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Clinical Study of Chinese Herbal Compound Qidan XiaoKe Granules After Coronary Revascularization

Study Type: Experimental Study

Study Centers:

The Third Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Zhongshan Hospital) (Lead Site)

Zhejiang Chinese Medical University Jinhua Research Institute

Zhejiang Provincial People's Hospital

Zhejiang Provincial Hospital of Chinese Medicine, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Dongfang Hospital)

Zhejiang Chinese Medical University

Department Undertaking the Study at This Site: Department of Cardiovascular Medicine

Signature of Site Principal Investigator: _____

Date: April 2026

This study will be conducted in accordance with the clinical study protocol and GCP.

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Study Protocol

I. Background of the Study

Coronary heart disease (CHD) is a major non-communicable disease causing death and disability worldwide, seriously endangering human health[1]. Percutaneous coronary intervention (PCI), as a core revascularization method, mechanically restores blood flow in occluded or stenotic coronary arteries, greatly reducing the mortality of acute myocardial infarction and saving countless lives[2]. However, patients still face multiple challenges after revascularization, including recurrent angina, in-stent restenosis, coronary microvascular dysfunction, peri-procedural myocardial injury, and psycho-cardiac issues[3]. Studies have shown that 20%–30% of CHD patients may still have recurrent angina after successful PCI revascularization[4]; in-stent restenosis 3–6 months after PCI is the main mechanical cause of angina recurrence and repeat revascularization[5]. Other non-mechanical factors such as incomplete revascularization, peri-procedural myocardial injury, and coronary microvascular dysfunction cannot be ignored[6]. Together, these factors lead to major adverse cardiovascular events (MACE) in about 10%–18% of patients within one year after surgery, seriously affecting long-term prognosis and quality of life[7].

Although conventional secondary prevention medications are effective, some patients have persistent symptoms, and there is a lack of systematic, holistic regulation[8]. Traditional Chinese medicine (TCM) has unique advantages in holistic regulation and multi-target intervention, matching the pathogenesis characteristics of "deficiency in origin and excess in superficiality, complex and changeable" after revascularization[9]. Systematic reviews indicate that TCM can exert synergistic effects in post-PCI patients through multiple mechanisms including antiplatelet, anti-inflammatory, inhibition of smooth muscle proliferation, vasodilation, improvement of microcirculation, and endothelial protection[10]. Our team previously developed a TCM compound, "Qidan XiaoKe Granules", with the effects of benefiting qi, activating blood circulation, resolving phlegm, and dissipating nodules, focusing on the syndrome of qi deficiency, blood stasis, and phlegm obstruction[11].

Preliminary studies have shown that this formula can effectively relieve residual symptoms, improve microcirculation, inhibit inflammation and plaque instability, and show potential to reduce MACE incidence[12]. At present, the drug component analysis and preparation technology have been preliminarily completed.

However, high-quality, large-sample, randomized controlled trial evidence supporting its widespread clinical application is still lacking[13]. Therefore, this study aims to scientifically evaluate the efficacy and safety of Qidan XiaoKe Granules combined with standardized Western medicine in patients after coronary revascularization through a standardized multicenter, randomized, double-blind, placebo-controlled trial, providing high-level evidence-based medical evidence for TCM prevention and treatment of CHD and laying the foundation for the development of a hospital preparation.

II. Main Research Content, Objectives, Plan, Progress, and Key Issues

1. Research Content

Patients after coronary revascularization will be enrolled and divided into an experimental group (standardized Western medicine + Qidan XiaoKe Granules) and a control group (standardized Western medicine + placebo). The intervention lasts 12 weeks, with follow-up at baseline (day of enrollment), 6 weeks, 12 weeks, 24 weeks, 36 weeks, and 48 weeks. The primary outcome is the incidence of major adverse cardiovascular events (MACE). Secondary outcomes include TCM syndrome score, echocardiography, Holter monitoring, Minnesota Living with Heart Failure Questionnaire (MLHFQ), cardiac enzymes, blood lipids, and blood glucose. Safety outcomes include vital signs, complete blood count, liver and kidney function, other adverse reactions, and adverse events.

2. Research Objectives

(1) To evaluate the efficacy and safety of Qidan XiaoKe Granules in patients after coronary revascularization;
(2) To develop a TCM rehabilitation treatment plan and evaluation system for the use of Qidan XiaoKe Granules after coronary revascularization;
(3) To demonstrate the advantages of TCM rehabilitation in post-revascularization management and provide high-level evidence-based medical evidence for TCM rehabilitation treatment plans.

3. Study Plan

3.1 Sample Size Estimation

Based on previous literature and preliminary experiments, the 48-week MACE rate in

the control group (standard Western medicine) is estimated to be about 30%, and in the experimental group (Western medicine + Qidan XiaoKe Granules) it is expected to be reduced to 15%. Taking α=0.05, β=0.20 (power 80%), using the formula for comparison of two proportions, approximately 70 patients per group are needed. Considering a 15% dropout rate, the sample size is increased to 82 per group, with a total of 164 patients.

$$n_1 = n_2 = \frac{\left[Z_{1-\alpha/2}\cdot\sqrt{2P(1-P)}+Z_{1-\beta}\cdot\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right]^2}{(P_1-P_2)^2}$$

3.2 Randomized Controlled Design and Implementation

This is a multicenter, prospective, randomized, double-blind, placebo-controlled, superiority trial. A computer-generated randomization list with stratified block randomization (stratified by center) will be used. Patients are strictly screened according to diagnostic, inclusion, and exclusion criteria. After confirmation of eligibility, they are randomized 1:1 to the experimental group (standard Western medicine + Qidan XiaoKe Granules) or control group (standard Western medicine + placebo). Personnel involved in randomization do not participate in data analysis. Outcome assessors are blinded to group allocation (separate roles for researchers, operators, and statisticians).

Study subjects are patients after coronary revascularization from the Department of Cardiovascular Medicine of the following institutions: The Third Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Zhongshan Hospital), Zhejiang Chinese Medical University Jinhua Research Institute, Zhejiang Provincial People's Hospital, Zhejiang Provincial Hospital of Chinese Medicine, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Dongfang Hospital).

Before the study begins, the investigator explains the study, its potential risks and benefits to the patient or their legal representative in clear, lay language. Only after signing informed consent can the patient be screened and enrolled.

After signing informed consent, the following assessments are performed:

(1) Demographic data;

(2) Vital signs, medical history, concomitant medications, allergy history;

(3) Procedural characteristics: radial/femoral artery access, target vessel (number, location), stent data (number, length, diameter), time since revascularization.

3.3 Diagnostic Criteria

Diagnosis of coronary heart disease follows the *2025 ACC/AHA/ACEP/NAEMSP/SCAI Guidelines for Acute Coronary Syndromes* and the 2025 Chinese Guidelines for Percutaneous Coronary Intervention.

3.4 Inclusion Criteria

① Age 18–80 years;

② No gender restriction;

③ Meets diagnostic criteria for coronary heart disease;

④ Has undergone successful PCI;

⑤ Voluntarily signs informed consent.

3.5 Exclusion Criteria

① Severe liver or kidney dysfunction;
② Severe electrolyte imbalance;
③ Severe hematologic disease or malignancy;
④ Pregnancy or breastfeeding;
⑤ Psychiatric disorder;
⑥ Cognitive impairment (e.g., dementia, post-stroke cognitive impairment) preventing normal communication;
⑦ Planned repeat revascularization in the near future;
⑧ Other severe cardiovascular diseases: uncontrolled hypertension, angina, tachyarrhythmias, high-degree or complete AV block (without pacemaker), severe aortic stenosis, decompensated heart failure (NYHA IV), deep vein thrombosis, obstructive hypertrophic cardiomyopathy, acute pericarditis/myocarditis, infective endocarditis, acute aortic dissection, etc.;
⑨ Acute pulmonary embolism or chronic lung disease with dyspnea at rest or on minimal exertion;
⑩ Bleeding risk within 1 month: history of bleeding, active bleeding, bleeding diathesis, current use of anticoagulants;
⑪ Participation in another interventional clinical trial within the last 1 month;
⑫ Known allergy to any ingredient of Qidan XiaoKe Granules;
⑬ Any other condition that the investigator deems unsuitable for participation.

3.6 Withdrawal and Dropout Criteria

Withdrawal (exclusion from efficacy analysis): (1) found after enrollment not to meet inclusion/exclusion criteria; (2) experienced significant adverse reactions during treatment; (3) did not receive treatment as per protocol after enrollment. Note: Withdrawn cases are documented, original records retained; they are not included in efficacy analysis but may be included in safety analysis if they received at least one dose.

Dropout (premature termination): (1) patient voluntarily withdraws or lost to follow-up; (2) serious adverse reaction or event during treatment.

Note: Follow the Drug Trial Quality Management Standards (2020 No. 57 document).

3.7 Discontinuation Criteria

(1) Serious adverse reaction during the study; the specialist evaluates whether to continue or terminate;
(2) Serious complication or other severe disease requiring emergency measures;
(3) Any other reason preventing continuation.

3.8 Adverse Events

Detailed recording of adverse events and reasons for dropouts.

3.9 Treatment Plan

The study period is from January 1, 2026, to December 31, 2028.

3.9.1 Experimental Group (Standard Western Medicine + Qidan XiaoKe Granules)

Standard Western medicine: all patients receive guideline-directed secondary

prevention medications including but not limited to dual antiplatelet therapy, statins, beta-blockers, ACEI/ARB, etc.

Qidan XiaoKe Granules composition: Astragalus membranaceus 15g, Pheretima 9g, Salvia miltiorrhiza 15g, Curcuma aromatica 12g, Citrus aurantium 12g, Oyster shell 30g, Siegesbeckia orientalis 15g. Form: formula granules. Dosage: 1 sachet per dose, twice daily, dissolved in warm water.

3.9.2 Control Group (Standard Western Medicine + Placebo)

Same Western medicine as experimental group. Placebo is made from 5% active ingredients with edible excipients and colorants, identical in appearance, taste, and packaging.

Source of drugs: Qidan XiaoKe Granules and placebo are both provided by Zhejiang Zuoli Baicao Pharmaceutical Co., Ltd., with quality inspection reports.

The study period is 48 weeks, with 12 weeks of treatment and 48 weeks of follow-up. Observation time points: baseline, 6 weeks, 12 weeks, 24 weeks, 36 weeks, 48 weeks.

3.9.3 Outcome Measures

(1) Primary Outcome

Incidence of major adverse cardiovascular events (MACE) within 48 weeks, defined as a composite of: all-cause death, subacute stent thrombosis, peri-procedural myocardial infarction, recurrent myocardial infarction, recurrent unstable angina, repeat revascularization, and rehospitalization due to angina or heart failure.

(2) Secondary Outcomes

① TCM syndrome score (developed according to the 2021 guideline, 0–3 scale, see table below).

Symptom/Sign	None (0)	Mild (1)	Moderate (2)	Severe (3)
Fatigue				
Shortness of breath				
Reluctance to speak				
Spontaneous sweating				
Palpitations				
Chest pain	□dull □stabbing □vague □other_____			
Dark/purple complexion or lips				
Scaly skin				
Chest tightness				
Epigastric fullness, poor appetite				
Obesity				
Cough/sputum or throat phlegm	□profuse □scanty color/texture_____ □other_____			
Heavy sensation in head				

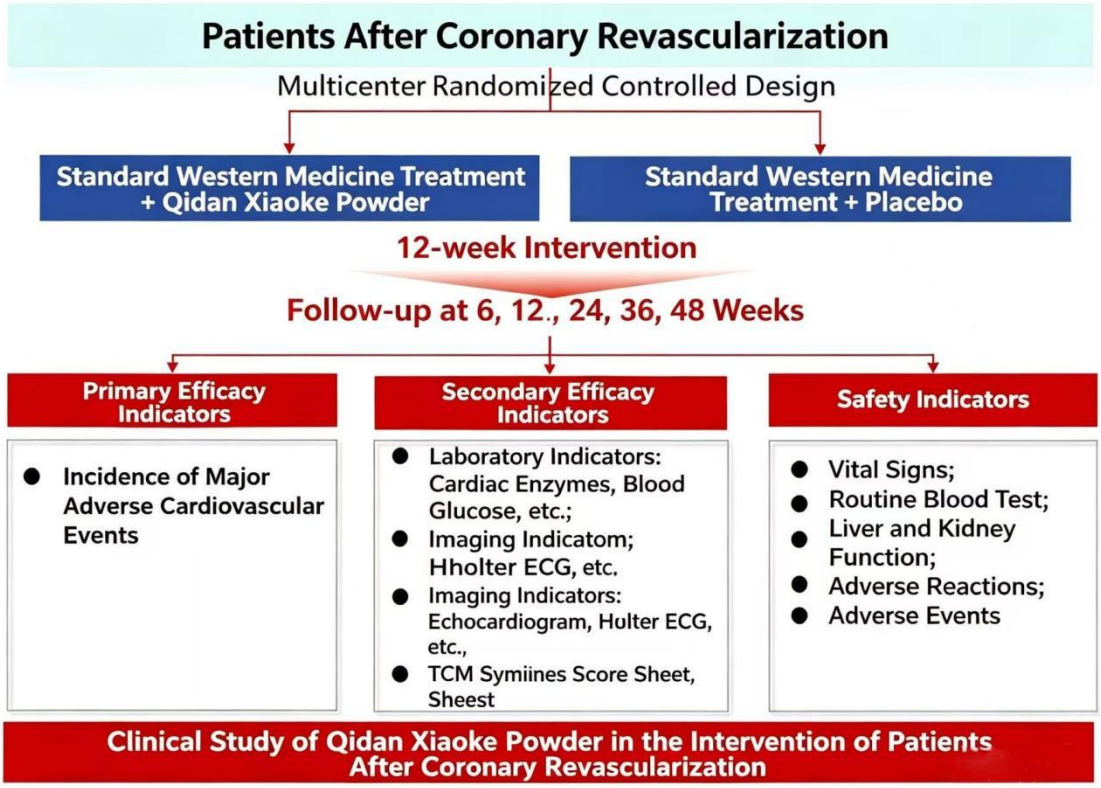
Chilliness and cold limbs				
Tidal fever and night sweats				
Dry mouth and throat				
Pale conjunctiva				
Severe bitter taste				
Depression / frequent sighing				
Bowel/urine abnormalities				
Tongue body color				
Tongue shape				
Tongue motility				
Tongue coating				
Sublingual collaterals				
Pulse	□deep □wiry □ slippery □thready □hesitant □other_____			
Other symptoms				
Basic syndrome pattern:□qi deficiency□yang deficiency□yin deficiency□blood deficiency□phlegm obstruction□blood stasis□heat toxin□qi stagnation□cold congealing□other_____				

② Echocardiography.
③ Holter monitoring.
④ Minnesota Living with Heart Failure Questionnaire (MLHFQ).
⑤ Cardiac enzymes.
⑥ Blood lipids.
⑦ Blood glucose.
(3) General Information
① Demographics: age, sex, marital status, height, weight, ethnicity.
② Clinical data: vital signs, medical history, concomitant medications, allergy history.
③ Procedural characteristics: access site, target vessels, stent data, time since revascularization.
(4) Safety Outcomes
Vital signs, complete blood count, liver and kidney function, other adverse reactions, and adverse events.

3.10 Emergency Management

If a patient's condition worsens or does not respond to treatment, the treating physician may implement emergency measures, adjust treatment, and decide whether to discontinue the study. All emergency medications and interventions must be recorded.

3.11 Flow Chart



4. Study Progress

(1) Jan 2026 – Jun 2026: Finalize study protocol, inclusion/exclusion criteria, develop clinical data collection forms, complete staff training, ethics review, and trial registration.

(2) Jul 2026 – Jun 2027: Enroll all patients for the RCT, collect clinical data. Publish 1 paper, complete interim report.

(3) Jul 2027 – Jun 2028: Complete follow-up of RCT, validate the prognostic risk model in ≥3 centers with prediction accuracy ≥85%.

(4) Jul 2028 – Dec 2028: Develop ≥1 TCM rehabilitation treatment plan and evaluation system, ≥1 expert consensus, publish 1 paper.

5. Key Issues to be Solved

(1) Verify the efficacy and safety of Qidan XiaoKe Granules in reducing MACE after coronary revascularization;

(2) Establish a standardized TCM rehabilitation treatment plan and comprehensive evaluation system for Qidan XiaoKe Granules that integrates TCM syndrome assessment with modern objective indicators;

(3) Elucidate the relative advantages of Qidan XiaoKe Granules versus placebo in improving quality of life, cardiac function, and inflammatory status, providing high-level evidence for its TCM rehabilitation value.

III. Adverse Events

1. Definitions of Adverse Events (AE) and Serious Adverse Events (SAE)

(1) Adverse Event (AE): Any untoward medical occurrence from the time of informed consent until the last study visit, regardless of causal relationship with the

investigational product. An AE can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with study participation.

AEs include:

-All suspected adverse reactions;

-All reactions due to overdose, abuse, withdrawal, allergy, toxicity, or failure of expected pharmacological action;

-Unrelated diseases, including worsening of pre-existing conditions;

-Injury or accident (note: if a medical condition causes an injury, both should be reported as separate AEs);

-Abnormal physical exam or laboratory results requiring further investigation (excluding repeat testing).

(2) Serious Adverse Event (SAE): Any event that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, causes persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not be immediately life-threatening but could jeopardize the patient or require intervention to prevent the above outcomes also qualify as SAEs.

2. Collection of AE Information

Investigators use concise medical terminology to record all AEs reported by patients or observed directly. At each visit, patients are asked: “Have you had any health problems since your last visit?”

3. Observation and Recording of AEs

All symptoms, signs, and abnormal laboratory findings from informed consent through the last visit are recorded, including time of onset, severity, duration, interventions, and outcome. AEs are recorded on the CRF AE page.

4. Management of AEs and SAEs

(1) Severity grading:

Mild: transient, easily tolerated.

Moderate: interferes with normal activities.

Severe: incapacitating or life-threatening.

(2) AE management: Regardless of causality, investigators provide necessary medical care. All AEs are followed until resolution or stabilization.

(3) SAE reporting: Any SAE must be reported within 24 hours to the Principal Investigator and Ethics Committee by telephone, followed by a written SAE report.

IV. Ethics and Quality Assurance

The study will be approved by the Ethics Committee before initiation. Written informed consent is obtained from each patient. Patient confidentiality is protected: only initials and subject number appear on CRFs. Data consistency across centers will be checked, and queries will be sent to investigators for clarification.

V. Data Management

1. Completion and Transfer of CRF

Completed CRFs are reviewed by the investigator and monitor, then sent to the data management unit.

2. Data Entry and Modification

Data entry is performed by two independent data entry personnel (double entry). Queries are generated and resolved through the clinical monitor.

3. Database Lock

After blind review and confirmation of data correctness, the database is locked by the PI and statistician.

4. Unblinding

After data lock, unblinding is performed by a third-party statistician for final analysis.

VI. Statistical Analysis

1. Statistical Software

SPSS 25.0 or equivalent.

2. Data Description

Continuous variables as mean±SD, median (IQR), min, max; categorical variables as frequencies and percentages.

3. Statistical Methods

All tests are two-sided, $p<0.05$ considered significant. Group comparisons: t-test or Mann-Whitney U test for continuous variables; chi-square or Fisher's exact test for categorical variables; Wilcoxon or CMH for ordinal variables.

4. Statistical Analysis Plan

A detailed SAP will be prepared before database lock.

VII. Final Report and Publication

A final clinical study report will be prepared and submitted for publication regardless of outcome.

VIII. Quality Control

(1) Standard operating procedures (SOPs) will be developed.
(2) All study personnel receive training before study initiation.
(3) All data are verified against source documents.
(4) Independent data management.
(5) Monthly quality control checks.

IX. References

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