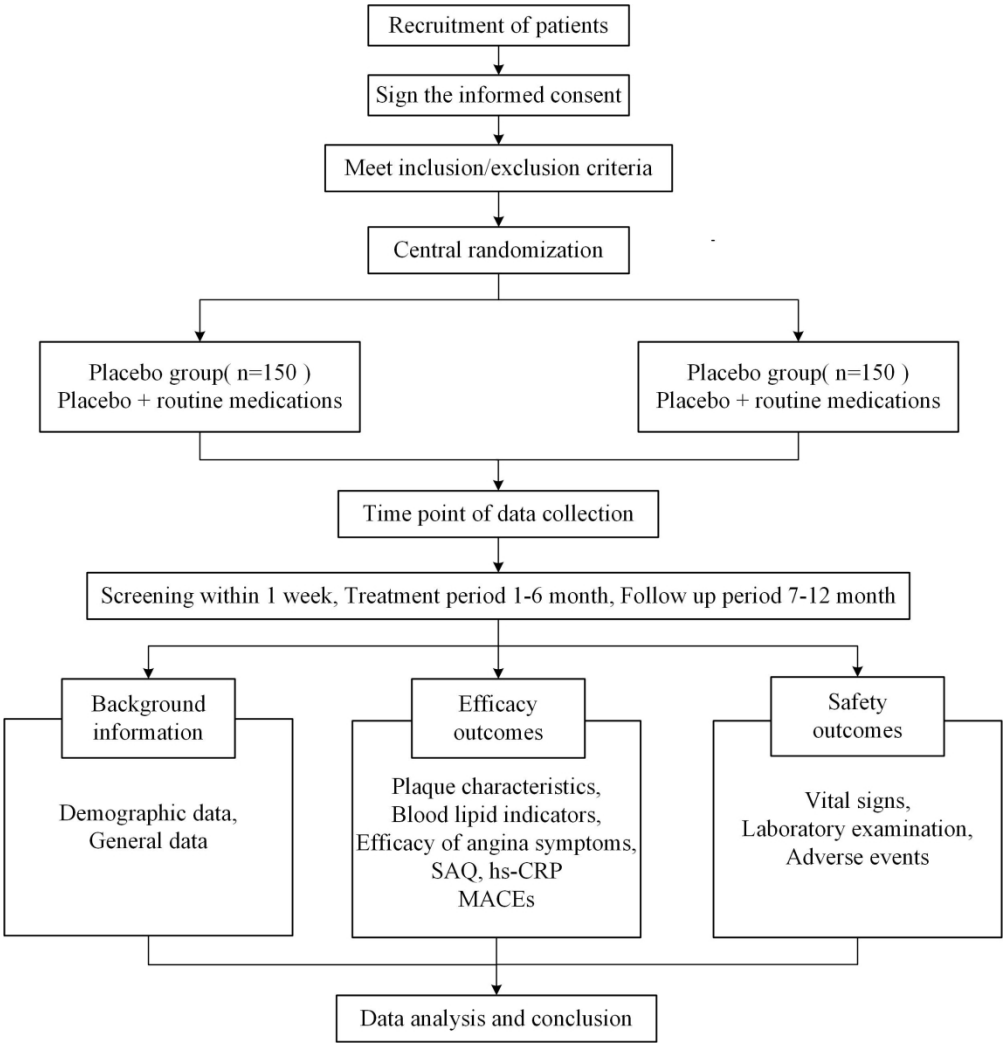

Figure 1 Study flow chart

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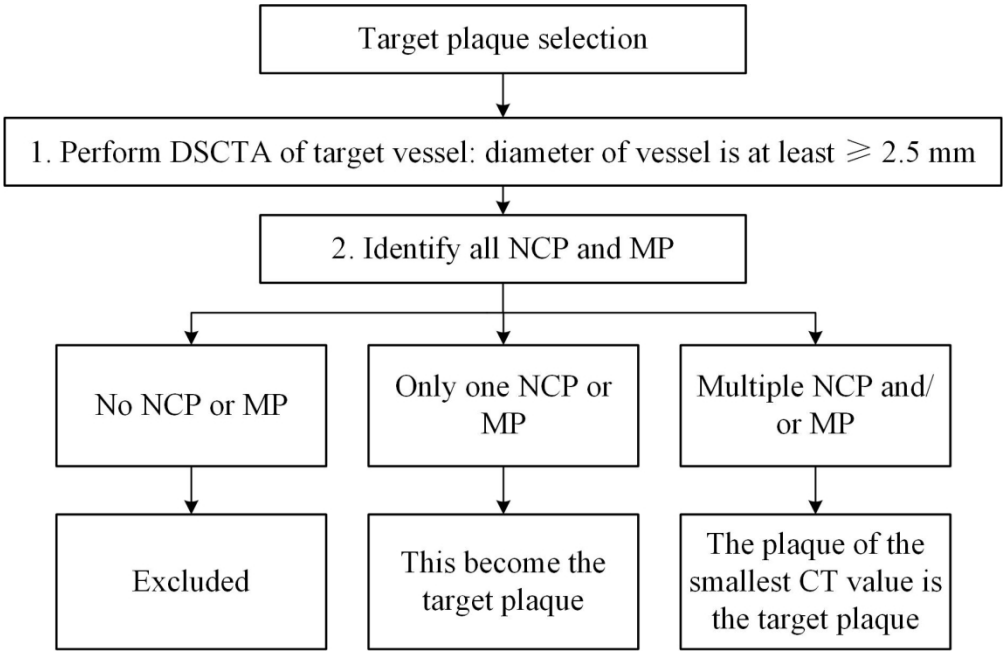

Figure 2 Flow chart of target plaque selection.

158x102mm (300 x 300 DPI)

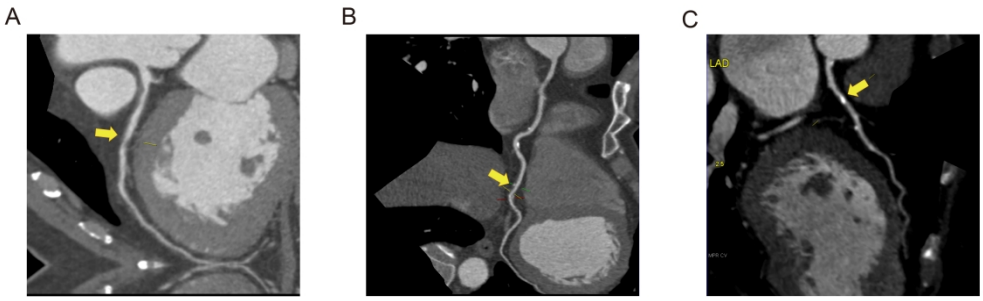

Figure 3 Subtypes of coronary plaques determined by DSCTA

537x162mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,12
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4-5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5-7
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	7

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset,	11

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Effectiveness and safety of Chinese herbal medicine xuanbi antong granules for the treatment of borderline coronary lesions: study protocol for a randomized, double-blind, placebo-controlled, multicenter clinical trial

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Chinese herbal medicine, borderline coronary lesions, randomized controlled trial, protocol

Effectiveness and safety of Chinese herbal medicine xuanbi antong granules for the treatment of borderline coronary lesions: study protocol for a randomized, double-blind, placebo-controlled, multicenter clinical trial

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ABSTRACT

Introduction： As the early stage of coronary heart disease (CHD), borderline coronary lesion (BCL) is defined as a 30% to 70% diameter stenosis. Previous studies have demonstrated that BCL may progress to acute coronary syndrome easily. However, routine medications available for the treatments of BCL have some limitations. Xuanbi Antong Granule (XAG) has been used for the treatment of BCL in China for many years. Previous studies have shown that XAG has effectiveness in improving clinical symptoms and quality of life in patients with CHD. This study aims to evaluate the effectiveness and safety of XAG in patients with BCL.

Methods and analysis： This is a multicenter, randomized, double-blinded, placebo-controlled clinical trial. A total of 300 participants will be randomly assigned to the intervention group and the placebo group. Based on routine medications, the intervention group will be treated with XAG and the placebo group will be treated with XAG placebo. All participants will receive a 6-month treatment and then be followed up for another 6 months. The primary outcomes are the changes of target plaque characteristics (including target plaque volume, degree of stenosis, CT value and calcification score) measured by dual source computed tomography angiography. The secondary outcomes include blood lipid indicators, efficacy of angina symptoms, Seattle Angina

Questionnaire, high-sensitivity C-reactive protein and occurrence of major adverse cardiac events. All the data will be recorded in electronic case report forms and analyzed by SPSS 20.0.

Ethics and dissemination： This study has been approved by Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (No. 2017-083-KY-01). Written informed consent will be obtained from all participants. The results of this study will be disseminated to the public through academic conferences and peer-reviewed journals.

Trial registration number： Chinese Clinical Trial Registry (ChiCTR-IOR-17013189); Pre-results.

Key words: Chinese herbal medicine, borderline coronary lesions, randomized controlled trial, protocol.

Word Count: 4324

Strengths and limitations of this study

Strength 1: This multicenter, randomized, double-blinded, placebo-controlled clinical trial is exploring the effectiveness and safety of Xuanbi Antong Granule (XAG) for the treatment of borderline coronary lesions (BCL).

Strength 2: We used a noninvasive test dual source computed tomography angiography (DSCTA) to evaluate the degree of coronary artery stenosis and plaque compositions, which is easy for investigators to operate and more acceptable to participants.

Strength 3: Participants are randomized in a 1:1 ratio using central randomization system (CRS), and the blinding codes will be kept by the manufacturer of CRS, which effectively guarantees the implementation of blinding in clinical trials.

Strength 4: The data from all participating centers will be recorded in electronic case report forms (eCRF) and imported into public clinical trial management platform (www.medresman.org) within six months after the trial completes.

Limitations: Our experiments will be conducted in three regions of China, and whether similar effects are available to other ethnic groups and regions remains uncertain.

Introduction

In China, cardiovascular disease（CVD） remains the leading cause of mortality, which accounts for 44.8% and 41.9% of deaths in rural and urban area, respectively. In Europe, CVD is still the most common cause of deaths, which accounts for 45% of all deaths. Among them, coronary heart disease (CHD) is the most common cause, which accounts for 20% of all death. The incidence of CHD is continuously increasing and the burden of CHD remains heavy, which has become a major public health issue [1, 2]. As the early stage of CHD, borderline coronary lesion (BCL), also called intermediate lesion, is defined as a 30% to 70% diameter stenosis [3]. Although the presence of severe coronary stenosis has been traditionally explained as indication of myocardial ischemia, yet it has been reported that coronary occlusion and myocardial infarction most frequently evolve from mild to moderate stenosis [4]. Some other studies have recently demonstrated that approximately 87% of lesions requiring subsequent percutaneous coronary

intervention (PCI) were ⩽ 60% in severity during original PCI, and 6% of patients with intermediate lesions needed PCI in 1 year because of acute coronary syndrome (ACS) [5]. There is evidence that BCL may become unstable and can be the starting point for ACS [6]. Studies have shown that patients with BCL have a higher burden of mixed plaque (MP, 46%) and non-calcified plaques (NCP, 33%), also known as vulnerable plaque [7]. The number of deaths resulting from BCL continues to rise despite the use of currently recommended antiplatelet therapy, lipid-lowering therapy, revascularization procedures as appropriate, and other evidence-based secondary preventive measures [8]. It has been demonstrated that plaque regression was associated with a lower rate of major adverse cardiac events (MACEs) [9]. Therefore, it is necessary to develop multidisciplinary management method that can relay or reverse plaque progression and eventually reduce the occurrence of MACEs in patients with BCL.

Currently, the main treatment methods for BCL include lifestyle changes, medical treatment and coronary revascularization. Among these treatments, revascularization, including PCI and coronary artery bypass grafting (CABG), is recommended for patients with significant anatomic (⩾ 50% Left Main or ⩾ 70% Non-Left Main) coronary artery stenosis to improve survival and symptoms [3]. In the era of drug-eluting stents, some might suggest that stenting all BCL is a suitable therapy. However, there are still some procedural complications related to revascularization, such as in-stent restenosis and stent thrombosis [10]. Moreover, research shows that revascularization is not relevant to improved long-term survival which may not be warranted in patients with BCL [11]. Among routine medications, antiplatelet and lipid-lowering therapy are mostly important in the treatment of BCL. Aspirin and clopidogrel are the most commonly used antiplatelet medications, which can reduce MACEs in patients with BCL. Whereas, studies have found that in patients with CHD, 5% to 45% are aspirin-resistant, 4% to 30% are clopidogrel-resistant and 10% are resistant to both [12]. Previous study has demonstrated that aggressive lipid-lowering therapy using high-dose statins could reduce coronary plaque volume obviously and stabilize plaque to improve long-term progression [8]. However, long-term statin therapy may cause symptomatic adverse events such as myopathy, defined as muscle pain or weakness with creatine kinase increasing in blood concentrations, and haemorrhagic stroke [13]. In addition, many patients do not receive the conventional treatments because of the side effects, contraindications, and unsatisfied relief of symptoms [14]. It is therefore crucial to develop supplementary therapeutic approaches for the treatment of BCL.

Chinese herbal medicine (CHM), a popular type of supplementary and alternative medicine, plays a significant role in treating BCL in China. Within the framework of Traditional Chinese Medicine (TCM) theory, all the related symptoms at a certain stage of a disease are summarized as a syndrome (‘Zheng’ in TCM), which has been used in China for more than 3000 years [15]. Patients with BCL can be divided into varied syndromes. In the diagnosis of BCL, ‘phlegm, blood stasis and heat syndrome’ is an important syndrome based on the viewpoint of TCM theory and our previous clinical practice [16]. Therefore, the principle of ‘clearing away heat, resolving phlegm, promoting blood circulation and removing blood stasis’ is applied in the treatment of BCL. TCM practitioners always attach importance to preventing disease before it arises and controlling the development of existing disease. Therefore, there are some special advantages for TCM in controlling the plaque progression of BCL.

Xuanbi Antong Granule (XAG) is a commonly used CHM based on the TCM theory of 'clear up heat, resolve phlegm and promoting blood circulation' for prevention of BCL in China. Clinical trials have found that XAG is effective in improving clinical symptoms and improving the quality of life in patients after PCI by protecting endothelial cells and regulating platelet function [17]. Experimental studies have found that XAG can significantly improve the heart function of ventricular remodeling rats after myocardial infarction, by down-regulating inflammatory factors of TNF-a [18]. XAG consists of eight herbal medicines (table 1), including salviae miltiorrhizae (Dan Shen), puerariae lobatae radix (Ge Gen), peaoniae radix rubra (Chi Shao), cistanches herba (Rou Cong Rong), pinellia rhizoma (Ban Xia), ginseng radix et rhizoma (Ren Shen), coptis chinensis (Huang Lian), panax notoginseng (San Qi). Among them, salvia miltiorrhiza, panax notoginseng and coptis chinensis are the principal pharmacologically active components. They have various pharmacological effects, including anti-oxidation, anti-atherosclerotic, lipid-lowering, anti-platelet aggregation, protecting vascular endothelial cells, anti-inflammatory and so on [19-22]. However, there is no evidence for XAG in the treatment of BCL. Therefore, we designed a central-randomized, double-blinded, multicenter trial aiming to evaluate effectiveness and safety of XAG for the treatment of BCL.

Table 1 Components and dose of XAG.

Chinese name	English name	Origin	Pharmacological effects	Weight (%)*
Dan Shen	Salvia miltiorrhiza	The dried root or rhizome of Salvia miltiorrhiza Bge	Improve microcirculatory, anti-coagulant, anti-thrombotic, and anti-inflammatory	20.83%
Ge Gen	Puerariae lobatae radix	The dried root of pueraria lobata (wild.) Ohwi	Antihypertensive, slow heart rate, and dilate coronary vessels	20.83%
Chi Shao	Peaoniae radix rubra	The dried root of paeonia lactiflora Pall	Antiplatelet aggregation, anti-erythrocyte aggregation, anti-coagulant, anti-thrombotic and protect myocardial cells	16.67%
Rou Cong Rong	Cistanches herba	The dried scaled fleshy stalk of Cistanche deserticola Y.C.Ma	Protect ischemic myocardium，and antioxidant	13.89%
Ban Xia	Pinellia rhizoma	The dried tubers of Pinellia (Thunb.) Breit	Hypolipidemic，lower blood viscosity, antilipid peroxidation, and anti-thrombotic	8.33%

Ren Shen	Ginseng radix et rhizoma	The dried roots and rhizomes of Panax ginseng C. A. Mey.	Bidirectional regulation of blood pressure, and protect myocardial cells	8.33%
Huang Lian	Coptis chinensis	The dried rhizome of Coptis chinensis Franch	Antiplatelet, antihypertensive, protect myocardial cells, and anti-inflammatory	6.94%
San Qi	Panax notoginseng	The dried root or rhizome of Panax notoginseng F.H.Chen	Anti-atherosclerotic，antioxidant, anti-inflammatory, anti-hyperlipidemic , and anti-coagulation，	4.18%

*The weight of every single herb in each bag of XAG (7.72g).

Methods and Design

Study Design

This is a multicenter, randomized, double-blinded, placebo-controlled, parallel-group clinical trial. The protocol, electronic case report form (eCRF) of this study and written informed consent were approved by the Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences on September 20, 2017 (No. 2017-083-KY-01). The study was registered at the Chinese Clinical Trial Registry on October 31, 2017 (ChiCTR-IOR-17013189). This study complies with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. We will rigorously follow the latest Consolidated Standards of Reporting Trials (CONSORT 2017) for CHM recommendations [23], Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and 2013 statement [24] for herbal interventions. Written informed consent will be acquired from all patients prior to their participation in this study. Totally 300 participants diagnosed BCL will be enrolled in the trial, which consists of a 1-week screening period, a 6-month treatment period, and another 6-month follow-up period. The recruited patients will be randomized and allocated to either the intervention group or the placebo group in a 1:1 ratio using central randomization system (CRS). In addition to routine medications, they will be given 7.72g XAG or placebo in granule form twice a day for 6 months. The participants flowchart is briefly illustrated in figure 1.

Patient and Public Involvement

This trial was designed to evaluate the effectiveness and safety of XAG in patients with BCL. In our previous clinical practice, early intervention of BCL may prevent the occurrence of MACEs and it is considered very important in BCL patients. XAG, a type of Chinese herbal medicine, is easily accepted by patients. Adding XAG to routine medications may increase the effectiveness in preventing the progression of BCL, thus significantly improve patients' quality of life and reduce the occurrence of MACEs. The outcome measures used in this trial were considered as important endpoints in clinical practice. The participants of this trial will be recruited from 3 participating hospitals. However, patients were not directly involved in design, recruitment or conduct of the study. After the trial

completes, the results of this study will be disseminated to the public through academic conferences and peer-reviewed journals. Once the manuscript is published, the results will be briefly summarized in a simple language and sent to all trial participants through e-mail and phone. The burden of intervention will not be assessed by trial participants.

Participant Recruitment

Consecutive patients undergoing coronary dual source computed tomography angiography (DSCTA) for a clinical indication will be evaluated for the entry into the study. Inpatients and outpatients at the 3 participating hospitals (table 2) will be screened according to the inclusion and exclusion criteria by two experienced cardiologists separately. When two cardiologists both confirm that patients conform to the criteria for recruitment, the participants will be enrolled in the trial. In addition, recruitment advertisements of the study will be posted on webpages and notice boards in 3 participating hospitals and resident communities. It includes a brief description of the subjects needed, the medicines, medical examinations and the ways to participate in this study. For those people who are ineligible or decline to participate, we will record the basic demographic information and reasons for non-participation. The trial began in December 2017 and will continue until December 2020.

Table 2 The hospitals participating in this study

Code	Participating Hospitals
01	Guang'anmen Hospital, China Academy of Chinese Medical Sciences
02	Yunnan Provincal Hospital of Traditional Chinese Medicine
03	The First Affiliated Hospital of Xinxiang Medical University

Diagnostic Criteria of BCL

The diagnosis of BCL will refer to the criteria published in "ACC/AHA Guidelines for Coronary Angiography", which is defined as 30% to 70% diameter stenosis [3]. The diameter stenosis of the main coronary, including left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA), is between 30% to 70% measured by DSCTA.

Diagnostic Criteria of CHD

Two types of CHD will be recruited, including stable angina and unstable angina. The diagnostic criteria will refer to the "Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease" [25] (2012 edition) and the "Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes" [26] (2014 edition).

Diagnostic Criteria of TCM syndrome

Diagnostic criteria of 'phlegm, blood stasis and heat' syndrome in TCM will based on the "Syndrome Elements Diagnostic Criteria of Coronary Heart Disease of Angina" published by Chinese Society of Traditional Chinese Medicine Cardiovascular Disease Branch on March 2018

[27]. Syndrome elements are the smallest diagnostic unit for the diagnosis of TCM syndromes. 'Phlegm, blood stasis and heat' syndrome is the combination of 'phlegm', 'blood stasis' and 'heat' syndrome elements. TCM syndrome of each participant will be estimated by two TCM experts blindly. The consistency will be checked on by kappa test.

Inclusion Criteria:

(1) Provision of written informed consent by participants or surrogates voluntarily;

(2) Patients aged 30 to 75 years at the time of their consent;

(3) Demonstration of at least one obstruction with 30% to 70% diameter narrowing with NCP or MP (target plaque) in at least one main coronary artery (the diameter of the target vessel is ⩾ 2.5mm) determined by DSCTA.

Exclusion Criteria:

(1) Chest pain caused by severe left main coronary artery lesions, severe valvular heart disease (aortic stenosis), severe psychoneurosis, climacteric syndrome, hyperthyroidism, cervical spondylosis, gallbladder heart syndrome, gastroesophageal reflux disease;

(2) Uncontrolled hypertension with SBP ⩾ 160mmHg or DBP ⩾ 100mmHg, severe cardiac insufficiency with EF < 35%, severe arrhythmia (Fast Atrial Fibrillation, Atrial Flutter, paroxysmal ventricular tachycardia, atrioventricular block higher that second degree subtype II, complete bundle branch block);

(3) Patients with severe primary diseases like heart, brain, liver, kidney, hemopoietic system related diseases, and patients whose ALT or AST is higher than 1.5 times of the upper limit, patients with abnormal renal function or insulin dependent diabetes mellitus;

(4) Reference vessel diameter of the target vessel < 2.5mm, or there is no NCP or MP in the main coronary artery, or severe tortuosity of the target vessel or any other anatomical reasons that the investigator deems inappropriate for DSCTA procedure;

(5) Patients have undergone revascularization including PCI or CABG;

(6) Patients with depression or anxiety;

(7) Stroke or resuscitated sudden death in the past 6 months;

(8) Hyperthyroidism with TSH levels more than 1.5 times upper limit of normal;

(9) Patients with malignant tumor;

(10) Pregnant women or breast feeding women;

(11) Chronic disease requiring treatment with oral, intravenous, or intra-articular corticosteroids (use of topical, inhaled, or nasal corticosteroids is permissible);

(12) Patients with allergic constitution or are allergic to many kinds of TCM herbs and iodine;

(13) Patients with low compliance, who might miss the follow-up;

(14) Participation in other clinical trials in last 1 month.

Removal, Dropout and Termination Criteria

During the course of the study, a participant may be removed if one was not taken medication after inclusion, occurrence of myocardial infarction, revascularization (PCI or CABG) or sudden cardiac death during the treatment period. Participants can voluntarily drop out at any time during

the trial. Eligible subjects failing to complete the observation period presented in the trial will be considered as dropout cases regardless of the time and reason. Reasons for dropout will be recorded in eCRFs, and the last data recorded for these participants will be included in the data analysis. The trial will be suspended in a specific participant if 1) serious adverse events (AEs) relevant to the XAG occur; 2) the participant decides to join in another clinical research project in terms of cardiovascular diseases; 3) the participant demonstrates hypersensitivity towards XAG, such as abnormal thirsty, stomachache and diarrhea; 4) the participant suffers from acute life-threatening disease. The whole research would be terminated in the following circumstances: 1) masking of the randomization fails; 2) unblinding rate exceeds 20% of the sample size; 3) assessments of all follow-up are completed.

Randomization and Blinding

Participants are randomized in a 1:1 ratio using CRS for Clinical Research (Web Edition) to achieve computerized randomization in blocks of 4, stratified by center. CRS could not only avoid factitious randomization mistake but also promote the real-time track for the progress of the participant enrollment, which is successfully developed and widely applied to multicenter clinical trials [28]. The CRS achieved the functions of subject screening, randomization, emergency exposure, drug delivery and drug supply management. It has the advantage of shortening the clinical trial cycle, improving the efficiency of clinical trials, and saving drug use. The researcher uses the screening module to input some basic information of the subject such as date of birth, sex, and answer tests to identify the subject and then obtain the subject's unique identification number. After the subjects pass the screening period, subjects are randomized into either XAG or placebo group by using a randomization module. In addition, CRS effectively guarantees the implementation of blinding in clinical trials. In order to ensure that the blinding method in randomized controlled clinical trials is effectively guaranteed, the random number and the drug number are separated in the system. The researcher uses the drug designation module to obtain the drug number for the subject. All patients, laboratory and inspection staff, attending physicians and statisticians will be blinded to treatment assignment until the entire research is completed. Emergency unblinding process should only occur when the knowledge of intervention allocation is essential to guide the clinical magenement. The blinding codes will be kept by the manufacturer of CRS (Clinical Evaluation Center of China Academy of Chinese Medical Sciences). All the participants and investigators in this trial will be asked to complete a questionnaire about which treatment the patents received to evaluate the success of blinding at the last visit.

Target Plaque Selection and Analysis by DSCTA

The target plaque to be monitored will be determined in NCP or MP on the main coronary vessel (diameter of the target vessel is $\geqslant$2.5mm such as LAD, CX, and/or RCA), and the diameter stenosis is between 30% to 70%. The distance from the target plaque to the coronary opening will be measured as a reproducible fiduciary index to guarantee the accuracy of the after-treatment measurement. The target plaque will be selected in each subject according to the standard operating procedures (SOP) illustrated in the figure 2, which will be evaluated as representative effect of XAG. Investigators will be required to use the same DSCTA operating system

(SOMATOM Definition Flash, Siemens Healthineers, Erlangen, Germany) for both the baseline and after-treatment DSCTA image acquisition in order to make sure that each center can keep in same standard level in terms of data collection for DSCTA parameters. The DSCTA images of target plaque characteristics include plaque volume, CT values, degree of stenosis and calcification scores by using the same workstation (Syngo.via VB10B). The images will be logged, and quantitative analysis of DSCTA will be performed by two independent blinded experienced investigators who are blinded to the patient group allocation in the Radiology Department of Guang'anmen Hospital of China Academy of Chinese Medical Sciences so that the data assessment for DACTA parameters could be conducted within the same standard for each center. We will use kappa test to evaluate the consistency of the results of the two investigators.

Interventions

Eligible patients will be allocated to receive XAG or placebo granules for 6 months randomly using CRS, based on routine medications including lipid-lowering, antiplatelet, antihypertensive or antidiabetic therapy [3]. Eligible participants are prohibited from using other TCM therapies for treating BCL. The XAG and placebo granules (7.72g/ bag, one bag at a time, twice a day, 6 months) will be provided by Sichuan New Green Pharmaceutical Technology Development Co. Ltd. (Peng Zhou, China). Both XAG and placebo have the same outer packaging, color, shape and flavor, so that neither the participant nor the investigator could recognize which group of intervention the participants are receiving before unblinding. After the treatment, the packaging will be returned to the investigators.

Data collection

Background Information

Background information includes demographic data and general clinical data, which will be recorded during the 1-week screening period. Demographic data consists of gender, age, height, weight and so on. General clinical data consists of medical history, course of disease, treatment history, combined diseases, concomitant medications and so on. The participants' information and privacy will be strictly protected and forbidden to the public.

Safety Outcomes

Safety is assessed by vital signs, laboratory examinations and AEs. Vital signs include body temperature, breathing, blood pressure and heart rate. Laboratory examinations include blood, urine and stool routine, liver and kidney function. AEs will be recorded all the time during the treatment. The development of AEs will also be observed until the adverse reactions disappear.

Primary and Secondary Outcomes

The primary outcome measures of the study are plaque characteristics including target plaque volume, degree of stenosis, CT value, and calcification score measured by DSCTA, which will be measured at baseline and 6 months after randomization. Secondary outcomes include the efficacy of angina symptoms, Seattle Angina Questionnaire (SAQ), which will be recorded at baseline and every month during the treatment period (1 to 6 months after randomization), blood lipid indicators, including cholesterol, triglycerides, low-density lipoprotein and high-density

lipoprotein, and high-sensitivity C-reactive protein (hs-CRP) which will be recorded at baseline, 3 months, and 6 months after randomization. At the same time, the trial also observes the occurrence of MACEs defined as the composites of deaths from any cardiac causes, myocardial infarction, and revascularization (PCI or CABG) at 9 months and 12 months after randomization. Items to be measured and the time window of data collection are shown in table 3.

Table 3 Schedule of data collection

Items	Screening Period within 1 week	Treatment Period 1-6 month	Follow-up Period 7-12 month
Signed informed consent	√		
Inclusion/exclusion criteria	√		
Demographic data	√		
Medical history, course of disease, treatment history	√		
Combined diseases	√		
Concomitant medications	√	√	
Plaque characteristics	√	√	
Blood lipid indicators	√	√	
Efficacy of angina symptoms	√	√	
SAQ	√	√	
MACEs			√
hs-CRP	√	√	
Vital signs	√	√	
Blood, urine and stool routine	√	√	
Liver and kidney function	√	√	
Adverse events		√	√

eCRF examination	√

√ represents the indicators tested in the specific time period.

Vital signs: temperature, heart rates, breathing and blood pressure.

Sample Size Calculation

The formula used to calculate the sample size is as follows，which is based on superiority clinical trial interval hypothesis test sample size estimation [29]. The sample size was calculated on the basis of expected reduction in plaque volume. One previous study suggested that the reducing value for plaque volume after interventional treatment is 1mm^3, and the combined standard deviation is 2.75mm^3. Therefore, we assume the reduction in plaque volume as 1 mm^3 in this study. In the following formula, c is the ratio between two sample cases. $n_1 = n_2$, so c=1. σ is the combined standard deviation and δ is the expected effect size, so σ=2.75, δ=1. Given a type I error rate of α = 0.05, a power of 90 % (type II error rate of β = 0.1), so $u_{1-\alpha}$=1.64, $u_{1-\beta}$=1.28. n1=n2≈128，the sample size for one group needs to be 128, resulting n=2×128=256 patients. Considering the maximum possible dropout rate is 15%, a total of 294 patients need to be allocated to reach the required number of patients for the efficacy analysis. For convenience of randomization, we decided to recruit 300 patients.

$$n_1 = \left[\frac{(u_{1-\alpha} + u_{1-\beta})\sigma}{\delta}\right]^2 \frac{(1+\mathrm{c})}{c}, \quad n_2 = cn_1$$

$n_1 = n_2 \approx 128$

Adverse Events

AEs are defined as negative or unintended clinical manifestations following the treatment. Patients will be asked to report to the investigators any abnormal reactions occurring at any time during the trial. In addition, investigators will collect information about abnormal reactions monthly. All details of related and unexpected AEs, such as time of occurrence, degree and duration of AEs, suspected causes, and the effective measures and outcomes will be recorded on eCRFs. Any AEs, such as subjective discomfort and laboratory abnormalities, should be taken seriously. Careful analysis and immediate measures are taken to protect the safety of the subjects until the adverse events disappeared. There is also a data safety monitoring board to oversee the trial.

Quality Control of Data

eCRFs will be used for data collection, and data from all participating centers will be imported into public clinical trial management platform (www.medresman.org) within six months after the trial completes. To maintain the quality of the data, we will adopt valid measures to ensure information accuracy, integrity, and authenticity. First, all investigators will receive pre-trial training on patients screening, data filling, medication use, AEs reporting and other matters. Second, a trial inspector will visit each site regularly to check the electronic database and ensure the trial is strictly following the protocol. Third, the Data Coordination Center will be in charge of

data validation. Fourth, the researchers should take measures to control the incidence rate of drop-out within 15%.

Planned Analysis

All the efficacy and safety analyses will be conducted within the full analysis set (FAS) according to the intention-to-treat (ITT) principle, with all randomly assigned participants included. Furthermore, we will also conduct the per-protocol set (PPS) analysis to compare the results from FAS and PPS. The data from all participating centers will be combined for statistical analysis of the primary and secondary outcomes as well as AEs. Demographic and laboratory characteristics will be calculated at baseline and after-treatment period for all patients. The primary endpoint will be analyzed by the absolute change in DSCTA-defined total plaque volume and degree of stenosis within the target segment, CT value, and calcification score measured by DSCTA workstation from baseline to follow-up. A safety analysis will be performed in all patients. The analysis will be done at Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing. Continuous variables will be expressed by mean ± SD; Categorical variables will be shown as counts and percentages. Whether the hypothesis of superiority is available will be judged by comparing the 95% CI of the difference in intergroup efficacy. The comparability of the characteristics between the two study groups will be assessed by using t test for continuous variables with normal distribution, while the nonparametric Mann–Whitney–Wilcoxon test will be used for the comparison of data with non-normal distribution. Specifically, the paired t test will be used to compare the difference of the outcome between pre-intervention and post-intervention in each group and independent t test will be used to compare the difference between the two groups. Categorical variables will be compared using chi-square statistics, while the Fisher exact test will be used when the theoretical frequency is less than 5 in more than 25% of the cells. In order to control the center and baseline effects, covariance analysis will be applied for the intergroup comparison with continuous variables and Cochran-Mantel-Haenszel (CMH) test for categorical variables. We will also use the Bonferroni test for multiplicity correction of the change in each of 4 parameters (total plaque volume, degree of stenosis, CT value, and calcification score). We will also conduct the subgroup analyses stratified by whether or not the participant is receiving statin therapy at the time of randomization and by subtypes of the target segment of coronary plaque determined by DSCTA. The subtypes include NCP, calcified plaque (CP) and MP, as shown in figure 3. All statistical tests are unilateral test, P <0.05 will be considered as statistically significant. All statistical analyses will be performed using SPSS 20.0.

Ethics and dissemination

The procedures were approved by the Guang'anmen Hospital Ethics Committee on September 20, 2017 (The approved number is 2017-083-KY-01). And this trial has been registered at Chinese Clinical Trial Registry http://www.chictr.org.cn/ (The register number is ChiCTR-IOR-17013189). The data of this trial will be managed by ResMan at http://www.medresman.org/ and posted on Chinese Clinical Trial Registry. The results of this study will be disseminated to the public through academic conferences and peer-reviewed journals.

Discussion

Most of the plaques in BCL are thin-cap fibroatheromas or characterized by a large plaque burden, also called vulnerable plaques [4], which may progress to ACS easily. The main pathogenesis of myocardial infarction is the rupture of vulnerable plaques and thrombosis [30, 31]. Coronary atherosclerotic plaque assessment provides improved discrimination of ischaemia compared with stenosis assessment alone [32]. Coronary artery angiography is considered as the gold standard for diagnosis of coronary artery stenosis [33]. However, it cannot observe the characterisistics of plaque. DSCTA, a noninvasive testing, is widely used in clinical practice, which can not only measure the degree of coronary artery stenosis but also measure plaque compositions. As the primary outcome indicators, target plaque volume, degree of stenosis, CT value and calcification score can not only reflect the size of the plaque but also reflect the stability of the plaque. CT value demonstrates the density of the plaque. The vulnerable lesions demonstrate low-attenuation plaques and NCP with $<$ 30 HU (CT value) density identified by multi-slice computed tomography [34, 35]. In this study, we will investigate whether XAG has the effect on relaying or reversing plaque progression by reducing plaque volume and stabilizing plaque via turning NCP and MP into calcified plaque (figure 3).

Integrative medicine, combined TCM with routine medicine, emerges as an optimal approach for achieving better effectiveness in patients with BCL. As a supplementary and alternative medicine, TCM is attracting our attention. With lifestyle and dietary changes, the number of patients with obesity and abnormal lipid metabolism increase significantly. In TCM studies, the level of low-density lipoprotein cholesterol was obviously increased in BCL patients with 'intermingled phlegm and blood stasis' syndrome [36]. People are getting more and more anxious under increasing pressure, which is related to 'heat' syndrome in TCM theory. 'Phlegm, blood stasis and heat syndrome' is the core pathogenesis in patients with BCL. XAG has the effect of 'clear up heat, resolve phlegm and promoting blood circulation'. As the principal active components, pharmacological studies have shown that salvia miltiorrhiza could perform the function of anti-oxidation, adjusting lipid metabolism, inhibiting thrombosis and expanding the coronary artery [19, 20]. Panax notoginseng is reported to protect vascular endothelial cells against hypoxia and have the anti-atherosclerotic, lipid-lowering, anti-platelet aggregation and anti-thrombosis effects [21]. Previous studies have shown that coptis chinensis can stabilize plaque by anti-inflammatory therapy [22]. However, whether XAG is effective in the patients with BCL still requires confirmation by large-sample, multi-centre and randomised controlled clinical trials. This study is a multicenter, central-randomized, double-blinded, placebo-controlled clinical trial with the objective of determining the effectiveness and safety of XAG for treating BCL.

There are also some limitations in this study. Firstly, DSCTA is easy for investigators to operate and more acceptable to participants, but plaques with diffuse irregular calcification always produce the image artifacts of DSCTA, which might cause deviation in the degree of stenosis of CP. It is recommended that the use of IVUS on the evaluation of plaque characteristics of coronary lesions would enhance the accuracy of the plaque evaluation. Secondly, our experiments will be conducted in three regions of China. Whether similar effects are available to other ethnic groups and regions remains uncertain.

Author Contributions JW is the principal investigator of this study. MYH and GC contributed equally to the article, who conceptualized the study design and wrote the manuscript. JW, KY and JL modified the manuscript. XJX, CL, QYG and HQH participated in the establishment of the eCRF. QZ, FL and XHH participated in the recruitment of patients. YQZ and MH designed the method for statistic analysis. YL, ZPZ and YML will participate in the data collection and analysis. All authors read and approved the final manuscript.

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Competing Interest The authors declare that they have no competing interests.

Patient consent Obtained.

Ethics approval This study has been approved by Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (No. 2017-083-KY-01).

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure 1 CONSORT flow diagram for XAG clinical trial

XAG: Xuanbi Antong Granules

Figure 2 Flow chart of target plaque selection.

Figure 3 Subtypes of coronary plaques determined by DSCTA

A reflects non-calcified plaque (NCP), B reflects mixed plaque (MP), C reflects calcified plaque (CP).

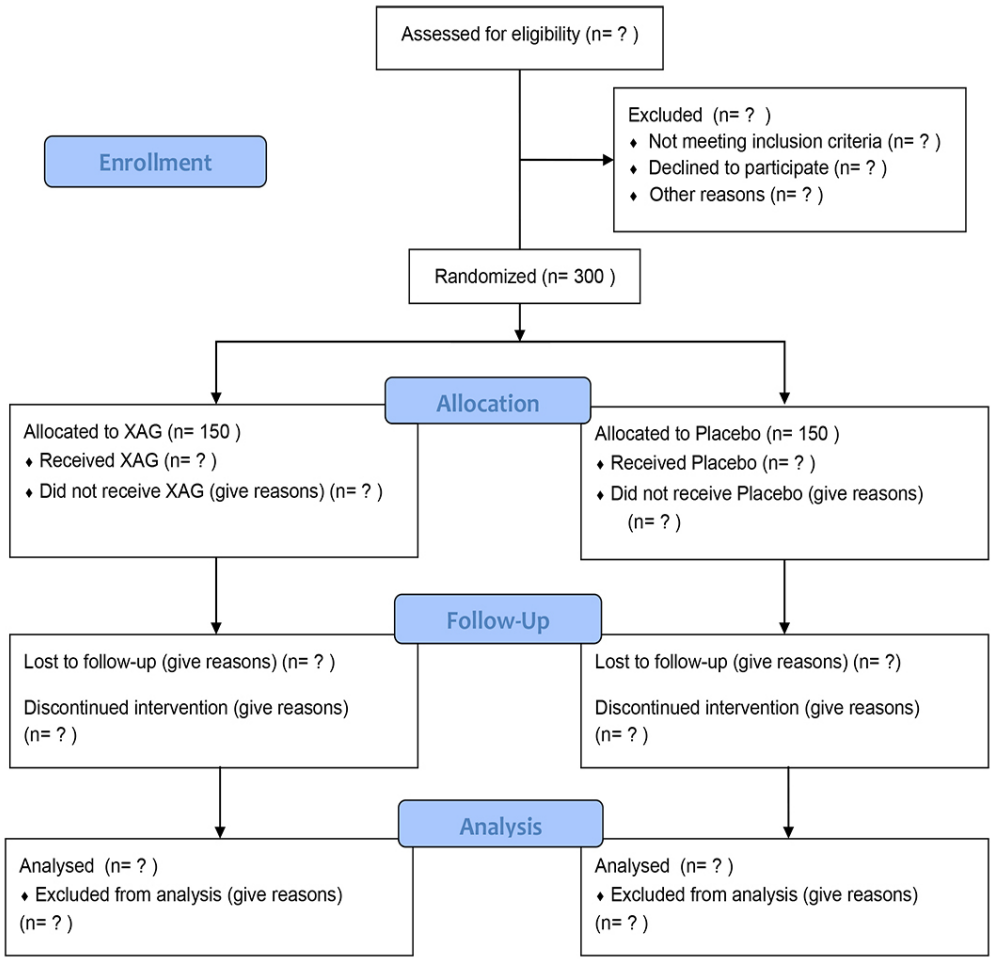

Figure 1 CONSORT flow diagram for XAG clinical trial

90x90mm (300 x 300 DPI)

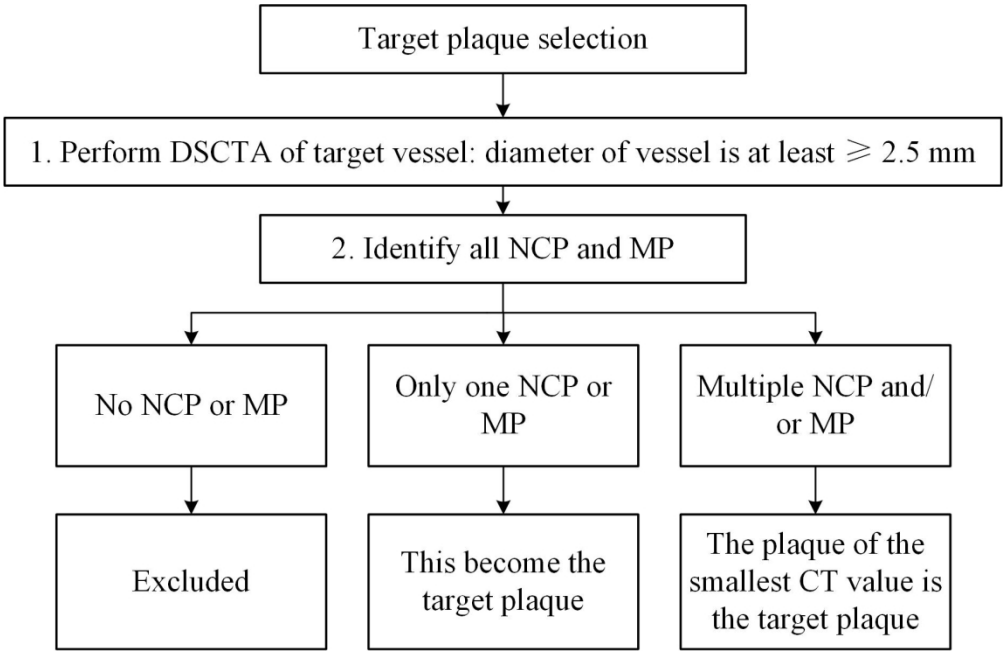

Figure 2 Flow chart of target plaque selection.

158x102mm (300 x 300 DPI)

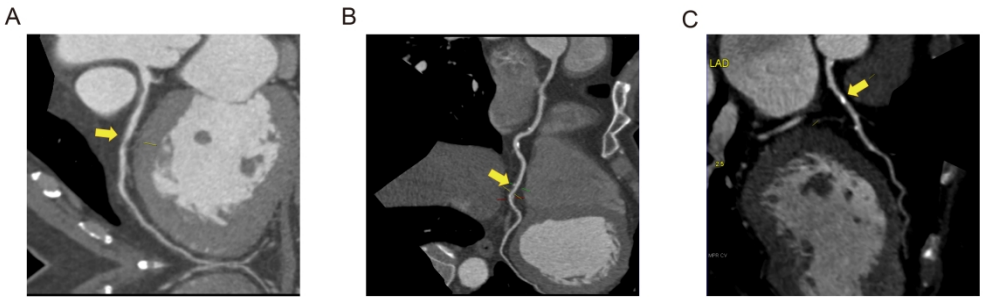

Figure 3 Subtypes of coronary plaques determined by DSCTA

537x162mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,12
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	n/a

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4-5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5-7
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	7

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset,	11

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a