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Efficacy and safety of Shexiang Baoxin Pill on coronary artery disease not amenable to revascularization: study protocol for a randomised, placebo-controlled, double-blinded trial.

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Efficacy and safety of Shexiang Baoxin Pill on coronary artery disease not amenable to revascularization: study protocol for a randomised, placebo-controlled, double-blinded trial.

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Keywords Coronary artery disease; revascularization; Shexiang Baoxin Pill; randomised controlled trial.

Word count About 2767 words.

ABSTRACT

Introduction: Coronary artery disease (CAD) is a common disease with high incidence and mortality rate around the world. CAD not amenable to revascularization mainly indicates that the coronary arteries have sever diffuse lesion, calcification, or CAD complicated with severe multiple organ disease. Currently, the western medicine treatment for CAD not amenable to revascularization is limited. Shexiang Baoxin Pill (SBP), a kind of Chinese patent medicine, has been widely used for treating CAD in China for many years. Numerous researches have identified that SBP can improve myocardial ischemia and promote therapeutic angiogenesis. However, whether SBP is effective in treating CAD not amenable to revascularization is still unknown. This study aims to evaluate the efficacy and safety of SBP in patients with CAD not amenable to revascularization.

Methods and analysis: This is a multicentre, placebo-controlled, double-blinded, randomised controlled clinical trial. A total of 440 participants are randomly allocated to two groups: the intervention group and the placebo group. On the basis of conventional western medicine treatment, the intervention group is treated by SBP, and the placebo group is treated by SBP placebo. The patients is treated by either SBP or placebo three times daily for 24 weeks. The primary outcomes include major adverse cardiovascular events (including myocardial infarction, mortality and other unexpected incidents). The secondary outcomes include C-reactive protein, B-type natriuretic peptide, electrocardiogram, echocardiographic parameters (ejection fraction percentage, E/A ratio), and hospital readmission rates due to CAD. The assessment is performed at baseline (before randomisation), and 24 weeks after randomisation.

Ethics and dissemination: The protocol has been approved by the Research Ethical Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China (reference: 2016-129-KY-01). The trial will be helpful in identifying the efficacy and safety of SBP on coronary heart disease not amenable to revascularization.

Trial registration number: NCT03072121.

BACKGROUND

Coronary artery disease (CAD) is a narrowing or blockage of the

arteries and vessels that provide oxygen and blood to the heart. It is the leading cause of death among 235 causes of death in human currently and kills more than 7 million people annually worldwide and will continuously be ranked as the top cause of death in next 20 years according the prediction [1]. CAD not amenable to revascularization mainly refers to the left main coronary artery and three-vessel severe diffuse stenosis, calcification or dilated lesions, or CAD complicated with severe multiple organ disease such as severe heart failure, infection, blood diseases, cancer cachexia, lung dysfunction or renal insufficiency [2]. Currently, the main treatment methods for CAD include lifestyle changes, medical treatment (cholesterol lowering medications, beta-blockers, nitroglycerin, calcium antagonists, etc), coronary interventions and surgery [3-5]. Among these treatments, coronary revascularization including PCI and CABG is an advanced effective therapeutic method for CAD, especially for acute coronary syndrome. However, there are about 5-10% CAD patients because of their sever and diffuse coronary disease, it's not eligible for revascularization, besides the conventional western medicine therapy don't work well on them [2]. Even Medicare has no classification code for those patients with CAD not amenable to revascularization, and the United States Task Force addressing this situation stresses the urgent need for studies[6] .

Chinese herbal medicine (CHM), as one kind of popular complementary and alternative medicine, plays an important role in treating CAD in China. According to the theory of traditional Chinese medicine (TCM), all the related symptoms and signs in a certain disease phase are generalized to a syndrome (*'Zheng'* in Chinese medicine), which is the basic unit and key concept of TCM [7]. Patients with CAD can be divided into different syndromes. In the diagnosis of CAD, the '*Qi* deficiency and blood stasis syndrome' is an important type diagnosed from the viewpoint of TCM and our previous clinical practice [8]. Therefore, the principle of 'tonifying *Qi* and activating blood" is applied in the treatment of CAD not amenable to revascularization. Shexiang Baoxin pill (SBP), one kind of Chinese patent medicine, originates from Suhexiang pill documented in Prescription of Peaceful Benevolent Dispensary (*Taiping Huimin Hejiju Fang*) in the *Song* Dynasty. It consists of seven herbal medicines, including Musk (Moschus, *Shexiang*), Ginseng Root (Radix Ginseng, *Renshen*), Cow-bezoar (Calculus Bovis, *Niuhuang*), Storax (Styrax, *Suhexiang*), Cassia Bark (Cortex Cinnamomi, *Rougui*), Toad Venom (Venenum Bufonis, *Chansu*), and Borneol (Borneolum Syntheticum, *Bingpian*). It has been widely used for treating CAD in China for many years. Modern researches have indicated that the major pharmacological mechanisms of SBP include improving endothelial cell function, inhibiting the reaction of vascular inflammation

through decreasing the level of C reactive protein and plasma homocysteine, stabilizing atherosclerotic plaque, promoting therapeutic angiogenesis, inhibiting the abnormal proliferation of vascular smooth muscle cells, reversing myocardial fibrosis, dilating coronary arteries, improving myocardial ischemia and reducing Myocardial infarct range [9-12]. Clinical studies found that long-term SBP administration could reduce the occurrence of angina pectoris events and some other clinical events, and cut down the dosage of nitrates used in patients with stable angina pectoris [13-14]. However, whether SBP is effective on treating CAD not amenable to revascularization is still unknown. The aim of this multicentre, randomised, double-blind, placebo controlled trial is to evaluate the efficacy and safety of Shexiang Baoxin pill in patients with CAD not amenable to revascularization.

METHODS/DESIGN

Ethics

The study was approved by the Research Ethical Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China (reference: 2016-129-KY-01).

Study population

A total of 440 patients are recruited from 7 centres: Wangjing Hospital, China Academy of Chinese Medical Sciences; Beijing Anzhen Hospital; The Second Affiliated Hospital of Henan University of

Traditional Chinese Medicine; Guangdong Provincial Hospital of Traditional Chinese Medicine; Shandong University of Traditional Chinese Medicine; Shaanxi Hospital of Traditional Chinese Medicine. The trial is executed from June 2017 to February 2019.

Recruitment of participants

Two strategies are used to recruit patients with CAD not amenable to revascularization. Firstly, we display recruitment posters outside the clinics. The posters contain brief introductions about the population needed, the medicine offered to eligible participants, and the contact information of the researcher. Secondly, we recruit participants in outpatient clinics from *Wangjing* Hospital, China Academy of Chinese Medical Sciences; *Beijing Anzhen* Hospital; The Second Affiliated Hospital of *Henan* University of Traditional Chinese Medicine; *Guangdong* Provincial Hospital of Traditional Chinese Medicine; *Shandong* University of Traditional Chinese Medicine; *Shaanxi* Hospital of Traditional Chinese Medicine. The patients that meet the study criteria will be requested to sign a written informed consent. They are also given enough time to decide whether they are willing to participate in the trial or not.

Inclusion criteria

Participants are included if they meet these requirements: aged between 45 and 75 years, diagnosed with sever CAD through coronary

arteriography which shows that the left main coronary artery and three-vessel have sever diffuse stenosis, calcification or vascular ectasia, and be in accordance with TCM syndrome type "*Qi* deficiency and blood stasis syndrome". Western medicine diagnostic criteria refer to "Guidelines for the Prevention and Management of Chronic Stable Angina in China" [15] (2007 edition), "Guidelines for the Diagnosis and Management of Non-ST-segment Elevation Myocardial Infarction Acute Coronary Syndromes" [16] (2012 edition), "Guidelines for the Diagnosis and Management of Acute ST-segment Elevation Myocardial Infarction" [17] (2010 edition), which were made by Cardiology Branch of Chinese Medical Association. And TCM diagnostic criteria refer to "Guideline of Clinical Research of New Drugs of Traditional Chinese Medicine·Chest Obstruction" [18] (2002 edition). Finally, it's decided by both cardiologists and cardiac surgeons whether the CAD patients are in accordance with the inclusive criteria.

Exclusion criteria

The exclusion criteria are listed as below: a) patients with severe valvular disease, congenital cardiomyopathy discompensation; b) patients with CAD complicated with severe multiple organ disease such as severe heart failure, severe lung, liver or renal dysfunction, peptic ulcer in active stage, or intracranial hemorrhage; c) patients that use high-dose steroids due to connective tissue disease; d) patients with serious infections; e)

patients with malignant tumor; f) patients with hematopoietic diseases. g) pregnant or lactating women.

Handling of withdrawal and data management

Participants may withdraw from the study at any time for any reason. If any patients want to withdraw, clinicians should ask whether they would be willing to complete the assessments according to the study schedule and write down their last time of taking the medicine. Incidences of patients loss to follow-up and withdrawal will be recorded and reported. The data collected in this trial comprises information recorded in case report forms. When every visits completed at each centre, data will be entered using the double entry method.

Interventions

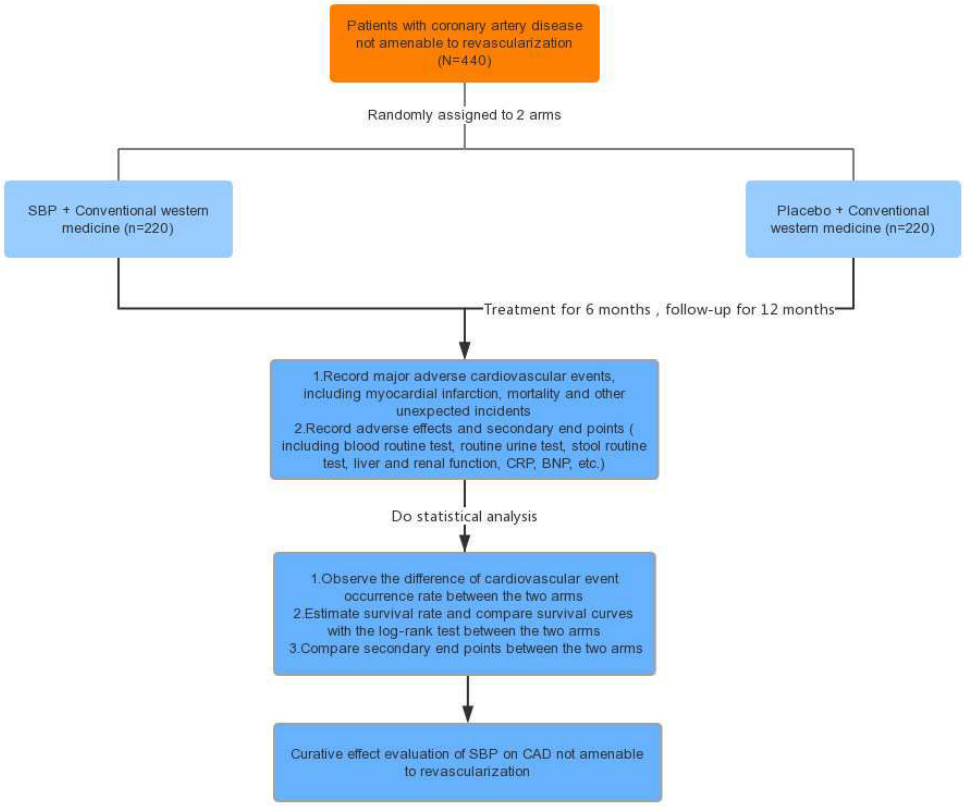
In addition to conventional western medicine treatment including antiplatelet, lipid-lowing, antihypertensive or anti-diabetic therapy, eligible patients will be allocated to receive SBP or placebo for 24 successive weeks. The SBP and placebo were produced and packed in a single batch (Production batch number: 160299) by Shanghai Hutchison Pharmaceuticals Limited, Shanghai, China. The test results of drug quality were consistent with the Chinese Medicine Standards of the State Food and Drug Administration (SFDA). The placebo pills have the identical appearance, smell, and scent as the active treatment pills. Patients will take the pills orally three times daily for 24

successive weeks. Any other Chinese herbal decoction or Chinese patent medicine for treating CAD is prohibited during the study.

Randomisation and blinding

Randomisation is performed by an independent statistician. The randomisation sequence (blocked, stratified for centres) is generated by use of SAS 9.4 software. Each centre receives consecutively coded drugs. All of the drugs provided by the pharmaceutical company are numbered with a label according to the randomisation schedule. This trial is a double-blind trial. The first level is for the case number corresponding to groups (group A and group B), and the second level is for the group corresponding to the intervention (the intervention and placebo groups). The numbers are kept in opaque sealed envelopes. The double levels of blinding are sealed separately and given to the leader of the clinical research. Emergency letters are sent to each of the centres, saved with the test drug, and properly preserved until the end of the trial. Treatment assignments are not revealed and are blinded to the patients and investigators (including statisticians) until the entire study is completed. Time points are as shown in Figure 1.

Figure 1 Flow chart.



Primary outcomes

The primary outcomes include major adverse cardiovascular events (including myocardial infarction, mortality and other unexpected incidents).

Secondary outcomes

The secondary outcomes include C-reactive protein, B-type natriuretic peptide, electrocardiogram, echocardiographic parameters (EF %, E/A ratio), and hospital readmission rates due to CAD.

Safety outcomes

Safety outcomes include: measurement of the vital signs:

temperature, blood pressure, respirations, heart rate; b) the routine blood test, routine urine test, routine stool test; c) blood lipids test, blood glucose test; d) liver function test (ALT, AST, γ-GT, ALP, TBIL), renal function test (BUN, Cr); e) electrocardiogram; f) recording adverse events at any time.

These biological indicators are monitored since these patients are grouped until the end of the follow-up.

Adverse events

Any unexpected symptom, vital sign or sickness, as long as they cause discomfort, will be recorded as an adverse event. The starting date, ending date, degree, relations with the trial medicine, andwhether they drop out of the study will be recorded correspondingly. Severe adverse events are required to be reported to the leader of the trial, ethics committees and sponsors within 24h, and participants will be provided with every necessary treatment. If the adverse event still exists, the follow-up will continue until the adverse event disappears.

Sample size

The incidence of major adverse cardiovascular events will be compared between both groups. The sample size is calculated using the concept of efficiency as presented by Xie [19]. The efficiency is 80% in the intervention group and 60% in the placebo group, respectively, as a previous study has suggested. The following formula is used for a

two-group trial:

$$n = (U_\alpha + U_\beta)^2 2P(1-P)/(P_1 - P_0)$$

On the basis of α=0.05, β=0.2, the required sample size per group is approximately 90 participants for each group. Allowing for 15% attrition, we should recruit 208 participants, with 104 in each group. Data analysis will be conducted by statisticians who are independent from the research team. An intent-to-treat analysis (ITT) for the patients, who have received treatment at least once, will be carried out. Missing data will be adjusted using the last observation carried forward method. The per-protocol analysis will be restricted to participants who strictly follow the protocol and complete the study. We will build up the database with the software Excel. The raw data are typed in computers by two statisticians independently. Every analysis is conducted using the SPSS software (SPSS 26.0). We calculate frequency and percentage of variables with Descriptive statistics program. Pearson's $\chi 2$ test will be performed on categorical variables, Student's t test on measurement variables. Log-rank test is used to assess the difference between the survival distributions of two groups with respect to some failure-time outcome.

DISCUSSION

Coronary artery disease has become a frequently–occurring and common disease in elderly people in many countries. With the rapid increase of diabetes and obesity patients, patients with CAD not

amenable to revascularization is expected to increase exponentially [20]. In a contemporary series of patients undergoing coronary angiography, 28.8% of patients had significant CAD and did not undergo complete revascularization, including 12.8% partially revascularized, 9.3% managed medically, and 6.7% with "no-option". These patients had higher mortality at 3 years when compared with completely revascularized patients [21].

In the treatment of CAD, antiplatelet therapy is the cornerstone. It's very important in the prevention of acute, subacute thrombosis and severe cardiovascular events. Currently, aspirin and clopidogrel are the most commonly used antiplatelet drugs. Aspirin is playing an important role in the acute phase, primary and secondary prevention of CAD. Clopidogrel is safe and effective in reducing acute coronary syndrome and ischemic events in percutaneous coronary intervention patients. And dual therapy with aspirin and clopidogrel has emerged as the gold standard therapy for patients treated with drug-eluting stents. However, there is variability in patients' responses to this antiplatelet therapy. Studies have identified that of the patients with CAD, 5%~45% were aspirin resistant, 4%~30% were clopidogrel resistant, 10% were both resistant [22]. Besides, medication compliance of patients is another problem. The middle-aged and elderly are the high-risk groups of CAD. The elderly patients with CAD are always combined with hypertension, diabetes, hyperlipidemia, cerebral

infarction, obstructive pulmonary disease and so on. Lifelong medication is necessary for them to control disease development. However, more than 60% of elders fail to adhere to their medication regimen due to too many drugs but insufficient relief of symptoms [23]. Therefore, it's necessary to identify other safe and effective treatment methods that can alleviate the symptoms and improve the quality of CAD patients' life.

As one of the alternative and complementary medicine, Chinese herb medicine is attracting more and more people's attention [24-25]. A large number of traditional Chinese medicine researches have implied that either single traditional Chinese medicine or compound preparations both have the multiple target effect in the prevention and treatment of cardiovascular disease [26-27]. The composition of Chinese herbal compound is more complicated. It can intervene in each link of the disease occurrence and development. The synthetical effects of the multiple targets reflect the advantages of traditional Chinese Herb Medicine [28-29].

Treatment with syndrome differentiation is one of the characteristics of TCM theoretical system. *Qi* deficiency and blood stasis syndrome is the core pathogenesis of CAD [30-31]. SBP as a kind of Chinese patent medicine has the effect of Supplementing *Qi* and activating blood which is consistent with the core pathogenesis. Numerous studies have identified the efficacy and safety of SBP on treating CAD. However,

among these researches, most studies were about clinical experience, case reports, case series, experts' opions. Large sample, rospective, randomized controlled studies on treatment are scarce [32]. Whether SBP is effective in treating CAD not amenable to revascularization still need to be confirmed by evidence medical research through large samples, multi-center, randomised controlled clinical trials. To facilitate appropriate high-quality methodology and strict quality control, this protocol has been developed according to the CONSORT statement [33]. This is a randomized double-blind parallel controlled multiple-centered clinical study design. It may be significant to improve the prognosis and quality of life of patients.

There are also some limitations that need to be taken into account in this study. Due to the restriction of research project funds and period, the treatment duration is so short that more RCTs with long term follow-up are wanted to determine the efficacy and safety of SBP in the future study.

Contributors Jun Li are the principal investigators of this study. Panpan Tian wrote the first draft of the manuscript. Jun Li involved in program design and modifying articles. Ying Li and Jian Gao contributed to the statistical acquisition and analysis of data. All authors revised the protocal critically for important intellectual content and approved the final manuscript.

Competing interests None declared.

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Data sharing No additional unpublished data are available.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1-2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6-8
	4b	Settings and locations where the data were collected	12
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	11-12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	2
	14b	Why the trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-15
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Authors Pan-pan Tian[1], Jun Li[2], Jian Gao[1], Ying Li[1]

Keywords Coronary artery disease; revascularization; Shexiang Baoxin pill; randomised controlled trial.

Word count About 3269 words.

ABSTRACT

Introduction: Coronary artery disease (CAD) not amenable to revascularization indicates that the coronary arteries have severe diffuse lesions, or calcification or that the CAD is complicated with severe multiple-organ disease. Currently, the Western medicines available for the treatment of CAD not amenable to revascularization are limited. Shexiang Baoxin pill (SBP), type of Chinese patent medicine, has been widely used to treat CAD in China for many years. Previous studies have shown that long-term administration of the SBP (1-2 pills three times daily, for at least 6 months) for the tratment of CAD is effective and safe with a significant, long-term effect. This study aims to evaluate the efficacy and safety of the SBP in patients with CAD not amenable to revascularization.

Methods and analysis: This is a multicentre, randomised, double-blinded, placebo-controlled clinical trial. A total of 440 participants will be randomly allocated to two groups: the intervention group and the placebo group. Based on conventional treatment with Western medicine, the intervention group will be treated with the SBP, and the placebo group will be treated with SBP placebo. The primary outcomes include major adverse cardiovascular events (including angina, acute myocardial infarction, pulmonary embolism and aortic dissection). The secondary outcomes include C-reactive protein, B-type natriuretic peptide,

electrocardiogram, echocardiographic parameters (ejection fraction percentage and the E/A ratio) and hospital readmission rates due to CAD. The assessment will be performed at baseline (before randomisation) and at 24 weeks after randomisation.

Ethics and dissemination: The protocol has been approved by the Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (reference: 2016-129-KY-01). The results from this study will be published in a peer-reviewed journal and be used as a basis for a multisite trial.

Trial registration number: NCT03072121(Clinical Trials); Pre-results.

BACKGROUND

Coronary artery disease (CAD) is characterised by the narrowing or blockage of arteries and vessels that provide oxygen and blood to the heart. It is the leading cause of death among 235 causes of death in humans; CAD currently kills more than 7 million people annually worldwide and is predicted to remain the top cause of death for the next 20 years.[1] CAD not amenable to revascularization mainly refers to severe diffuse left main coronary artery and three-vessel stenosis, calcification or lesions or CAD complicated with severe multiple- organ disease, such as severe heart failure, infection, blood diseases, cancer cachexia, lung dysfunction or renal insufficiency.[2] With the rapid increase in patients with diabetes and obesity, patients with CAD not amenable to revascularization are expected to increase exponentially.[3] Currently, the main treatment methods for CAD include lifestyle changes, medical treatment (cholesterol lowering medications, beta-blockers, nitroglycerin, calcium antagonists, etc), coronary interventions and surgery.[4-6] Among these treatments, coronary revascularization including percutaneous coronary intervention and coronary artery bypass surgery, is an advanced

and effective therapeutic method for CAD, especially acute coronary syndrom. However, in a contemporary series of patients undergoing coronary angiography, 28.8% of patients had significant CAD and did not undergo complete revascularization, among which 12.8% was partially revascularized, 9.3% was managed medically, and 6.7% had "no-options"; these patients exhibited higher mortality at 3 years compared with completely revascularized patients.[7] Even Medicare has no classification code for patients with CAD not amenable to revascularization, and the United States Task Force addressing this situation stresses the urgent need for studies .[8]

Chinese herbal medicine (CHM), a popular type of complementary and alternative medicine, plays an important role in treating CAD in China. According to the theory of traditional Chinese medicine (TCM), all the related symptoms and signs in a certain disease phase are generalized as a syndrome (*'Zheng'* in Chinese medicine), which is the basic unit and key concept of TCM.[9] Patients with CAD can be divided into different syndromes. In the diagnosis of CAD, '*Qi* deficiency and blood stasis syndrome' is an important type diagnosed from the viewpoint of TCM and our previous clinical practice.[10] Therefore, the principle of 'tonifying *Qi* and activating blood" is applied in the treatment of CAD not amenable to revascularization. Shexiang Baoxin pill (SBP), is based on the Suhexiang pill documented in the Prescription of Peaceful Benevolent Dispensary (*Taiping Huimin Hejiju Fang*) from the *Song* Dynasty. It consists of seven herbal medicines, including musk (Moschus, *Shexiang*), ginseng root (Radix Ginseng, *Renshen*), cow-bezoar (Calculus Bovis, *Niuhuang*), Storax (Styrax, *Suhexiang*), cassia bark (Cortex Cinnamomi, *Rougui*), toad venom (Venenum Bufonis, *Chansu*) and borneol (Borneolum Syntheticum, *Bingpian*). It has been widely used for the treatment of CAD in China for many years. Modern studies have

indicated that the major pharmacological mechanisms of the SBP include improving endothelial cell function, inhibiting vascular inflammation through decreasing the level of C-reactive protein and plasma homocysteine, stabilizing atherosclerotic plaque, promoting therapeutic angiogenesis, inhibiting the abnormal proliferation of vascular smooth muscle cells, reversing myocardial fibrosis, dilating coronary arteries, improving myocardial ischaemia and reducing myocardial infarct size.[11-14] Experimental studies have shown that SBP is quickly absorbed in the body, is quickly eliminated and has a short duration of action. Although toad venom (Venenum Bufonis, *Chansu*) is toxic when administered alone, its toxicity may be reduced by extending the peak time of toad steroid ingredients via other compatible ingredients in the SBP thus showing the scientific nature of compound compatibility.[15] In addition, clinical studies have found that long-term SBP administration could reduce the occurrence of angina pectoris events and several other clinical events and reduce the dosage of nitrates used in patients with stable angina pectoris.[16-19] In addition, the adverse reactions to the SBP are mild, and studies have not shown that the SBP is harmful to liver or kidney function.[19 20] However, whether the SBP is effective for the treatment of CAD not amenable to revascularization is still unknown. The aim of this multicentre, randomised, double-blind, placebo-controlled trial is to evaluate the efficacy and safety of the Shexiang Baoxin pill in patients with CAD not amenable to revascularization.

METHODS/DESIGN

Trial organisation

The funders will not participate in the study design, data collection, analyses and interpretation, and manuscript preparation. An independent data and safety monitoring board will monitor the conduct and safety of

the trial to ensure patient safety. Stopping guidelines and monitoring practices have been established.

Study population

A total of 440 patients will be recruited from 7 centres: *Wangjing* Hospital, China Academy of Chinese Medical Sciences; *Beijing Anzhen* Hospital; The Second Affiliated Hospital of *Henan* University of Traditional Chinese Medicine; *Guangdong* Provincial Hospital of Traditional Chinese Medicine; *Shandong* University of Traditional Chinese Medicine; and *Shaanxi* Hospital of Traditional Chinese Medicine. The trial began in June 2017 and will continue until February 2019.

Recruitment of participants

Two strategies are being used to recruit patients with CAD not amenable to revascularization. First, we are displaying recruitment posters outside the clinics. The posters contain brief introductions about the population required, the medicine offered to eligible participants, and the contact information of the researcher. Second, we are recruiting participants in outpatient clinics from *Wangjing* Hospital, China Academy of Chinese Medical Sciences; *Beijing Anzhen* Hospital; The Second Affiliated Hospital of *Henan* University of Traditional Chinese Medicine; *Guangdong* Provincial Hospital of Traditional Chinese Medicine; *Shandong* University of Traditional Chinese Medicine; and *Shaanxi* Hospital of Traditional Chinese Medicine. The patients who meet the study criteria are requested to sign a written informed consent form. The consent form includes the nature, objectives and potential benefits and consequences of the study. Additionally, the consent details the required length of follow-up, supportive care, the name of the principal investigator (Jun Li) responsible for the protocol and the patient's right to accept or refuse treatment and to terminate participation and withdraw from the protocol.

Inclusion criteria

Participants will be included if they met the following requirements: between 55 and 75 years old, diagnosed with sever CAD through coronary arteriography, which showed that the left main coronary artery and three vessels have severe diffuse stenosis, calcification or vascular ectasia, and have "*Qi* deficiency and blood stasis syndrome" according to TCM. For the Western medicine diagnostic criteria, we refer to "Guidelines for the Prevention and Management of Chronic Stable Angina in China"[21] (2007 edition), "Guidelines for the Diagnosis and Management of Non-ST-segment Elevation Myocardial Infarction Acute Coronary Syndromes"[22] (2012 edition), and "Guidelines for the Diagnosis and Management of Acute ST-segment Elevation Myocardial Infarction"[23] (2010 edition), which were published by Cardiology Branch of the Chinese Medical Association. In addition, for the TCM diagnostic criteria we refer to "Guideline of Clinical Research of New Drugs of Traditional Chinese Medicine·Chest Obstruction"[24] (2002 edition). Finally, both cardiologists and cardiac surgeons will decide whether the CAD patients are in accordance with the inclusion criteria.

Exclusion criteria

The exclusion criteria are as follows: a) patients with severe valvular disease or congenital decompensated cardiomyopathy; b) patients with CAD complicated with severe multiple-organ disease, such as severe heart failure, severe lung, liver or renal dysfunction, peptic ulcer in the active stage or intracranial haemorrhage; c) patients who use high-dose steroids due to connective tissue disease; d) patients with serious infections; e) patients with malignant tumours; f) patients with haematopoietic diseases; g) female patients who are pregnant or lactating; h) patients who are eligible for revascularization.

Handling of withdrawal and data management

Participants may withdraw from the study at any time for any reason. If any patients want to withdraw, clinicians should ask whether they would be willing to complete the assessments according to the study schedule and record the last day of medicine intake. Patients lost to follow-up and patients who withdraw from the study will be recorded and reported. The data collected in this trial comprises information recorded in case report forms. After every visit at each centre, the data will be entered using the double-entry method.

Interventions

In addition to conventional Western medical treatment, including antiplatelet, lipid-lowing, antihypertensive or anti-diabetic therapy, eligible patients will be allocated to receive SBP or placebo two pills three times daily for 24 successive weeks. The SBP and placebo were produced and packed in a single batch (Production batch number: 160299) by Shanghai Hutchison Pharmaceuticals Limited in Shanghai, China. The test results of drug quality were consistent with the Chinese Medicine Standards of the State Food and Drug Administration (SFDA). The SBP is a compound prepared with Chinese herbs, and their main components are shown in Table 1. The placebo pills have an identical appearance and scent as the active treatment pills. Patients will take the pills orally three times daily for 24 successive weeks. Intake of any other Chinese herbal decoction or Chinese patent medicine for treating CAD is prohibited during the study.

Table 1 Main components of traditional Chinese medicines

Chinese name	Description	Comments
She Xiang	A substance with a penetrating odour that is obtained from a gland of the male musk deer	The original material is banned from use due to the endangered status of the musk deer; a synthetic compound (muscone) is used in its place

Ren Shen	Root of Chinese ginseng	An extract that specifically includes ginsensosides
Niu Huang	The gallstone of an ox (water buffalo)	The original material is too rare and costly to use in patent medicines and is substituted by a mixture of substances that have a similar effect
Su He Xiang	An aromatic extract of the Liquidambar tree (styrax; storax)	It has antiplatelet aggregation, anti-thrombosis, anti-myocardial ischaemia and other effects
Rou Gui	Bark of the cinnamon	Cinnamon aqueous solution is rich in antioxidants and can reduce the risk of heart disease and diabetes
Chan Su	The venom of a toad (*Bufo bufo*)	This agent is known as a cardiotonic, but it can also exhibit cardiotoxicity depending on dosage; it exhibits neurotoxicity. The amount of Chan Su in the SBP pill is small (28 μg/22.5 mg)
Bing Pian	Crystalline aromatic component of certain plants that predominantly contains borneol	Due to high cost, the patent medicine contains synthetic borneol; borneol is known as a cardiac stimulant

Randomisation and blinding

Randomisation was performed by an independent statistician. The randomisation sequence (blocked and stratified for centres) was generated using SAS 9.4 software. Each centre received consecutively coded drugs. All of the drugs provided by the pharmaceutical company are labelled according to the randomisation schedule. This trial is a double-blind trial. The first level is for the case number corresponding to groups (group A and group B), and the second level is for the group corresponding to the intervention (the intervention and placebo groups). The numbers are kept in opaque sealed envelopes. The two levels of blinding are sealed

separately and given to the lead clinical researcher. Emergency letters have been sent to each of the centres, are kept with the test drug and will be properly preserved until the end of the trial. Treatment assignments will not be revealed to the patients and investigators (including statisticians) until the entire study is completed. The time points are shown in Figure 1.

Primary outcomes

The primary outcomes include mortality and major adverse cardiovascular events (including angina, acute myocardial infarction, pulmonary embolism and aortic dissection).

Secondary outcomes

The secondary outcomes include C-reactive protein, B-type natriuretic peptide, electrocardiogram (abnormal ST-T changes), echocardiographic parameters (EF% and the E/A ratio) and hospital readmission rate due to CAD.

Safety outcomes

Safety outcomes include the following (a) the measurement of vital signs, including temperature, blood pressure, respiration and heart rate; (b) routine blood tests, routine urine tests and routine stool tests; (c) blood lipid tests and blood glucose tests; (d) liver function tests (ALT, AST, γ-GT, ALP and TBIL), and renal function tests (BUN and Cr); (e) electrocardiogram (mainly ST-T changes); and (f) records of adverse events at any time.

These biological indicators are monitored from the grouping of these patients until the end of follow-up.

Adverse events

Any unexpected symptoms, vital signs or sicknesses, as long as they cause discomfort, will be recorded as an adverse event. The start date, end date, degree, relationship with the trial medicine and whether the patients

drop out of the study will be recorded. Severe adverse events are required to be reported to the lead researcher of the trial, ethics committees and sponsors within 24 hours, and the participants will be provided with every necessary treatment. If the adverse event persists, follow-up will continue until the adverse event disappears.

Sample size

The incidence of major adverse cardiovascular events will be compared between both groups. The sample size was calculated using the concept of efficiency as presented by Xie.[25] The efficiency is 80% in the intervention group and 60% in the placebo group, as suggested by a previous study. The following formula was used for a two-group trial:

$$n = (U_\alpha + U_\beta)^2 2P(1-P)/(P_1 - P_0)$$

Based on $\alpha = 0.05$ and $\beta = 0.2$, the required sample size per group is approximately 90 participants. Allowing for 15% attrition, we should recruit 208 participants, with 104 patients in each group. Data analysis will be conducted by statisticians who are independent from the research team. An intent-to-treat analysis (ITT) will be carried out for patients who have received treatment at least once. Missing data will be adjusted using the last observation carried forward method. Per-protocol analysis will be restricted to participants who strictly follow the protocol and complete the study. The database will be maintained using Excel software. The raw data will be independently typed into computers by two statisticians. Every analysis will be conducted using SPSS software (SPSS 26.0). We will calculate the frequency and percentage of variables with the Descriptive statistics program. Pearson's $\chi 2$ test will be performed on categorical variables, and Student's ttest will be performed on measurement variables. The log-rank test will be used to assess the difference in survival distributions between the two groups with respect

to some failure time outcome.

Ethics and Dissemination

The study was approved by the Research Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences in Beijing, China (reference: 2016-129-KY-01). Final trial results will be disseminated via publication and clinicaltrials.gov. Authorship will be determined based on BMJ Open guidelines.

DISCUSSION

Antiplatelet therapy is the cornerstone treatment for CAD. It's very important in the prevention of acute or subacute thrombosis and severe cardiovascular events. Currently, aspirin and clopidogrel are the most commonly used antiplatelet drugs. Aspirin plays an important role in the acute phaseas well as the primary and secondary prevention of CAD. Clopidogrel is safe and effective in reducing acute coronary syndrome and ischaemic events in percutaneous coronary intervention patients. In addition, dual therapy with aspirin and clopidogrel has emerged as the gold standard therapy for patients treated with drug-eluting stents. However, there is variability in patient responses to antiplatelet therapy. Studies have identified that among patients with CAD, 5%~45% is aspirin resistant, 4%~30% is clopidogrel resistant and 10% is resistant to both.[26] In addition, medication compliance among patients is another problem. Middle-aged and elderly patients are at high risk for CAD. Elderly patients with CAD are always comorbid with hypertension, diabetes, hyperlipidaemia, cerebral infarction, obstructive pulmonary disease, etc. Lifelong medication is necessary to control disease development among this patient population. However, more than 60% of elderly patients fail to adhere to their medication regimen due to an abundance of drugs but insufficient relief of symptoms.[27] Therefore, it's

necessary to identify other safe and effective treatment methods that can alleviate symptoms and improve the quality of life for CAD patients.

As an alternative and complementary medicine, Chinese herbal medicine is attracting attention.[28 29] Many traditional Chinese medicine studies have implied that either single traditional Chinese medicines or compound preparations can have multiple target effects in the prevention and treatment of cardiovascular disease.[30 31] The composition of Chinese herbal compounds is more complicated. They can intervene at each phase of disease occurrence and development. The multiple target effects reflect the advantages of traditional Chinese herb medicine.[32 33]

Treatment with syndrome differentiation is one of the characteristics of the TCM system. *Qi* deficiency and blood stasis syndrome is the core pathogenesis of CAD.[34 35] The SBP has the effect of supplementing *Qi* and activating blood, which is consistent with the core pathogenesis. Numerous studies have identified the efficacy and safety of the SBP in treating CAD. However, among these studies, most are based on clinical experience, case reports, case series and expert opinionswhereas large-sample, retrospective, randomized controlled studiesare scarce.[36] Whether the SBP is effective for the treatment of CAD not amenable to revascularization still requires confirmation by evidence-based medical research through large-sample, multicentre, randomised controlled clinical trials. To ensure appropriate high-quality methodology and strict quality control, this protocol has been developed according to the the SPIRIT 2013,[37] and the new extension of the CONSORT statement.[38] This study has a randomized, double-blind, parallel, controlled, multiple-centre clinical study design. It may be significant for the improvement of patient prognosis and quality of life.

There are also some limitations in this study that should be considered. Due to the restriction of research project funds and trial period, the

treatment duration will be short, and thus, additional RCTs with long-term follow-up are warranted to determine the efficacy and safety of the SBP.

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Contributors Jun Li is the principal investigator of this study. Pan-pan Tian wrote the first draft of the manuscript. Jun Li was involved in programme design and modifying the articles. Ying Li and Jian Gao contributed to the statistical acquisition and analysis of data. All authors critically revised the protocol for important intellectual content and approved the final manuscript.

Protocol version V1.1; Aug 20, 2017.

Patient consent Obtained.

Competing interests None declared.

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Data sharing No additional unpublished data are available.

Figure legends Flow chart.

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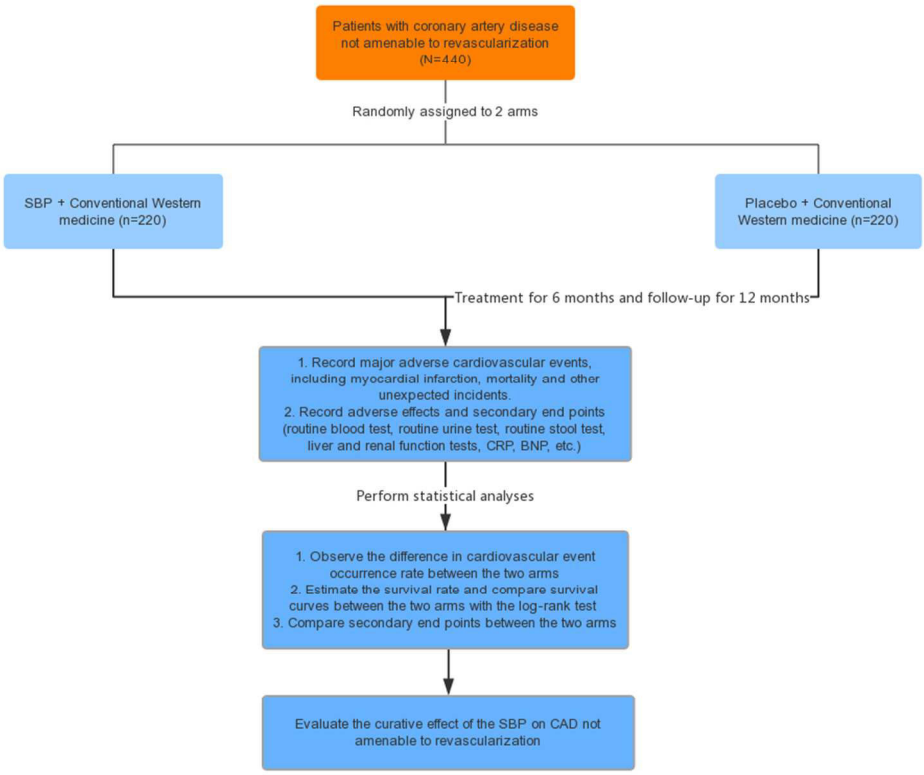

Flow chart

Checklist of Items for Reporting Trials of Chinese Herbal Medicine Formulas*

Section/Topic	Item Number	Standard CONSORT Checklist Item	Extension for CHM Formulas	Reported on Page Number
Title, abstract, and keywords	1a	Identification as a randomized trial in the title	*Statement of whether the trial targets a TCM* Pattern*, a Western medicine–defined disease, or a Western medicine–defined disease with a specific TCM* Pattern*, if applicable*	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts [26, 27])	*Illustration of the name and form of the formula used, and the TCM* Pattern *applied, if applicable*	1、2
	1c		*Determination of appropriate keywords, including "Chinese herbal medicine formula" and "randomized controlled trial"*	1
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	*Statement with biomedical science approaches and/or TCM approaches*	2-4
	2b	Specific objectives or hypotheses	*Statement of whether the formula targets a Western medicine–defined disease, a TCM* Pattern*, or a Western medicine–defined disease with a specific TCM* Pattern	4
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio		4、5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	*Statement of whether participants with a specific TCM* Pattern *were recruited, in terms of 1) diagnostic criteria and 2) inclusion and*	6

			exclusion criteria. All criteria used should be universally recognized, or reference given to where detailed explanation can be found.	
	4b	Settings and locations where the data were collected		5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	*Description(s) for different types of formulas should include the following:* ***5a. For fixed CHM formulas*** *1. Name, source, and dosage form (e.g., decoctions, granules, powders)* *2. Name, source, processing method, and dosage of each medical substance. Names of substances should be presented in at least 2 languages: Chinese (*Pinyin*), Latin, or English. Names of the parts of the substances used should be specified.* *3. Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible* *4. Principles, rationale, and interpretation of forming the formula* *5. Reference(s) as to the efficacy of the formula, if any* *6. Pharmacologic study results of the formula, if any* *7. Production method of the formula, if any* *8. Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible.* *9. Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and*	3、7、8

			acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible. *10. Dosage of the formula, and how the dosage was determined* *11. Administration route (e.g., oral, external)* ***5b. For individualized CHM formulas*** *1. See recommendations 5a 1–11* *2. Additional information: how, when, and by whom the formula was modified* ***5c. For patent proprietary CHM formulas*** *1. Reference to publicly available materials, such as pharmacopeia, for the details about the composition, dosage, efficacy, safety, and quality control of the formula* *2. Illustration of the details of the formula, namely 1) the proprietary product name (i.e., brand name), 2) name of manufacturer, 3) lot number, 4) production date and expiry date, 5) name and percentage of added materials, and 6) whether any additional quality control measures were conducted* *3. Statement of whether the patent proprietary formula used in the trial is for a condition that is identical to the publicly available reference* ***5d. Control groups*** *Placebo control* *1. Name and amount of each ingredient* *2. Description of the similarity of placebo with the intervention (e.g., color, smell, taste, appearance, packaging)* *3. Quality control and safety assessment, if any* *4. Administration route, regimen, and dosage*	

			5. Production information: where, when, how, and by whom the placebo was produced *Active control* *1. If a CHM formula was used, see recommendations 5a–5c* *2. If a chemical drug was used, see item 5 of the CONSORT Statement (24)*	
Outcomes	6a	Completely defined, prespecified primary and secondary outcome measures, including how and when they were assessed	*Illustration of outcome measures with* Pattern *in detail*	9、2
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined		10
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomization				
Sequence generation	8a	Method used to generate the random allocation sequence		8
	8b	Type of randomization; details of any restriction (such as blocking and block size)		8、9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		8、9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and		8、9

		how		
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes		10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome		9
	13b	For each group, losses and exclusions after randomization, together with reasons		
Recruitment	14a	Dates defining the periods of recruitment and follow-up		5
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group		
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups		
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)		9
	17b	For binary outcomes, presentation of both absolute and relative effect		

		sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory		
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms [28])	*(There is no extension for this item)*	10
Discussion				
Limitations	20	Trial limitations; addressing sources of potential bias; imprecision; and, if relevant, multiplicity of analyses		12、13
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	*Discussion of how the formula works on different TCM* Patterns *or diseases*	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	*Interpretation with TCM theory*	11、12
Other information				
Registration	23	Registration number and name of trial registry		2
Protocol	24	Where the full trial protocol can be accessed, if available		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		13

CHM = Chinese herbal medicine; CONSORT = Consolidated Standards of Reporting Trials; TCM = traditional Chinese medicine.

* The original CONSORT items are provided; elaborations for CHM formulas are in italicized text. We strongly recommend reading this checklist in conjunction with the CONSORT 2010 Explanation and Elaboration (29) for important clarifications on all original items of CONSORT Statement.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry P2
	2b	All items from the World Health Organization Trial Registration Data Set P2
Protocol version	3	Date and version identifier P13
Funding	4	Sources and types of financial, material, and other support P13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors P13
	5b	Name and contact information for the trial sponsor P13
	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
	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)
Introduction		
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 P2-P4
	6b	Explanation for choice of comparators P4
Objectives	7	Specific objectives or hypotheses P2 P4

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, noninferiority, exploratory) P4
Methods: Participants, interventions, and outcomes		
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 P5
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) P6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P7
	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)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial P7
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 P9
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) P9
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 P10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size P5
Methods: Assignment of interventions (for controlled trials)		
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 P8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned P8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P5 P8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P8 P9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	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 P2
	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 P6 P7
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 P10
Statistical methods	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 P10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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) P10

Methods: Monitoring

Data monitoring	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. P7 Alternatively, an explanation of why a DMC is not needed
	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 P5
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 P9 P10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval P2
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)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable P11
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site P13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators P10
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 P9 P10

Dissemination policy	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 P11
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates P5
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and safety of the Shexiang Baoxin pill for the treatment of coronary artery disease not amenable to revascularization: Study protocol for a randomised, placebo-controlled, double-blinded trial

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Efficacy and safety of the Shexiang Baoxin pill for the treatment of coronary artery disease not amenable to revascularization: Study protocol for a randomised, placebo-controlled, double-blinded trial

Authors Pan-pan Tian[1,2], Jun Li[1], Jian Gao[1,2], Ying Li[1,2]

Keywords Coronary artery disease; revascularization; Shexiang Baoxin pill; randomised controlled trial.

Word count About 3271 words.

ABSTRACT

Introduction: Coronary artery disease (CAD) not amenable to revascularization indicates that the coronary arteries have severe diffuse lesions, or calcification or that the CAD is complicated with severe multiple-organ disease. Currently, the Western medicines available for the treatment of CAD not amenable to revascularization are limited. Shexiang Baoxin pill (SBP), type of Chinese patent medicine, has been widely used to treat CAD in China for many years. Previous studies have shown that long-term administration of the SBP (1-2 pills three times daily, for at least 6 months) for the tratment of CAD is effective and safe with a significant, long-term effect. This study aims to evaluate the efficacy and safety of the SBP in patients with CAD not amenable to revascularization.

Methods and analysis: This is a multicentre, randomised, double-blinded, placebo-controlled clinical trial. A total of 440 participants will be randomly allocated to two groups: the intervention group and the placebo group. Based on conventional treatment with Western medicine, the intervention group will be treated with the SBP, and the placebo group will be treated with SBP placebo. The primary outcomes include major adverse cardiovascular events (including angina, acute myocardial infarction, pulmonary embolism and aortic dissection). The secondary outcomes include C-reactive protein, B-type natriuretic peptide,

electrocardiogram, echocardiographic parameters (ejection fraction percentage and the E/A ratio) and hospital readmission rates due to CAD. The assessment will be performed at baseline (before randomisation) and at 24 weeks after randomisation.

Ethics and dissemination: The protocol has been approved by the Research Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing, China (reference: 2016-129-KY-01). The results from this study will be published in a peer-reviewed journal and be used as a basis for a multisite trial.

Trial registration number: NCT03072121(Clinical Trials); Pre-results.

BACKGROUND

Coronary artery disease (CAD) is characterised by the narrowing or blockage of arteries and vessels that provide oxygen and blood to the heart. It is the leading cause of death among 235 causes of death in humans; CAD currently kills more than 7 million people annually worldwide and is predicted to remain the top cause of death for the next 20 years.[1] CAD not amenable to revascularization mainly refers to severe diffuse left main coronary artery and three-vessel stenosis, calcification or lesions or CAD complicated with severe multiple- organ disease, such as severe heart failure, infection, blood diseases, cancer cachexia, lung dysfunction or renal insufficiency.[2] With the rapid increase in patients with diabetes and obesity, patients with CAD not amenable to revascularization are expected to increase exponentially.[3] Currently, the main treatment methods for CAD include lifestyle changes, medical treatment (cholesterol lowering medications, beta-blockers, nitroglycerin, calcium antagonists, etc), coronary interventions and surgery.[4-6] Among these treatments, coronary revascularization including percutaneous coronary intervention and coronary artery bypass surgery, is an advanced

and effective therapeutic method for CAD, especially acute coronary syndrom. However, in a contemporary series of patients undergoing coronary angiography, 28.8% of patients had significant CAD and did not undergo complete revascularization, among which 12.8% was partially revascularized, 9.3% was managed medically, and 6.7% had "no-options"; these patients exhibited higher mortality at 3 years compared with completely revascularized patients.[7] Even Medicare has no classification code for patients with CAD not amenable to revascularization, and the United States Task Force addressing this situation stresses the urgent need for studies .[8]

Chinese herbal medicine (CHM), a popular type of complementary and alternative medicine, plays an important role in treating CAD in China. According to the theory of traditional Chinese medicine (TCM), all the related symptoms and signs in a certain disease phase are generalized as a syndrome (*'Zheng'* in Chinese medicine), which is the basic unit and key concept of TCM.[9] Patients with CAD can be divided into different syndromes. In the diagnosis of CAD, '*Qi* deficiency and blood stasis syndrome' is an important type diagnosed from the viewpoint of TCM and our previous clinical practice.[10] Therefore, the principle of 'tonifying *Qi* and activating blood" is applied in the treatment of CAD not amenable to revascularization. Shexiang Baoxin pill (SBP), is based on the Suhexiang pill documented in the Prescription of Peaceful Benevolent Dispensary (*Taiping Huimin Hejiju Fang*) from the *Song* Dynasty. It consists of seven herbal medicines, including musk (Moschus, *Shexiang*), ginseng root (Radix Ginseng, *Renshen*), cow-bezoar (Calculus Bovis, *Niuhuang*), Storax (Styrax, *Suhexiang*), cassia bark (Cortex Cinnamomi, *Rougui*), toad venom (Venenum Bufonis, *Chansu*) and borneol (Borneolum Syntheticum, *Bingpian*). It has been widely used for the treatment of CAD in China for many years. Modern studies have

indicated that the major pharmacological mechanisms of the SBP include improving endothelial cell function, inhibiting vascular inflammation through decreasing the level of C-reactive protein and plasma homocysteine, stabilizing atherosclerotic plaque, promoting therapeutic angiogenesis, inhibiting the abnormal proliferation of vascular smooth muscle cells, reversing myocardial fibrosis, dilating coronary arteries, improving myocardial ischaemia and reducing myocardial infarct size.[11-14] Experimental studies have shown that SBP is quickly absorbed in the body, is quickly eliminated and has a short duration of action. Although toad venom (Venenum Bufonis, *Chansu*) is toxic when administered alone, its toxicity may be reduced by extending the peak time of toad steroid ingredients via other compatible ingredients in the SBP thus showing the scientific nature of compound compatibility.[15] In addition, clinical studies have found that long-term SBP administration could reduce the occurrence of angina pectoris events and several other clinical events and reduce the dosage of nitrates used in patients with stable angina pectoris.[16-19] In addition, the adverse reactions to the SBP are mild, and studies have not shown that the SBP is harmful to liver or kidney function.[19 20] However, whether the SBP is effective for the treatment of CAD not amenable to revascularization is still unknown. The aim of this multicentre, randomised, double-blind, placebo-controlled trial is to evaluate the efficacy and safety of the Shexiang Baoxin pill in patients with CAD not amenable to revascularization.

METHODS/DESIGN

Trial organisation

The funders will not participate in the study design, data collection, analyses and interpretation, and manuscript preparation. An independent data and safety monitoring board will monitor the conduct and safety of

the trial to ensure patient safety. Stopping guidelines and monitoring practices have been established.

Study population

A total of 440 patients will be recruited from 7 centres: *Wangjing* Hospital, China Academy of Chinese Medical Sciences; *Beijing Anzhen* Hospital; The Second Affiliated Hospital of *Henan* University of Traditional Chinese Medicine; *Guangdong* Provincial Hospital of Traditional Chinese Medicine; *Shandong* University of Traditional Chinese Medicine; and *Shaanxi* Hospital of Traditional Chinese Medicine. The trial began in June 2017 and will continue until February 2019.

Recruitment of participants

Two strategies are being used to recruit patients with CAD not amenable to revascularization. First, we are displaying recruitment posters outside the clinics. The posters contain brief introductions about the population required, the medicine offered to eligible participants, and the contact information of the researcher. Second, we are recruiting participants in outpatient clinics from *Wangjing* Hospital, China Academy of Chinese Medical Sciences; *Beijing Anzhen* Hospital; The Second Affiliated Hospital of *Henan* University of Traditional Chinese Medicine; *Guangdong* Provincial Hospital of Traditional Chinese Medicine; *Shandong* University of Traditional Chinese Medicine; and *Shaanxi* Hospital of Traditional Chinese Medicine. The patients who meet the study criteria are requested to sign a written informed consent form. The consent form includes the nature, objectives and potential benefits and consequences of the study. Additionally, the consent details the required length of follow-up, supportive care, the name of the principal investigator (Jun Li) responsible for the protocol and the patient's right to accept or refuse treatment and to terminate participation and withdraw from the protocol.

Inclusion criteria

Participants will be included if they met the following requirements: between 55 and 75 years old, diagnosed with sever CAD through coronary arteriography, which showed that the left main coronary artery and three vessels have severe diffuse stenosis, calcification or vascular ectasia, and have "*Qi* deficiency and blood stasis syndrome" according to TCM. For the Western medicine diagnostic criteria, we refer to "Guidelines for the Prevention and Management of Chronic Stable Angina in China"[21] (2007 edition), "Guidelines for the Diagnosis and Management of Non-ST-segment Elevation Myocardial Infarction Acute Coronary Syndromes"[22] (2012 edition), and "Guidelines for the Diagnosis and Management of Acute ST-segment Elevation Myocardial Infarction"[23] (2010 edition), which were published by Cardiology Branch of the Chinese Medical Association. In addition, for the TCM diagnostic criteria we refer to "Guideline of Clinical Research of New Drugs of Traditional Chinese Medicine·Chest Obstruction"[24] (2002 edition). Finally, both cardiologists and cardiac surgeons will decide whether the CAD patients are in accordance with the inclusion criteria.

Exclusion criteria

The exclusion criteria are as follows: a) patients with severe valvular disease or congenital decompensated cardiomyopathy; b) patients with CAD complicated with severe multiple-organ disease, such as severe heart failure, severe lung, liver or renal dysfunction, peptic ulcer in the active stage or intracranial haemorrhage; c) patients who use high-dose steroids due to connective tissue disease; d) patients with serious infections; e) patients with malignant tumours; f) patients with haematopoietic diseases; g) female patients who are pregnant or lactating; h) patients who are eligible for revascularization.

Handling of withdrawal and data management

Participants may withdraw from the study at any time for any reason. If any patients want to withdraw, clinicians should ask whether they would be willing to complete the assessments according to the study schedule and record the last day of medicine intake. Patients lost to follow-up and patients who withdraw from the study will be recorded and reported. The data collected in this trial comprises information recorded in case report forms. After every visit at each centre, the data will be entered using the double-entry method.

Interventions

In addition to conventional Western medical treatment, including antiplatelet, lipid-lowing, antihypertensive or anti-diabetic therapy, eligible patients will be allocated to receive SBP or placebo two pills three times daily for 24 successive weeks. The SBP and placebo were produced and packed in a single batch (Production batch number: 160299) by Shanghai Hutchison Pharmaceuticals Limited in Shanghai, China. The test results of drug quality were consistent with the Chinese Medicine Standards of the State Food and Drug Administration (SFDA). The SBP is a compound prepared with Chinese herbs, and their main components are shown in Table 1. The placebo pills have an identical appearance and scent as the active treatment pills. Patients will take the pills orally three times daily for 24 successive weeks. Intake of any other Chinese herbal decoction or Chinese patent medicine for treating CAD is prohibited during the study.

Table 1 Main components of traditional Chinese medicines

Chinese name	Description	Comments
She Xiang	A substance with a penetrating odour that is obtained from a gland of the male musk deer	The original material is banned from use due to the endangered status of the musk deer; a synthetic compound (muscone) is used in its place

Ren Shen	Root of Chinese ginseng	An extract that specifically includes ginsensosides
Niu Huang	The gallstone of an ox (water buffalo)	The original material is too rare and costly to use in patent medicines and is substituted by a mixture of substances that have a similar effect
Su He Xiang	An aromatic extract of the Liquidambar tree (styrax; storax)	It has antiplatelet aggregation, anti-thrombosis, anti-myocardial ischaemia and other effects
Rou Gui	Bark of the cinnamon	Cinnamon aqueous solution is rich in antioxidants and can reduce the risk of heart disease and diabetes
Chan Su	The venom of a toad (*Bufo bufo*)	This agent is known as a cardiotonic, but it can also exhibit cardiotoxicity depending on dosage; it exhibits neurotoxicity. The amount of Chan Su in the SBP pill is small (28 μg/22.5 mg)
Bing Pian	Crystalline aromatic component of certain plants that predominantly contains borneol	Due to high cost, the patent medicine contains synthetic borneol; borneol is known as a cardiac stimulant

Randomisation and blinding

Randomisation was performed by an independent statistician. The randomisation sequence (blocked and stratified for centres) was generated using SAS 9.4 software. Each centre received consecutively coded drugs. All of the drugs provided by the pharmaceutical company are labelled according to the randomisation schedule. This trial is a double-blind trial. The first level is for the case number corresponding to groups (group A and group B), and the second level is for the group corresponding to the intervention (the intervention and placebo groups). The numbers are kept in opaque sealed envelopes. The two levels of blinding are sealed

separately and given to the lead clinical researcher. Emergency letters have been sent to each of the centres, are kept with the test drug and will be properly preserved until the end of the trial. Treatment assignments will not be revealed to the patients and investigators (including statisticians) until the entire study is completed. The time points are shown in Figure 1.

Primary outcomes

The primary outcomes include mortality and major adverse cardiovascular events (including angina, acute myocardial infarction, pulmonary embolism and aortic dissection).

Secondary outcomes

The secondary outcomes include C-reactive protein, B-type natriuretic peptide, electrocardiogram (abnormal ST-T changes), echocardiographic parameters (EF% and the E/A ratio) and hospital readmission rate due to CAD.

Safety outcomes

Safety outcomes include the following (a) the measurement of vital signs, including temperature, blood pressure, respiration and heart rate; (b) routine blood tests, routine urine tests and routine stool tests; (c) blood lipid tests and blood glucose tests; (d) liver function tests (ALT, AST, γ-GT, ALP and TBIL), and renal function tests (BUN and Cr); (e) electrocardiogram (mainly ST-T changes); and (f) records of adverse events at any time.

These biological indicators are monitored from the grouping of these patients until the end of follow-up.

Adverse events

Any unexpected symptoms, vital signs or sicknesses, as long as they cause discomfort, will be recorded as an adverse event. The start date, end date, degree, relationship with the trial medicine and whether the patients

drop out of the study will be recorded. Severe adverse events are required to be reported to the lead researcher of the trial, ethics committees and sponsors within 24 hours, and the participants will be provided with every necessary treatment. If the adverse event persists, follow-up will continue until the adverse event disappears.

Sample size

The incidence of major adverse cardiovascular events will be compared between both groups. The sample size was calculated using the concept of efficiency as presented by Xie.[25] The efficiency is 80% in the intervention group and 60% in the placebo group, as suggested by a previous study. The following formula was used for a two-group trial:

$$n = (U_\alpha + U_\beta)^2 2P(1-P)/(P_1 - P_0)$$

Based on $\alpha = 0.05$ and $\beta = 0.2$, the required sample size per group is approximately 90 participants. Allowing for 15% attrition, we should recruit 208 participants, with 104 patients in each group. Data analysis will be conducted by statisticians who are independent from the research team. An intent-to-treat analysis (ITT) will be carried out for patients who have received treatment at least once. Missing data will be adjusted using the last observation carried forward method. Per-protocol analysis will be restricted to participants who strictly follow the protocol and complete the study. The database will be maintained using Excel software. The raw data will be independently typed into computers by two statisticians. Every analysis will be conducted using SPSS software (SPSS 26.0). We will calculate the frequency and percentage of variables with the Descriptive statistics program. Pearson's $\chi 2$ test will be performed on categorical variables, and Student's ttest will be performed on measurement variables. The log-rank test will be used to assess the difference in survival distributions between the two groups with respect

to some failure time outcome.

Ethics and Dissemination

The study was approved by the Research Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences in Beijing, China (reference: 2016-129-KY-01). Final trial results will be disseminated via publication and clinicaltrials.gov. Authorship will be determined based on BMJ Open guidelines.

DISCUSSION

Antiplatelet therapy is the cornerstone treatment for CAD. It's very important in the prevention of acute or subacute thrombosis and severe cardiovascular events. Currently, aspirin and clopidogrel are the most commonly used antiplatelet drugs. Aspirin plays an important role in the acute phaseas well as the primary and secondary prevention of CAD. Clopidogrel is safe and effective in reducing acute coronary syndrome and ischaemic events in percutaneous coronary intervention patients. In addition, dual therapy with aspirin and clopidogrel has emerged as the gold standard therapy for patients treated with drug-eluting stents. However, there is variability in patient responses to antiplatelet therapy. Studies have identified that among patients with CAD, 5%~45% is aspirin resistant, 4%~30% is clopidogrel resistant and 10% is resistant to both.[26] In addition, medication compliance among patients is another problem. Middle-aged and elderly patients are at high risk for CAD. Elderly patients with CAD are always comorbid with hypertension, diabetes, hyperlipidaemia, cerebral infarction, obstructive pulmonary disease, etc. Lifelong medication is necessary to control disease development among this patient population. However, more than 60% of elderly patients fail to adhere to their medication regimen due to an abundance of drugs but insufficient relief of symptoms.[27] Therefore, it's

necessary to identify other safe and effective treatment methods that can alleviate symptoms and improve the quality of life for CAD patients.

As an alternative and complementary medicine, Chinese herbal medicine is attracting attention.[28 29] Many traditional Chinese medicine studies have implied that either single traditional Chinese medicines or compound preparations can have multiple target effects in the prevention and treatment of cardiovascular disease.[30 31] The composition of Chinese herbal compounds is more complicated. They can intervene at each phase of disease occurrence and development. The multiple target effects reflect the advantages of traditional Chinese herb medicine.[32 33]

Treatment with syndrome differentiation is one of the characteristics of the TCM system. *Qi* deficiency and blood stasis syndrome is the core pathogenesis of CAD.[34 35] The SBP has the effect of supplementing *Qi* and activating blood, which is consistent with the core pathogenesis. Numerous studies have identified the efficacy and safety of the SBP in treating CAD. However, among these studies, most are based on clinical experience, case reports, case series and expert opinionswhereas large-sample, retrospective, randomized controlled studiesare scarce.[36] Whether the SBP is effective for the treatment of CAD not amenable to revascularization still requires confirmation by evidence-based medical research through large-sample, multicentre, randomised controlled clinical trials. To ensure appropriate high-quality methodology and strict quality control, this protocol has been developed according to the the SPIRIT 2013,[37] and the new extension of the CONSORT statement.[38] This study has a randomized, double-blind, parallel, controlled, multiple-centre clinical study design. It may be significant for the improvement of patient prognosis and quality of life.

There are also some limitations in this study that should be considered. Due to the restriction of research project funds and trial period, the

treatment duration will be short, and thus, additional RCTs with long-term follow-up are warranted to determine the efficacy and safety of the SBP.

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Contributors Jun Li is the principal investigator of this study. Pan-pan Tian wrote the first draft of the manuscript. Jun Li was involved in programme design and modifying the articles. Ying Li and Jian Gao contributed to the statistical acquisition and analysis of data. All authors critically revised the protocol for important intellectual content and approved the final manuscript.

Protocol version V1.2; Aug 20, 2017.

Patient consent Obtained.

Competing interests None declared.

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Data sharing No additional unpublished data are available.

Figure legends Flow chart.

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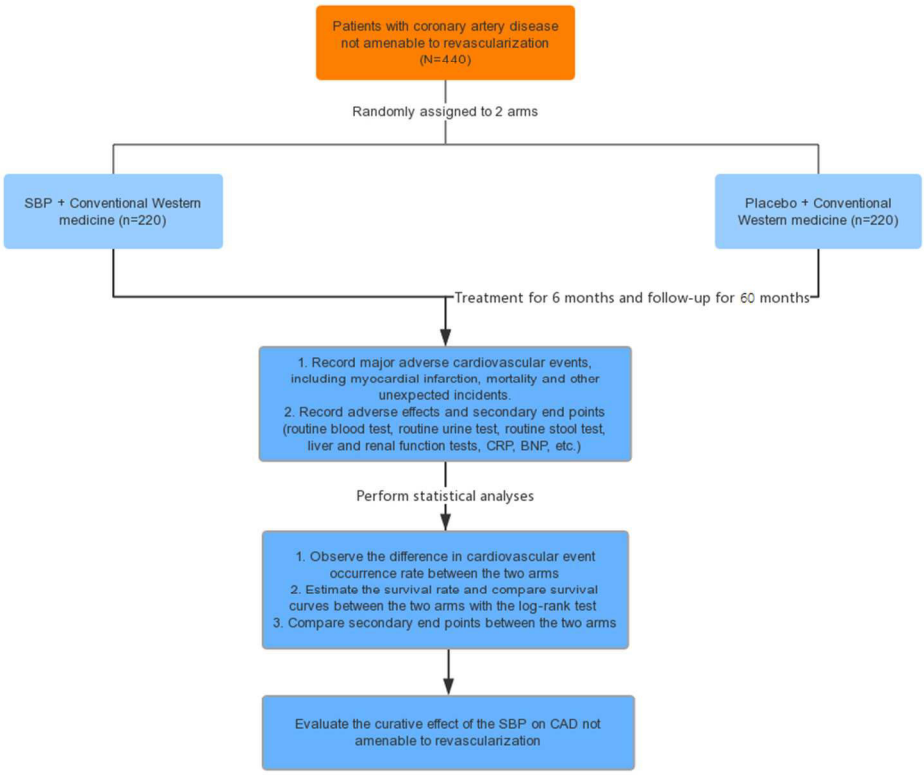

Checklist of Items for Reporting Trials of Chinese Herbal Medicine Formulas*

Section/Topic	Item Number	Standard CONSORT Checklist Item	Extension for CHM Formulas	Reported on Page Number
Title, abstract, and keywords	1a	Identification as a randomized trial in the title	*Statement of whether the trial targets a TCM* Pattern*, a Western medicine–defined disease, or a Western medicine–defined disease with a specific TCM* Pattern*, if applicable*	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts [26, 27])	*Illustration of the name and form of the formula used, and the TCM* Pattern *applied, if applicable*	1、2
	1c		*Determination of appropriate keywords, including "Chinese herbal medicine formula" and "randomized controlled trial"*	1
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	*Statement with biomedical science approaches and/or TCM approaches*	2-4
	2b	Specific objectives or hypotheses	*Statement of whether the formula targets a Western medicine–defined disease, a TCM* Pattern*, or a Western medicine–defined disease with a specific TCM* Pattern	4
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio		4、5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	*Statement of whether participants with a specific TCM* Pattern *were recruited, in terms of 1) diagnostic criteria and 2) inclusion and*	6

			exclusion criteria. All criteria used should be universally recognized, or reference given to where detailed explanation can be found.	
	4b	Settings and locations where the data were collected		5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	*Description(s) for different types of formulas should include the following:* ***5a. For fixed CHM formulas*** *1. Name, source, and dosage form (e.g., decoctions, granules, powders)* *2. Name, source, processing method, and dosage of each medical substance. Names of substances should be presented in at least 2 languages: Chinese (*Pinyin*), Latin, or English. Names of the parts of the substances used should be specified.* *3. Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible* *4. Principles, rationale, and interpretation of forming the formula* *5. Reference(s) as to the efficacy of the formula, if any* *6. Pharmacologic study results of the formula, if any* *7. Production method of the formula, if any* *8. Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible.* *9. Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and*	3、7、8

			acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible. *10. Dosage of the formula, and how the dosage was determined* *11. Administration route (e.g., oral, external)* ***5b. For individualized CHM formulas*** *1. See recommendations 5a 1–11* *2. Additional information: how, when, and by whom the formula was modified* ***5c. For patent proprietary CHM formulas*** *1. Reference to publicly available materials, such as pharmacopeia, for the details about the composition, dosage, efficacy, safety, and quality control of the formula* *2. Illustration of the details of the formula, namely 1) the proprietary product name (i.e., brand name), 2) name of manufacturer, 3) lot number, 4) production date and expiry date, 5) name and percentage of added materials, and 6) whether any additional quality control measures were conducted* *3. Statement of whether the patent proprietary formula used in the trial is for a condition that is identical to the publicly available reference* ***5d. Control groups*** *Placebo control* *1. Name and amount of each ingredient* *2. Description of the similarity of placebo with the intervention (e.g., color, smell, taste, appearance, packaging)* *3. Quality control and safety assessment, if any* *4. Administration route, regimen, and dosage*	

			5. Production information: where, when, how, and by whom the placebo was produced *Active control* *1. If a CHM formula was used, see recommendations 5a–5c* *2. If a chemical drug was used, see item 5 of the CONSORT Statement (24)*	
Outcomes	6a	Completely defined, prespecified primary and secondary outcome measures, including how and when they were assessed	*Illustration of outcome measures with* Pattern *in detail*	9、2
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined		10
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomization				
Sequence generation	8a	Method used to generate the random allocation sequence		8
	8b	Type of randomization; details of any restriction (such as blocking and block size)		8、9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		8、9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and		8、9

		how		
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes		10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome		9
	13b	For each group, losses and exclusions after randomization, together with reasons		
Recruitment	14a	Dates defining the periods of recruitment and follow-up		5
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group		
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups		
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)		9
	17b	For binary outcomes, presentation of both absolute and relative effect		

		sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory		
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms [28])	*(There is no extension for this item)*	10
Discussion				
Limitations	20	Trial limitations; addressing sources of potential bias; imprecision; and, if relevant, multiplicity of analyses		12、13
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	*Discussion of how the formula works on different TCM* Patterns *or diseases*	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	*Interpretation with TCM theory*	11、12
Other information				
Registration	23	Registration number and name of trial registry		2
Protocol	24	Where the full trial protocol can be accessed, if available		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		13

CHM = Chinese herbal medicine; CONSORT = Consolidated Standards of Reporting Trials; TCM = traditional Chinese medicine.

* The original CONSORT items are provided; elaborations for CHM formulas are in italicized text. We strongly recommend reading this checklist in conjunction with the CONSORT 2010 Explanation and Elaboration (29) for important clarifications on all original items of CONSORT Statement.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry P2
	2b	All items from the World Health Organization Trial Registration Data Set P2
Protocol version	3	Date and version identifier P13
Funding	4	Sources and types of financial, material, and other support P13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors P13
	5b	Name and contact information for the trial sponsor P13
	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
	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)
Introduction		
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 P2-P4
	6b	Explanation for choice of comparators P4
Objectives	7	Specific objectives or hypotheses P2 P4

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, noninferiority, exploratory) P4
Methods: Participants, interventions, and outcomes		
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 P5
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) P6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P7
	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)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial P7
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 P9
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) P9
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 P10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size P5
Methods: Assignment of interventions (for controlled trials)		
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 P8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned P8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P5 P8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P8 P9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	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 P2
	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 P6 P7
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 P10
Statistical methods	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 P10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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) P10

Methods: Monitoring

Data monitoring	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. P7 Alternatively, an explanation of why a DMC is not needed
	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 P5
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 P9 P10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval P2
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)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable P11
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site P13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators P10
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 P9 P10

Dissemination policy	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 P11
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates P5
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.