

Efficacy and Safety of Kuoxin Formula in the Treatment of Dilated Cardiomyopathy-Related Heart Failure: Study Protocol of a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Clinical Trial

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Background: Dilated cardiomyopathy (DCM) is a severe heterogeneous cardiomyopathy characterized by cardiac enlargement and declining heart function, often leading to refractory heart failure and life-threatening outcomes, particularly prevalent in China. The challenge lies in the scarcity of targeted therapies with substantial efficacy for DCM. Additionally, traditional anti-heart failure drugs are constrained due to hypotension propensity or limited symptom improvement. Kuoxin Formula (KXF), internally endorsed at Longhua Hospital, demonstrates clear biological evidence for enhancing cardiac function and myocardial remodeling. Previous clinical studies suggest its potential to enhance patients' quality of life. This trial aims to further evaluate KXF's safety and efficacy in managing DCM-related heart failure.

Methods: This prospective, randomized, double-blind, placebo-controlled, multicenter trial aims to recruit 230 DCM patients from five centers. Participants will be randomly assigned to either KXF or placebo for 12 weeks, with careful monitoring of key indicators and adverse events. The primary outcome measures the proportion of patients with NT-proBNP reduction exceeding 30%. Secondary outcomes include New York Heart Association functional classification, Traditional Chinese Medicine syndrome scores, 6-minute walk test, Lee's heart failure score, and Minnesota Heart Failure Quality of Life Scale score. Ventricular remodeling will be assessed using cardiac ultrasound and ELISA. Safety metrics and adverse events will be meticulously recorded.

Discussion: This study will be the first multicentered research conducted in China that utilizes a randomized, double-blind, placebo-controlled design to investigate the use of TCM in the treatment of DCM. It seeks to develop new theoretical frameworks and provide solid clinical data to support the integration of TCM and modern medicine in treating heart failure in DCM patients.

Trial Registration: China Clinical Trial Registry, ChiCTR2300068937. Registered on March 1, 2023. <https://www.chictr.org.cn/bin/project/edit?pid=190926>.

Keywords: dilated cardiomyopathy, heart failure, Kuoxin Formula, traditional Chinese medicine, clinical trials

Introduction

Dilated cardiomyopathy (DCM) is a type of primary mixed cardiomyopathy depicted by high rate of sudden death and poor prognosis, leading to the enlargement of the heart and the steady reduction of myocardial contractile function caused by ventricular remodeling.^{1,2} The clinical manifestations of DCM are principally intractable heart failure, malignant arrhythmias, thromboembolism, cardiogenic shock and even sudden death.³ DCM has an unknown etiology, sophisticated pathogenesis, and a lack of focused cure, it remains a leading cause of heart transplantation in children and adults worldwide.^{4,5} Existing treatments such as anti-heart failure therapies, calibration of arrhythmias, anticoagulation, and prevention of sudden death have been constantly concentrating on symptomatic management, but not target treatment. DCM-related heart failure, which imposes dramatic burden on patients' well-being, home budget and social healthcare resource, is a pressing social problem that we urgently need to solve.^{6,7}

According to Guidelines for the Diagnosis and Treatment of Dilated Cardiomyopathy in China,¹ Western medical treatments for DCM primarily involve pharmaceutical therapy, implantable devices and immunotherapy. Pharmaceutical options include the use of renin-angiotensin system inhibitors, beta-blockers and other conventional medications. Whereas some DCM patients are unable to tolerate anti-heart failure and myocardial remodeling reversal treatments due to low blood pressure, which leads to poor prognosis and unsatisfactory therapeutic outcomes. Additionally, implantable devices like cardiac resynchronization therapy defibrillators (CRT-D) and left ventricular assist devices (LVAD) are costly, invasive, and typically used only in advanced stages of the disease, necessitating strict adaptation criteria.⁸ Immunotherapy, such as venous adsorption, is not widely used and remains controversial.⁹

TCM employs a unique personalized treatment approach based on syndrome differentiation, modifying herbal formulas according to patients' different signs and symptoms. This approach not only efficiently alleviates clinical symptoms and reduces the side effects of modern medicine but also delays myocardial abnormalities and reverses myocardial fibrosis at the cellular and molecular levels. It has embodied achievements in mortality reduction, better life standard and potent healing.¹⁰⁻¹² According to Traditional Chinese Medicine Diagnosis and Treatment Guidelines for Chronic Heart Failure (2022)¹³ the pathology of heart failure is identified by an underlying inadequacy of Qi, Blood, Yin and Yang, while stagnation of Blood, retention of phlegm and fluids is the predominant surficial pattern. KXF comprises Astragalus membranaceus, Polygonatum kingianum, Ganoderma lucidum, Salvia miltiorrhiza, Hirudo nipponica, Trichosanthes kirilowii peel, Cinnamomum cassia, Cassia obtusifolia, Ilex pubescens, and Acanthopanax senticosus (Table 1). Also, its chemical constituents were analyzed using UPLC. KXF has been used for years at Longhua Hospital

Table 1 Components of KXF

No.	Chinese Pinyin Name	Latin Scientific Name/Scientific Name	Part and Form Used	Place of Origin(China)
1	Sheng Huang Qi	Astragali Radix/Astragalus membranaceus(Fisch.) Bge. Var. mongholicus(Bge.) Hsiao	Dried root	Neimenggu
2	Huang Jing	Polygonati Rhizoma/Polygonatum kingianum Coll. Et Hemsl.	Dried rhizome	Yunnan
3	Ling Zhi	Ganoderma/Ganoderma lucidum(Leyss. Ex Fr.) Karst.	Dried fruiting body	Guizhou
4	Dan Shen	Salviae Miltiorrhizae radix Et Rhizoma/Salvia miltiorrhiza Bge.	Dried root and rhizome	Hebei
5	Shui Zhi	Hirudo/Whitmania pigra Whitman	Dried whole body	Jiangsu
6	Gua Lou Pi	Trichosanthis Pericarpium/Trichosanthes kirilowii maxim.	Dried and ripe peel	Shandong
7	Gui Zhi	Cinnamomi Ramulus/Cinnamomum cassia presl	Dried twig	Guangdong
8	Huang Jing Zi	Vitidis Negundo Fructus/Vitex negundo L. var. cannabifolia (Sieb. et Zucc.)	Dried and ripe fruit	Jiangsu
9	Mao Dong Qing	Pubescent Holly Root/Ilex pubescens Hook. and Arn.	Dried root	Zhejiang
10	Mao Ren Shen	Actinidia valvata Dunn/Actinidia valvata Dunn.	Dried root	Anhui

for early-to-mid-stage DCM treatment, addressing Qi-Yin deficiency combined with Blood stasis syndrome, showing promising results in reducing patient readmission rates and indicating the need for more in-depth research.

Experimental studies have shown that KXF can improve myocardial hypertrophy, necrosis, and reduce myocardial fibrosis in rat models of doxorubicin-induced DCM.^{14,15} Additionally, zebrafish experiments have demonstrated KXF's effectiveness in increasing the Bcl2/Bax ratio, decreasing Caspase 3 and Caspase 9 mRNA expression, and improving cell apoptosis in a Tnnt2a mutant DCM zebrafish model.¹⁶ Previous clinical trials have indicated that combining KXF with conventional modern medicine therapy effectively improves symptoms, cardiac function, and quality of life in DCM patients with Qi-Yin deficiency and blood stasis syndrome.^{10,17} However, these studies had limitations such as non-blinding, no placebo control, and KXF being prepared as a decoction based on clinical diagnosis. Therefore, this project aims to build upon prior research, employing randomized, double-blind, placebo-controlled, multicenter research methods to systematically evaluate KXF's clinical efficacy in DCM patients. This evaluation will cover aspects such as clinical symptoms, cardiac functional classification, ventricular remodeling, exercise endurance, and quality of life. Drawing on the clinical experience of prestigious Chinese physicians and relevant literature on KXF treating DCM, and funded by two National Natural Science Foundation of China grants (81873264 and 82004319), our team has conducted clinical observations and research on the extraction of effective components, pharmacological screening, cardiovascular precaution, and mechanisms of KXF. We hope to contribute more evidence of KXF's effectiveness in DCM treatments.

Methods

Objectives

This study aims to further evaluate the safety and efficacy of KXF in treating DCM -related heart failure. It seeks to develop new theoretical frameworks and provide solid clinical data to support the integration of TCM and modern medicine in treating DCM.

Design and Settings

This study is a multicenter, randomized, double-blind, placebo-controlled clinical trial. Patients meeting the primary screening requirements will first undergo a screening period (−7 to 0 days) before enrollment. Eligible participants will then be randomly assigned to receive either Kuoxin Formula (KXF) or a placebo for 12 weeks. [Figure 1](#) presents a flowchart of the study design. Additionally, a Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure outlining the schedule of enrollment, interventions, and assessments is provided in [Table 2](#).

Participants

Western Diagnostic Criteria

- (1) Diagnostic criteria for DCM are based on the Chinese Guidelines for the Diagnosis and Treatment of Dilated Cardiomyopathy (2018).¹
- (2) Diagnostic criteria for heart failure refer to the Guidelines for Diagnosis and Treatment of Heart Failure in China (2018).¹⁸
- (3) Cardiac function classification is based on the NYHA.¹⁹
- (4) Patients must have a history of chronic heart failure (CHF) for at least 3 months or clinical symptoms of HF for a similar duration.
- (5) Patients must have received standard medical treatment for at least 2 weeks with no dosage modification or intravenous administration.

TCM Syndrome Differentiation Criteria

According to the Guidelines for Clinical Research of Chinese Medicine New Drugs (2002)²⁰ Traditional Chinese Medicine Diagnosis and Treatment Guidelines for Chronic Heart Failure (2022)¹³ and opinions from domestic cardiologists, a patient must exhibit at least four main symptoms and three secondary symptoms, along with specific tongue and pulse conditions, to be diagnosed with Qi-Yin deficiency combined with blood stasis syndrome. Syndrome differentiation will be independently determined by two qualified TCM cardiologists according to TCM differentiation criteria.

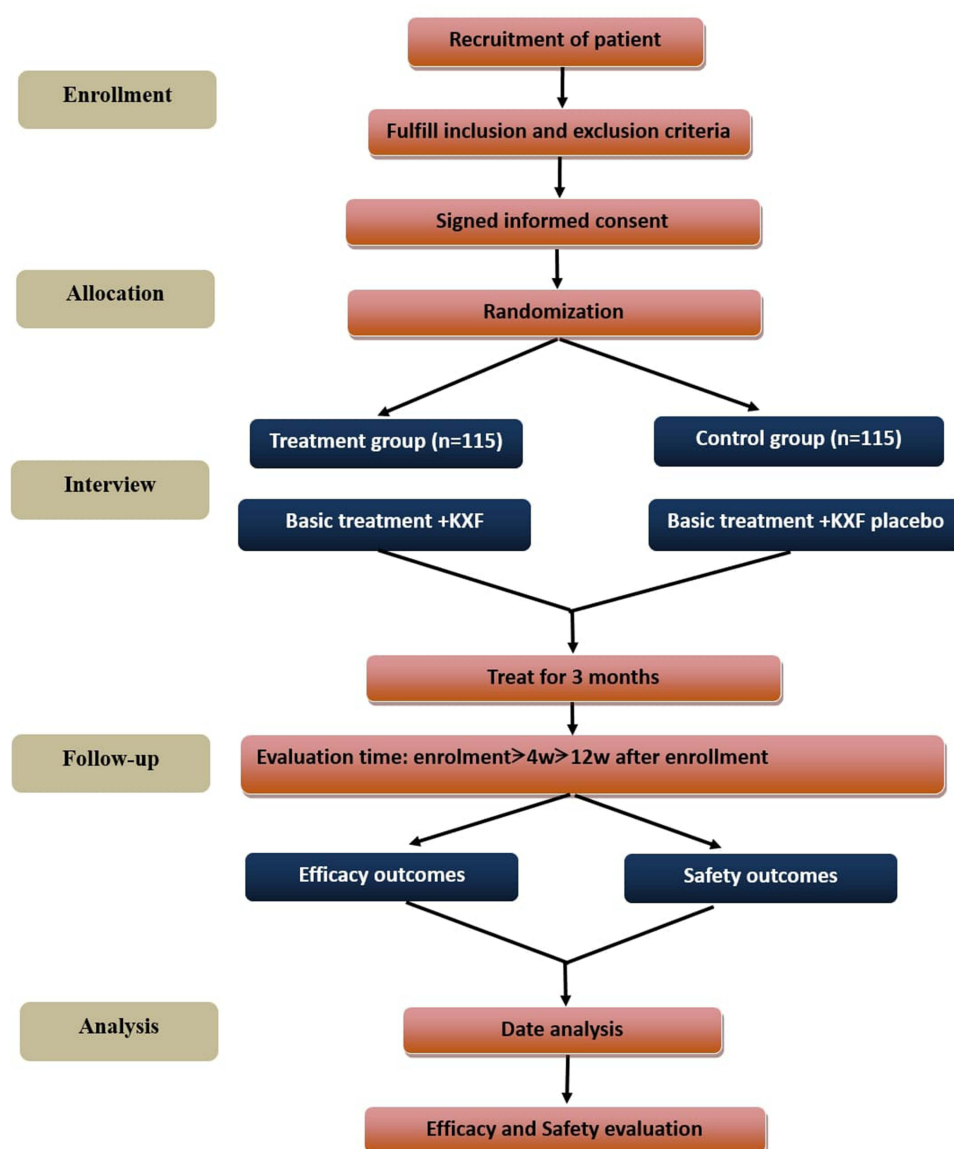


Figure 1 Trial flow chart.

- (1) The main symptoms: palpitations, shortness of breath, distending pain in the hypochondriac area (or chest stuffiness), lassitude, and spontaneous sweating or night sweats.
- (2) The secondary symptoms: dizziness, dysphoria, dry mouth and throat, a dark complexion, bluish-purple lips and fingernails, exposed veins in the neck, and edema of lower limb.
- (3) Tongue characteristic is a red tongue with a scanty coating, or a dark-purple tongue with petechia or suggillation.
- (4) Pulse manifestation is a deep thready, feeble rapid, and hesitant or knotted or intermittent pulse.

Inclusion Criteria

Patients must fulfill the following criteria:

- (1) The diagnostic criteria of DCM, details are as follows:¹

Objective evidence of ventricular enlargement and reduced myocardial systolic function: ① Left ventricular end diastolic diameter (LVEDd) > 5.0cm (female) and LVEDd > 5.5cm (male) (or 117% of the predicted value of age and body surface

Table 2 Schedule of Enrollment and Assessments

	Study Period			
	Enrolment	Allocation	Post-Allocation	
	-1 week	Week 0	Week 4	Week 12
Enrolment				
Eligibility screen	x			
Informed consent	x			
Allocation		x		
Interventions				
KXF		x	x	x
KXF placebo		x	x	x
Outcome assessments				
NT-proBNP		x		x
Cardiac function		x	x	x
Integral TCM syndrome score		x	x	x
Echocardiogram		x		x
TGF- β 1		x		x
PICP, C1TP		x		x
Galectin-3		x		x
ST2		x		x
MLHFQ		x	x	x
Lee's scale		x	x	x
6MWT		x	x	x
Safety assessments		x	x	x
Blood routine		x		x
Urine routine		x		x
Electrocardiography		x		x
Liver and kidney function		x		x
Adverse events		x	x	x

area, 2 times SD + 5%), ②LVEF <45% (Simpsons method), LVFS <25%,③except hypertension, heart valve disease, congenital heart disease or ischemic heart disease.

- (2) Cardiac function classification by NYHA (Class II to IV).
- (3) TCM syndrome differentiation criteria: Qi-Yin deficiency combined with blood stasis syndrome.
- (4) Age between 45 and 80 years.
- (5) Volunteered to participate in clinical trial observation and signed the informed consent form.

Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

- (1) Patients with shock, uncontrolled severe arrhythmias, acute myocardial infarction, acute pulmonary infarction, infectious endocarditis, pericardial filling, narrowing of pericarditis, and left ventricular outflow canal stenosis.
- (2) Patients with severe liver, kidney, anemia and electrolyte imbalance disorder, uncontrolled hyperthyroidism, hypothyroidism. Specifically, patients were excluded if they had a serum creatinine level >194.5 mmol/l or

serum potassium level >5.5 mmol/l; had alanine aminotransferase levels >1.5 times the upper normal limit; had hemoglobin < 9 g/dl.

- (3) Pregnant or lactating women.
- (4) Within 3 years, patients with cancer or other common malignant disease, such as respiratory, digestive, blood, immune, mental, or potentially dangerous diseases of clinical significance, which can reduce life expectancy for less than the duration of the trial.
- (5) Allergic constitution or history of allergy to common drugs.
- (6) Participate in other clinical researchers of TCM within 3 months or those who do not want to stop using other TCM.
- (7) Patients with mental illness or poor adherence with TCM treatment.

Discontinuing and Dropout Criteria

Patients will be discontinued and dropped out of the study if they meet any of the following criteria:

- (1) If severe adverse events occur, the clinical trial should be stopped according to the judgment of doctors.
- (2) If the patients' situation worsens or other diseases affect the observation during the trial, it should be stopped according to the assessment of doctors, and the case should be regarded as invalid.
- (3) Significant deviations in the design or implementation of clinical study protocol, such as poor adherence, make it difficult to evaluate drug effects.
- (4) The subjects are unwilling to continue the clinical trial and request withdrawal from the clinical trial.

Recruitment

Patients will be recruited from the outpatient and inpatient cardiology departments of five centers in China, including Longhua Hospital affiliated to Shanghai University of TCM, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated to Shanghai University of TCM, Shanghai Fifth People's Hospital affiliated Fudan University, Shuguang Hospital affiliated Shanghai University of TCM, and Shanghai Jiading Nanxiang Hospital. Trained study investigators will provide detailed explanations to potential participants. Upon agreeing to consent, eligible participants will be invited to sign written informed consent forms regarding participation in the trial (including procedures, risks, and options for dropping out), use of laboratory data, and the collection, storage, and use of biological specimens. To ensure adequate participant enrollment, we will implement three major strategies: (1) Disseminating recruitment information in hospital areas such as the outpatient hall. (2) Spreading recruitment information on WeChat, a popular communication platform in China. (3) Introducing potential patients to the trial during consultations and inquiring if they are interested in participating.

Randomization, Allocation and Blinding

This trial will use center-based stratification and block-randomization to assign participants in a 1:1 ratio to either the treatment group or the control group. An independent statistician, unaware of the trial's design and purpose, will generate the randomization sequences and grouping using SAS 9.4 statistical software. The random distribution results and the intervention drugs will then be delivered to the participating centers.

Blinding will be maintained throughout the trial for both participants and study personnel. The KXF and placebo granules, manufactured by Jiangyin Tianjiang Pharmaceutical Co., Ltd. (Jiangyin, China), will be indistinguishable in color, size, shape, and taste. Blinding codes will be assigned post-randomization by a designated operator, using the sequence number of the subject, corresponding random numbers, and grouping results (Group A or Group B) as the primary blinding base. This will be followed by secondary blinding to the medication (determining which group receives TCM and which receives placebo), with each subject's drug number prepared randomly in sequence. The blinding codes will remain sealed until all clinical data are entered into a database and locked, except in emergencies. In such cases, the envelope opener will be required to sign, date, and state the reason for unsealing on the envelope cover. Unblinding will be performed after all data has been recorded and locked.

Intervention

Basic Treatment

Following the Chinese guidelines for the diagnosis and treatment of dilated cardiomyopathy (2018) and Heart Failure in China (2018)^{1,18} this trial adopts conventional Western medications. Eligible patients will receive diuretics, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitors (ARNI), aldosterone receptor antagonists, beta-blockers, nitrates, and positive inotropic drugs as per their condition. Patients must have received standard medical treatment for at least 2 weeks without any modification of dosage or intravenous administration before qualifying for the study. Additionally, patients are advised to maintain a low-salt diet, bed rest, and, if necessary, oxygen treatment. During the treatment period, each patient will continue with the standard treatment plan established before enrollment. Any required adjustments in drug dosage or type due to changes in condition will be recorded in the CRF table, along with composite endpoint events and adverse events.

Treatment Group

Patients in the treatment group will receive basic treatment plus KXF granules (3 bags at 7.3 mg each, orally, twice daily, with warm water) for 12 weeks. KXF is prepared from Radix Astragali (Huangqi, 30g), Polygonati Rhizoma (Huangjing, 30g), Ganoderma lucidum (Lingzhi, 9g), Salvia miltiorrhiza (Danshen, 15g), Hirudo nipponica (Shuizhi, 6g), Trichosanthes kirilowii peel (Gualoupi, 30g), Cinnamomum cassia (Guizhi, 3g), Vitex negundo (Huangjingzi, 9g), Ilex pubescens (Maodongqing, 30g), and Actinidia valvata (Maorenshen, 30g).

Control Group

Patients in the control group will receive basic treatment plus a placebo, identical in appearance, taste, and smell to KXF. They will consume the placebo following the same dosage and schedule as the treatment group.

Outcomes

Primary Outcome

The proportion change in patients with a decrease in serum N-terminal-pro hormone B-type natriuretic peptide level (NT-proBNP) of more than 30% after 12 weeks of treatment(from baseline to weeks 12).

Secondary outcomes

The New York Heart Association (NYHA) Functional Classification (from Baseline to Weeks 4, 12)

Based on the NYHA functional classification, the investigators will grade the severity of functional limitation.

Integral TCM Syndrome Score (from Baseline to Weeks 4, 12)

Referring to Guidelines for Clinical Research of Chinese Medicine New Drugs(2002).¹⁹ A scale of 0–6 points and semi-quantitative integral methods will be scored according to the severity of clinical symptoms. The details are presented in Table 3.

- (1) Significant effect: symptoms and signs significantly improved and TCM syndrome score decreased $\geq 70\%$.
- (2) Effective: symptoms and signs improved, and TCM syndrome score decreased $\geq 30\%$.
- (3) Invalid: no significant improvement in symptoms and signs, TCM syndrome score decreased $< 30\%$.
- (4) Deterioration: symptoms and signs aggravated, post-treatment score exceeded pre-treatment score.

Echocardiographic Examinations (from Baseline to Week 12)

Left ventricular end-diastolic volume(LVEDV), left ventricular end-systolic volume(LVESV), stroke volume(SV), E and A-wave velocities and their ratio(E/A), left ventricular ejection fraction (LVEF) will be examined. All echocardiographic examinations will be performed by the same physician, blinded to patient grouping, using the Simpson method over three consecutive cardiac cycles.

Table 3 Traditional Chinese Medicine symptom score

Primary Symptoms	None (0)	Mild (2)	Moderate (4)	Severe (6)
Palpitations	No symptom	Slight; do not affect daily life and work	Obvious; can relieved after rest, and barely adhere to daily activity	No symptom at rest; slight activity will cause; unable to carry out daily activity
Shortness of breath	No symptom	General activity will cause	Slight activity will cause	Inactivity will cause
Chest stuffiness(pain)	No symptom	Vague	Intermittent	Obvious
Lassitude	No symptom	Low spirit, poor strength; can still adhere to daily work and activity	Mental fatigue, general weakness, barely adhere to daily activity	Severe mental fatigue, difficult to adhere to daily activity
Spontaneous sweating	No symptom	Slightly sweating after activity	Heavy sweating without any activity	Profuse sweating
Night sweats	No symptom	Occasional occurrence; sweats primarily in the head	Regular occurrence; sweats primarily on the chest and back	Frequent occurrence; sweats all over the body
Secondary symptoms	None (0)	Mild (1)	Moderate (2)	Severe (3)
Dry mouth	No symptom	Slight; no need to drink water	Severe; need to drink water occasionally	Intolerable; need to drink water frequently
Dizziness	No symptom	Sometimes break out, sometimes stop	Visual rotation, unable to walk	Almost fall, cannot stand
Feverish sensations in palm, soles, and chest	No symptom	Slight fever in hands and feet	Upset, hands and feet are burning	Feverish sensation, do not want clothes and quilts
Dark complexion	No symptom	Lusterless complexion	Dark complexion	Bluish-purple complexion
Bluish-purple lips and fingernails	No symptom	Slight purplish	Bluish-purple	Dark purple
Scanty urine	No symptom	24 hours >1000mL	24 hours < 400mL	24 hours < 100mL
Edema in the lower limbs	No symptom	Slightly	Pitting edema, +-++	Pitting edema, more than ++

2.6.2.4 transforming growth factor- β (TGF- β), type I procollagen carboxyterminal peptide (PICP), type I collagen carboxyterminal crosslinked peptide (CITP), galectin-3, soluble suppression of tumorigenicity-2 (ST2) levels (from baseline to week 12).

Fasting blood samples will be collected from patients, and levels of these indicators will be detected via enzyme-linked immunosorbent assay.

Minnesota Heart Failure Quality of Life Scale (MLHFQ) Score (from Baseline to Weeks 4, 12)

Lee's Heart Failure Score(from Baseline to Weeks 4, 12). Lee's scale will also be adopted with details as follows:

- (1) Significant effect: a decrease in score by $>75\%$ after 12 weeks.
- (2) Effective: a decrease in score by $50\%–75\%$ after 12 weeks.
- (3) Invalid: a decrease in score by $<50\%$ after 12 weeks.
- (4) Deterioration: the score remains unchanged or is higher than the pre-treatment score.

Minute Walk Trial (6MWT) (from Baseline to Weeks 4, 12).

Safety outcomes

Routine blood and urine analyses, electrocardiography, and liver and kidney function tests will be conducted before and after treatment. Adverse events and severe adverse events will be recorded at each visit.

Sample Size

Sample size calculation is based on the level of NT-proBNP, the main efficacy indicator. The literature showed that after 12 weeks of conventional basic treatment combined with placebo, NT-proBNP levels decreased by more than 30% in 31.98% of the patients, and after 12 weeks of conventional basic treatment combined with TCM, NT-proBNP levels decreased by more than 30 in 47.95% of the patients.²¹ Therefore, we estimate that after 12 weeks of conventional basic treatment combined with KXF, the NT-proBNP levels will decrease by more than 30 in 52% of the patients. Thus, assuming $\alpha = 0.05$ and $\beta = 0.20$, the calculated sample size required for each group is 92 cases, after substituting the above values in PASS 15 Considering that 20% will miss visits, the sample size is adjusted to 115 cases in each group.

Statistical Analysis

Statistical analysis will be performed using SAS software, version 9.4 (SAS Institute), following a pre-established statistical analysis plan. Data analysis for efficacy will be performed following the intention-to-treat (ITT) principle. The full analysis set (FAS), per protocol set (PPS), and safety set (SS) were included for analysis by SAS software. The two groups' baseline characteristics will be summarized by descriptive statistics. For the primary and secondary outcomes, a *t*-test or Mann–Whitney *U*-test will be employed for continuous variables with normal or unknown distributions; Chi-squared test or Fisher's exact test will be used for categorical variables. Any change across time among the primary or secondary outcomes will be analyzed by the generalized estimated equation model or a mixed-effects model, as appropriate. Sub-group analysis will also be conducted according to the pre-established statistical analysis plan. All hypothesis tests were two-sided, with $\alpha=0.05$; thus, results where $p<0.05$ were considered statistically significant. All results are presented with a 95% confidence interval (95% CI).

Adherence

Adherence refers to the extent to which participants comply with the intervention. We use the following methods to improve patient adherence: ① Create a WeChat group called “DCM patient group” to share general information about traditional Chinese and modern medicine related to DCM. ② Ensure that all researchers treat participants respectfully, answering any questions they may have. ③ Notify participants by phone or WeChat two or three days before follow-up. ④ Provide economic compensations such as transportation, food, and communication reimbursement. ⑤ Offer all participants 100 Chinese yuan as transportation subsidies.

Data Collections and Management

In this trial, the case report Form (CRF) will be filled out by the researchers to collect relevant data. The CRF will be checked by the supervisors with the original medical records of the patients. To ensure the reliability of the data, the Data Monitoring Committee will conduct data monitoring. The Data Monitoring Committee consists of a researcher who is not involved in data collection, data manager, biostatistician, and ethicist (independent of sponsors and not subject to competitive interests). The Data Monitoring Committee will conduct periodic mid-term assessments and will suspend the trial if there are significant differences between the two groups.

The final data will be submitted to the Shanghai Science and Technology Committee in the form of a research report by the researchers after completion of the study. The results will be published in a peer-reviewed academic journal to share the findings with the general public and healthcare professionals.

Trial Management and Quality Control

The trial management structure includes a Coordinating Committee and a supervisor. The coordinating center is Longhua Hospital Shanghai University of TCM, with the head of each research unit a committee member. The committee is responsible for trial implementation and meets every three months. The supervisor, appointed by the principal investigator, will ensure participant rights, data accuracy, and adherence to the trial protocol.

Continuous monitoring of adverse events will be conducted. In case of severe adverse events, the investigator will contact the project leader and initiate the emergency response plan, adhering to the principle of “free treatment priority”, and report to the organizer and ethics committee within 24 hours using the “serious adverse event report form”.

Discussion

Traditional Chinese Medicine (TCM) offers significant potential in enhancing both the systolic and diastolic functions of the heart, improving the quality of life for patients, and serving as a supplementary or alternative therapeutic approach for treating DCM.^{10–12} While DCM is not explicitly defined within the TCM framework, its clinical manifestations and characteristics allow for its categorization under “heart distention”, “water in heart”, or “blood obstruction in heart”. Dr. Duan Zhou, a renowned TCM expert and lifelong professor at Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, has proposed a novel understanding of DCM. According to his theory, DCM results from a combination of congenital disorders, acquired malnutrition, and prolonged illness, leading to the depletion of essential life forces, especially Qi and Yin. This depletion hinders blood flow and circulation, causing an obstruction in the heart meridian and leading to fluid accumulation and heart swelling. The essential pathogenesis of DCM can be summarized as “deficiency of the vital energy (Qi-Yin deficiency) and obstruction by pathogenic factors (stagnation of blood)”. Thus, the treatment focuses on supplementing Qi, nourishing Yin, and activating blood circulation. A common issue in conventional heart failure treatment is the side effects of diuretics, which can include dry mouth, excessive sweating, and a sensation of heat, leading to considerable discomfort. These symptoms are frequently insufficiently addressed by modern medications. In TCM, they are commonly linked to Qi-Yin deficiency. This serves as another crucial reason for our selection of this syndrome type for study. Such a holistic approach is vital in managing complex conditions like DCM, where symptoms typically cannot be easily resolved.

KXF, a prospective herbal prescription, is composed of several key ingredients including *Astragalus membranaceus*, *Polygonatum sibiricum*, *Salvia miltiorrhiza*, *Cinnamomum cassia*, *Trichosanthes kirilowii* peel, and *Vitex negundo* seed, etc. *Astragalus membranaceus* and *Polygonatum sibiricum* serve as the primary herbs, effectively replenishing Qi-Yin and essence. *Salvia miltiorrhiza* and *Trichosanthes kirilowii* peel, acting as minister herbs, are known for their blood-activating, stasis-dissolving, and Qi-regulating properties. *Cinnamomi ramulus* is included to warm Yang and aid in fluid circulation, while *Vitex negundo* is utilized for its abilities to relieve wheezing and resolve phlegm. Modern pharmacological studies support the clinical efficacy of many herbs contained in KXF in treating DCM. *Astragalus membranaceus* can enhance cardiac function by increasing the ejection fraction, reducing the left ventricular end-diastolic diameter, extending walking distances, alleviating heart rate, and decreasing BNP levels.^{22–24} *Polygonatum sibiricum* exhibits anti-inflammatory, antioxidant, and anti-apoptotic effects.²⁵ *Salvia miltiorrhiza* can ameliorate myocardial remodeling potentially through the inhibition of angiotensin I receptors (AT1) and the blockade of the TGF- β /Smads signaling pathway.²⁶ Rest of the herbs in KXF also plays specific role in treating cardiac remodeling.^{27–29} Therefore, from the perspective of TCM, the composition of KXF is reasonable and treats both the symptoms and the root cause. From the perspective of modern pharmacology, many of the herbs it contains do have the effect of treating DCM, so they are worthy of study. Moreover, previous clinical studies conducted by our research team in a single-blind, randomized controlled design have revealed KXF can improve cardiac function and life quality of DCM patients.¹⁷ However, there is little explicit information focused on DCM-related heart failure and double-blind, placebo-controlled methods were not performed

in the existing studies. This study will be the first multi-centered research conducted in China that utilizes a randomized, double-blind, placebo-controlled design to investigate the use of TCM in the treatment of DCM-related heart failure.

In this study, the proportion of patients whose serum NT-proBNP decreased by more than 30% serves as the primary outcome. NT-proBNP is a cardiovascular neurohormone produced by ventricular myocytes. It is widely utilized for diagnosing heart failure, distinguishing between different types of heart failure, assessing risk, and predicting prognosis. Its advantages lie in its ease of measurement, precision, repeatability, and its frequent use in evaluating the clinical effectiveness of drugs.³⁰ In addition, We utilize the NYHA functional classification to gauge the severity of heart failure based on exercise tolerance. This classification system plays a critical role in guiding treatment decisions and forecasting patient outcomes.^{31,32} In DCM, ventricular remodeling is a major pathological development and a fundamental cause of heart failure, which can be monitored through cardiac ultrasound.^{33,34} TGF- β , a principal fibrillogenic factor, plays a significant role in myocardial fibrosis by promoting cardiac fibroblast proliferation and collagen synthesis, thus triggering the TGF- β /Smad pathway and contributing to ventricular remodeling.^{35,36} Additionally, Galectin-3, a pro-inflammatory factor, is crucial in various pathological processes like cell growth, apoptosis, and inflammatory responses, acting as a key mediator in cardiac remodeling and the progression of heart failure.³⁷ Furthermore, Type I procollagen carboxyterminal peptide (PICP) and Type I collagen carboxyterminal crosslinked peptide (CITP) are valuable markers for assessing fibrosis.³⁸ Therefore, it is highly pertinent for us to select these indicators as objective measures to assess the efficacy of KXF.

In this research, we aim to methodically evaluate the clinical efficacy and impact of KXF on ventricular remodeling in treating DCM-related heart failure patients characterized by Qi-Yin deficiency combined with blood stasis syndrome. Our goal is to gather definitive and reliable clinical data, offering new perspectives and laying the groundwork for an evidence-based approach to TCM in treating DCM.

Abbreviations

DCM, Dilated cardiomyopathy; KXF, Kuoxin Formula; LVEF, Left ventricular ejection fraction; TCM, Traditional Chinese Medicine; 6MWT, 6-min walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; LVESV, Left ventricular end-systolic volume; LVEDV, Left ventricular end-diastolic volume; SV, Stroke volume; E/A, E and A-wave velocities and their ratio; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide level; TGF- β , transforming growth factor- β ; PICP, Type I procollagen carboxyterminal peptide; CITP, Type I collagen carboxyterminal crosslinked peptide; ST2, Soluble suppression of tumorigenicity-2; CO, cardiac output; CI, cardiac index; LVEDD, Left ventricular end diastolic; LVFS, Left ventricular fraction shortening; NYHA, New York Heart Association; GCP, Good clinical practice; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockage;; CRF, Case Report Form; ATI, angiotensin I receptor.

Trial Status

The trial has been registered at [http://www.chictr.org.cn\(ChiCTR2300068937\)](http://www.chictr.org.cn(ChiCTR2300068937)). Recruitment started on April 1, 2023 and will be completed on December 31, 2025.

Ethics Approval and Consent to Participate

This study conformed to the ethics principles set forth by the Declaration of Helsinki and was approved by the Ethics Committee of Longhua Hospital Shanghai University of TCM (2022LCSY078). The participants will provide their signed informed consent to enroll in the trial and be asked whether their data can be used and share with another relevant department.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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