Efficacy and safety of Chinese herbal medicine Guanxinshutong capsule for the treatment of chronic heart failure with ejection fraction decrease (<50%) caused by coronary heart disease: study protocol for a randomized controlled trial

Yu Wang
Zhejiang Chinese Medical University
Jiaping Xu
Zhejiang Chinese Medical University
Jie-hong Yang
Zhejiang Chinese Medical University
Ling Zhang
Zhejiang Chinese Medical University
Yuan-jiang Pan
Zhejiang University
Li-ping Dou
Second Affiliated Hospital of Zhejiang Chinese Medical University
Peng Zhou
Zhejiang Chinese Medical University
Yi-zhou Xu
Hangzhou First People's Hospital
Chang Li
Zhejiang Chinese Medical University
Yu He
Zhejiang Chinese Medical University
Hui-fen Zhou
Zhejiang Chinese Medical University
Li Yu
Zhejiang Chinese Medical University
Jing-wen Chen
Second Affiliated Hospital of Zhejiang Chinese Medicial University
Shu-wei Huang
Second Affiliated Hospital of Zhejiang Chinese Medical University

Wei Fu
Yinchuan Cardiac-Cerebral Treatment Internet Hospital
Hai-tong Wan (haitongw@163.com)
Zhejiang Chinese Medical University https://orcid.org/0000-0003-4459-8246

Study protocol

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Abstract

Background

Chronic Heart failure (CHF) is a global epidemic and common cardiovascular disease with high mortality and poor prognosis, which bring heavy burdens to society and family. Traditional Chinese medicine (TCM) has been extensively used in China as an adjunct treatment for CHF. Guanxinshutong capsule (GXST), approved by the China Food and Drug Administration (CFDA) in 2002 (No. Z20020055), is commonly used Chinese herbal medicine (CHM) for the treatment of coronary heart disease (CHD) currently. Both experimental research and small-sample clinical trials have shown that GXST could attenuate CHF. However, the effects of GXST on CHF as an adjunct therapy are lack of high-quality clinical evidence. This study is a large-scale, multi-center, double-blinded clinical trial to explore the efficacy and safety of GXST in CHF with ejection fraction decrease (<50%) caused by CHD.

Methods

This study is a multi-center, randomized, double-blind, placebo-controlled clinical trial. After 1week baseline period, a total of 480 participants will be randomly assigned to the intervention group and placebo group in ratio 2:1. Based on routine medications, the intervention group will be treated with GXST while the control group will be treated with placebo (both 0.3g/capsule, op, 3 capsules/time, thrice daily) for 12 weeks, and then be followed-up for another 40 weeks. The primary outcome is the effect of 6 min walk test (6MWT). The secondary outcomes include NT-proBNP, classification of the New York Heart Association (NYHA) heart function, Minnesota heart failure quality of life scale (MLHFQ), echocardiographic parameters, blood stasis syndrome symptom scale and clinical endpoint events. Metabolomics and proteomics will also be assessed. Adverse events (AEs) will be monitored throughout the trial. All the data will be recorded in electronic case report forms (eCRF) system database and analyzed in accordance with a predefined statistical analysis plan. Ethical approval of this trial has been granted by the Research Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University (ID: 2019-Y-003-02). Written informed consent of patients will be required. The results will be disseminated to the public through peer-reviewed journals and academic conferences.

Discussion

This study integrates the advantages of TCM and western medicine in the treatment of CHF, the result of this study will offer the efficacy and safety evidence of GXST on CHF with ejection fraction decrease (<50%).

Background

Chronic Heart failure (CHF) is a complex clinical syndrome characterized by decreased cardiac output, insufficient organ perfusion and venous congestion due to cardiac dysfunction [1, 2]. And it is a global epidemic, affecting about 26 million people worldwide, with more than 1 million hospitalized people in

the United States and Europe each year [3]. In China, it is estimated that 4.5 million aged from 35 to 74 suffered from CHF, and with the growing aging of population and changes of lifestyle, the incidence of common cardiovascular diseases such as hypertension, coronary heart disease (CHD), and CHF continues to rise [4, 5]. CHF has resulted in a growing economic and public health burden on individuals, their families and society and calls for new therapies, as well as prevention.

Currently, angiotensin converting enzyme inhibitors (ACEI), β-blockers and aldosterone receptor antagonists are called "Golden Triangle", which are listed as the standard and basic treatment for CHF. According to 2018 China HF diagnosis and treatment guidelines, "Golden Triangle" should be used for CHF as soon as possible without waiting for the poor curative effect of the combined use of ACEI and β-blockers or the left ventricular ejection fraction (LVEF) must be less than 35% [6]. However, the improvement of the curative effect results in more side effects, such as electrolyte disorder, the increase of serum creatinine, and even renal function impairment. Furthermore, due to the contraindications, side effects, and unsatisfied relief of symptoms, the compliance of patients receiving conventional drug treatment needs to be improved. Therefore, it is crucial to develop supplementary therapeutic approaches for the treatment of CHF.

TCM has been widely and successfully used in treating cardiovascular diseases in China for more than 2000 years and has great advantages in less harmful side effects, high safety, and ideal effects. As early as the Han Dynasty, CHF was classified as “palpitation” or “heartache” according to its symptoms. Based on thousands of years clinical practice, TCM has accumulated many experiences in the treatment of CHF, currently, CHM combined with western routine therapy have shown promising benefits in controlling symptoms, reducing mortality, improving cardiac function and promoting life quality in patients with CHF [7]. Within the framework of TCM theory, all the related symptoms, signs, tongue appearances and pulse feelings at a certain stage of disease are summarized as a syndrome (‘Zheng’ in TCM) [8]. Syndrome is not only the core of TCM theory but also the base of definite diagnosis and effective therapies [9]. In TCM, patients with CHF can be divided into varied syndromes, and according to previous data the syndrome of ‘blood stasis’ is the most common and important subtype[10].

Guanxinshutong capsule (GXST), which is commonly used to treat CHD in China, was developed by Shaanxi Buchang Pharmaceutical Co., Ltd, and approved by China Food and Drug Administration (CFDA) for the treatment of CHD in 2002 (approval number Z20020055). GXST consists of five herbal medicines (Table 1), and was reported to promote blood circulation, remove blood stasis and relieve pain [11]. Experimental studies showed that GXST inhibited the ventricular remodeling process through increasing mitochondrial productivity [11, 12], repressing the expression of matrix metalloprotein 9, angiotensin receptors 1 and extracellular regulated protein kinases 2 [13, 14], and transforming growth factor-β/Smad signaling pathway [15] and finally to treat patients with CHF. A clinical trial with 61 patients reported that compared to conventional treatment, combination with GXST could significantly increase LVEF and cardiac output and reduce end-systolic and diastolic volume in acute myocardial infarction patients with CHF [16]. Meanwhile, in our previous clinical study, GXST exerted obvious effect on CHF (unpublished data) which implied it might be the potentially promising CHM for the treatment of CHF. However, current

data of GXST as complementary therapy in CHF are insufficient, and the present clinical trials are limited in the methodology and sample size. Therefore, in this study, we conduct a large-scale, multi-center, double-blinded clinical trial to investigate the efficacy and safety of GXST in CHF caused with ejection fraction decrease (< 50%) by CHD.

Table 1
Components of GXST (intervention drug)

Main composition	Chinese Pinyin	Latin scientific name	Plant part
Choerospondiatis Fructus	Guang Zao	Choerospondiatis Fructus	Fruit
Salvia miltiorrhiza	Dan Shen	Salvia miltiorrhiza Bunge	Rhizome
Clove	Ding Xiang	Caryophylli Flos	Flower
Borneol	Bing Pian	Borneolum Syntheticum	Resin
Tabasheer	Tian Zhu Huang	Concretio Silcea Bambusae	Resin

Methods

In this trial, we aim to assess the efficacy and safety of GXST for CHF with ejection fraction decrease (< 50%) caused by CHD.

Design and settings

This study is a prospective, randomized, double-blind, placebo-controlled, multicenter, superior trial.

Researchers must explain to participants the trial properties, purpose, potential benefits and risks, alternative treatment options, and the rights of participants under the Helsinki declaration, Participants fully understand and voluntarily sign the informed consent. After the participants have enrolled and signed the informed consent, participants will be randomized in a 2:1 ratio to the intervention group and the placebo group. The trial will be conducted by 11 medical centers throughout China (Table 2), and a total of 480 participants will be recruited. This trial consists of 1-week baseline period, 12-week intervention period and 40-week follow-up period. A flow diagram of the study procedures is illustrated in Fig. 1.

Table 2. Research setting

Code	Participating hospitals
01	Second Affiliated Hospital of Zhejiang Chinese Medical University
02	Zhoukou Central Hospital
03	Pingdingshan First People's Hospital
04	Hangzhou First People's Hospital
05	Fenyang Hospital of Shanxi Province
06	The Affiliated Hospital of Liaoning University of Traditional Chinese Medicine
07	Lishui Traditional Chinese Medicine Hospital
08	First People's Hospital of Huzhou
09	PizhouTraditional Chinese Medicine Hospital
10	Zhumadian Central Hospital
11	First Affiliated Hospital of Xinxiang Medical University

Study population

Inclusion criteria

The inclusion criteria are as follows: (1) meet the diagnosis of CHD [17] and CHF[6, 18]; (2) meet the diagnostic criteria of blood stasis syndrome in TCM [19]; (3) aged 40 to 80, both male and female; (4) NYHA class II ~ III; (5) LVEF < 50% (by two-dimensional echocardiographic Simpson method); (6) course of disease ≥ 3 months, stable condition in recent 1 month or receiving routine treatment with stable doses more than 1 month; (7) plasma NT-proBNP ≥ 125 ng/L; (8) volunteer, understand and sign informed consent.

Exclusion criteria

The exclusion criteria for recruitment of participants into the study are: (1) acute coronary syndrome occurred in the past 1 month; (2) plan to take cardiac surgery during the trial; (3) with severe diseases like cardiogenic shock, acute myocarditis, uncontrollable malignant arrhythmia, hypertrophic obstructive cardiomyopathy, pulmonary embolism or severe valvular disease requiring surgery; (4) uncontrolled hypertension with systolic blood pressure ≥ 180 mmHg, diastolic blood pressure > 110 mmHg, or hypotension < 90/50 mmHg; (5) with severe liver or kidney dysfunction or active liver disease, or AST, ALT ≥ 3 times the upper limit of normal; (6) psychiatric patients, or patients with severe depression, or a history of alcohol or drug abuse; (7) pregnant women, or breast-feeding women, or those who are trying to get pregnant during the trial; (8) with allergic constitution, or be allergic to test drug; (9) with previous or

present tumor history, or with precancerous lesions confirmed by pathological examination; (10) participate in other clinical studies 3 months before this trial.

Randomization, allocation concealment mechanism and blinding

Participants are randomized to the intervention group or the placebo group in a 2:1 ratio using the Central Randomization System to achieve computerized randomization in blocks of 6, stratified by center. The random sequence will be placed in an envelope and subsequently sealed. According to the randomization number, the statistician will send the envelope directly to the Shaanxi Buchang Pharmaceutical Co., Ltd for the labeling of the invention and placebo drugs. All researchers, subjects, physicians, drug administrators and dispensing nurses will be blinded until the study is completed. The blinding codes can't be broken until all the clinical data are entered into eCRF database and locked, except subjects experience an SAE or need to be rescued in an emergency situation. Once unblinded, the cases will withdraw from the study, and researchers should report the reasons to the inspector within 24 h and the precise cause, date, treatment situation, and results should be recorded in eCRF.

Interventions

Eligible patients will be randomly allocated to the intervention group and the placebo group, both of which are given conventional therapies.

Intervention group

GXST, 0.3 g/capsule, op, 3capsules/time, thrice daily;

Placebo group

capsule stimulants, 0.3 g/capsule, op, 3capsules/time, thrice daily.
The GXST and capsule stimulants are both provided by Shaanxi Buchang Pharmaceutical Co. Ltd. The capsule stimulant's primary content is starch and dextrin, adding food colorants and flavoring agents, and achieves a smell, color, taste, and texture comparable to GXST. After the treatment, the packaging will be returned to the researches.

Outcomes

Primary and secondary outcomes

The primary outcome is the difference in 6 MWT [20]. The secondary outcomes are as follows: (1) changes in NT-proBNP; (2) improvement in heart function assessed by NYHA classifications [21]; (3) improvement of MLHFQ [22]; (4) improvement in echocardiographic parameters of left ventricular end-diastolic diameter and LVEF; (5) incidence rate of clinical endpoint events (rehospitalization for CHF acute aggravation, cardiogenic death, and all-cause death); (6) improvement of blood stasis syndrome symptom scale score. According to the degree of the symptoms from normal, mild, moderate to severe,

the scores of 0, 2, 4 and 6 will be given respectively of the primary symptoms and signs, and 0, 1, 2 and 3 of the secondary symptoms and signs. The higher the score, the severer the symptoms. The patient with syndrome scores decreasing by more than 70% are considered as effective cases, which will be counted as a percentage of all cases. The details of items to be measured and the time window of data collection are shown in Table 3.

Table 3. Study schedule

Study phase Time	Baseline period	Intervention period			Follow-up period
	Visit 1	Visit 2	Visit 3	Visit 4	every 4 weeks until 52 weeks
	-7□0 days	4 weeks	8 weeks	12weeks	
Baseline data collection					
Informed consent	×				
Inclusion/exclusion criteria	×				
Demographic data	×				
Get the central random number	×				
Previous history□medical history and allergies	×				
Concomitant disease and treatment	×				
Safety evaluation					
Vital signs	×	×	×	×	
Physical examination	×	×	×	×	
Blood routine	×			×	
Urine routine	×			×	
Blood biochemistry	×			×	
Myocardial Zymogram and troponin	×			×	
ECG	×			×	
Chest X-ray or CT	×			×	
Urine pregnancy test	×			×	
Efficiency evaluation					
6MWT	×			×	
NT-proBNP	×			×	
NYHA class	×	×	×	×	
MLHFQ	×	×	×	×	
Echocardiographic parameters	×			×	
Blood stasis syndrome symptom	×	×	×	×	

scale					
Clinical endpoint events		×	×	×	×
Other work					
Dispense drug	×	×	×		
Recovery and record of study drug		×	×	×	
Metabolomics and proteomics	×			×	
Record AE		×	×	×	×
Concomitant medications		×	×	×	
Evaluate the adherence		×	×	×	×

Abbreviations: CT-computed tomography, 6MWT-6 min walk test, NYHA class classification of the New York Heart Association heart function, MLHFQ Minnesota Heart Failure Quality of Life Scale, AE adverse event.

Safety outcomes

Safety outcomes include vital signs (temperature, heart rate, breathing, and blood pressure), image examinations (X-ray or CT), laboratory examinations (blood and urine test, blood biochemistry test, myocardial zymogram, and troponin test, and urine pregnancy test) and AEs. AEs will be recorded throughout the trial.

Metabolomics and proteomics

50 subjects are randomly selected and blood samples are taken for metabolomics and proteomics examination to explore the therapeutic biomarkers and pharmacodynamic material basis of GXST in treating CHF.

Metabolomics: gas chromatography-mass spectrometer (GC-MS) and liquid chromatograph-mass spectrometer (LC-MS) techniques are used to detect the chemical and biological fingerprints, describe the possible metabolic pathways, and identify biomarkers of GXST for the treatment of CHF.

Proteomics: two-dimensional difference gel electrophoresis (2D-DIGE) method is used to establish the protein patterns; Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS) is applied to identify differentially expressed proteins; bioinformatics is used to analyze the biological functions of differentially expressed proteins; String analysis and ingenuity pathway analysis (IPA) are applied to establish the protein network and explore the pharmacodynamic material basis of GXST for the treatment of CHF.

Data Management

The data management will be performed by the department of Medical Statistics, First Hospital of Peking University with electronic data management system (EDC). According to the requirements of Good Clinical Practice (GCP) and research plan, two researchers entry electronic case report form (eCRF) accurately, timely, completely and normatively. Clinical research associate adopt system automatic and manual logic verification to check the consistency of eCRF data and source data, and issues questions online at any time in case of any problem. After all subjects have completed the trial, all medical records have been entered into EDC, and the primary researcher, sponsor, statistical analyst and data management personnel review and confirm the data, then the data will be locked and submitted to the statistician for statistical analysis by the administrator. After the data is locked, data can be corrected in the statistical analysis program after confirmation, and if there is exact evidence to prove that it is necessary to unlock, the researcher and the sponsor need to sign relevant documents. After the trial, the data management report will be written according to the actual implementation of the project.

In this study, due to CHM is added to the basic treatment of western medicine, which can guarantee the rights and therapeutic effects of patients, no data monitoring committee is established. Personal information about potential and enrolled participants will be protect confidentiality before, during, and after the trial, and researchers should keep the data for five years after the termination of the clinical trial.

Sample size

The formula for calculating the sample size is as follows, which is based on the superior clinical trial sample size estimation [23]. The sample size is driven by the expected improvement in 6MWT. Referring to previous clinical researches [24–27], we assumed that the improvement in 6MWT is 30 meters, and the combined standard deviation (SD) is 100 meters in this study. Given a type I error rate of α = 0.025, a power of 80% (type II error rate of β = 0.2), considering of 20% possible dropout rate, a total of 470 patients need to be allocated. For the convenience of randomization, the final sample size was 320 cases in the intervention group and 160 cases in the placebo group, total of 480 cases.

$$n_1 = \left[\frac{(\mu_\alpha+\mu_\beta)\sigma}{\delta}\right]^2 \frac{(1+k)}{k} \ , \ n_2 = k\mathrm{n}_1$$

In this formula k is the ratio between two sample cases, δ is the expected improvement in 6MWT, σ is the combined SD.

Statistical analysis

The statistical analysis plan (SAP) will be specified before data analysis. The statistical analysis will be performed by the department of Medical Statistics, First Hospital of Peking University using SAS software version 9.4 (or higher version). The full analysis set (FAS) includes patients who received allocated treatment and provided assessable outcome data. The safety analysis set (SAS) includes patients who

received allocated treatment at least once. The per protocol set (PPS) includes patients who received allocated treatment and for whom planned outcome data as per the protocol are available. According to the intention-to-treat (ITT) principle, the FAS is used for the primary endpoint, and the FAS and PPS are used for the important secondary and other secondary endpoints. For quantitative data, we will calculate the mean, SD, median, minimum, maximum, interquartile range, and for classified data, we will describe various cases and percentages.

Inter-group comparisons will be analyzed by appropriate methods according to the type of data, independent t-test (homogeneity of variance, normal distribution) or Mann-Whitney-Wilcoxon test (nonnormal distribution) will be used for comparison of quantitative data, chi-square test or Fisher's exact test (if chi-square test is not applicable) will be used for classified data, and Wilcoxon rank-sum test or Cochran-Mantel-Haenszel test will be used for ranking data. Paired t-test will be applied to assess the difference of outcome before and after treatment in the same group. Significance will be assumed at a p level of less than 5%. The superiority of the GXST group to the placebo group in terms of 6MWT will be examined with a superiority of 30 metres. The last observation carried forward (LOCF) method is used for missing values.

Adverse events

Any AEs that occur during the observation period must be recorded. AEs within one week after the end of the trial are recorded by the patient's initiative reporting method. The development of AEs will also be observed until all the AEs disappear. The classification and coding of AEs are formulated with reference to Common Terminology Criteria for AEs 4.03.

Quality control of the intervention

In order to further ensure the quality of this trial, a multi-center trial Coordination Committee and the general director are set up to implement and solve related problems. The Coordination Committee includes the leaders of each center and the head of sponsor, and all passes pre-clinical training. All staff including the operators, researchers, physicians, data collectors, and analyzers can fully understand the purpose and content of the trial. This trial is inspected by the CFDA, sponsor and clinical research organization throughout the trial.

Ethics and dissemination

This study has approved by the Research Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University (No. 2019-Y-003-02), and all participate centers will receive approval from their local ethics committee. All data will be recorded in eCRF and imported into public clinical trial management platform (www.medresman.org) and posted on Chinese Clinical Trial Registry within 6 months after completion of the trial. Study results will be published in academic conferences and peer-reviewed journals.

Discussion

CHF is a global public health problem. According to the 2018 China Cardiovascular report [5], hypertension and CHD are the main causes of HF. An analysis of the predisposing factors of 426 elderly patients with HF suggests that CHD is the leading cause of HF, accounting for 43.2% [28]. GXST was approved by CFDA for the treatment of CHD in 2002. Experimental studies and small-sample clinical trials have confirmed that GXST could reduce the symptoms of the patients with CHF [11–16]. Therefore, we choose CHF with ejection fraction decrease (< 50%) caused by CHD as the inclusion criteria.

Currently, there are three methods for the assessment of functional capacity and exercise tolerance in patients with HF. First, the self-assessed or physician-reported categorization of patients' physical status which is mainly dependent on the patients' perceives. Second, peak oxygen consumption, which is a maximal symptom-limited exercise test (cardiopulmonary exercise test; CPET), will explain the reason of dyspnea and fatigue based on the assessment of all systems involved in physical activity. However, because of the demand for special equipment and trained personnel, it is unavailable in some hospital settings. Third, submaximal exercise tests including 6MWT, which is well-tolerated by patients. 6MWT is a simple and inexpensive test that requires no special equipment and advanced training for physicians and assesses the submaximal level of functional capacity of patients while walking on a flat barrier-free corridor in a period of 6 min [20]. NT-proBNP, as an important biomarker of cardiac function, is recommended for the diagnosis, screening, differential diagnosis, severity and prognosis evaluation of HF [29–33]. In this study, we choose 6MWT as the primary outcome and NT-proBNP as the secondary outcome. In order to reduce the possible differences caused by the detection of each center, metabolomics, proteomics, and NT-proBNP adopt centralized detection methods. The samples are tested in the Central Laboratory of Zhejiang Chinese Medical University.

TCM has developed for thousands of years and is one of the positive signs of globalization in the world. An increasing proofs demonstrates that integrative medicine, combined with TCM and western medicine, emerges as an optimal approach for achieving better effectiveness in patients with CHF [34–36]. According to the TCM theory and syndrome differentiation, blood stasis syndrome is the core pathogenesis of CHF [37–38], and GXST play an important role in promoting blood circulation and removing blood stasis and is optimal for treating CHF. As the principal active components, salvia miltiorrhiza and choerospondiatis fructus were showed to perform the function of microcirculation improvement, vascular endothelial cells protection, anti-arrhythmia, and antioxidation [39–41]. Caryophylliflos was effective in anticoagulation, antiplatelet aggregation and antithrombotic [42]. However, whether GXST as the supplementary therapy is better than western medicine alone in patients with CHF still requires confirmation by large sample, multicentre and randomized controlled clinical trials. This study is a multicentre, double-blinded, placebo-controlled clinical trial with the hope of verifying the effectiveness and safety of GXST for the treatment of CHF with ejection fraction decrease (< 50%) caused by CHD.

There are also some limitations in this study. Firstly, this experiment will be conducted in five provinces of China. Whether similar effects are obtainable to other regions and ethnic groups remain uncertain. Secondly, this study is only 52 weeks in duration; further data on long-term clinical effect and safety are

needed. Thirdly, GXST used in this trial is designed for the treatment of CHF with blood stasis syndrome; thus, the findings may not be applicable to other CHF syndromes.

Abbreviations

CHF
Chronic Heart failure;
TCM
Traditional Chinese medicine;
GXST
Guanxinshutong capsule;
CHM
Chinese herbal medicine;
CFDA
China Food and Drug Administration;
CHD
coronary heart disease;
6MWT
6 min walk test;
NYHA
New York Heart Association;
MLHFQ
Minnesota heart failure quality of life scale;
AEs
Adverse events;
eCRF
Electronic case report forms;
SAS
Statistical Analysis System;
ACEI
Angiotensin converting enzyme inhibitors;
LVEF
Left ventricular ejection fraction;
GC-MS
Gas chromatography-mass spectrometer;
LC-MS
Liquid chromatograph-mass spectrometer;
2D-DIGE
Two-dimensional difference gel electrophoresis;
MALDI-TOF-MS

Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry;
IPA
ingenuity pathway analysis;
SAP
statistical analysis plan;
FAS
full analysis set;
SAS
safety analysis set;
PPS
per protocol set;
ITT
intention to treat;
LOCF
last observation carried forward;
EDC
electronic data management system;
GCP
Good Clinical Practice;
eCRF
electronic case report form
SD
standard deviation;
CPED
Cardiopulmonary exercise test.

Declarations

Ethics approval and consent to participate

Research Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University has approved this study (No. 2019-Y-003-02), and all participate centers will receive approval from their local ethics committee.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HW, SH, and FW designed the study. YW and JX contributed equally to the article, who conceptualized the study design and wrote the manuscript. LZ, JY modified the manuscript. YP, YH, and CL are responsible for the quality control of the test drug. LD, YX, JC, HZ, and LY participated in the modification of this protocol. PZ, JY designed the method for statistical analysis. All authors read and approved the final manuscript.

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Contributions To The Literature

- This study is a double-blind, placebo-controlled trial of Guanxinshutong capsule as add-on therapy, provides a strategy with the combination of Chinese and western medicine in chronic heart failure patients.
- This is a pilot study to explore the efficacy and safety of Guanxinshutong capsule on chronic heart failure with ejection fraction decrease, provides a preliminary basis for expanding the scope of application of Guanxinshutong capsule.
- This study will apply metabolomics and proteomics examination to explore the therapeutic biomarkers and pharmacodynamic material basis of Guanxinshutong capsule in treating chronic heart failure, provides a novel ideas for precision treatment.

Figures

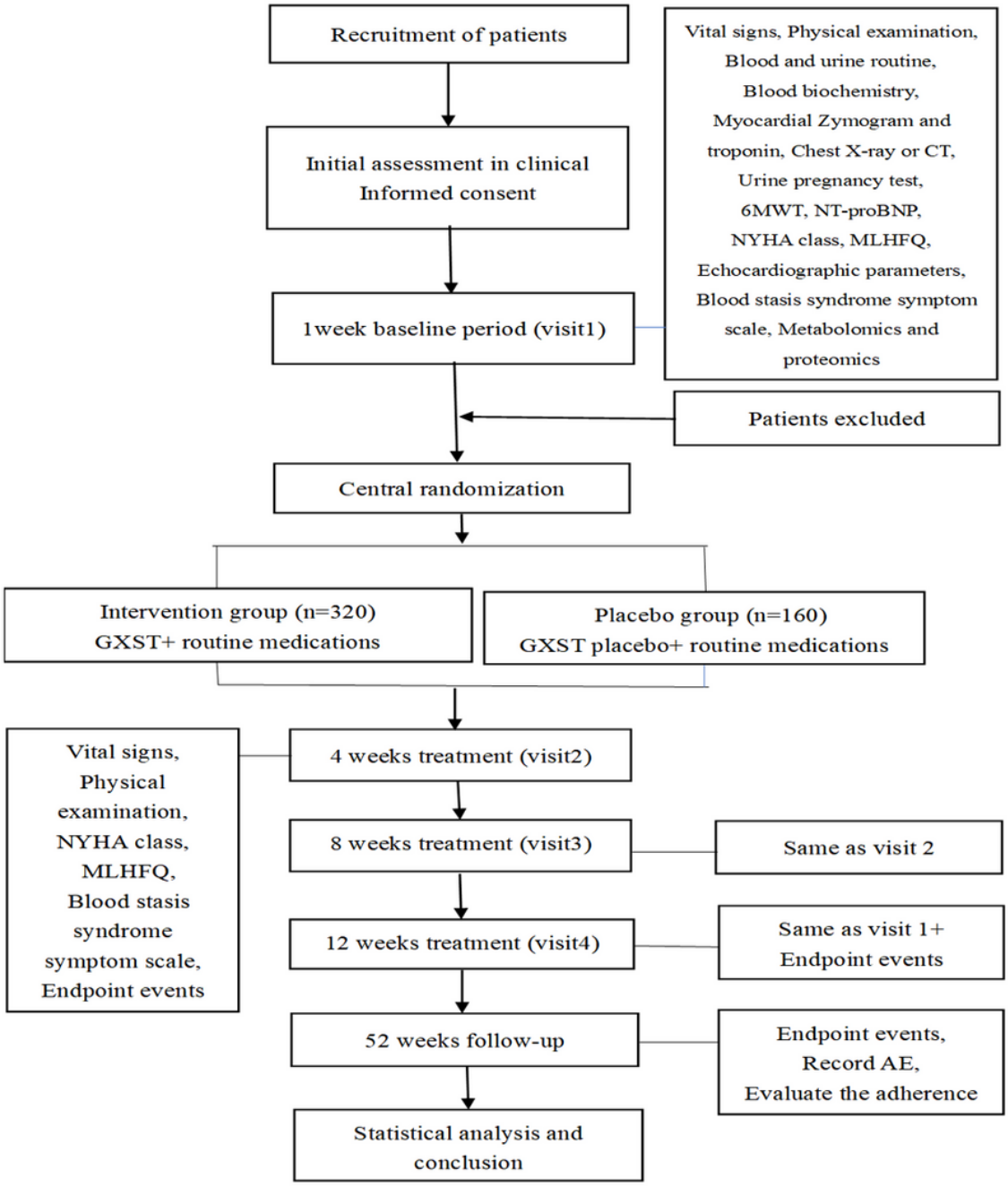

Figure 1

CONSORT flow diagram for GXST clinical trial.

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