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Efficacy and safety of Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

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4 **Efficacy and safety of Xueshuantong injection (lyophilized) in reducing the**
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6 **incidence of major adverse cardiovascular events in patients with unstable**
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8 **angina: A randomized, parallel-arm, controlled, double-blind, and multicenter**
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10 **clinical trial based on dual antiplatelet therapy**
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14 **Running title:** Efficacy and safety of Xueshuantong injection in patients with UA

15
16 Wenjie Long PhD^{1,3†}, Huili Liao MD^{1†}, Xi Huang MD^{2†}, Qingqing Liu MD², Yaqing
17
18 Tang MD⁴, Liming Lu PhD⁵, Jianhong Liu MD¹, Tianhui Yuan MD⁴, Yan Ling PhD¹,
19
20 Yu Hong MD¹, Jiao Duan MD¹, Weiji Lin MD¹, Shaoxiang Xi PhD^{1,3*}, Zhongqi
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22 Yang PhD^{1,3*}
23
24
25

26
27 ¹Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of
28
29 Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R.
30
31 China
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33

34
35 ²The First Clinical College, Guangzhou University of Chinese Medicine, No.12
36
37 Jichang Road, Baiyun District, Guangzhou, 510405, P.R. China
38
39

40
41 ³Lingnan Medical Research Center, Guangzhou University of Chinese Medicine,
42
43 Jichang road No.12, Guangzhou, Guangdong 510000, China
44
45

46
47 ⁴National Drug Clinical Trial Agency Office , The First Affiliated Hospital of
48
49 Guangzhou University of Chinese Medicine, No.16 Jichang Road, Baiyun District,
50
51 Guangzhou, 510405, P.R. China.
52

53
54 ⁵Clinical Research Center, South China Research Center for Acupuncture and
55
56 Moxibustion, Medical College of Acu-Moxi and Rehabilitation, Guangzhou
57
58
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3
4 University of Chinese Medicine, No.232 Waihuan Dong Road, Guangzhou, 510006,
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6 Guangdong, China.

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8 †These authors contributed equally to this work.
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14 ***Corresponding Author:**

15
16 Shaoxiang Xi

17
18 Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of
19
20 Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R.
21
22 China
23

24
25
26 Lingnan Medical Research Center, Guangzhou University of Chinese Medicine,
27
28 Jichang road No.12, Guangzhou, Guangdong 510000, China
29

30
31
32 Tel: +86-13560231626

33
34
35 Fax: +86-21-57643271

36
37
38 E-mail: Shaoxiangx@hotmail.com

39
40
41 Zhongqi Yang

42
43
44 E-mail: Yang_zhongqi@163.com
45
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Abstract

Objective: Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection having the potential to treat ACS. This clinical trial aims to examine the efficacy and safety of XST.

Design: A randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial.

Setting and Participants: A total of 1200 participants with UA will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group and 600 with one-twentieth dose in the control group.

Interventions: All participants will receive the conventional treatment. XST group will be treated via intravenous drip with 500 mg XST diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days, while the patients in control group will be treated via intravenous drip with 25 mg XST diluted with 250–500 mL of 5% glucose injection or sodium chloride injection.

Primary and secondary outcome measures: The primary outcome will include the incidence of composite endpoints for major adverse cardiovascular events(MACE), including cardiovascular death, nonfatal myocardial infarction, and revascularization. The secondary outcomes, the efficacy of angina pectoris will be observed and the myocardial injury markers will be monitored.

Results: The efficacy assessment and MACE will be observed, and angina pectoris

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4 will be examined at the start and end of the run-in period. All AEs will be recorded,
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6 regardless of severity, to assess the safety of XST. The baseline characteristics of
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8 patients will be summarized and compared using the *t* test or nonparametric statistical
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10 test. Qualitative data will be analyzed using the chi-square or Fisher exact tests,
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12 Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.
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17 **Conclusions:** Clinical evidence for the efficacy and safety of XST in reducing the
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19 incidence of MACE in patients with UA.
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22 **Trial registration:** This study was registered on the Chinese Clinical Trial Registry
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24 (<http://www.chictr.org.cn/>) with the ID ChiCTR180001591.
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27 **Key words:** Acute coronary syndrome, clinical trial, traditional Chinese herbal
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29 injection, unstable angina
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Strengths and limitations of this study

- This is a randomized, double-blind, placebo-controlled and multicenter trial to assess the efficacy and safety of Xuanshuantong injection(lyophilized) in patients with unstable angina
- A multicenter trial is carried out in 17 medical centers across China, which can improve the external validity and representativeness of the sample and reduce the risk of selection bias.
- A long-term follow-up (1, 3, and 6 months) will be conducted after the supervised intervention.
- The treatment period of 7-14 days may be a bit short.

1.Introduction

Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Reduced blood flow to the heart muscle is the most common cause of UA because the coronary arteries are narrowed by atherosclerosis, leading to the rupture of coronary blood vessels and hence blood clotting, which blocks the flow of blood to the heart muscle. The risk factors for UA include diabetes, obesity, family history of heart disease, high blood pressure, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, male sex, and use of any form of tobacco^{1, 2}. With the wide application of percutaneous coronary intervention (PCI) in patients with ACS, current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after ACS management with PCI. However, the greatest anti-ischemic benefit of potent antiplatelet drugs over the less-potent clopidogrel occurs early, while most excess bleeding events occur during chronic treatment. It is related to the efforts of physicians to reduce the adverse incidence of cardiovascular events, promote the patient's early recovery, and improve their health-related quality of life.

Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection comprising a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and People's Republic of China Pharmacopoeia, respectively. It has been

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4 reported to have anti-inflammatory effects that correct endothelial dysfunction *in*
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6 *vivo*³ and *in vitro*⁴. Clinically, as a common medicine in China's Grade-A Tertiary
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8 Hospital, XST has been reported to be beneficial in treating ACS^{5, 6}. In preliminary
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10 studies, including small samples, XST reduced the incidence of major adverse
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12 cardiovascular events (MACE). The high-quality trials and evidence are needed to
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14 prove the efficacy of XST. This randomized, parallel, controlled, double-blind, and
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16 multicenter clinical trial aims to examine the efficacy and safety of XST in patients
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18 with UA. The results of this trial may provide clinical evidence for treating patients
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20 with UA.
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30 **2. Method and design**

31 **2.1 Study design**

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35 This randomized, parallel-arm, controlled, double-blind, and multicenter clinical
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37 trial will be conducted in 17 medical centers in China: The First Affiliated Hospital of
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39 Guangzhou University of Chinese Medicine, The First Affiliated Hospital of the
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41 Henan University of Chinese Medicine, Luoyang No. 1 Hospital of Traditional
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43 Chinese Medicine, Shanxi Fenyang Hospital, The First Affiliated Hospital of Henan
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45 University of Science and Technology, Zhengzhou People's Hospital, Zhengzhou
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47 Central Hospital, Ruikang Hospital Affiliated to Guangxi University of Traditional
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49 Chinese Medicine, Nanjing Hospital of Chinese Medicine, Shuguang Hospital
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51 Affiliated to Shanghai University of Chinese Medicine, Changsha Fourth Hospital,
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4 The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine,
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6 The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese
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9 Medicine, The Second Affiliated Hospital of Tianjin University of Traditional
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11 Chinese Medicine, Affiliated Hospital of Tianjin Academy of Chinese Medicine,
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13 Tianjin Beichen District Hospital of Traditional Chinese Medicine, and Wenzhou
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15 Hospital of Traditional Chinese Medicine. A total of 1200 patients with UA who met
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17 the selection will be enrolled in a 1:1 ratio, with 600 patients included in the XST
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19 treatment group and 600 with 1/20th dose in the control group.
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24 All the visits will be recorded in electronic care report forms through the
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26 Electronic Data Capture system, which is accessed online via the Internet for data
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28 collection and management. The protocol of this study was developed in accordance
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30 with the standard protocol project: Interventional Trial Recommendations guidelines⁷.
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38 **2.2 Ethics**

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40 This study has been approved by the ethics committee of the First Affiliated
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42 Hospital of Guangzhou University of Chinese Medicine (approval number:
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44 ZYYEC[2017]002) and registered on the Chinese Clinical Trial Registry with the ID
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46 ChiCTR1800015911.
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53 **2.3 Study population**

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55 Patients will be included after written informed consent and enrolled in the study
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57 when the inclusion and exclusion criteria are met (Table 1).
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2.3.3 Withdrawal criteria

1. Patients with some comorbidities, complications, or special physiological changes during the trial
2. Patients with poor compliance in the trial; the use of the drug not reaching 80% (except for those recovered in advance) or exceeding 120% of the prescribed amount
3. Patients with blindness or emergency unblinding during the trial
4. Patients with serious adverse events and those not appropriate to continue the test
5. Patients failing to use the test drug
6. Patients misdiagnosed or not matching the inclusion criteria and accidentally included
7. Patients with no follow-up records
8. Patients failing to comply with the treatment during the trial, changing the medicines, or adding nonspecified therapeutic medications by themselves, especially those medications that may affect the evaluation of the test drug, affecting the validity and safety.

2.4 Study setting and recruitment

Between December 2018 and December 2020, 1200 patients will be recruited at the 17 centers mentioned earlier through the official website of the hospitals, posters, and networks. The physicians will diagnose the participants, and the research assistants will manage the recruitment.

2.5 Randomization

After the recruitment is completed, statistical analysis system software will be used to generate the random arrangement of 1200 people in 2 groups (XST and placebo groups) with the method of central stratified regional group randomization. The randomization numbers will be kept in opaque sealed envelopes. The physicians and patients will not be aware of the grouping and intervention.

2.6 Blinding

This study has a double-blind design, with a very low dose used as control. The number of cases in the study and control groups will be in the ratio of 1:1. The blinding work will be completed by statisticians. To ensure the blinding of investigators and participants to study treatment, the study drug or placebo will be provided in identical packaging and labeling. Due to some natural variability in the color of the study drug, which is batch dependent, the color of the placebo will be matched to be the same as the average color of the study drug. Study drug and placebo will be labeled with a unique label letter that will be used to assign treatment to the patient but will not indicate treatment allocation to investigators or participants. No member of the study team and their extended staff, except for pharmacists and biostatisticians, will have access to the randomization scheme during the conduct of the study. In the event of a medical emergency, where breaking the blind is required

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4 to provide medical care to the participant, the investigator will obtain the treatment
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6 assignment from the trial pharmacists.
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10 11 12 **2.7 Sample size calculation**

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14 MACE will be used as the effect index according to the statistical requirements of
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16 the optimal validity test design.
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19 Based on the expert advice combined with clinical practical considerations and
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21 according to the loss rate of less than 20% estimated beforehand, the study sample
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23 was 1200 cases (600 cases in each group), assuming that the incidence of MACE was
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25 12% after dual antiplatelet therapy for 6 months, which was reduced by 6% after
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27 lyophilization (alpha = 0.05; power = 0.9).
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35 **2.8 Interventions**

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37 All participants will receive dual antiplatelet therapy (aspirin 100 mg/d +
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39 clopidogrel 75 mg/d) and anticoagulation therapy (unfractionated heparin) according
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41 to the 2014 American College of Cardiology/American Heart Association Guidelines
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43 for the Diagnosis and Treatment of Non-ST-Segment Acute Coronary Syndrome, and
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45 in accordance with the guidelines to accept statins, angiotensin-converting enzyme
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47 inhibitors, beta-blockers, and nitrates. Patients with mild UA will undergo a
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49 standardized baseline assessment before the treatment, including detailed medical
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51 history, physical examination, and laboratory testing. Meanwhile, the following
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4 treatments will be given to different groups:
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6 (1) XST treatment group: The patients will be treated via an intravenous drip with
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8 500 mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or
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10 sodium chloride injection, once per day for 7–14 days.
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14 (2) Control group: The patients will be treated via an intravenous drip with 25 mg
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16 XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium
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18 chloride injection, once per day for 7–14 days.
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22 The experimental drugs will be distributed by a drug administrator and injected
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24 by trained nurses.
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27 Patients who continue to use the drug for more than 7 days until discharge will
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29 end the medication and move directly to the follow-up period. The efficacy and safety
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31 of XST will be assessed after treatment for 7–14 days and follow-up for 1, 3, and 6
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33 months (Figs. 1 and Table 2).
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40 **2.7 Outcome measurements**

41 **2.7.1 Primary outcomes**

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43 The primary endpoints will include the incidence of composite endpoints for
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45 MACE, including cardiovascular death, nonfatal myocardial infarction, and
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47 revascularization.
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53 The primary endpoint is the time from the enrollment to the end of the study
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55 (including the medication observation period and follow-up period) when any of the
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4 MACE events occur for the first time. Patients without MACE during the study will
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6 be defined as censored at the end of the study. For patients who quit the trial early due
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8 to reasons other than MACE, the time of occurrence is defined as censoring at the
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10 time of early termination. Deaths not due to cardiovascular diseases or that occur after
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12 the MACE will not be evaluated.
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19 **2.7.2 Secondary outcomes**

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22 The efficacy of angina pectoris will be observed at the time of enrollment and at
23
24 the end of treatment.
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27 Myocardial injury markers [serum creatine kinase MB; cardiac troponin T/cardiac
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29 troponin I (cTnI)/high-sensitivity troponin I] will be monitored.
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35 **2.7.3 Safety assessment**

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37 The observation of vital signs; testing of blood and urine samples, renal function, and
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39 liver function; electrocardiograms; and physical examinations will be examined at the
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41 start and end of the run-in period. The researchers will record the abnormal changes at
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43 any time. An adverse event (AE) is any adverse medical event that occurs during the
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45 trial. Patients will be required to report all AEs at each visit. All AEs will be recorded,
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47 regardless of severity, to assess the safety of XST.
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53 If an AE occurs, the researchers will have to determine whether to stop the
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55 observation and proceed with the diagnosis and corresponding treatment. If any
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4 severe AE occurs, the researchers must take immediate action to ensure the safety of
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6 the participants. They must also report to the ethics committee within 24 h. The
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8 responsible staff from The First Affiliated Hospital of Guangzhou University of
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10 Chinese Medicine must promptly notify other participating centers and initiate any
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12 necessary legal procedures.
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19 **2.8 Follow-up**

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22 All included participants will be evaluated for the occurrence of MACE after 1, 3,
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24 and 6 months through phone calls after the end of the medication. The trial will be
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26 ended if the following endpoints occur: death, nonfatal myocardial infarction, or
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28 revascularization (including PCI and CABG). The academic research on hemorrhage
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30 in Europe and the United States proposed a unified definition of hemorrhage type 3–
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38 The occurrence of the MACE must be recorded in an original supporting
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40 document, including but not limited to a copy of the discharge summary, a copy of the
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42 medical record, or other documents that can be used to verify the occurrence of the
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44 MACE and the date of its occurrence.
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50 **2.9 Statistical analysis**

51 ***2.9.1 Enrollment and case completion***

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56 The completion of the trial at each center must be recorded and described. All
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4 cases of shedding must be listed.
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6 **2.9.2 Baseline comparability analysis**

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9 The baseline characteristics of patients will be summarized and compared using
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11 the t test or nonparametric statistical test. Qualitative data will be analyzed using the
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13 chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and
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15 Wilcoxon test.
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18 **2.9.3 Analysis of efficacy**

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20 (1) Baseline comparability analysis: This includes the description of demographic
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22 data, symptoms, and general conditions. The t test or nonparametric statistical method
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24 will be used for quantitative data. Qualitative data will be determined using the
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26 chi-square test, Fisher's exact probability method, CMH test, and Wilcoxon rank-sum
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28 test.
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35 (2) Primary and secondary outcomes: The incidence of composite endpoints for
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37 MACE and the efficacy of angina pectoris will be compared between the two groups
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39 and analyzed using the chi-square or Fisher exact tests and two-sample t tests or
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41 Wilcoxon rank-sum test. The laboratory data on myocardial injury markers will be
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43 analyzed for the changes before and after the intervention. The average value of each
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45 laboratory data after the treatment will be compared.
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50 (3) For cases of rejection and shedding, statistical descriptions will be performed
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52 one by one. Adverse reactions will be statistically described. The incidence of adverse
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54 reactions will be compared using the chi-square or Fisher exact tests.
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3. Discussion

XST is a traditional Chinese herbal injection consisting of a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the “2012 national essential drugs list” and the People’s Republic of China Pharmacopoeia, respectively. Total saponins, isolated from the root and rhizome of *P. notoginseng*, are the main components of XST.

P. notoginseng is known for promoting blood circulation, preventing thrombosis, and dilating blood vessels. It is widely applied to treat acute cerebral infarction, stroke, and coronary heart disease in clinical practice^{8, 9}. Gan et al.¹⁰ evaluated the efficacy and safety of the *P. notoginseng* extract via intracoronary injection for treating the post-PCI slow-reflow phenomenon in patients with ST-segment elevation myocardial infarction and its impact on patients' prognosis. They found that coronary injection with tirofiban and XST was more effective in improving the coronary blood flow and showed no increase in the incidence of hemorrhagic complications compared with the injection with tirofiban only. *P. notoginseng* has been found to be beneficial to patients with UA. The use of the extract has been recommended for patients with UA in clinical practice as a complementary and alternative therapy¹¹. However, more randomized controlled trials with reliable designs, large samples, and long-term observations are needed for further evaluations.

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4 The meta-analysis of XST injection combined with routine basic treatment was
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6 superior to routine basic treatment alone in alleviating clinical symptoms, with
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8 statistically significant differences between the groups. XST injection combined with
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10 routine basic treatment could alleviate UA pectoris. However, due to the low quality
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12 of included studies, further well-designed, multicenter, and large-scale RCTs are still
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14 needed to evaluate the efficacy of XST injection [14]. Moreover, the total revenue from
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16 XST in the Chinese market in 2013 was over \$700 million [15]. Therefore, the
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18 enormous consumption requires stricter and accurate evidence on its safety. However,
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20 many reports of XST were case reports, and hence large-sample and high-level
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22 evidence for the efficacy and safety of XST is still lacking. Therefore, this study will
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24 be conducted to investigate the efficacy and safety of XST in reducing the incidence
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26 of MACE in patients with UA. The findings of this study will provide clinical
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28 evidence for the use of XST in reducing the incidence of MACE in patients with UA.
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41
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44 Chinese Medicine for his guidance during this study. They also thank Miss Jingyi Xu,
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46 who carefully checked the references.
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53 This study has been supported by the project “Efficacy and safety of Xueshuantong
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4 injection (lyophilized) in reducing the incidence of MACE in patients with unstable
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6 angina: A randomized, parallel-arm, controlled, double-blind, and multicenter clinical
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8 trial based on dual antiplatelet therapy” (no. 10600216) and the second batch of
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10 national TCM clinical research base project (no. 2018131).
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14 **Trial status**

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17 Currently the participants are being enrolled for the trial.

18 **Conflicts of interest**

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21 All authors declare no any conflicts of interest.
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23 **Author contribution**

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XSX, LHL and YZQ carried out the studies, LJH, DJ, HY and LY participated in
collecting data, and drafted the manuscript. LWJ, LLM and LQQ performed the
statistical analysis and participated in its design. TYQ, YTH, HX and LWJ
participated in acquisition, analysis, or interpretation of data and draft the manuscript.

All authors read and approved the final manuscript.

38 **Patient Consent Form**

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All participants provided written informed consent.

43 **Data Sharing Statement**

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The datasets used and/or analysed during the current study are available from the
corresponding author on reasonable request.

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4 **Figure legends**
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6 Figure 1. Flowchart of the study procedure.
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For peer review only

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ● Patients diagnosed with coronary heart disease who met at least one of the following diagnostic criteria^[1]: <ul style="list-style-type: none"> (1) a clear history of myocardial infarction (MI); (2) prior coronary revascularization; (3) coronary angiography or coronary angiography suggesting at least one coronary artery stenosis with catheter stenosis $\geq 50\%$; (4) cardiac magnetic resonance imaging or radionuclide myocardial perfusion imaging to confirm myocardial ischemia in the patient having coronary heart disease 	<ul style="list-style-type: none"> ◆ Patients with cardiac function class IV (New York Heart Association cardiac function grading); or patients at a high risk of UA short-term risk stratification
<ul style="list-style-type: none"> ● Patients complying with the diagnosis of UA and having at least one of the following conditions: <ul style="list-style-type: none"> (1) electrocardiograph with a transient or persistent ST-segment depression of 0.1 mV and even more on one or more leads; (2) Thrombolysis In Myocardial 	<ul style="list-style-type: none"> ◆ Patients with uncontrolled grade III hypertension having systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg; severe cardiopulmonary insufficiency; severe arrhythmia; severe primary diseases of the liver, kidney, and hematopoietic system; or serious diseases (such as tumors) and mental diseases ◆ Patients also having other clinical conditions that might increase the risk of bleeding, such as a history of important organ bleeding in the last 6 months (such as intracerebral hemorrhage and upper gastrointestinal bleeding), decreased platelet count, abnormal coagulation function, and recent active bleeding ◆ Patients with abnormal function indexes of the liver and kidney

<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p>	<p>Infarction (TIMI) risk score^[9] ≥ 3</p> <ul style="list-style-type: none"> ● Patients receiving dual antiplatelet therapy (aspirin + clopidogrel) ● Patients aged 40–75 years, irrespective of sex ● Patients willing to accept the drug treatment and provide written informed consent, conforming to the relevant regulations of Good Clinical Practice 	<p>[blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level more than two times the upper normal reference range; glomerular filtration rate (GFR) $<60 \text{ mL}/(\text{min} \times 1.73 \text{ m}^2)$]. Simplified Modification of Diet in Renal Disease formula^[4]: $\text{GFR} [\text{mL}/(\text{min} \times 1.73 \text{ m}^2)] = 186.3 \times \text{serum creatinine (Scr)}^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ female})$; Scr in mg/dL and age in years</p> <ul style="list-style-type: none"> ◆ Patients who planned to undergo revascularization [PCI or coronary artery bypass grafting (CABG)] recently ◆ Patients allergic to a variety of foods, or with known allergy to study drugs, including their components ◆ Patients pregnant, preparing for pregnancy, or lactating ◆ Patients participating in other clinical trials during the same period ◆ Patients considered inappropriate to participate in this study
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Table 2. Study schedule of assessments

	Study period			
	Enrollment	Allocation	Intervention	Follow-up
Time point	-2 week	0	7-14 days	1,3 and 6 months
ENROLLMENT:	X			
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
SXT treatment			X	
Placebo treatment			X	
ASSESSMENTS:				
MACE			X	X
CK-MB		X	X	
cTnT		X	X	
cTnI		X	X	
hsTnI		X	X	
Adverse events			X	X

Abbreviations: CK-MB, creatine kinase MB; MACE, major adverse cardiac events; cTn, cardiac troponin; hsTn, high-sensitivity Troponin; UA, unstable angina.

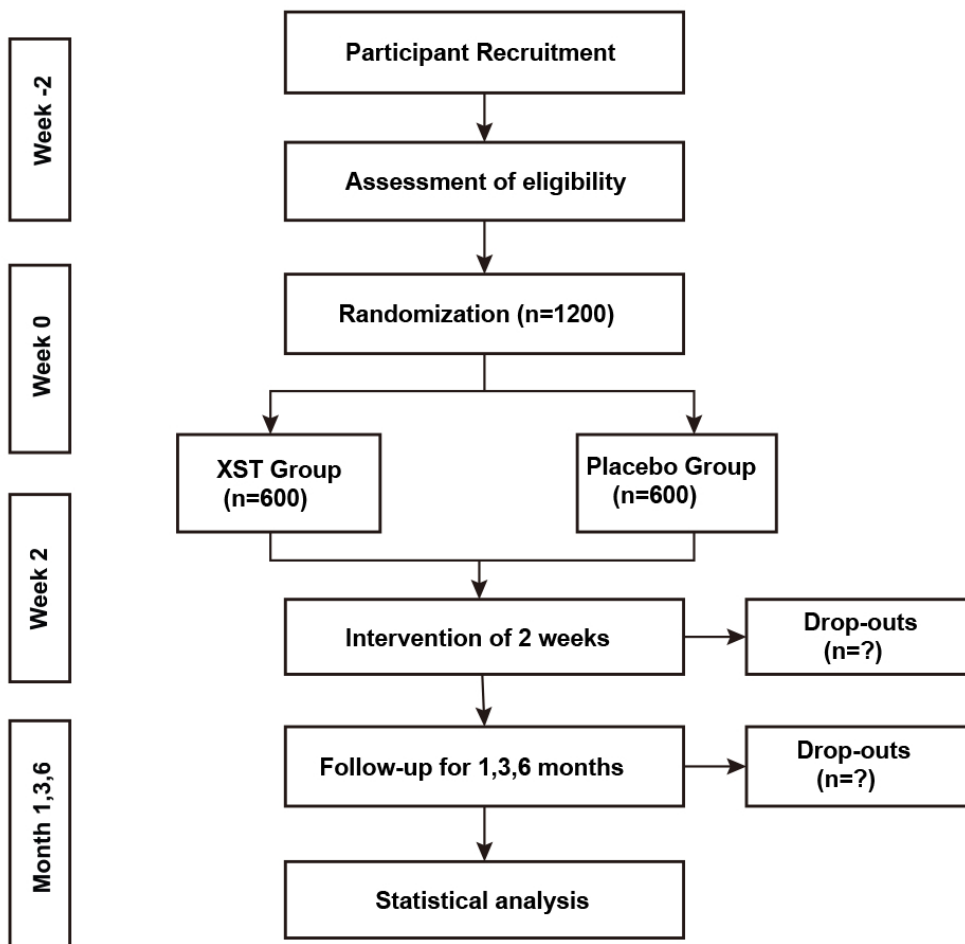


fig 1

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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)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8-9
Sample size	7a	How sample size was determined	8-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8-10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8-10
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	8-10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8-10

1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
2				
3		11b	If relevant, description of the similarity of interventions	8
4	Statistical	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
5	methods	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
6				
7	Results			
8	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended	6
9	diagram is strongly		treatment, and were analysed for the primary outcome	
10	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	
11				
12	Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
13		14b	Why the trial ended or was stopped	8
14				
15	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
16	Numbers	16	For each group, number of participants (denominator) included in each analysis and whether the	
17	analysed		analysis was by original assigned groups	
18				
19	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	
20	estimation		precision (such as 95% confidence interval)	
21		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
22				
23	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses,	
24			distinguishing pre-specified from exploratory	
25	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
26				
27	Discussion			
28	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of	11
29			analyses	
30	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
31				
32	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant	11
33			evidence	
34				
35	Other information			
36	Registration	23	Registration number and name of trial registry	1
37	Protocol	24	Where the full trial protocol can be accessed, if available	
38	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11
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*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.

BMJ Open

Efficacy and safety of Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

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Complete List of Authors:	<p>Long, Wenjie; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital; Guangzhou University of Chinese Medicine, Lingnan Medical Research Center</p> <p>Liao, Huili; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics,</p> <p>Huang , Xi ; Guangzhou University of Chinese Medicine, The First Clinical College</p> <p>Liu, Qingqing; Guangzhou University of Chinese Medicine, The First Clinical College,</p> <p>Tang, Yaqing ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, National Drug Clinical Trial Agency Office</p> <p>Lu, Liming; Guangzhou University of Chinese Medicine, Clinical Research Center</p> <p>Liu, Jianhong; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Yuan, Tianhui ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, National Drug Clinical Trial Agency Office</p> <p>Ling, Yan ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Hong, Yu; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Duan , Jiao ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Lin , Weiji ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Xian, Shaoxiang; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Yang, Zhongqi; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p>
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	CARDIOLOGY, Adult cardiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY

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4 **Efficacy and safety of Xueshuantong injection (lyophilized) in reducing the**
5 **incidence of major adverse cardiovascular events in patients with unstable**
6 **angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and**
7 **multicenter clinical trial based on dual antiplatelet therapy**
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12 **Running title: Efficacy and safety of Xueshuantong injection in patients with**
13 **UA**
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17 Wenjie Long PhD^{1,3†}, Huili Liao MD^{1†}, Xi Huang MD², Qingqing Liu MD², Yaqing
18
19 Tang MD⁴, Liming Lu PhD⁵, Jianhong Liu MD¹, Tianhui Yuan MD⁴, Yan Ling PhD¹,
20
21 Yu Hong MD¹, Jiao Duan MD¹, Wei Ji Lin MD¹, Shaoxiang Xian PhD^{1,3*}, Zhongqi
22
23 Yang PhD^{1,3*}
24
25

26
27 ¹ Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of
28
29 Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R.
30
31 China
32
33

34
35 ² The First Clinical College, Guangzhou University of Chinese Medicine, No.12
36
37 Jichang Road, Baiyun District, Guangzhou, 510405, P.R. China
38
39

40
41 ³ Lingnan Medical Research Center, Guangzhou University of Chinese Medicine,
42
43 Jichang road No.12, Guangzhou, Guangdong 510000, China
44
45

46
47 ⁴ National Drug Clinical Trial Agency Office, The First Affiliated Hospital of
48
49 Guangzhou University of Chinese Medicine, No.16 Jichang Road, Baiyun District,
50
51 Guangzhou, 510405, P.R. China.
52

53
54 ⁵ Clinical Research Center, South China Research Center for Acupuncture and
55
56 Moxibustion, Medical College of Acu-Moxi and Rehabilitation, Guangzhou University
57
58

1
2
3
4 of Chinese Medicine, No.232 Waihuan Dong Road, Guangzhou, 510006, Guangdong,
5
6
7 China.

8 † These authors contributed equally to this work.
9

10
11
12
13
14 ***Corresponding Author:**

15
16 Shaoxiang Xi

17
18 Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of
19
20 Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R.
21
22
23 China

24
25
26
27 Lingnan Medical Research Center, Guangzhou University of Chinese Medicine,
28
29 Jichang road No.12, Guangzhou, Guangdong 510000, China

30
31
32 Tel: +86-18620602046

33
34 Fax: +86-21-57643271

35
36
37 E-mail: Shaoxiangx@hotmail.com

38
39
40 Zhongqi Yang

41
42 Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of
43
44 Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R.
45
46
47 China

48
49
50 Lingnan Medical Research Center, Guangzhou University of Chinese Medicine,
51
52 Jichang road No.12, Guangzhou, Guangdong 510000, China

53
54
55 Tel: +86-13560231626

1
2
3
4 Fax: +86-21-57643271
5
6
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8

9 E-mail: Yang_zhongqi@163.com; Yangzhongqi@gzucm.edu.cn
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16 **List of abbreviation**

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19 ACS, Acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitors;
20 CABG, coronary artery bypass grafting; cTn, cardiac troponin; CK-MB, creatine
21 kinase MB; HDL-C, low high-density lipoprotein cholesterol; LDL-C, high low-
22 density lipoprotein cholesterol; MACE, major adverse cardiac events; PCI,
23 percutaneous coronary intervention; STEMI, ST-segment elevation myocardial
24 infarction; hsTn, high-sensitivity troponin; UA, unstable angina
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Abstract

Introduction: Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection having the potential to treat ACS. However, no clinical trial has been performed in this field. This clinical trial aims to examine the efficacy and safety of XST.

Methods and Analysis: This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial. A total of 1200 participants with UA will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group and 600 with one-twentieth dose in the control group. The efficacy assessment and major adverse cardiovascular events (MACE) will be observed, and the frequency of angina attack, angina pectoris will be examined at the start and end of the run-in period. All AEs will be recorded, regardless of severity, to assess the safety of XST. The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

Ethics and Dissemination: This trial has been approved by Research Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine, China (approval number: ZYYEC [2017] 0021). Written informed consent will be obtained from all participants. The results of this trial will be disseminated to the public through academic conferences and peer-reviewed journals.

Trial registration: This study was registered on the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/>) with the ID ChiCTR1800015911.

Key words: Acute coronary syndrome, clinical trial, traditional Chinese herbal injection, unstable angina

Strengths and limitations of this study:

1. This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial.
2. The trial will be conducted in 17 medical centers with 1200 participants.
3. In our study, to better implement the blind method, the extremely low dose 25mg is used as the control group.
4. The efficacy assessment and major adverse cardiovascular events (MACE) will be observed, and the frequency of angina attack, angina pectoris will be examined at the start and end of the run-in period.
5. Our experiments will be conducted in different regions of China, and whether similar effects are available to other ethnic groups and regions remains uncertain.

Introduction

Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Reduced blood flow to the heart muscle is the most common cause of UA because the coronary arteries are narrowed by atherosclerosis, leading to the rupture of coronary blood vessels and hence blood clotting, which blocks the flow of blood to the heart muscle. The risk factors for UA include diabetes, obesity, family history of heart disease, high blood pressure, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, male sex, and use of any form of tobacco^[1, 2]. With the wide application of percutaneous coronary intervention (PCI) in patients with ACS, current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after ACS management with PCI. However, the greatest anti-ischemic benefit of potent antiplatelet drugs over the less-potent clopidogrel occurs early, while most excess bleeding events occur during chronic treatment. It is related to the efforts of physicians to reduce the adverse incidence of cardiovascular events, promote the patient's early recovery, and improve their health-related quality of life.

Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection comprising a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and People's Republic of China Pharmacopoeia, respectively. It has been reported to have anti-inflammatory effects that correct endothelial dysfunction *in vivo*^[3] and *in vitro*^[4]. Clinically, as a common medicine in China's Grade-A Tertiary Hospital, XST has been reported to be beneficial in treating ACS^[5, 6]. In preliminary studies, including small samples, XST has been found to platelet aggregation inhibition, anti-myocardial ischemia, anti-inflammation, anti-oxidation, protecting endothelial cells, which could reduce the incidence of major adverse cardiovascular events (MACE)^[7]. As the primary component^[8], *Panax notoginseng*, has been extensively verified that it can ameliorate ischemia-reperfusion (IR)-induced injury in cardiovascular and neuronal systems

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4 mainly by upregulating the activity of estrogen receptor α -dependent
5 phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and nuclear factor erythroid-
6 2-related factor 2 (NRF2) pathways and downregulating nuclear factor- κ B (NF- κ B)
7 and mitogen-activated protein kinase (MAPK) pathways. The high-quality trials and
8 evidence are needed to prove the efficacy of XST. This randomized, parallel, controlled,
9 double-blind, and multicenter clinical trial aims to examine the efficacy and safety of
10 XST in patients with UA. The results of this trial may provide clinical evidence for
11 treating patients with UA.
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22 **2. Method and design**

23 **2.1 Study design**

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27 This randomized, parallel-arm, controlled, double-blind, and multicenter clinical
28 trial will be conducted in 17 medical centers in China: The First Affiliated Hospital of
29 Guangzhou University of Chinese Medicine, The First Affiliated Hospital of the
30 Henan University of Chinese Medicine, Luoyang No. 1 Hospital of Traditional
31 Chinese Medicine, Shanxi Fenyang Hospital, The First Affiliated Hospital of Henan
32 University of Science and Technology, Zhengzhou People's Hospital, Zhengzhou
33 Central Hospital, Ruikang Hospital Affiliated to Guangxi University of Traditional
34 Chinese Medicine, Nanjing Hospital of Chinese Medicine, Shuguang Hospital
35 Affiliated to Shanghai University of Chinese Medicine, Changsha Fourth Hospital,
36 The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine,
37 The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese
38 Medicine, The Second Affiliated Hospital of Tianjin University of Traditional
39 Chinese Medicine, Affiliated Hospital of Tianjin Academy of Chinese Medicine,
40 Tianjin Beichen District Hospital of Traditional Chinese Medicine, and Wenzhou
41 Hospital of Traditional Chinese Medicine. A total of 1200 patients with UA who met
42 the selection will be enrolled in a 1:1 ratio, with 600 patients included in the XST
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4 treatment group and 600 in the control group.
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6 All the visits will be recorded in electronic care report forms through the
7 Electronic Data Capture system, which is accessed online via the Internet for data
8 collection and management. The protocol of this study was developed in accordance
9 with the standard protocol project: Interventional Trial Recommendations
10 guidelines^[9].
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19 **2.2 Ethics**

20 This study has been approved by the ethics committee of the First Affiliated
21 Hospital of Guangzhou University of Chinese Medicine (approval number:
22 ZYYEC[2017]002) and 17 other medical centers, which have been approved by the
23 ethics committee by the respective medical centers. The trial has been registered on
24 the Chinese Clinical Trial Registry with the ID ChiCTR1800015911.
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35 **2.3 Patient and public involvement**

36 This clinical trial was designed to evaluate the efficacy and safety of XST in
37 patients with UA. Clinically, XST has been found to be beneficial in treating ACS,
38 which had been widely used in China's Grade-A Tertiary Hospital. More high-quality
39 trials and evidence are needed to prove the efficacy of XST. The outcome measures
40 used in this trial were considered as important endpoints in clinical practice. The
41 participants of this trial will be recruited from 17 medical centers in China. However,
42 patients were not directly involved in the design, recruitment, or conduct of the study.
43 After the trial completes, the results of this study will be disseminated to the public
44 through academic conferences and peer-reviewed journals. Once the manuscript is
45 published, the results will be briefly summarized in a simple language and inform all
46 trial participants through the telephone. The burden of intervention will not be assessed
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4 by the trial participants.
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8 9 **2.4 Study population**

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11 Patients will be included after written informed consent and enrolled in the study
12 when the inclusion and exclusion criteria are met (Table 1).
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15 **2.4.1 Withdrawal criteria**

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17 1. Patients with some comorbidities, complications, or special physiological changes
18 during the trial
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21 2. Patients with poor compliance in the trial; the use of the drug not reaching 80%
22 (except for those recovered in advance) or exceeding 120% of the prescribed
23 amount
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27 3. Patients with blindness or emergency unblinding during the trial
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- 29
30 4. Patients with serious adverse events and those not appropriate to continue the test
31
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33 5. Patients failing to use the test drug
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36 6. Patients misdiagnosed or not matching the inclusion criteria and accidentally
37 included
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40 7. Patients with no follow-up records
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43 8. Patients failing to comply with the treatment during the trial, changing the
44 medicines, or adding nonspecified therapeutic medications by themselves,
45 especially those medications that may affect the evaluation of the test drug,
46 affecting the validity and safety.
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51 **2.5 Study setting and recruitment**

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54 Between December 2018 and December 2020, 1200 outpatients or inpatient will
55 be recruited at the 17 centers mentioned earlier through the official website of the
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4 hospitals, posters, and networks. The physicians will diagnose the participants, and
5
6 the research assistants will manage the recruitment.
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10 **2.6 Randomization**

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13 On the day of enrollment, statistical analysis system software will be used to
14
15 generate the random arrangement of 1200 people in 2 groups (XST and placebo groups)
16
17 with the method of central stratified regional group randomization. The randomization
18
19 numbers will be kept in opaque sealed envelopes. The physicians and patients will not
20
21 be aware of the grouping and intervention.
22
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27 **2.7 Blinding**

28
29 This study has a double-blind design. Because XST was lyophilized powder form
30
31 in this study, which was a kind of white or light yellow amorphous powder or loose
32
33 solid, and was dissolved with an appropriate amount of injection sodium chloride
34
35 injection before use, there were color changes and a small amount of powder
36
37 precipitation. Therefore, in order to better implement the blind method, an extremely
38
39 low dose (25mg) was used as the control group, which is invalid for UA from our
40
41 previous pharmacokinetic experiment, did not increase the efficacy of the
42
43 experimental group.
44
45

46 The number of cases in the study and control groups will be in the ratio of
47
48 1:1. The blinding work will be completed by statisticians. To ensure the blinding of
49
50 investigators and participants to study treatment, the study drug or placebo will be
51
52 provided in identical packaging and labeling. Due to some natural variability in the
53
54 color of the study drug, which is batch dependent, the color of the placebo will be
55
56 matched to be the same as the average color of the study drug. Study drug and
57
58 placebo will be labeled with a unique label letter that will be used to assign treatment
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4 to the patient but will not indicate treatment allocation to investigators or participants.
5
6 No member of the study team and their extended staff, except for pharmacists and
7
8 biostatisticians, will have access to the randomization scheme during the conduct of
9
10 the study. In the event of a medical emergency, where breaking the blind is required
11
12 to provide medical care to the participant, the investigator will obtain the treatment
13
14 assignment from the trial pharmacists.
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19 **2.8 Sample size calculation**

20
21 MACE will be used as the effect index according to the statistical requirements of
22
23 the optimal validity test design.
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25

26 Based on the expert advice combined with clinical practical considerations and
27
28 according to the loss rate of less than 20% estimated beforehand, the study sample was
29
30 1200 cases (600 cases in each group), assuming that the incidence of MACE was 12%
31
32 after dual antiplatelet therapy for 6 months, which was reduced by 6% after
33
34 lyophilization ($\alpha = 0.05$; power = 0.9).
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39 **2.9 Interventions**

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41 All participants will receive dual antiplatelet therapy (aspirin 100 mg/d +
42
43 clopidogrel 75 mg/d) and anticoagulation therapy (unfractionated heparin) according
44
45 to the 2014 American College of Cardiology/American Heart Association Guidelines
46
47 for the Diagnosis and Treatment of Non-ST-Segment Acute Coronary Syndrome, and
48
49 in accordance with the guidelines to accept statins, angiotensin-converting enzyme
50
51 inhibitors, beta-blockers, and nitrates. Patients with mild UA will undergo a
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53 standardized baseline assessment before the treatment, including detailed medical
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55 history, physical examination, and laboratory testing. Meanwhile, the following
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57 treatments will be given to different groups:
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4 (1) XST treatment group: The patients will be treated via an intravenous drip with
5 500 mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or
6 sodium chloride injection, once per day for 7–14 days.
7
8

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10 (2) Control group: The patients will be treated via an intravenous drip with 25 mg
11 XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium
12 chloride injection, once per day for 7–14 days.
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16 The experimental drugs will be distributed by a drug administrator and injected by
17 trained nurses.
18

19
20 Patients will be admitted to the hospital on the day of registration for the first
21 intervention, and patients who discharge will move directly to the follow-up period.
22 The efficacy and safety of XST will be assessed after treatment for 7–14 days and
23 follow-up for 1, 3, and 6 months (Figs. 1 and Table 2).
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31 **2.10 Outcome measurements**

32 **2.10.1 Primary outcomes**

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34 The primary endpoints will include the incidence of composite endpoints for
35 MACE, which is a commonly used indicator to evaluate the prognosis of patients with
36 coronary heart disease or UA [10], including cardiovascular death, nonfatal myocardial
37 infarction, and revascularization.
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45 The primary endpoint is the time from the enrollment to the end of the study
46 (including the medication observation period and follow-up period) when any of the
47 MACE events occur for the first time. The researchers will record through telephone
48 interviews, in-patient and outpatient medical records of patients, and information
49 provided by their family members. Patients without MACE during the study will be
50 defined as censored at the end of the study. For patients who quit the trial early due to
51 reasons other than MACE, the time of occurrence is defined as censoring at the time
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4 of early termination. Deaths not due to cardiovascular diseases or that occur after the
5 MACE will not be evaluated.
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10 **2.10.2 Secondary outcomes**

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13 The efficacy of angina pectoris will be observed at the time of enrollment and at
14 the end of treatment, including the frequency of angina attack, the clinical
15 manifestations, ECG and laboratory examination.
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20 Myocardial injury markers [serum creatine kinase MB; cardiac troponin T/cardiac
21 troponin I (cTnI)/high-sensitivity troponin I] will be monitored, in order to observe
22 changes in myocardial injury during treatment and to assess efficacy and safety during
23 treatment.
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31 **2.10.3 Safety assessment**

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33 An adverse event (AE) is any adverse medical event that occurs during the trial.
34 The researchers will record the observation of vital signs, testing of blood and urine
35 samples, renal and liver function at the start and end of the run-in period, and recorded
36 abnormal changes and AEs at any time.
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42 In view of the particularity of the disease, the condition of the participants may
43 change significantly during the observation, including the need for hospitalization for
44 the deterioration of the disease, or even life-threatening. Since cardiovascular death,
45 non-fatal myocardial infarction, and revascularization were the endpoints of this study,
46 the above events would not be reported as serious adverse events (and described in the
47 study history). Known adverse reaction of the XST: systemic injury: fever, chills,
48 anaphylactic reaction, anaphylactic shock, etc.; the respiratory system damage: chest
49 tightness, breathing difficulties, shortness of breath, asthma, laryngeal edema, etc.; skin
50 and its appendages damage: rash, pruritus, dermatitis exfoliating; heart rate and
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4 arrhythmia: palpitations, tachycardia, etc.; central and peripheral nervous system
5 damage: dizziness, headache, convulsions, tremor, etc.; gastrointestinal system damage:
6 nausea, vomiting, etc.; cardiovascular system damage: cyanosis, flushing, decreased
7 blood pressure, elevated blood pressure, etc.; other damage: blood in the urine,
8 abnormal liver function, etc.
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14 Patients will be required to report all AEs at each visit. All AEs will be recorded,
15 regardless of severity, to assess the safety of XST.
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19 If an AE occurs, the researchers will have to determine whether to stop the
20 observation and proceed with the diagnosis and corresponding treatment. If any severe
21 AE occurs, the researchers must take immediate action to ensure the safety of the
22 participants. They must also report to the ethics committee within 24 h. The responsible
23 staff from The First Affiliated Hospital of Guangzhou University of Chinese Medicine
24 must promptly notify other participating centers and initiate any necessary legal
25 procedures.
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35 **2.11 Follow-up**

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38 All included participants will be evaluated for the occurrence of MACE after 1, 3,
39 and 6 months through phone calls after the end of the medication. The trial will be
40 ended if the following endpoints occur: death, nonfatal myocardial infarction, or
41 revascularization (including PCI and CABG). The academic research on hemorrhage
42 in Europe and the United States proposed a unified definition of hemorrhage type 3–5.
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48 The occurrence of the MACE must be recorded in an original supporting document,
49 including but not limited to a copy of the discharge summary, a copy of the medical
50 record, or other documents that can be used to verify the occurrence of the MACE and
51 the date of its occurrence.
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2.12 Statistical analysis

2.12.1 Enrollment and case completion

The completion of the trial at each center must be recorded and described. All cases of shedding must be listed.

2.12.2 Baseline comparability analysis

The baseline characteristics of patients will be summarized and compared using the t test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

2.12.3 Analysis of efficacy

(1) Baseline comparability analysis: This includes the description of demographic data, symptoms, and general conditions. The t test or nonparametric statistical method will be used for quantitative data. Qualitative data will be determined using the chi-square test, Fisher's exact probability method, CMH test, and Wilcoxon rank-sum test.

(2) Primary and secondary outcomes: The incidence of composite endpoints for MACE and the efficacy of angina pectoris will be compared between the two groups and analyzed using the chi-square or Fisher exact tests and two-sample t tests or Wilcoxon rank-sum test. The laboratory data on myocardial injury markers will be analyzed for the changes before and after the intervention. The average value of each laboratory data after the treatment will be compared.

(3) For cases of rejection and shedding, statistical descriptions will be performed one by one. Adverse reactions will be statistically described. The incidence of adverse reactions will be compared using the chi-square or Fisher exact tests.

3. Discussion

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4 XST is a traditional Chinese herbal injection consisting of a series of saponins
5 extracted from *Panax notoginseng*. It has been approved by the China Food and Drug
6 Administration (China drug approval number: Z 20025652) and collected according to
7 the “2012 national essential drugs list” and the People’s Republic of China
8 Pharmacopoeia, respectively. Total saponins, isolated from the root and rhizome of *P.*
9 *notoginseng*, are the main components of XST.
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16 *P. notoginseng* is known for promoting blood circulation, preventing thrombosis,
17 and dilating blood vessels. It is widely applied to treat acute cerebral infarction, stroke,
18 and coronary heart disease in clinical practice^[11, 12]. Wang et al.^[13] found that in a rat
19 model of middle cerebral artery occlusion-reperfusion, administration of XST
20 combined with salvianolate lyophilized (SLI) injection not only significantly decreased
21 neurological deficit scores and infarct volumes, and increased regional cerebral blood
22 flow. Gan et al.^[14] evaluated the efficacy and safety of the *P. notoginseng* extract via
23 intracoronary injection for treating the post-PCI slow-reflow phenomenon in patients
24 with ST-segment elevation myocardial infarction and its impact on patients' prognosis.
25 They found that coronary injection with tirofiban and XST was more effective in
26 improving the coronary blood flow and showed no increase in the incidence of
27 hemorrhagic complications compared with the injection with tirofiban only. *P.*
28 *notoginseng* has been found to be beneficial to patients with UA. The use of the extract
29 has been recommended for patients with UA in clinical practice as a complementary
30 and alternative therapy^[15]. However, more randomized controlled trials with reliable
31 designs, large samples, and long-term observations are needed for further evaluations.
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48 The meta-analysis of XST injection combined with routine basic treatment was
49 superior to routine basic treatment alone in alleviating clinical symptoms, with
50 statistically significant differences between the groups. XST injection combined with
51 routine basic treatment could alleviate UA pectoris. However, due to the low quality of
52 included studies, further well-designed, multicenter, and large-scale RCTs are still
53 needed to evaluate the efficacy of XST injection^[16]. Moreover, the total revenue from
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4 XST in the Chinese market in 2013 was over \$700 million^[17]. Therefore, the enormous
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6 consumption requires stricter and accurate evidence on its safety. However, many
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8 reports of XST were case reports, and hence large-sample and high-level evidence for
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10 the efficacy and safety of XST is still lacking. Therefore, this study will be conducted
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12 to investigate the efficacy and safety of XST in reducing the incidence of MACE in
13
14 patients with UA. The findings of this study will provide clinical evidence for the use
15
16 of XST in reducing the incidence of MACE in patients with UA.

17 18 19 20 **Acknowledgments**

21
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23
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25
26 who carefully checked the references.
27
28
29
30

31 32 **Contributors**

33
34 ZY and WL wrote the study protocol. SX, HL, TY and YT developed the original
35
36 study design. XH, JL, YH, JD, YL and WL were all involved in the revision of the
37
38 study design and contributed in the review process of the protocol manuscript. YT and
39
40 QL are jointly responsible for the collection of data and administration of study
41
42 participants. LL provides methodological guidance on research statistics. ZY is the
43
44 principal investigator and responsible for the funding and overall management of the
45
46 trial.
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49
50

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53
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55
56 injection (lyophilized) in reducing the incidence of MACE in patients with unstable
57
58 angina: A randomized, parallel-arm, controlled, double-blind, and multicenter clinical
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4 trial based on dual antiplatelet therapy” (no. 10600216) and the second batch of
5 national Traditional Chinese Medicine(TCM) clinical research base project (no.
6 2018131).
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13 **Disclaimer**

14
15
16 The funders have no role in the study design, data collection and analysis, decision to
17 publish or preparation of the manuscript.
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23 **Trial status**

24
25 Currently the participants are being enrolled for the trial.
26
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29 **Conflicts of interest**

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31 All authors declare no conflicts of interest.
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7 doi: 10.1001/jama.284.7.835
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18 Table 1. Inclusion and exclusion criteria
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Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ● Patients who meet all the following requirements ● Patients diagnosed with coronary heart disease who met at least one of the following diagnostic criteria^[1]: <ol style="list-style-type: none"> (1) a clear history of myocardial infarction (MI); (2) prior coronary revascularization; (3) coronary angiography or coronary angiography suggesting at least one coronary artery stenosis with catheter stenosis $\geq 50\%$; (4) cardiac magnetic resonance imaging or radionuclide myocardial perfusion imaging to confirm myocardial ischemia in the patient having coronary heart disease 	<ul style="list-style-type: none"> ◆ Patients with cardiac function class IV (New York Heart Association cardiac function grading); or patients at a high risk of UA short-term risk stratification ◆ Patients with uncontrolled grade III hypertension having systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg; severe cardiopulmonary insufficiency; severe arrhythmia; severe primary diseases of the liver, kidney, and hematopoietic system; or serious diseases (such as tumors) and mental diseases ◆ Patients also having other clinical conditions that might increase the risk of bleeding, such as a history of important organ bleeding in the last 6 months (such as intracerebral

<ul style="list-style-type: none"> ● Patients complying with the diagnosis of UA and having at least one of the following conditions: <ul style="list-style-type: none"> (1) electrocardiograph with a transient or persistent ST-segment depression of 0.1 mV and even more on one or more leads; (2) Thrombolysis In Myocardial Infarction (TIMI) risk score^[18] ≥ 3 ● Patients receiving dual antiplatelet therapy (aspirin + clopidogrel) ● Patients aged 40–75 years, irrespective of sex ● Patients willing to accept the drug treatment and provide written informed consent, conforming to the relevant regulations of Good Clinical Practice 	<p>hemorrhage and upper gastrointestinal bleeding), decreased platelet count, abnormal coagulation function, and recent active bleeding</p> <ul style="list-style-type: none"> ◆ Patients with abnormal function indexes of the liver and kidney [blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level more than two times the upper normal reference range; glomerular filtration rate (GFR) $< 60 \text{ mL}/(\text{min} \times 1.73 \text{ m}^2)$]. Simplified Modification of Diet in Renal Disease formula: $\text{GFR} [\text{mL}/(\text{min} \times 1.73 \text{ m}^2)] = 186.3 \times \text{serum creatinine (Scr)}^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ female})$; Scr in mg/dL and age in years ◆ Patients who planned to undergo revascularization [PCI or coronary artery bypass grafting (CABG)] recently ◆ Patients allergic to a variety of foods, or with known allergy to study drugs, including their components ◆ Patients pregnant, preparing for pregnancy, or lactating ◆ Patients participating in other clinical trials during the same period ◆ Patients considered inappropriate to
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	participate in this study
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Table 2. Study schedule of assessments

Abbreviations: CK-MB, creatine kinase MB; MACE, major adverse cardiac events; cTn, cardiac troponin; hsTn, high-sensitivity Troponin; UA, unstable angina.

	Study period			
	Enrollment	Allocation	Intervention	Follow-up
Time point	-3 ~ 0 days	0	7 ~ 14 days	1, 3 and 6 months
ENROLLMENT:	X			
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
SXT treatment			X	
Placebo treatment			X	
ASSESSMENTS:				
MACE			X	X

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3				
4	CK-MB		X	X
5				
6				
7	cTnT		X	X
8				
9				
10	cTnI		X	X
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12				
13	hsTnI		X	X
14				
15				
16				
17	Adverse events		X	X
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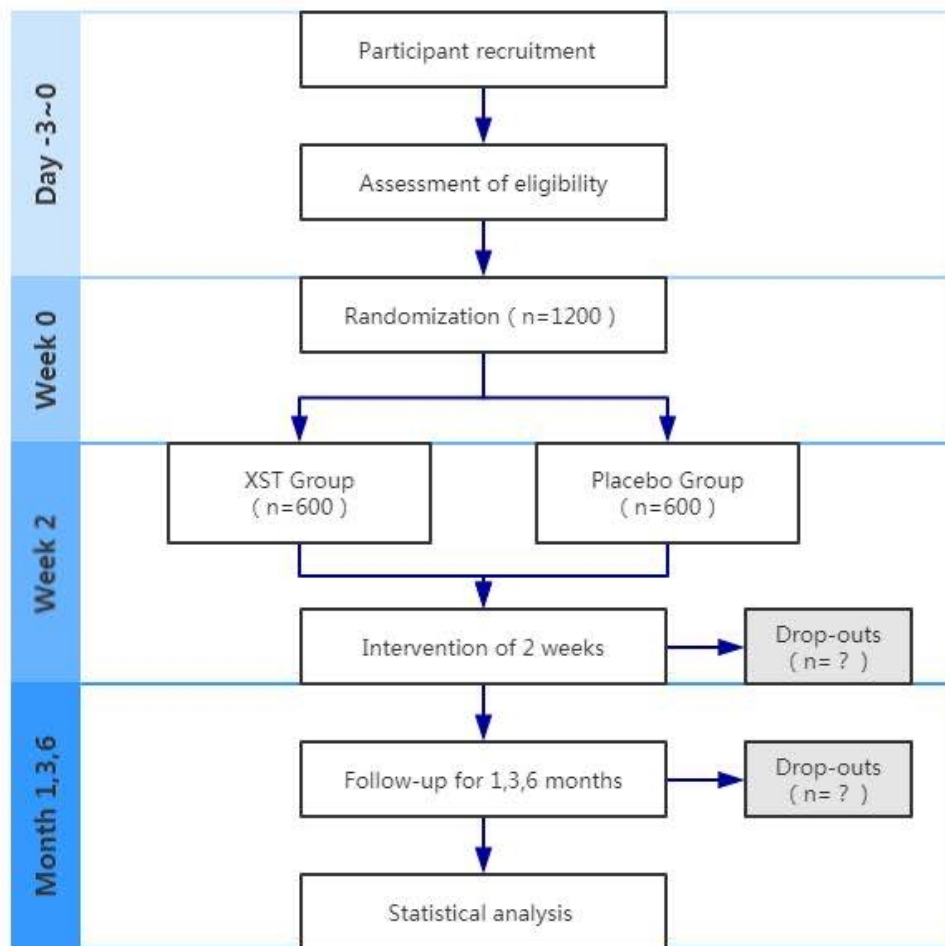
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Figure legends

Figure 1. Flowchart of the study procedure.

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159x155mm (96 x 96 DPI)



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

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,17
	5b	Name and contact information for the trial sponsor	17
	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	17-18
	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)	17
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	5,6
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	5,6

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2	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)	6
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7				
8	Methods: Participants, interventions, and outcomes			
9				
10	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	6-7
11				
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14	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)	7-8 21-22
15				
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
20				
21				
22		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)	11-12
23				
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
27				
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31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
32				
33				
34	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	12-13
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42	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)	23-24
43				
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46				
47	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	23-24
48				
49				
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51	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
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54	Methods: Assignment of interventions (for controlled trials)			
55				
56	Allocation:			
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1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	10-11
3	generation		generated random numbers), and list of any factors for stratification.	
4			To reduce predictability of a random sequence, details of any planned	
5			restriction (eg, blocking) should be provided in a separate document	
6			that is unavailable to those who enrol participants or assign	
7			interventions	
8				
9				
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	10-11
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
12	mechanism		describing any steps to conceal the sequence until interventions are	
13			assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	10-11
16			and who will assign participants to interventions	
17				
18				
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	10-11
20	(masking)		participants, care providers, outcome assessors, data analysts), and	
21			how	
22				
23		17b	If blinded, circumstances under which unblinding is permissible, and	10-11
24			procedure for revealing a participant's allocated intervention during	
25			the trial	
26				
27				

Methods: Data collection, management, and analysis

28				
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	13
31	methods		trial data, including any related processes to promote data quality (eg,	
32			duplicate measurements, training of assessors) and a description of	
33			study instruments (eg, questionnaires, laboratory tests) along with	
34			their reliability and validity, if known. Reference to where data	
35			collection forms can be found, if not in the protocol	
36				
37				
38		18b	Plans to promote participant retention and complete follow-up,	15
39			including list of any outcome data to be collected for participants who	
40			discontinue or deviate from intervention protocols	
41				
42	Data	19	Plans for data entry, coding, security, and storage, including any	13,15
43	management		related processes to promote data quality (eg, double data entry;	
44			range checks for data values). Reference to where details of data	
45			management procedures can be found, if not in the protocol	
46				
47				
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	15
49	methods		Reference to where other details of the statistical analysis plan can be	
50			found, if not in the protocol	
51				
52		20b	Methods for any additional analyses (eg, subgroup and adjusted	15
53			analyses)	
54				
55		20c	Definition of analysis population relating to protocol non-adherence	15
56			(eg, as randomised analysis), and any statistical methods to handle	
57			missing data (eg, multiple imputation)	
58				
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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. Alternatively, an explanation of why a DMC is not needed	17
	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	17
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	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
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)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8,17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	17
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	NA

1				
2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	NA
3	policy		participants, healthcare professionals, the public, and other relevant	
4			groups (eg, via publication, reporting in results databases, or other	
5			data sharing arrangements), including any publication restrictions	
6				
7		31b	Authorship eligibility guidelines and any intended use of professional	17
8			writers	
9				
10		31c	Plans, if any, for granting public access to the full protocol, participant-	NA
11			level dataset, and statistical code	
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13				

Appendices

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16	Informed consent	32	Model consent form and other related documentation given to	NA
17	materials		participants and authorised surrogates	
18				
19	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
20	specimens		specimens for genetic or molecular analysis in the current trial and for	
21			future use in ancillary studies, if applicable	
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*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Efficacy and safety of High-Dose Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

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Complete List of Authors:	<p>Long, Wenjie; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital; Guangzhou University of Chinese Medicine, Lingnan Medical Research Center</p> <p>Liao, Huili; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics,</p> <p>Huang , Xi ; Guangzhou University of Chinese Medicine, The First Clinical College</p> <p>Liu, Qingqing; Guangzhou University of Chinese Medicine, The First Clinical College,</p> <p>Tang, Yaqing ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, National Drug Clinical Trial Agency Office</p> <p>Lu, Liming; Guangzhou University of Chinese Medicine, Clinical Research Center</p> <p>Liu, Jianhong; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Yuan, Tianhui ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, National Drug Clinical Trial Agency Office</p> <p>Ling, Yan ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Hong, Yu; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Duan , Jiao ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Lin , Weiji ; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Xian, Shaoxiang; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p> <p>Yang, Zhongqi; Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Department of Geriatrics</p>
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Secondary Subject Heading:	Complementary medicine
Keywords:	CARDIOLOGY, Adult cardiology < CARDIOLOGY, Coronary heart disease

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Efficacy and safety of High-Dose Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

Running title: Efficacy and safety of Xueshuantong injection in patients with UA

Wenjie Long PhD^{1,3†}, Huili Liao MD^{1†}, Xi Huang MD², Qingqing Liu MD², Yaqing Tang MD⁴, Liming Lu PhD⁵, Jianhong Liu MD¹, Tianhui Yuan MD⁴, Yan Ling PhD¹, Yu Hong MD¹, Jiao Duan MD¹, Wei Ji Lin MD¹, Shaoxiang Xian PhD^{1,3*}, Zhongqi Yang PhD^{1,3*}

¹ Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R. China

² The First Clinical College, Guangzhou University of Chinese Medicine, No.12 Jichang Road, Baiyun District, Guangzhou, 510405, P.R. China

³ Lingnan Medical Research Center, Guangzhou University of Chinese Medicine, Jichang road No.12, Guangzhou, Guangdong 510000, China

⁴ National Drug Clinical Trial Agency Office. The First Affiliated Hospital of Guangzhou University of Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R. China.

⁵ Clinical Research Center, South China Research Center for Acupuncture and Moxibustion, Medical College of Acu-Moxi and Rehabilitation, Guangzhou University of Chinese Medicine, No.232 Waihuan Dong Road, Guangzhou, 510006,

1
2
3
4 Guangdong, China.

5 † These authors contributed equally to this work.
6
7
8
9

10
11 ***Corresponding Author:**
12

13
14 Shaoxiang Xian

15
16 Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of
17 Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R.
18
19 China
20
21

22
23
24 Lingnan Medical Research Center, Guangzhou University of Chinese Medicine,
25
26 Jichang road No.12, Guangzhou, Guangdong 510000, China
27

28
29 Tel: +86-18620602046

30
31 Fax: +86-21-57643271

32
33 E-mail: Shaoxiangx@hotmail.com
34

35
36
37 Zhongqi Yang

38
39 Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of
40 Chinese Medicine, No.16 Jichang Road, Baiyun District, Guangzhou, 510405, P.R.
41
42 China
43
44

45
46 Lingnan Medical Research Center, Guangzhou University of Chinese Medicine,
47
48 Jichang road No.12, Guangzhou, Guangdong 510000, China
49

50
51 Tel: +86-13560231626

52
53 Fax: +86-21-57643271
54
55
56
57
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59
60

E-mail: Yang_zhongqi@163.com; Yangzhongqi@gzucm.edu.cn

List of abbreviation

ACS, Acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass grafting; cTn, cardiac troponin; CK-MB, creatine kinase MB; HDL-C, low high-density lipoprotein cholesterol; LDL-C, high low-density lipoprotein cholesterol; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; hsTn, high-sensitivity troponin; UA, unstable angina

Abstract

Introduction: Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection having the potential to treat ACS. However, no clinical trial has been performed in this field. This clinical trial aims to examine the efficacy and safety of XST.

Methods and Analysis: This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial. A total of 1200 participants with UA will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group and 600 with one-twentieth dose in the control group. The efficacy assessment and major adverse cardiovascular events (MACE) will be observed, and the frequency of angina attack, angina pectoris will be examined at the start and end of the run-in period. All AEs will be recorded, regardless of the severity, to assess the safety of XST. The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenzel (CMH) test, and Wilcoxon test.

Ethics and Dissemination: This trial has been approved by the Research Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine, China (approval number: ZYYEC [2017] 0021). Written informed consent will be obtained from all participants. The results of this trial will be disseminated to the public through academic conferences and peer-reviewed journals.

Trial registration: This study was registered on the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/>) with the ID ChiCTR1800015911.

Key words: Acute coronary syndrome, clinical trial, traditional Chinese herbal injection, unstable angina

Strengths and limitations of this study:

1. This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial.
2. The trial will be conducted in 17 medical centers with 1200 participants.

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4 3. In our study, to better implement the blind method, the extremely low dose
5 25mg is used as the control group.
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8 4. The efficacy assessment and major adverse cardiovascular events (MACE)
9 will be observed, and the frequency of angina attack, angina pectorals will be
10 examined at the start and end of the run-in period.
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13 5. Our experiments will be conducted in different regions of China, and whether
14 similar effects are available to other ethnic groups and regions remains uncertain.
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For peer review only

Introduction

Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Reduced blood flow to the heart muscle is the most common cause of UA because the coronary arteries are narrowed by atherosclerosis, leading to the rupture of coronary blood vessels and hence blood clotting, which blocks the flow of blood to the heart muscle. The risk factors for UA include diabetes, obesity, family history of heart disease, high blood pressure, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, male sex, and use of any form of tobacco^[1, 2]. With the wide application of percutaneous coronary intervention (PCI) in patients with ACS, current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after ACS management with PCI. However, the greatest anti-ischemic benefit of potent antiplatelet drugs over the less-potent clopidogrel occurs early, while most excess bleeding events occur during chronic treatment. It is related to the efforts of physicians to reduce the adverse incidence of cardiovascular events, promote the patient's early recovery, and improve their health-related quality of life.

Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection comprising a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and People's Republic of China Pharmacopoeia, respectively. It has been reported to have anti-inflammatory effects that correct endothelial dysfunction *in vivo*^[3] and *in vitro*^[4]. Clinically, as a common medicine in China's Grade-A Tertiary Hospital, XST has been reported to be beneficial in treating ACS^[5, 6]. In preliminary studies, including small samples, XST has been found to platelet aggregation inhibition, anti-myocardial ischemia, anti-inflammation, anti-oxidation, protecting endothelial cells, which could reduce the incidence of major adverse cardiovascular events (MACE)^[7]. The recent study found that XST inhibits platelet activation and suppresses leukocytes adhesion

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4 to injured endothelial cells (ECs) under controlled shear stress in vitro, which not only
5 dose-dependent and showed stronger anti-platelet activation and adhesion effect under
6 low shear stress^[8]. XST also played an effect in fighting against thrombosis induced
7 by k-carrageenan in rats. High dose could significantly increase the microcirculatory
8 blood flow perfusion of the tail and significantly inhibit platelet aggregation rate^[9].
9 Besides, XST could significantly inhibit platelet piezo1 protein expression which may
10 improve blood flow and antithrombotic. The Meta-analysis reported that
11 Xueshuantong Injection combined with routine basic treatment (RBT) can alleviate
12 unstable angina pectorals, especially for frequency...relief of angina, frequency
13 reduction of nitroglycerin and the effective rate is more than 80%. It can significantly
14 reduce blood high-sensitivity C-reactive protein(hs-CRP),
15 fibrinogen(FIB) concentration^[10]. As the primary component^[11], Panax notoginseng,
16 has been extensively verified that it can ameliorate ischemia-reperfusion (IR)-induced
17 injury in cardiovascular and neuronal systems mainly by upregulating the activity of
18 estrogen receptor α -dependent phosphoinositide 3-kinase (PI3K)/protein kinase B
19 (AKT) and nuclear factor erythroid-2-related factor 2 (NRF2) pathways and
20 downregulating nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase
21 (MAPK) pathways. Therefore, high-quality trials and evidence are needed to prove
22 the efficacy of XST. This randomized, parallel, controlled, double-blind, and
23 multicenter clinical trial aims to examine the efficacy and safety of XST in patients
24 with UA. The results of this trial may provide clinical evidence for treating patients
25 with UA.
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50 **2. Method and design**

51 **2.1 Study design**

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55 This randomized, parallel-arm, controlled, double-blind, and multicenter clinical
56 trial will be conducted in 17 medical centers in China: The First Affiliated Hospital of
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4 Guangzhou University of Chinese Medicine, The First Affiliated Hospital of Henan
5 University of Chinese Medicine, Luoyang No. 1 Hospital of Traditional Chinese
6 Medicine, Shanxi Fenyang Hospital, The First Affiliated Hospital of Henan
7 University of Science and Technology, Zhengzhou People's Hospital, Zhengzhou
8 Central Hospital, Ruikang Hospital Affiliated to Guangxi University of Traditional
9 Chinese Medicine, Nanjing Hospital of Chinese Medicine, Shuguang Hospital
10 Affiliated to Shanghai University of Chinese Medicine, Changsha Fourth Hospital,
11 The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine,
12 The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese
13 Medicine, The Second Affiliated Hospital of Tianjin University of Traditional
14 Chinese Medicine, Affiliated Hospital of Tianjin Academy of Chinese Medicine,
15 Tianjin Beichen District Hospital of Traditional Chinese Medicine, and Wenzhou
16 Hospital of Traditional Chinese Medicine. A total of 1200 patients with UA who met
17 the selection will be enrolled in a 1:1 ratio, with 600 patients included in the XST
18 treatment group (high-dose, 500mg) and 600 in the control group (extremely low
19 dose, 25mg).

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36 All the visits will be recorded in electronic case report forms through the
37 Electronic Data Capture system, which is accessed online via the Internet for data
38 collection and management. The protocol for this study was developed in accordance
39 with the standard protocol project: Interventional Trial Recommendations
40 guidelines^[12].

41 42 43 44 45 46 47 48 49 **2.2 Ethics**

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This study has been approved by the ethics committee of the First Affiliated
Hospital of Guangzhou University of Chinese Medicine (approval number:
ZYYEC[2017]002) and 17 other medical centers: the Ethics Committee of Drug
Clinical Trials of Zhengzhou People's Hospital (approval number: YW201800501) ,

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4 the Ethics Committee of Shanxi Fenyang Hospital (approval number: 2018002) , the
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6 Ethics Committee of Ruikang Hospital Affiliated to Guangxi University of
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8 Traditional Chinese Medicine (approval number: RK201709) , the Ethics Committee
9
10 of Changsha Fourth Hospital (approval number: CSSDSYY-LL-SC-2017-03-03) ,
11
12 the Ethics Committee of The First Affiliated Hospital of the Henan University of
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14 Chinese Medicine (approval number: 2018HL-046-01) , the Ethics Committee of
15
16 the Second Affiliated Hospital of Heilongjiang University of Chinese Medicine
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18 (approval number: 2015R000774), the Ethics Committee of The First Affiliated
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20 Hospital of Hunan University of Traditional Chinese Medicine (approval number:
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22 HN-LL-2017-018-01) , the Medical Ethics Committee of Luoyang NO.1 Hospital of
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24 TCM (approval number: 2018-01), the Ethics Committee of Zhengzhou Central
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26 Hospital (approval number: 2018-006-02), the Ethics Committee of Tianjin Beichen
27
28 District Hospital of Traditional Chinese Medicine (approval number:
29
30 BCZYK201901) , the Ethics Committee of Nanjing Hospital of Chinese Medicine
31
32 (approval number: 2017NJL033) , the Ethics Committee of Shuguang Hospital
33
34 Affiliated to Shanghai University of Chinese Medicine (approval number:
35
36 2017-563-46-01) , the Ethics Committee of Affiliated Hospital of Tianjin Academy
37
38 of Chinese Medicine (approval number: LLSY207-04) , the Ethics Committee of
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40 The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine
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42 (approval number: EC.AT/03.19-02/08.0) , the Ethics Committee of The First
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44 Affiliated Hospital of Henan University of Science and Technology (approval
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46 number: 2018-0020) and the Ethics Committee of Wenzhou Hospital of Traditional
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48 Chinese Medicine (approval number: WTCM-H-2017024-2018-002) .The trial has
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50 been registered on the Chinese Clinical Trial Registry with the ID
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52 ChiCTR1800015911.
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55 **2.3 Patient and public involvement**

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58 This clinical trial was designed to evaluate the efficacy and safety of high-dose
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4 XST in patients with UA. Clinically, XST has been found to be beneficial in treating
5 ACS, which had been widely used in China's Grade-A Tertiary Hospital. More
6 high-quality trials and evidence are needed to prove the efficacy of XST. The
7 outcome measures used in this trial were considered as important endpoints in clinical
8 practice. The participants in this trial will be recruited from 17 medical centers in
9 China. However, patients were not directly involved in the design, recruitment, or
10 conduct of the study. After the trial completes, the results of this study will be
11 disseminated to the public through academic conferences and peer-reviewed journals.
12 Once the manuscript is published, the results will be briefly summarized in a simple
13 language and inform all trial participants through the telephone. The burden of
14 intervention will not be assessed by the trial participants.
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28 **2.4 Study population**

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30 Patients will be included after written informed consent and enrolled in the study
31 when the inclusion and exclusion criteria are met (Table 1).
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34 **2.4.1 Withdrawal criteria**

- 35 1. Patients with some comorbidities, complications, or special physiological changes
36 during the trial
- 37 2. Patients with poor compliance in the trial; the use of the drug not reaching 80%
38 (except for those recovered in advance) or exceeding 120% of the prescribed
39 amount
- 40 3. Patients with blindness or emergency unblinding during the trial
- 41 4. Patients with serious adverse events and those not appropriate to continue the test
- 42 5. Patients failing to use the test drug
- 43 6. Patients misdiagnosed or not matching the inclusion criteria and accidentally
44 included
- 45 7. Patients with no follow-up records

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3 8. Patients failing to comply with the treatment during the trial, changing medicines,
4 or adding non specified therapeutic medications by themselves, especially those
5 medications that may affect the evaluation of the test drug, affecting the validity
6 and safety.
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10 11 12 13 14 **2.5 Study setting and recruitment**

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16 Between December 2018 and December 2020, 1200 outpatients or inpatient will
17 be recruited at 17 centers mentioned earlier through the official website of the
18 hospitals, posters, and networks. Physicians will diagnose the participants, and the
19 research assistants will manage the recruitment.
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27 28 **2.6 Randomization**

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30 On the day of enrollment, statistical analysis system software will be used to
31 generate the random arrangement of 1200 people in 2 groups (XST and placebo
32 groups) with the method of central stratified regional group randomization. The
33 randomization numbers will be kept in opaque sealed envelopes. Physicians and
34 patients will not be aware of the grouping and intervention.
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44 45 **2.7 Blinding**

46 This study has a double-blind design. Because XST was lyophilized powder form
47 in this study, which was a kind of white or light yellow amorphous powder or loose
48 solid, and was dissolved with an appropriate amount of injection sodium chloride
49 injection before use, there were color changes and a small amount of powder
50 precipitation. Therefore, in order to better implement the blind method, an extremely
51 low dose (25mg) was used as the control group, which is invalid for UA from our
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4 previous pharmacokinetic experiment, did not increase the efficacy of the
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6 experimental group.
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8 The number of cases in the study and control group will be in the ratio of
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10 1:1. The blinding work will be completed by statisticians. To ensure the blinding of
11
12 investigators and participants to study treatment, the study drug or placebo will be
13
14 provided in identical packaging and labeling. Due to some natural variability in the
15
16 color of the study drug, which is batch dependent, the color of the placebo will match
17
18 the same as the average color of the study drug. Study drug and placebo will label
19
20 with a unique label letter that will be used to assign treatment to the patient but will
21
22 not indicate treatment allocation to investigators or participants. No member of the
23
24 study team and their extended staff, except for pharmacists and biostatisticians, will
25
26 have access to the randomization scheme during the conduct of the study. In the event
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28 of a medical emergency, where breaking the blind is required to provide medical care
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30 to the participant, the investigator will obtain the treatment assignment from the trial
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32 pharmacists.
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37 **2.8 Sample size calculation**

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39 MACE will be used as the effective index according to the statistical
40
41 requirements of the optimal validity test design.
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44 Based on the expert advice combined with clinical practical considerations and
45
46 according to the loss rate of less than 20% estimated beforehand, the study sample
47
48 was 1200 cases (600 cases in each group), assuming that the incidence of MACE was
49
50 12% after dual antiplatelet therapy for 6 months, which was reduced by 6% after
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52 lyophilization ($\alpha = 0.05$; power = 0.9).
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56 **2.9 Interventions**

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4 All participants will receive dual antiplatelet therapy (aspirin 100 mg/d +
5 clopidogrel 75 mg/d) and anticoagulation therapy (unfractionated heparin) according
6 to the 2014 American College of Cardiology/American Heart Association Guidelines
7 for the Diagnosis and Treatment of Non-ST-Segment Acute Coronary Syndrome, and
8 in accordance with the guidelines to accept statins, angiotensin-converting enzyme
9 inhibitors, beta-blockers, and nitrates. Patients with mild UA will undergo a
10 standardized baseline assessment before the treatment, including detailed medical
11 history, physical examination, and laboratory testing. Meanwhile, the following
12 treatments will be given to different groups:
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22 (1) XST treatment group: The patients will be treated via an intravenous drip with
23 500mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or
24 sodium chloride injection, once per day for 7–14 days.
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28 (2) Control group: The patients will be treated via an intravenous drip with 25mg
29 XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium
30 chloride injection, once per day for 7–14 days.
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34 The experimental drugs will be distributed by a drug administrator and injected by
35 trained nurses.
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38 Patients will be admitted to the hospital on the day of registration for the first
39 intervention, and patients who discharge will move directly to the follow-up period.
40 The efficacy and safety of XST will be assessed after treatment for 7–14 days and
41 follow-up for 1, 3, and 6 months (Figs. 1 and Table 2).
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49 **2.10 Outcome measurements**

50 **2.10.1 Primary outcomes**

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52 The primary endpoints will include the incidence of the composite endpoints for
53 MACE, which is a commonly used indicator to evaluate the prognosis of patients with
54 coronary heart disease or UA ^[13], including cardiovascular death, nonfatal myocardial
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4 infarction, and revascularization.
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6 The primary endpoint is the time of enrollment to the end of the study (including
7 the medication observation period and follow-up period) when any of the MACE
8 events occur for the first time. The researchers will record through telephone
9 interviews, in-patient and outpatient medical records of patients, and information
10 provided by their family members. Patients without MACE during the study will be
11 defined as censored at the end of the study. For patients who quit the trial early due to
12 reasons other than MACE, the time of occurrence is defined as censoring at the time
13 of early termination. Death not due to cardiovascular diseases or that occurs after the
14 MACE will not be evaluated.
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27 **2.10.2 Secondary outcomes**

28 The efficacy of angina pectorals will be observed at the time of enrollment and by
29 the end of treatment, including the frequency of angina attack, the clinical
30 manifestations, ECG, and laboratory examination.
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36 Myocardial injury markers [serum creatine kinase MB; cardiac troponin T/cardiac
37 troponin I (cTnI)/high-sensitivity troponin I] will be monitored, to observe changes in
38 myocardial injury during treatment and to assess the efficacy and safety during
39 treatment.
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50 **2.10.3 Safety assessment**

51 An adverse event(AE) is any adverse medical event that occurs during the trial.
52 The researchers will record the observation of vital signs, testing of blood and urine
53 samples, renal and liver function at the start and end of the run-in period, and
54 recorded abnormal changes and AEs at any time.
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58 In view of the particularity of the disease, the condition of the participants may
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4 change significantly during the observation, including the need for hospitalization for
5 the deterioration of the disease, or even life-threatening. Since cardiovascular death,
6 non-fatal myocardial infarction, and revascularization were the endpoints of this
7 study, the above events would not be reported as serious adverse events (and
8 described in the study history). Known adverse reaction of the XST: systemic injury:
9 fever, chills, anaphylactic reaction, anaphylactic shock, etc.; respiratory system
10 damage: chest tightness, breathing difficulties, shortness of breath, asthma, laryngeal
11 edema, etc.; skin and its appendages damage: rash, pruritus, dermatitis
12 exfoliating; heart rate and arrhythmia: palpitations, tachycardia, etc.; central and
13 peripheral nervous system damage: dizziness, headache, convulsions, tremor, etc.;
14 gastrointestinal system damage: nausea, vomiting, etc.; cardiovascular system
15 damage: cyanosis, flushing, decreased blood pressure, elevated blood pressure, etc.;
16 other damage: blood in the urine, abnormal liver function, etc.

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Patients will be required to report all AEs at each visit. All AEs will be recorded, regardless of the severity, to assess the safety of XST.

If an AE occurs, the researchers will have to determine whether to stop the observation and proceed with the diagnosis and corresponding treatment. If any severe AE occurs, the researchers must take immediate action to ensure the safety of the participants. They must also report to the ethics committee within 24 h. The responsible staff from The First Affiliated Hospital of Guangzhou University of Chinese Medicine must promptly notify other participating centers and initiate any necessary legal procedures.

2.11 Follow-up

All included participants will be evaluated for the occurrence of MACE after 1, 3, and 6 months through phone calls after the end of the medication. The trial will be ended if the following endpoints occur: death, nonfatal myocardial infarction, or

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4 revascularization (including PCI and CABG). The academic research on hemorrhage
5 in Europe and the United States proposed a unified definition of hemorrhage type 3–
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10 The occurrence of the MACE must be recorded in an original supporting
11 document, including but not limited to a copy of the discharge summary, a copy of the
12 medical record, or other documents that can be used to verify the occurrence of the
13 MACE and the date of its occurrence.
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21 **2.12 Statistical analysis**

22 **2.12.1 Enrollment and case completion**

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24 The completion of the trial at each center must be recorded and described. All
25 cases of shedding must be listed.
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30 **2.12.2 Baseline comparability analysis**

31 The baseline characteristics of patients will be summarized and compared using
32 the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the
33 chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and
34 Wilcoxon test.
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42 **2.12.3 Analysis of efficacy**

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44 (1) Baseline comparability analysis: This includes the description of demographic
45 data, symptoms, and general conditions. The *t* test or nonparametric statistical method
46 will be used for quantitative data. Qualitative data will be determined using the
47 chi-square test, Fisher's exact probability method, CMH test, and Wilcoxon rank-sum
48 test.
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55 (2) Primary and secondary outcomes: The incidence of the composite endpoints
56 for MACE and the efficacy of angina pectorals will be compared between the two
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4 groups and analyzed using the chi-square or Fisher exact tests and two-sample *t* tests
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6 or Wilcoxon rank-sum test. The laboratory data on myocardial injury markers will be
7
8 analyzed for the changes before and after the intervention. The average value of each
9
10 laboratory data after the treatment will be compared.

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12 (3) For cases of rejection and shedding, statistical descriptions will be performed
13
14 one by one. Adverse reactions will be statistically described. The incidence of adverse
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16 reactions will be compared using the chi-square or Fisher exact tests.

21 3. Discussion

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23
24 XST is a traditional Chinese herbal injection consisting of a series of saponins
25
26 extracted from *Panax notoginseng*. It has been approved by the China Food and Drug
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28 Administration (China drug approval number: Z 20025652) and collected according
29
30 to the “2012 national essential drugs list” and the People’s Republic of China
31
32 Pharmacopoeia, respectively. Total saponins, isolated from the root and rhizome of *P.*
33
34 *notoginseng*, are the main components of XST.

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37 *P. notoginseng* is known for promoting blood circulation, preventing thrombosis,
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39 and dilating blood vessels. It is widely applied to treat acute cerebral infarction,
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41 stroke, and coronary heart disease in clinical practice^[14, 15]. Wang et al.^[16] found that in
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43 a rat model of middle cerebral artery occlusion-reperfusion, administration of XST
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45 combined with salvianolate lyophilized (SLI) injection not only significantly
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47 decreased neurological deficit scores and infarct volumes, and increased regional
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49 cerebral blood flow. Gan et al.^[17] evaluated the efficacy and safety of the *P.*
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51 *notoginseng* extract via intracoronary injection for treating the post-PCI slow-reflow
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53 phenomenon in patients with ST-segment elevation myocardial infarction and its
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55 impact on patients' prognosis. They found that coronary injection with tirofiban and
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57 XST was more effective in improving coronary blood flow and showed no increase in
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59 the incidence of hemorrhagic complications compared with the injection with
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4 tirofiban only. *P. notoginseng* has been found to be beneficial in patients with UA.
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6 The use of the extract has been recommended for patients with UA in clinical practice
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8 as a complementary and alternative therapy^[18]. However, more randomized controlled
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10 trials with reliable designs, large samples, and long-term observations are needed for
11
12 further evaluations.

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14 The meta-analysis of XST injection combined with routine basic treatment was
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16 superior to routine basic treatment alone in alleviating clinical symptoms, with
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18 statistically significant differences between the groups. XST injection combined with
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20 routine basic treatment could alleviate UA pectorals. However, due to the low quality
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22 of the included studies, further well-designed, multicenter, and large-scale RCTs are
23
24 still needed to evaluate the efficacy of XST injection^[19]. Moreover, the total revenue
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26 from XST in the Chinese market in 2013 was over \$700 million ^[20]. Therefore,
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28 enormous consumption requires stricter and accurate evidence on its safety. However,
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30 many reports of XST were case reports, and hence large-sample and high-level
31
32 evidence for the efficacy and safety of XST is still lacking. Therefore, this study will
33
34 be conducted to investigate the efficacy and safety of XST in reducing the incidence
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36 of MACE in patients with UA. The findings of this study will provide clinical
37
38 evidence for the use of XST in reducing the incidence of MACE in patients with UA.
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47
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49
50 of the manuscript.
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55 **Contributors**

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58 ZY and WL wrote the study protocol. SX, HL, TY and YT developed the original
59
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4 study design. XH, JL, YH, JD, YL and WL were all involved in the revision of the
5 study design and contributed to the review process of the protocol manuscript. YT and
6
7 QL are jointly responsible for the collection of data and administration of study
8
9 participants. LL provides methodological guidance on research statistics. ZY is the
10
11 principal investigator and responsible for the funding and overall management of the
12
13 trial.
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19
20
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22
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24
25 Medicine(TCM) clinical research base project (2018131).
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31 **Disclaimer**

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34 The funders have no role in the study design, data collection and analysis, decision to
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36 publish or preparation of the manuscript.
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41 **Trial status**

42
43 Currently the participants are being enrolled for the trial.
44
45

46 **Conflicts of interest**

47
48
49 All authors declare no conflicts of interest.
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44 Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ● Patients who meet all the following requirements ● Patients diagnosed with coronary heart disease who met at least one of the following diagnostic criteria^[1]: (1) a clear history of myocardial 	<ul style="list-style-type: none"> ◆ Patients with cardiac function class IV (New York Heart Association cardiac function grading); or patients at a high risk of UA short-term risk stratification ◆ Patients with uncontrolled grade III hypertension having systolic blood

<p>infarction (MI);</p> <p>(2) prior coronary revascularization;</p> <p>(3) coronary angiography or coronary angiography suggesting at least one coronary artery stenosis with catheter stenosis $\geq 50\%$;</p> <p>(4) cardiac magnetic resonance imaging or radionuclide myocardial perfusion imaging to confirm myocardial ischemia in the patient having coronary heart disease</p> <ul style="list-style-type: none"> ● Patients complying with the diagnosis of UA and having at least one of the following conditions^[21]: <ol style="list-style-type: none"> (1) electrocardiograph with a transient or persistent ST-segment depression of 0.1 mV and even more on one or more leads^[22]; (2) Thrombolysis In Myocardial Infarction (TIMI) risk score^[23] ≥ 3 ● Patients receiving dual antiplatelet therapy (aspirin + clopidogrel) ● Patients aged 40–75 years, irrespective of sex ● Patients willing to accept the drug treatment and provide written 	<p>pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg; severe cardiopulmonary insufficiency; severe arrhythmia; severe primary diseases of the liver, kidney, and hematopoietic system; or serious diseases (such as tumors) and mental diseases</p> <ul style="list-style-type: none"> ◆ Patients also having other clinical conditions that might increase the risk of bleeding, such as a history of important organ bleeding in the last 6 months (such as intracerebral hemorrhage and upper gastrointestinal bleeding), decreased platelet count, abnormal coagulation function, and recent active bleeding ◆ Patients with abnormal function indexes of the liver and kidney [blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level more than two times the upper normal reference range; glomerular filtration rate (GFR) < 60 mL/(min \times 1.73 m²)]. Simplified Modification of Diet in Renal Disease formula: GFR [mL/(min \times 1.73 m²)] = $186.3 \times$ serum creatinine (Scr)^{-1.154} \times (age)^{-0.203} \times (0.742 female); Scr in mg/dL and age in years
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<p>informed consent, conforming to the relevant regulations of Good Clinical Practice</p>	<ul style="list-style-type: none"> ◆ Patients who planned to undergo revascularization [PCI or coronary artery bypass grafting (CABG)] recently ◆ Patients allergic to a variety of foods, or with known allergy to study drugs, including their components ◆ Patients pregnant, preparing for pregnancy, or lactating ◆ Patients participating in other clinical trials during the same period ◆ Patients considered inappropriate to participate in this study
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Table 2. Study schedule of assessments

Abbreviations: CK-MB, creatine kinase MB; MACE, major adverse cardiac events; cTn, cardiac troponin; hsTn, high-sensitivity Troponin; UA, unstable angina.

	Study period			
	Enrollment	Allocation	Intervention	Follow-up
Time point	-3~0 days	0	7 ~ 14 days	1, 3 and 6 months
ENROLLMENT:	X			
Eligibility screen	X			
Informed consent	X			

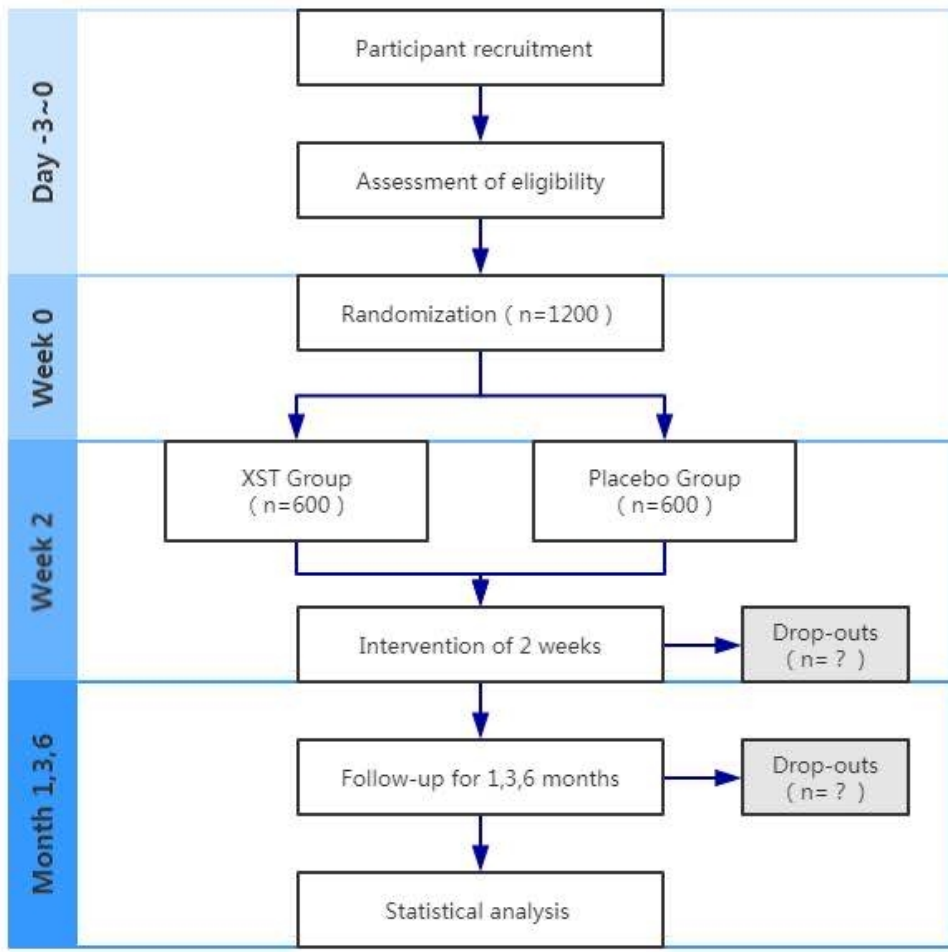
Allocation		X		
INTERVENTIONS:				
SXT treatment			X	
Placebo treatment			X	
ASSESSMENTS:				
MACE			X	X
CK-MB		X	X	
cTnT		X	X	
cTnI		X	X	
hsTnI		X	X	
Adverse events			X	X

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4 **Figure legends**
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6 Figure 1. Flowchart of the study procedure.
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For peer review only

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Flowchart of the study procedure.

159x155mm (96 x 96 DPI)



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

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,17
	5b	Name and contact information for the trial sponsor	17
	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	17-18
	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)	17
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	5,6
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	5,6

1				
2	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)	6
3				
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8	Methods: Participants, interventions, and outcomes			
9				
10	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	6-7
11				
12				
13				
14	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)	7-8 21-22
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
20				
21				
22		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)	11-12
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24				
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
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31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
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34	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	12-13
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42	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)	23-24
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47	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	23-24
48				
49				
50				
51	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
52				
53				

Methods: Assignment of interventions (for controlled trials)

Allocation:

1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	10-11
3	generation		generated random numbers), and list of any factors for stratification.	
4			To reduce predictability of a random sequence, details of any planned	
5			restriction (eg, blocking) should be provided in a separate document	
6			that is unavailable to those who enrol participants or assign	
7			interventions	
8				
9				
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	10-11
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
12	mechanism		describing any steps to conceal the sequence until interventions are	
13			assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	10-11
16			and who will assign participants to interventions	
17				
18				
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	10-11
20	(masking)		participants, care providers, outcome assessors, data analysts), and	
21			how	
22				
23		17b	If blinded, circumstances under which unblinding is permissible, and	10-11
24			procedure for revealing a participant's allocated intervention during	
25			the trial	
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27				

Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	13
31	methods		trial data, including any related processes to promote data quality (eg,	
32			duplicate measurements, training of assessors) and a description of	
33			study instruments (eg, questionnaires, laboratory tests) along with	
34			their reliability and validity, if known. Reference to where data	
35			collection forms can be found, if not in the protocol	
36				
37				
38		18b	Plans to promote participant retention and complete follow-up,	15
39			including list of any outcome data to be collected for participants who	
40			discontinue or deviate from intervention protocols	
41				
42	Data	19	Plans for data entry, coding, security, and storage, including any	13,15
43	management		related processes to promote data quality (eg, double data entry;	
44			range checks for data values). Reference to where details of data	
45			management procedures can be found, if not in the protocol	
46				
47				
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	15
49	methods		Reference to where other details of the statistical analysis plan can be	
50			found, if not in the protocol	
51				
52		20b	Methods for any additional analyses (eg, subgroup and adjusted	15
53			analyses)	
54				
55		20c	Definition of analysis population relating to protocol non-adherence	15
56			(eg, as randomised analysis), and any statistical methods to handle	
57			missing data (eg, multiple imputation)	
58				
59				
60				

Methods: Monitoring

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	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. Alternatively, an explanation of why a DMC is not needed	17
		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	17
	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	17
	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17

Ethics and dissemination

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Ethics and dissemination			
	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
	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)	8
	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8,17
	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
	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	17
	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	NA

1				
2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to	NA
3	policy		participants, healthcare professionals, the public, and other relevant	
4			groups (eg, via publication, reporting in results databases, or other	
5			data sharing arrangements), including any publication restrictions	
6				
7		31b	Authorship eligibility guidelines and any intended use of professional	17
8			writers	
9				
10		31c	Plans, if any, for granting public access to the full protocol, participant-	NA
11			level dataset, and statistical code	
12				
13				

Appendices

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16	Informed consent	32	Model consent form and other related documentation given to	NA
17	materials		participants and authorised surrogates	
18				
19	Biological	33	Plans for collection, laboratory evaluation, and storage of biological	NA
20	specimens		specimens for genetic or molecular analysis in the current trial and for	
21			future use in ancillary studies, if applicable	
22				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.