

METHOD

The effect of Qi-Shao-Tong-Mai-An-Shen herbal paste on coronary heart disease patients with depression and/or anxiety: Study protocol for a randomized controlled trial

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Abstract

Coronary heart disease (CHD) poses a significant threat to human life and well-being. The presence of psycho-cardiology diseases not only exacerbates the progression of CHD but also imposes a substantial financial burden. Consequently, there is a pressing need to prioritize the prevention and management of psycho-cardiology conditions. Given the complex adverse effects associated with antidepressants, it is imperative to investigate alternative, safer, and more efficacious early interventions for psycho-cardiology diseases. The trial will randomly divide 99 patients who meet the inclusion criteria into two groups in a ratio of 1:2. Both groups will be administered standard western medicine treatment for CHD. The Qi-Shao-Tong-Mai-An-Shen (QSTMAS) group will be treated with an additional 30 mL QSTMAS herbal paste orally twice daily for up to 12 weeks. The primary endpoints are the changes of Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 scores after the intervention for 12 weeks. The secondary endpoints include the scores of Traditional Chinese medicine syndromes, 6-min walking test, Insomnia severity index sleep scale, laboratory tests, and other examinations of both groups after the intervention for 12 weeks. The QSTMAS herbal paste exhibits potential and promise as a treatment modality for mild-to-moderate psychological disorders within the department of cardiology. The implementation of a rigorous trial design will facilitate an objective and scientific assessment of the clinical effectiveness and safety of combining QSTMAS herbal paste with standard western medicine for CHD patients with depression and/or anxiety. Trial Registration: China Clinical Trial Registry, ChiCTR2200065179. Registered 31 October 2022.

KEYWORDS

anxiety, coronary heart disease, depression, Qi-Shao-Tong-Mai-An-Shen herbal paste, traditional Chinese medicine

Ying Chen and Xiang Xiao have contributed equally to this work as the co-first author.

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BACKGROUND

Coronary heart disease (CHD) is a serious threat to human health and one of the leading causes of death worldwide [1–3]. With the increasing pressure of modern life, CHD complicated with depression and/or anxiety (namely psycho-cardiology disease) becomes more common. Cardiovascular disease (CVD) and mental disorders have become two major diseases that affect the physical and mental health of mankind [4–6]. Cardiac events or cardiac surgery may be so painful life events that the incidence of mental complications in patients with CVD is much higher than that in the general population [7]. Mental disorders are associated with poor outcomes, including increased nonfatal events [8, 9] and even greater mortality in healthy individuals and patients with CHD [10–14]. Also, it is reported that depression is the main reason for disability. It is estimated that as many as 264 million people are suffering from depression in the world [15] and about 15% of them die of suicide.

In the UNWIND trial, escitalopram was found to be effective for CHD patients with anxiety or depression [16]. However, adverse effects (AEs) of escitalopram, such as appetite problems, weight gain, insomnia, dizziness, or sleepiness, trouble those patients at the same time [17, 18]. Thus, current guidelines recommend non-psychotropic drug intervention as the initial treatment [19]. Yet, numerous clinical and experimental studies have confirmed that Traditional Chinese medicine (TCM) has a definite effect and relatively high safety in the treatment of psycho-cardiology disease [20–23]. Qi-Shao-Tong-Mai-An-Shen (QSTMAS) herbal paste, summarized by Professor Huang Li based on 40 years of clinical experience, is used to treat CHD with qi deficiency and blood stasis symptoms. The effects of QSTMAS herbal paste include supplementing qi, promoting blood circulation, nourishing the heart, and soothing the nerves. Preliminary data analysis results [24] showed that the core components of QSTMAS herbal paste were also effective for emotional problems or serious insomnia, and no serious AEs have been observed. On this basis, optimizing this recipe is expected to obtain a better clinical curative effect.

Whether QSTMAS herbal paste can be recommended for the management of CHD with qi deficiency and blood stasis syndrome combined with anxiety and/or

depression in the clinical situation is still absent of advanced evidence-based clinical proofs. Hence, we plan to conduct a randomized controlled trial to verify the efficacy of QSTMAS herbal paste on this kind of patients mentioned above.

METHODS

Preparation of QSTMAS and previous data

QSTMAS is composed of 9 traditional plants, such as Huangqi (*Astragalus membranaceus* (Fisch.) Bge.), Chishao (*Paeonia lactiflora* Pall.), Chuanxiong (*Ligusticum chuanxiong* Hort, *Rhodiola crenulata* (Hook. f. et Thoms.) H. Ohba.), Hongjingtian (*Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou.), and so on; main composition is shown in Table 1. Its effects include supplementing qi, promoting blood circulation, nourishing the heart, and soothing the nerves. Modern research shows that its main drug composition has the treatment effect of “psycho-cardiology”. For example, *Astragali radix*, it can protect cardiomyocytes from injury caused by ischemia and hypoxia [25, 26], alleviate myocardial ischemia-reperfusion injury [27, 28], regulate myocardial energy metabolism [29, 30], and inhibit calcium overload [31]. Figure 1 shows its main composition and modern pharmacological action. At the same time, it has certain antianxiety and antidepressant effects [32], which can eliminate anxiety, depression, and other psychological and emotional states. At the same time, our team conducted a single toxicity test of QSTMAS administration in Sprague Dawley rats in the early stage, and no significant abnormalities were found indicating that it was safe.

Study design, setting, and participants

This trial adhered to the Standard Protocol Items: Recommendations for Interventional Trials Statements [33]. Strictly follow the 2017 Consolidated Standards for Extension Reports of Chinese Herbal Medicine Formulation Tests (CONSORT-CHM Formulas 2017) [34]. We have registered the study at the website Chinese Clinical Trial Registry (China Clinical Trial Registry ID:

TABLE 1 Main composition of Qi-Shao-Tong-Mai-An-Shen (QSTMAS).

Common name	Botanical name	Family name
Astragali radix	<i>Astragalus membranaceus</i> (Fisch.) Bge.	Fabaceae
Paeoniae radix rubra	<i>Paeonia lactiflora</i> Pall.	Ranunculaceae
Chuanxiong rhizoma	<i>Ligusticum chuanxiong</i> Hort.	Umbelliferae
Rhodiola crenulatae radix et rhizoma	<i>Rhodiola crenulata</i> (Hook. f. et Thoms.) H. Ohba.	Crassulaceae
Ziziphi spinosae semen	<i>Ziziphus jujuba</i> Mill. var. <i>Spinosa</i> (Bunge) Hu ex H. F. Chou.	Rhamnaceae

QSTMAS

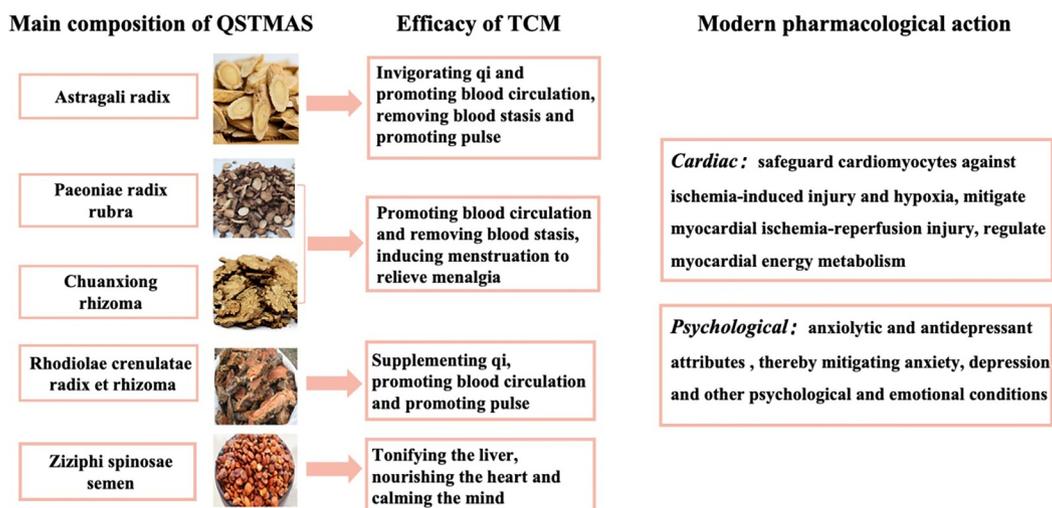


FIGURE 1 Main composition and modern pharmacological action of Qi-Shao-Tong-Mai-An-Shen (QSTMAS).

ChiCTR2200065179) in October 2022. This trial is approved by ethics committee of China–Japan Friendship Hospital (No.2022-KY-174-1, 23 September 2022). A total of 99 CHD patients combined with depression and/or anxiety in China–Japan Friendship Hospital will be recruited from November 2022 to August 2024. Subsequently, they will be randomly allocated to the control group or the QSTMAS group at a ratio of 1:2. Then, they will receive interventions for a treatment period of 12 weeks. Figure 2 presents the schedule of evaluations. Recruitment to the study started in November 2022. The trial is currently on going.

Participant recruitment

Participants will be recruited in the outpatient department and ward of Department of Cardiology of Integrated Traditional Chinese and Western Medicine in China–Japan Friendship Hospital. The “China–Japan Friendship Hospital Psychological Assessment and Early Warning System” will be used to evaluate the psychological status of every patient who is diagnosed with CHD with qi deficiency and blood stasis. The specific researcher responsible for recruiting participants will screen the patients who have mild-to-moderate depression and/or anxiety within 1 week.

ELIGIBILITY CRITERIA

Diagnostic criteria

Diagnostic criteria for CHD

It conforms to the diagnostic criteria of stable CHD in the Guidelines for Diagnosis and Treatment of Stable CHD in 2018 [35].

Diagnostic criteria for TCM syndrome of qi deficiency and blood stasis

According to the Consensus of Diagnosis and Treatment of Blood Stasis Syndrome of Integrated Traditional Chinese and Western Medicine [36], the diagnostic criteria of qi deficiency and blood stasis syndrome are: if there is more than one main disease and more than two secondary diseases, the diagnosis can be made by combining tongue pulse.

Main symptoms are chest distress and chest pain. Secondary symptoms include palpitation, shortness of breath, fatigue, sweating, and purple complexion. Tongue and pulse include lavender, and the pulse is thin and astringent.

Diagnostic criteria for mild-to-moderate depression and/or anxiety

According to the diagnostic criteria related to anxiety and depression in DSM-5, the Generalized Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) brief scales were applied, and the diagnosis of depression and anxiety will be completed by “The psychological assessment and early warning system of China–Japan Friendship Hospital”.

Referring to the GAD-7 anxiety disorder screening scale scoring and grading diagnostic criteria [37] [7 questions, Likert's 4-point scoring (0 = not at all and 4 = almost every day); the sum of scores was calculated as the total score, the higher the total score was, the higher the anxiety level was]: no: 0–4; mild: 5–9; moderate: 10–13 points; moderate-to-severe: 14–18 points; and severe: 19–21 points.

Referring to the PHQ-9 depression screening scale scoring and grading diagnostic criteria [38] [9 questions, Likert scored at 4 points (0 = not at all and 4 = almost

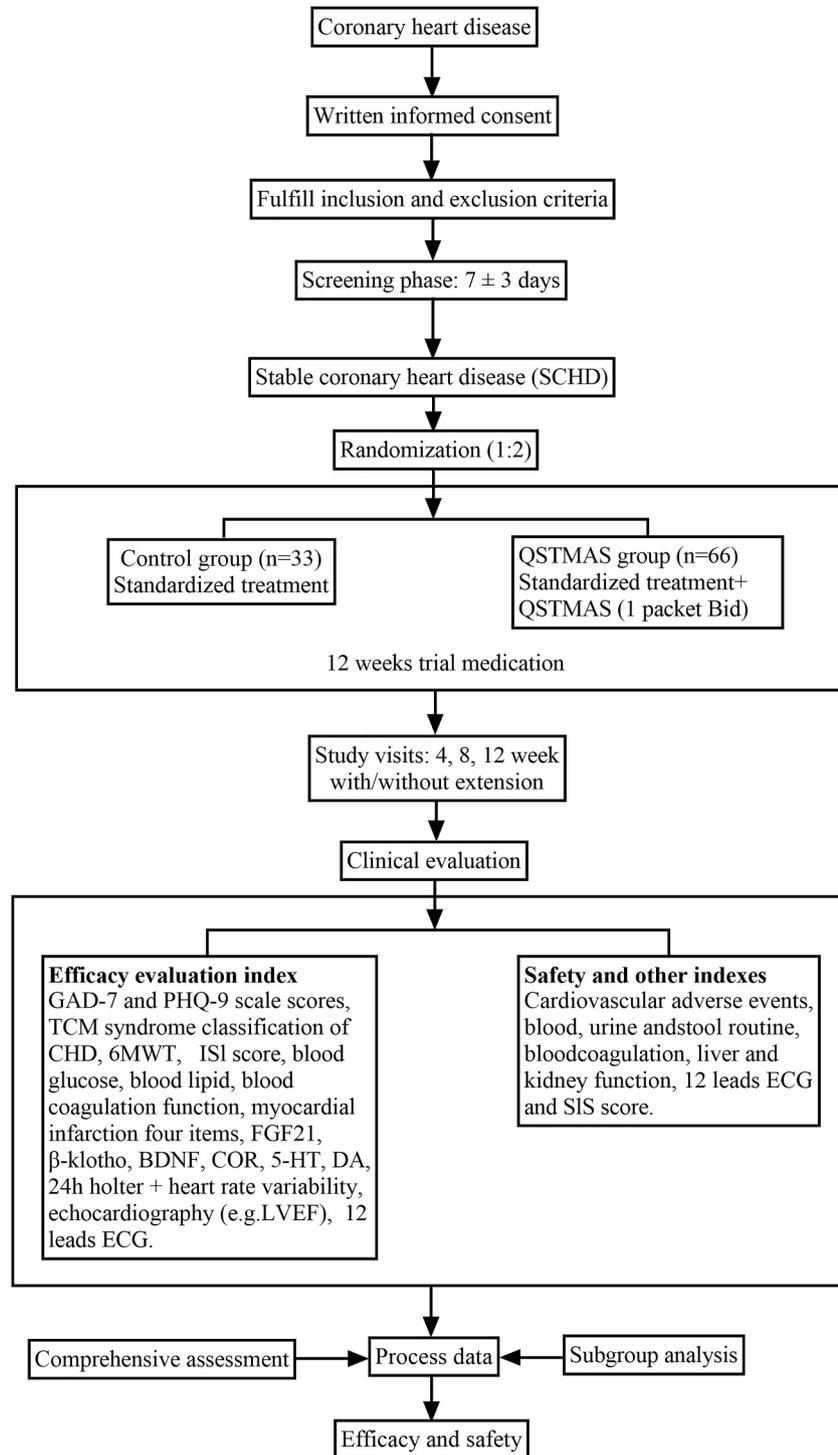


FIGURE 2 The schedule of evaluations.

every day); the sum of the scores was calculated as the total score, and the higher the total score was, the higher the anxiety level was]: no: 0–4; mild: 5–9; moderate: 10–14 points; moderate-to-severe: 15–19 points; and heavy: 20–27 points.

Inclusion criteria

1. Confirmed to the diagnostic criteria of CHD; confirmed to TCM syndrome of qi deficiency and blood stasis;

2. Confirmed to the diagnostic criteria of mild-to-moderate depression and/or anxiety using psychological evaluation scales and the early warning system of China–Japan Friendship Hospital;
3. Age 18–65 years old;
4. Accept and cooperate with the trial scheme;
5. Volunteer to participate in this study and sign the informed consent forms; people who meet the above requirements will be included in this study.

Exclusion criteria

1. Patients who are receiving anxiolytics, antidepressants, or drugs for other mental disorders within 1 month;
2. Combined with severe cardiac insufficiency, such as Killip grade II and above and New York Heart Association grade III and above;
3. Combined with other serious diseases, such as severe liver and kidney dysfunction (ALT > 3 × upper limits of normal, serum creatinine > 221 μmol/L); Severe consumption state or malignant tumor;
4. Pregnant or lactating women or those with pregnancy plans;
5. Suspicious or definite allergy to TCM or proprietary Chinese medicine;
6. Those who use TCM with similar efficacy within 2 weeks;
7. Those who are participating in other clinical studies now or within 1 month.

People who meet any of the above conditions will be excluded.

Randomization and blinding

We used the random number generator in SPSS (version 26.0) to generate the corresponding random numbers of 99 patients. Using the function of random case sample, 99 patients were randomly divided into group 1 and group 2 according to the ratio of 1:2. Test group 1 is marked as 1, and the test group 2 is marked as 2.

In this study, the single blind method is adopted, that is, the blind end point. Only the result evaluator is blind. Results assessors and data analysts are third-party personnel who do not know the distribution of group information and intervention measures.

Intervention

Test group 1: Take standard western medicine treatment for CHD regularly within 12 weeks, including antiplatelet agents, anticoagulants, β receptor blockers, nitrates, statins, and other drugs recommended by

guidelines and consensus. Routine coronary intervention is also acceptable according to the condition.

Test group 2: Standard western medicine treatment for CHD as mentioned above combined with QSTMAS herbal paste. Take QSTMAS herbal paste regularly for 80% or more of 12 weeks.

QSTMAS: Dosage form: paste formula; Dose: 30 mL paste decoction, twice daily, morning and evening; Route of administration: oral; and the treatment lasted for 12 weeks.

Outcome measures

Primary outcomes: GAD-7 and PHQ-9 scale scores after intervention for 12 weeks.

Secondary outcomes: Secondary outcome measures are as follows:

1. A quantitative score of TCM syndrome classification of CHD.
2. 6-min walk test (6-MWT); (c) 24 h Holter and Heart Rate Variability.
3. Insomnia severity index score.
4. Laboratory tests: blood glucose, blood lipid, blood coagulation function, and markers of myocardial infarction (Myo, CK-MB, cTnI (or cTnT) and NT-proBNP (or Brain Natriuretic Peptide)), fibroblast growth factor, β-klotho, brain derived neurotrophic factor, COR, 5-HT, and DA).
5. Examination: echocardiography, 12 leads electrocardiogram (ECG).

Safety index

Vital signs, the occurrence of cardiovascular adverse events, blood, urine and stool routine, blood coagulation, liver and kidney function, as well as 12 leads ECG changes.

Other indexes

Other index includes social impact scale score.

Study plan and follow-up

Subsequently, all patients are screened for 7 ± 3 days (V0). During this period, their use of western medicine will be checked and supervised according to the clinical situation of the 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes [39]. Standardized western medicine treatment includes antiplatelet, anticoagulant beta blockers, nitrate drugs, statins, and so on.

After screening, the patients will be randomly assigned to different groups at the baseline visit (V1). During the 12-week treatment, participants need to be interviewed three times (V2-4). The researcher will follow-up the patient for about 4 weeks (± 3 days) by telephone, patient's medical record and/or outpatient follow-up until the patient died of all causes, the consent form was withdrawn, and the follow-up was lost or the study was ended. They can quit the research at any time. All accesses and contents are described in Table 2.

The study drug should be taken regularly for 12 weeks, unless it is prohibited for some clinical conditions. In the case of complications (such as hypertension

or diabetes), appropriate western medicine treatment can be given according to relevant guidelines. The researcher should keep an up-to-date record of all medicines used. If necessary, patients should not hesitate to seek first aid care.

Supervision and quality control

A standard operating procedure guide has been developed for each trained investigator. The quality supervisor appointed by the China–Japan Friendship Hospital will carry out regular supervision. If it is really

TABLE 2 Study visits.

Item	Study phase				
	Screening	Baseline	Treatment phase		
Time	–1 week ± 3 days	0 week ± 3 days	4 week ± 3 days	8 week ± 3 days	12 week ± 3 days
Study visits	V0	V1	V2	V3	V4
Written informed consent	√				
Inclusion and exclusion criteria		√			
General data		√			
Blood pressure and heart rate	√	√	√	√	√
History of present illness		√			
History of past medical and allergies		√			
History of personal and family		√			
Medication records of CHD		√	√	√	√
Combined disease and medication records		√	√	√	√
Blood, urine, and stool routine		√			√
Blood biochemistry (liver and kidney function, blood glucose, and blood lipid)	√	√			√
Six-coagulation		√			√
Myocardial infarction four		√			√
FGF21, β -klotho, and BDNF		√			√
COR		√			√
5-HT, DA		√			√
24 h Holter + heart rate variability		√			√
Echocardiography		√			√
ECG (12 leads)		√	√	√	√
Quantitative score of TCM syndrome grading		√	√	√	√
6-MWT		√			√
Score of GAD-7, PHQ-9, and ISI		√	√	√	√
Score of SIS		√			√
MACE			√	√	√

Abbreviations: 5-HT, 5-hydroxytryptamine; 6-MWT, 6-minute walk test; BDNF, brain derived neurotrophic factor; COR, Cortisol (hormone); DA, Dopamine; ECG, electrocardiogram; FGF21, fibroblast growth factor; GAD-7, Generalized Anxiety Disorder-7; ISI, insomnia severity index; MACE, Major Adverse Cardiovascular Events; PHQ-9, Patient Health Questionnaire-9; SIS, social impact scale; β -klotho, human klotho beta ELISA Kit.

necessary to communicate important amendments to the agreement, the parties concerned should notify the applicant in writing.

Sample size estimation

The principle of minimum sample size is used. The dropout rate is calculated as 10%, and the patients were randomly divided into different groups according to the ratio of 1:2. It is planned to include 99 cases out of which 33 cases are in the experimental group 1 and 66 cases are in the another group.

Data collection and management

Patients will be followed up by a study investigator until the end of the trial. At each study visit, all general data and outcome evaluations will be recorded in the Case Report Form (CRF). The CRF will be carefully filed to protect confidentiality. Investigators will also update an electronic database using SPSS (version 26.0). Only investigators, researchers, and statistical analysts can access the final experimental data set.

Statistical analysis

Statistical analysis will be conducted by a third statistical team. Data analysis will use SPSS (version 26.0). The calculation of results will be based on a two-tailed test, except for the main results, which will be a one-tailed test (significance level $\alpha = 0.05$). In addition to the statistical comparison between baseline variables, the change of depression and anxiety score between the baseline, 4th week, 8th week, and 12th weeks in the treatment stage will be analyzed by adjusting the covariance between baseline and treatment so as to improve the efficiency and effectiveness of the tests. Survival analysis will be conducted using Kaplan–Meier and Cox regression models. Estimation equation or statistical model will be used to adjust the missing data analysis of the result measurement. Sensitivity analysis will be conducted to evaluate the robustness of the data.

DISCUSSION

In 1997, the introduction of psycho-cardiology medicine marked a significant advancement in the field of biomedicine, effectively surpassing its previous limitations and fostering the progress of the bio-psycho-social model [40]. The medical community has increasingly recognized the importance of psycho-cardiology medicine, attributing its appeal to its widespread applicability and high prevalence. A comprehensive global study [41] shows that besides the identified risk factors and

treatment methods, the secondary prevention of CHD should also give priority to the psychosocial burden. Furthermore, there is a strong interdependence and reciprocal causation between cardiovascular and psychosocial disorder [42, 43]. Long-term exposure to CVD and recurrent diseases can easily lead to psychological disorder, that is, depression and anxiety, thus affecting the prognosis of patients [44]. Consequently, timely detection and intervention of depression and anxiety assume paramount importance in the prevention and management of psycho-radiological conditions [41]. Although antidepressants are effective in relieving depression symptoms, their use is often associated with adverse cardiovascular outcomes [45].

While the Chinese expert consensus on psychological prescriptions for patients in the department of cardiology (version 2020) recommends syndrome differentiation by trained cardiologists and TCM intervention for patients with mild-to-moderate mental disorders [46]. This study aims to recruit patients with CHD and depression and/or anxiety. This trial will use “China–Japan Friendship Hospital Psychological Assessment and Early Warning System” to investigate the influence of QSTMAS ointment on these patients. The hypotheses of this study are as follows: (1) after receiving QSTMAS ointment for 12 weeks, the scores of depression and anxiety in patients with CHD with depression and/or anxiety will be significantly reduced; (2) the intervention of QSTMAS herbal paste for 12 weeks will reduce TCM syndrome score, decrease angina pectoris recurrence, and improve sleep status; and (3) after 12 weeks' intervention with QSTMAS, the laboratory examination and examination indexes will be improved obviously.

This study presents two significant innovations. First of all, we use “China–Japan Friendship Hospital Psychological Assessment and Early Warning System” to identify individuals who are suspected of mental health, thus improving the screening efficiency. This method not only improves the detection rate of depression and anxiety but also reduces the burden on medical personnel. Second, this study is expected to achieve substantial results by adopting early detection methods for patients with CHD who suffer from depression and/or anxiety. By integrating TCM interventions in the early stage, this trial aims to improve the clinical effect of psychological and cardiac rehabilitation of patients with CHD and improve their quality of life. Therefore, it is expected that the use of QSTMAS will help to reduce the incidence of Major Adverse Cardiovascular Events for a long time.

At present, there is still a lack of proprietary drugs specifically tailored for patients with CHD who suffer from depression and/or anxiety. Consequently, when faced with individuals suffering from psycho-cardiology ailments, healthcare practitioners must resort to prescribing psychotropic medications in addition to conventional CHD treatments. Therefore, the advantage of this study is that it investigates the clinical efficacy of a clinical empirical formula used to treat patients with

psycho-cardiology disease. However, it is important to recognize the limitations of this research. First of all, it should be pointed out that this study is exploratory, lacking any comparable research for reference. In addition, the sample size was not calculated. After consulting statisticians, it is suggested that the principle of minimum sample size should be adopted, and the ratio of clinical patient recruitment is 1:2. Finally, there is no placebo control and the results could have been subject to subjective bias. While, it is possible to ensure that subjective bias is excluded from the research results by hiring statistical analysts who are not aware of the intervention. The data will be released after the study is completed. In addition, the results of this study will provide substantial evidence for evaluating the effectiveness and safety of QSTMAS as a complementary and alternative treatment for patients with CHD accompanied by depression and/or anxiety.

Trial status

This trial started on 1 November 2022. Participant's recruitment and selection is ongoing at present in the China–Japan Friendship Hospital.

AUTHOR CONTRIBUTIONS

Ying Chen and Xiang Xiao contributed to the initial conception and design of the research. Lin Li, Hong Jiang, Chao-Zeng Si, Ming-Jing Shao, Xiao-Yan Lu and Shu-Liang Zheng provided methodological guidance and trial design. Tian-Gu Dai and Qing He were responsible for the collection, collation, and writing of the original manuscript. Li Huang and Xiang Xiao were responsible for managing and supervising the processes of the clinical research. Xiang Xiao critically revised the manuscript for important intellectual content. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The study results will be available as the manuscripts, and no additional unpublished data are available.

ETHICS STATEMENT

This study is carried out under the guidance of Good Clinical Practice and the Helsinki Declaration [47, 48]. It is approved by the ethics committee of China–Japan Friendship Hospital (No. 2022-KY-174-1, 23 September 2022). Before screening and recruitment, all participants or their legally authorized representatives must obtain written informed consent. Before registration, investigators will explain the detailed procedures of the study to the participants and answer the detailed questions and describe the use of the data.

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