Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Effect of Qishen Yiqi Dripping Pill on Clinical Outcomes in Patients with Ischemic Heart Failure: A Post-Hoc Analysis of the CACT-IHF Randomized Trial

Zhou Zhou[1,2,*], Shuai Wang[1,*], Yijia Du[1,2], Zhiqiang Zhao[1], Yingfei Bi[1], Quan Su[1], Yazhu Hou[1], Xianliang Wang[1], Jingyuan Mao[1]

[1]Cardiovascular Department, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, People's Republic of China; [2]Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jingyuan Mao; Xianliang Wang, Cardiovascular Department, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/ National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, No. 88 Changling Road, Xiqing District, Tianjin, 300381, People's Republic of China, Email jymao@126.com; xlwang1981@126.com

Purpose: This study aimed to evaluate whether the effect of Qishen Yiqi dropping pills (QSYQ) on the clinical outcome of patients with chronic ischemic heart failure (IHF) is related to the history of revascularization.

Patients and Methods: An exploratory post-hoc analysis was conducted using data from the CACT-IHF trial, a multicenter, randomized, double-blind, placebo-controlled study involving 640 patients with chronic IHF. Participants were randomized to receive either QSYQ or placebo for a duration of 6 months in addition to standard therapy, with a minimum follow-up period of 12 months.

Results: Among 638 patients (319 QSYQ, 319 placebo) in modified Intention-to-Treat (mITT) population (patients receive at least one trial drug or placebo treatment after randomization), 54.5% had prior revascularization. In the revascularized subgroup, QSYQ significantly reduced the risk of major adverse cardiac events (MACEs) (HR: 0.55, 95% CI: 0.36 to 0.82; P=0.003), second composite endpoint (HR: 0.60, 95% CI: 0.39 to 0.92; P=0.02) and hospitalization for heart failure (HHF) (HR: 0.57, 95% CI: 0.36 to 0.91; P=0.018) compared to placebo, while no significant difference was observed in non-revascularized patients. A significant interaction between revascularization and QSYQ treatment was noted (Pinteraction=0.009). It is suggested that the effect of QSYQ on the outcome of IHF patients is related to the history of revascularization. Adverse event rates were similar between groups.

Conclusion: QSYQ reduces MACEs risk in revascularized chronic IHF patients without increasing adverse events, suggesting its potential as a safe and effective adjunct therapy.

Registration: Clinical Trial Registry Identifier: NCT01555320.

Keywords: ischemic heart failure, Qishen Yiqi Dripping Pills, traditional Chinese medicine, major adverse cardiac events, revascularization

Introduction

Heart failure (HF) is a heterogeneous clinical syndrome characterized by high morbidity and mortality.[1] Globally, there are over 64 million HF patients, and more than half of HF cases are believed to be associated with ischemic heart disease (IHD).[2] Therefore, ischemic heart failure (IHF) is the primary type of HF. Currently, significant progress has been made in improving the prognosis and reducing cardiovascular events for HF patients through pharmacological treatment.[3,4] However, the age-adjusted mortality rate for heart failure continues to rise annually, and the majority of patients still

Received: 26 July 2025
Accepted: 6 November 2025
Published: 15 November 2025

suffer from reduced exercise tolerance and impaired quality of life.[1,5] Consequently, there is an urgent necessity to identify and develop effective and safe complementary therapies to further benefit IHF patients.

Traditional Chinese medicine (TCM) has steadily garnered recognition in both Asian and Western nations as a vital component of complementary therapy for HF.[6,7] Qishen Yiqi Dripping Pills (QSYQ) is a TCM formula consisting of *Astragalus membranaceus Bunge* (Leguminosae), *Salvia miltiorrhizae* C. Y.Wu (Lamiaceae), *Panax notoginseng* (Burkill), and extract of *Dalbergia odorifera* T.C.Chen (Fabaceae). It received approval from the China National Medical Products Administration in 2003 for the treatment of IHD. It is also recommended by Chinese HF guidelines for the management of ischemic heart failure (IHF).[8,9] Preclinical research has demonstrated that QSYQ exhibits benefits in mitigating myocardial fibrosis, enhancing myocardial energy metabolism, and alleviating myocardial microvascular inflammation.[10–12] Our prospective cohort study, registered with ChiCTR (ChiCTR-ONRC-14004407), revealed that the utilization of QSYQ was independently correlated with an increase in ejection fraction, an improvement in New York Heart Association (NYHA) functional class, and a reduction in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score among patients with IHF.[13] However, the impact of QSYQ on the clinical outcomes of IHF patients is currently unclear.

CACT-IHF trial (Complementary Treatment with Qishen Yiqi dripping pills on Ischemic Heart Failure) is a randomized double-blind placebo-controlled trial aimed at evaluating the efficacy and safety of QSYQ in patients with IHF.[14] QSYQ was incorporated into the established treatment protocol for chronic IHF patients, demonstrating promising outcomes. Specifically, six months of QSYQ treatment resulted in an increased 6-minute walk distance (6MWD), an improvement in NYHA functional class, and a decreased MLHFQ score. In the CACT-IHF trail, no difference was observed in the risk of composite endpoints between the QSYQ group and the placebo group over the 12-month follow-up period. It is noteworthy that heart failure patients exhibit substantial variability in their response to pharmacological interventions.[15] A short-term follow-up RCT study found that QSYQ treatment significantly reduced troponin I levels and decreased the incidence of microcirculatory dysfunction in patients after percutaneous coronary intervention (PCI).[16] Another observational study revealed that one-year QSYQ treatment can reduce the occurrence of clinical endpoints in patients with acute coronary syndrome (ACS) after PCI.[17] Therefore, to identify the subset of IHF patients most likely to benefit from QSYQ treatment, this study will utilize data from the CACT-IHF trial to examine the differential effects of QSYQ on the risk of MACEs in IHF patients who have or have not undergone revascularization (including PCI or CABG). The findings aim to provide a valuable reference for further research on QSYQ's role in improving clinical outcomes in IHF patients.

Materials and Methods

Trial Design and Patient Population

The CACT-IHF trial is a multicenter, double-blind, placebo-controlled, randomized clinical trial that conducted across 32 research centers in China from March, 2012, to August, 2014 (a detailed listing of these centers and investigators can be found in Supplement 1 eTable 1) and the trial has been registered on ClinicalTrials.gov (NCT01555320). The primary objective of this trial was to assess the effect of QSYQ on exercise tolerance, quality of life, and cardiovascular outcomes among patients with chronic IHF. The comprehensive protocol, encompassing trial design, statistical analysis methodologies, patient inclusion and exclusion criteria, as well as the key findings of the study, have all been published.[14,18]

The trial enrolled patients aged 40–79 years with a history of ischemic heart failure (IHF) for at least 3 months or longer, and with NYHA functional class II–IV. During a 10-day run-in phase, the HF treatment plan for all patients was standardized according to relevant guidelines, primarily including medications such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta-blockers, aldosterone receptor antagonists (MRA), diuretics, vasodilators, and digoxin, as well as daily HF management measures such as salt and water restriction, weight monitoring, and moderate exercise. The main exclusion criteria included other severe cardiovascular and cerebrovascular diseases (such as acute heart failure, acute coronary syndrome within the past 30 days, uncontrolled hypertension, etc)., patients who had already undergone cardiac resynchronization therapy, severe endocrine diseases, malignant tumors, and

patients with suspected or confirmed allergy to QSYQ or placebo. The complete inclusion and exclusion criteria can be found in Supplement 2 and the published protocol.[18]

This trial was conducted in accordance with the Declaration of Helsinki and relevant regulations in China. The study protocol was reviewed and approved by the ethics review committees of all participating centers, and all participants provided written informed consent before the start of the trial (TYLL2011[K]005). An independent data monitoring committee oversaw the trial.

This study conducted an exploratory post-hoc analysis of MACEs and various other outcomes derived from the CACT-IHF trial, stratifying the patients based on their history of revascularization therapy. The results of this study were written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized trials (Supplement 3).[19] The data used in this study has been approved by the CACT-IHF Steering Committee.

Randomization

The NYHA functional class, research center, and revascularization method (PCI or CABG) were used as stratification factors. Randomization codes were generated using a central randomization system (IWRS/IVRS software), and eligible participants were randomly assigned in a 1:1 ratio to receive QSYQ or placebo in addition to the standard treatment plan for HF. The researchers and participants were blinded to the treatment allocation. The trial drug and placebo were identical in packaging, appearance, odor, and taste.

Intervention and Follow-Up

Prior to participating in the study, patients signed a written informed consent form. During the screening period (V0), patients undergone screening for inclusion and exclusion criteria and received a standardized adjustment of their western medicine treatment plan for HF in a period of 10 days (±3 days). Eligible patients had their baseline information collected during the baseline period (V1) and were randomly assigned to receive either QSYQ or placebo treatment (provided by Tasly Pharmaceutical Co., Ltd., Tianjin, China), administered three times a day, one packet (0.52g) each time, for a duration of 6 months. Study visits (V2-V6) were conducted at 1, 3, 6, 9, and 12 months after randomization, and some patients may have received two additional visits (V7, V8) until the last enrolled patient completed the 12-month follow-up. During each visit, information on patients' vital signs, exercise testing, laboratory tests, quality of life scales, MACEs, adverse events, concomitant treatments, and adherence to study medication was recorded.

Outcomes

The primary efficacy outcome was a composite of the MACEs during the follow-up period, which included cardiovascular death and hospitalizations due to cardiovascular events (heart failure, acute coronary syndrome, stroke, unplanned revascularization). The secondary composite outcome is composed of cardiovascular death and hospitalization for heart failure (HHF). Secondary outcomes include BNP levels, left ventricular ejection fraction (LVEF), NYHA functional class, and MLHFQ scores at 6 months after randomization. Safety outcomes encompass all adverse events during the follow-up period, with adverse events being recorded at each study visit and serious adverse events being reported to the principal investigator within 24 hours. In cases where necessary treatment requires it, patients may be unblinded according to the unblinding procedure with the permission of the principal investigator.

Statistical Analysis

This study is an exploratory post hoc analysis without prior hypothesis, no adjustment for multiple testing was performed, and all analyses should be considered exploratory. Evaluate the efficacy of the main clinical outcomes MACEs to clarify the power of the obtained results. The hazard rates of MACE events in the control group of this study were 0.36 and 0.27 in the revascularization and non revascularization populations, respectively. The control group had a dropout rate of 0.04, and the QSYQ group had a dropout rate of 0.06. The hypothesis testing efficacy was 0.8, and the confidence level was 0.95. Based on the existing sample size, the highest hazard ratios that can be detected in the revascularization population and non-revascularization population are 0.59 and 0.51, respectively.

Baseline characteristics and outcomes were analyzed based on a modified intention to treat (mITT) population of 638 patients, the definition of mITT is that patients receive at least one trial drug or placebo treatment after randomization. Baseline characteristics were statistically described using mean (SD), medians (IQRs), and number of cases (percentages). The nearest neighbor interpolation method was used to process missing data. We employed the Cox hazard analysis to assess the hazard ratio (HR) and 95% confidence interval (CI) for the occurrence of MACEs in patients who had undergone or not undergone revascularization, comparing QSYQ with placebo. According to the baseline characteristics, the use of beta blockers and the history of diabetes were included as confounding factors in the models of people who received revascularization and people who did not receive revascularization, respectively. Cumulative endpoint curves were plotted using the Kaplan–Meier method, and differences between curves were tested using the log-rank method. Additionally, the number of events per 100 patient-years of follow-up and 1-years number needed to treat (NNT) was calculated, along with the absolute risk change in the QSYQ group compared to the placebo group. For other efficacy outcomes, Student's *t*-test and the Wilcoxon test were used for intergroup comparisons of continuous and categorical variables, respectively, while paired-sample *t*-test and Wilcoxon signed-rank test were used for intragroup comparisons. An interaction test between revascularization status and treatment assignment was conducted by adding these variables to the linear regression model. Sensitivity analyses were performed using the per-protocol set data to assess the robustness of the study results. The safety of QSYQ was analyzed in both the revascularized and non-revascularized populations using the safety analysis set. Statistical analyses were conducted using R 4.3.1 software (R Foundation for Statistical Computing, Vienna, Austria), two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristic

Between March, 2012 and August, 2014, a total of 640 patients were randomly assigned to the QSYQ group (n=320) and the Placebo group (n=320). Among them, 638 patients were included in the safety set and the mITT population (319 in the QSYQ group and 319 in the Placebo group), and 606 subjects were included in the per-protocol set (PPS, 300 in the QSYQ group and 306 in the Placebo group) (Figure 1). The median follow-up time was 12.3 months (interquartile range

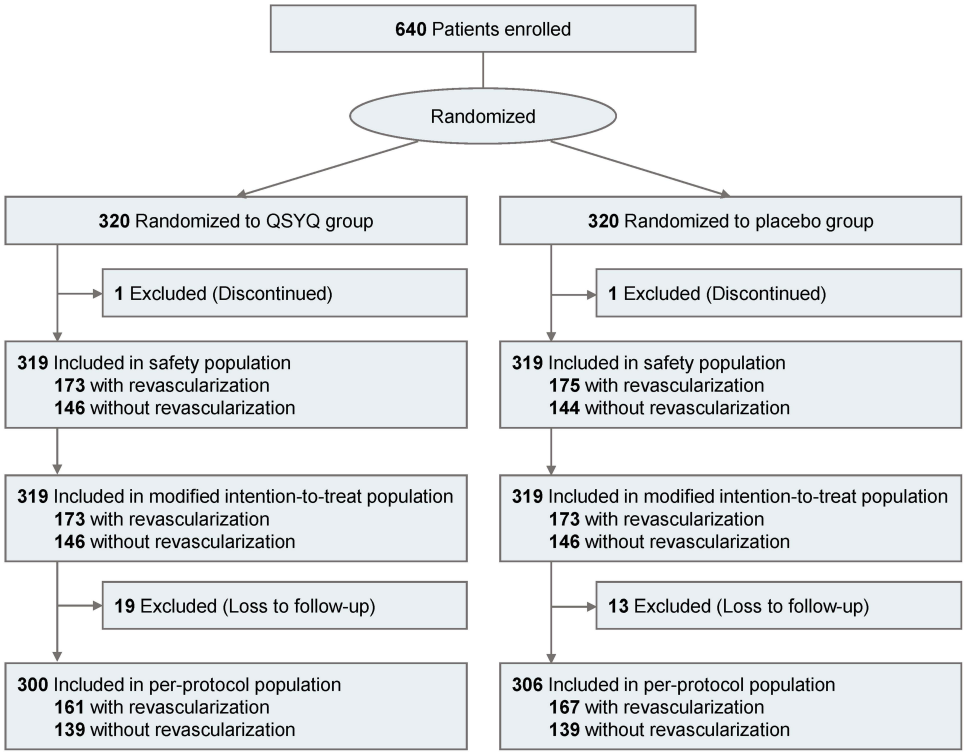

Figure 1 Study Flow Diagram.

[IQR] 12.1–18.2). The mean age of mITT population was 65±9 years, with 178 (28%) females. The mean LVEF was 37.7±7.2%, and the median BNP level was 420 pg/mL (IQR 65–480). In the mITT population, 348 (54.5%) patients had undergone revascularization (173 in the QSYQ group and 175 in the Placebo group). Overall, compared with the IHF population that had not undergone revascularization, those who had undergone revascularization were older, had more severe disease (higher BNP levels and NYHA functional class), poorer exercise tolerance, and lower quality of life (lower 6MWD and higher MLHFQ scores) (P<0.05). Baseline characteristics were balanced between the QSYQ and Placebo groups among IHF patients who had or had not undergone revascularization (Table 1). Among the patients who had undergone revascularization, 329 (94.5%) had undergone percutaneous coronary intervention (PCI), 72 (20.7%) had undergone coronary artery bypass grafting (CABG), and 53 (15.2%) had undergone both.

Table 1 Baseline Characteristics of the Modified Intention-to-Treat Population

Characteristics	Undergone Revascularization			Non-Undergone Revascularization		
	QSYQ (n=173)	Control (n=175)	P Value	QSYQ (n=146)	Control (n=144)	P Value
Age, mean (SD), y	66.28 (8.63)	65.45 (8.82)	0.371	63.49 (9.36)	64.24 (9.05)	0.489
Sex			0.517			0.288
Male	114 (65.9)	122 (69.7)		109 (74.7)	116 (80.6)	
Female	59 (34.1)	53 (30.3)		37 (25.3)	28 (19.4)	
BMI, mean (SD)	23.35 (3.44)	23.91 (3.22)	0.116	24.78 (3.64)	25.14 (3.45)	0.386
SBP, mean (SD), mmHg	126.62 (15.08)	125.66 (15.15)	0.553	125.87 (17.59)	124.81 (15.83)	0.589
Resting heart rate, mean (SD), beats per minute	73.40 (11.05)	72.71 (11.49)	0.572	71.34 (10.58)	71.56 (14.07)	0.877
Smoking	73 (42.2)	69 (39.4)	0.677	76 (52.1)	74 (51.4)	1
LVEF, mean (SD), %	37.28 (7.85)	37.26 (7.03)	0.983	37.78 (7.45)	38.58 (6.38)	0.329
BNP, median (IQR), $pg \cdot mL^{-1}$	269 (98.95–697.00)	259.5 (117.8–579.8)	0.484	148 (36.0–387.0)	130.0 (50.2–350.0)	0.602
Creatinine, mean (SD), $\mu mol \cdot L^{-1}$	87.22 (30.68)	88.77 (32.49)	0.649	83.77 (23.80)	82.64 (21.41)	0.67
BUN, mean (SD), $mmol \cdot L^{-1}$	7.16 (3.52)	7.70 (4.01)	0.183	6.66 (3.02)	6.33 (2.49)	0.303
NYHA functional class			0.455			0.513
II	70 (40.5)	64 (36.6)		79 (54.1)	69 (47.9)	
III	86 (49.7)	98 (56.0)		63 (43.2)	69 (47.9)	
IV	17 (9.8)	13 (7.4)		4 (2.7)	6 (4.2)	
MLHFQ, median (IQR), score	37.0 (24.0–55.0)	36.0 (23.5–53.0)	0.66	29.0 (17.25–42.0)	32.0 (16.75–48.5)	0.193
6MWD, mean (SD), m	319.95 (95.88)	323.77 (101.14)	0.718	355.25 (103.84)	347.30 (98.02)	0.504
History of HF and CAD, (median (IQR), y						
Time from initial diagnosis of heart failure	2.0 (1.0–5.0)	3.0 (1.25–5.0)	0.637	2.5 (1.0–5.0)	2.0 (1.0–5.0)	0.521
Time from initial diagnosis of CAD	6.0 (3.0–10.0)	7.0 (4.0–13.0)	0.06	6.0 (3.0–10.0)	5.0 (2.0–9.0)	0.066
PCI history	165 (95.4)	164 (93.7)	0.655	0 (0)	0 (0)	-
CABG history	33 (19.1)	39 (22.3)	0.544	0 (0)	0 (0)	-
Myocardial infarction	131 (75.7)	125 (71.4)	0.431	100 (68.5)	103 (71.5)	0.663
Medical history						

(*Continued*)

 https://doi.org/10.2147/DDDT.S556373

Table 1 (Continued).

Characteristics	Undergone Revascularization			Non-Undergone Revascularization		
	QSYQ (n=173)	Control (n=175)	P Value	QSYQ (n=146)	Control (n=144)	P Value
Arrhythmia	62 (35.8)	61 (34.9)	0.937	62 (35.8)	61 (34.9)	0.124
Hypertension	99 (57.2)	107 (61.1)	0.526	99 (57.2)	107 (61.1)	0.293
Diabetes mellitus	46 (26.6)	50 (28.6)	0.769	46 (26.6)	50 (28.6)	0.033
Hyperlipidemia	49 (28.3)	64 (36.6)	0.126	49 (28.3)	64 (36.6)	0.868
Family history	32 (18.5)	25 (14.3)	0.359	32 (18.5)	25 (14.3)	0.838
Medication						
Antiplatelet	153 (88.4)	165 (94.3)	0.08	143 (97.9)	143 (99.3)	0.624
β-blocker	122 (70.5)	141 (80.6)	0.04	121 (82.9)	112 (77.8)	0.345
ACEI	64 (37.0)	71 (40.6)	0.565	57 (39.0)	56 (38.9)	1
ARB	55 (31.8)	50 (28.6)	0.591	46 (31.5)	44 (30.6)	0.962
Statin	120 (69.4)	130 (74.3)	0.367	120 (82.2)	128 (88.9)	0.146
MRA	83 (48.0)	91 (52.0)	0.52	60 (41.1)	52 (36.1)	0.453
Diuretic	85 (49.1)	94 (53.7)	0.455	69 (47.3)	56 (38.9)	0.187
Nitrate	108 (61.7)	104 (60.1)	0.845	88 (60.3)	88 (61.1)	0.979
CCB	33 (19.1)	34 (19.4)	1	29 (19.9)	25 (17.4)	0.692
Digoxin	50 (28.9)	61 (34.9)	0.282	40 (27.4)	28 (19.4)	0.144

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, brain-type natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; LAD, left anterior descending branch; LCX, left circumflex artery; LM, left main; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QSYQ, Qishen Yiqi Dripping Pills; RCA, right coronary artery; SBP, systolic blood pressure; 6MWD, six minute walking distance.

Primary Outcome

As shown by the Kaplan–Meier curves (Figure 2), among patients with a history of revascularization, the risk of MACEs in the QSYQ group was reduced compared to the placebo group during follow-up (HR: 0.55, 95% CI: 0.36 to 0.82; P=0.003) (Figure 2a), this result is within the detectable effect range of this study (with 80% efficacy and 95% confidence), both events per 100 patient-years (18.7 vs 34.0) and 1-year estimated NNT values 9.9 (5.3 to 72.7) were beneficial for the QSYQ group (Figure 3). However, there was no statistical difference in the risk of MACEs among patients who had not undergo revascularization (P>0.05) (Figure 2b). The risk of the second composite endpoint of cardiovascular death and HHF was reduced by 40% among patients who had undergo revascularization (17.0 vs 28.2 events per 100 patient-years; HR: 0.60, 95% CI: 0.39 to 0.92; P=0.02), 1-year estimated NNT values was 12 (Figure 2c and 3), but there was no statistical difference among patients who had not (P>0.05) (Figure 2d). The risk of HHF was reduced by 43% (14.5 vs 25.1 events per 100 patient-years; HR: 0.57, 95% CI: 0.36 to 0.91; P=0.018), 1-year estimated NNT values was 11.7 (Figure 3). However, among patients who had not undergone revascularization, no statistically significant differences were observed in these outcomes between the QSYQ group and the placebo group (P>0.05). The results of the absolute risk analysis were consistent with those of the HR analysis (Figure 3). Interaction analysis revealed that whether or not revascularization was performed had significant interactions with the effect of QSYQ in reducing the MACEs ($P_{interaction}$ = 0.009), the composite endpoint ($P_{interaction}$ = 0.023), and HHF ($P_{interaction}$ = 0.04), but not with cardiovascular death ($P_{interaction}$ = 0.073) (Figure 3). Sensitivity analysis conducted on the PPS yielded conclusions consistent with the aforementioned results. In the PPS population, QSYQ reduced the risk of MACEs in patients who had undergone revascularization (HR: 0.50, 95% CI: 0.32 to 0.76; P=0.001), but had no effect on patients who had not

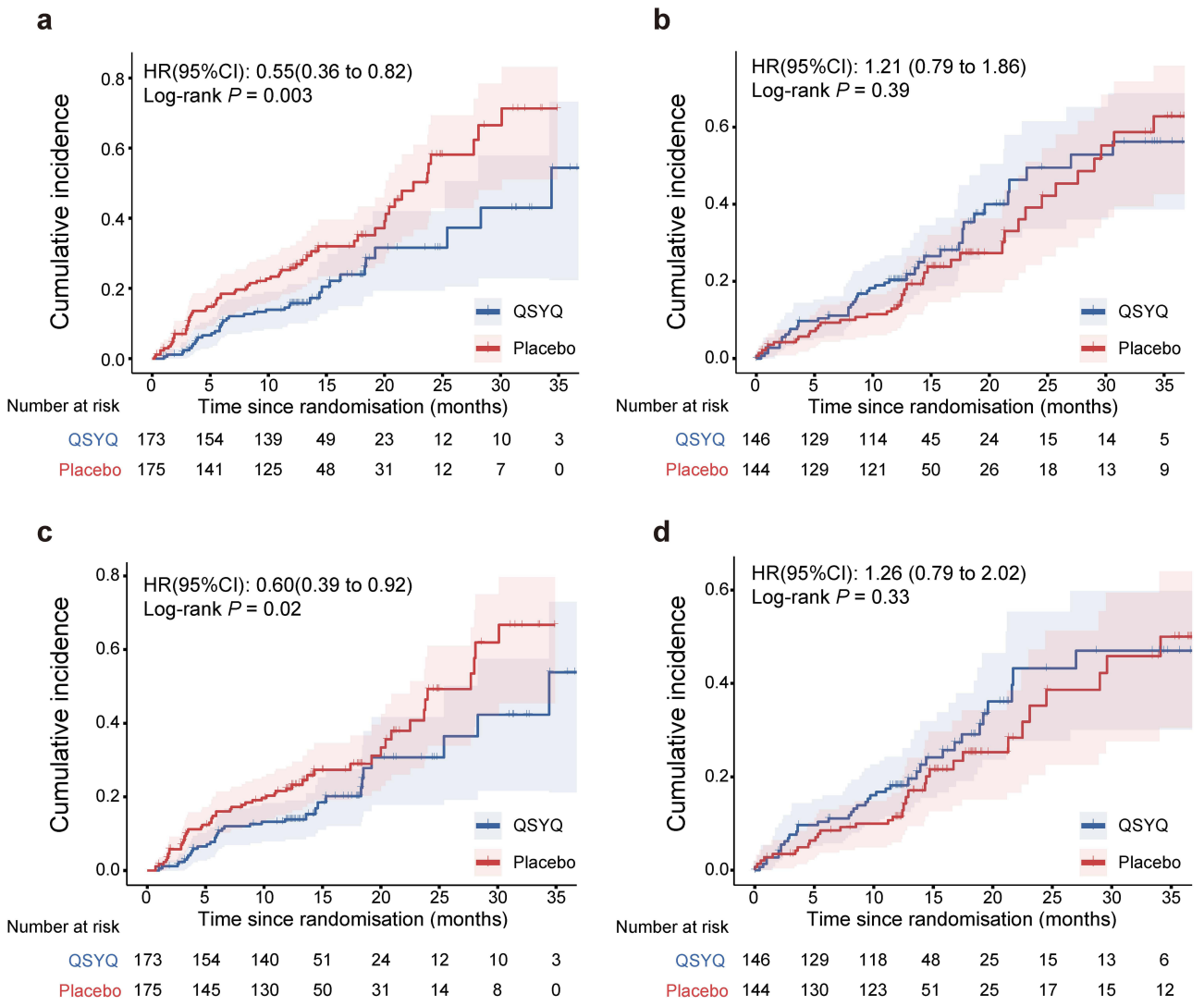

Figure 2 Cumulative Incidence Curve of Clinical Outcomes in Modified Intention-to-Treat Population. (**a**) MACEs of patients who have undergone revascularization; (**b**) MACEs in patients who have not undergone revascularization; (**c**) Secondary composite outcomes in patients who have undergone revascularization; (**d**) Secondary composite outcomes in patients who have not undergone revascularization.
Abbreviations: CI, confidence interval; QSYQ, Qishen Yiqi Dripping Pills; HR, hazard ratio.

undergone revascularization (HR: 1.2, 95% CI: 0.77 to 1.87; P=0.418) (eTable 2 in Supplement 1). To verify that the effect of QSYQ on the MACEs in IHF patients who had undergone revascularization was not attributed to other differences between the two population, we conducted an interaction analysis between QSYQ and multiple important variables, including age, gender, BMI, revascularization, LVEF, and NYHA functional class. The results indicated that only revascularization had an interaction with QSYQ (eFigure 1 in Supplement 1). This suggests that QSYQ may have a more significant effect in reducing the MACEs of IHF patients after coronary artery recanalization.

Secondary Outcomes

As shown in Table 2, for the secondary outcomes, QSYQ did not further improve BNP and LVEF in patients regardless of whether they undergone revascularization (P>0.05). However, six months of QSYQ treatment increased the 6MWD in both patients who undergone revascularization (361.37±98.72 vs 325.16±109.08; P=0.001) and those who did not (386.17±109.00 vs 359.29±95.71; P=0.026). In patients who undergone revascularization, the reduction in MLHFQ score from baseline was significantly greater in the QSYQ group than in the placebo group (−9.0 [IQR, −19 ~ 2] vs −6 [IQR, −16 ~ 0]; P=0.02). In patients who did not undergo revascularization, the changes of MLHFQ compared to baseline was no significant difference between the

https://doi.org/10.2147/DDDT.S556373

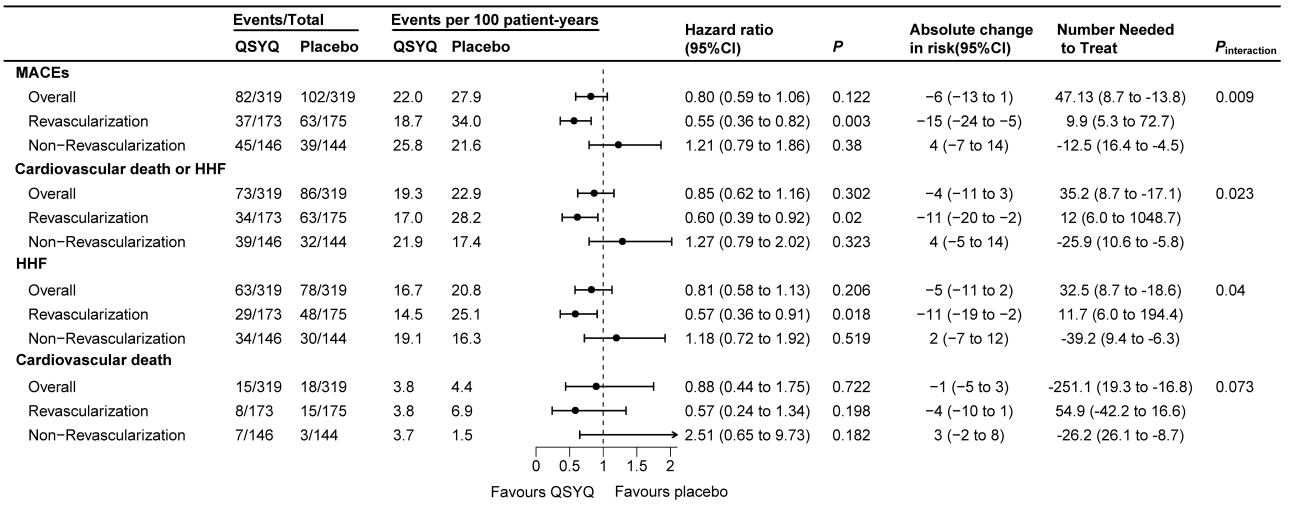

Figure 3 Forest Plot and Interaction Analysis of MACEs in Modified Intention-to-Treat Population.
Abbreviations: CI, confidence interval; QSYQ, Qishen Yiqi Dripping Pills; HR, hazard ratio; MACEs, major adverse cardiovascular events; HHF, hospitalized for heart failure.

two groups (−8.0 [IQR, −19 ~ −1] vs −6 [IQR, −16.25 ~ 0]; P=0.11). QSYQ improved the NYHA functional class in patients who undergone revascularization (P=0.045). In summary, the effects of QSYQ on secondary outcomes were similar in both patients who undergone revascularization and those who did not, improving exercise tolerance, quality of life, and NYHA functional class. This conclusion was confirmed in the interaction analysis, which showed no significant interaction between the effects of revascularization and QSYQ on BNP ($P_{interaction}$=0.94), LVEF ($P_{interaction}$=0.95), 6WMD ($P_{interaction}$=0.57), MLHFQ score ($P_{interaction}$=0.23), and NYHA functional class ($P_{interaction}$=0.84) in IHF patients. The same conclusion was reached in the PPS analysis (eTable 3 in Supplement 1).

Table 2 The Impact of QSYQ on Secondary Outcomes in Two Subgroups at 6 Months

Parameter	QSYQ (n=319[a])	Control (n=319[a])	Difference or RR (95% CI)	P Value	$P_{interaction}$
BNP at 6th month, median (IQR), pg·mL^{-1}					0.94
Revascularization	196.00 (73.95~489.50) [b]	182.50 (64.08~584.75) [c]	NA	0.92	
Non-Revascularization	104.00 (38.65~297.50) [b]	106.00 (44.65~280.00) [b]	NA	0.94	
LVEF at 6th month, mean (SD), %					0.95
Revascularization	42.08 (10.35) [b]	41.94 (9.49) [b]	0.14 (−1.95 to 2.24)	0.89	
Non-Revascularization	43.30 (11.53) [b]	43.25 (9.56) [b]	0.14 (−2.50 to 2.40)	0.97	
6MWD at 6th month, mean (SD), m					0.57
Revascularization	361.37 (98.72) [b]	325.16 (109.08) [c]	36.21 (14.28 to 58.14)	0.001	
Non-Revascularization	386.17 (109.00) [b]	359.29 (95.71) [b]	36.21 (3.18 to 50.59)	0.026	
Changes in MLHFQ compared to baseline at 6th month, median (IQR), score					0.23
Revascularization	−9 (−19 ~ −2)	−6 (−16 ~ 0)	NA	0.02	
Non-Revascularization	−8 (−19 ~ −1)	−6 (−16.25 ~ 0)	NA	0.11	

(*Continued*)

Table 2 (Continued).

Parameter	QSYQ (n=319[a])	Control (n=319[a])	Difference or RR (95% CI)	P Value	$P_{interaction}$
NYHA functional class at 6th month					0.84
Revascularization					
Improved	66 (38.2)	52 (29.7)	1.28 (0.94 to 1.75)	0.045	
Remained	105 (60.7)	115 (65.7)	0.92 (0.76 to 1.11)		
Deteriorated	2 (1.2)	8 (4.6)	0.25 (0.05 to 1.39)		
Non-Revascularization					
Improved	61 (41.8)	46 (31.9)	1.31 (0.94 to 1.82)	0.07	
Remained	82 (56.2)	93 (64.6)	0.87 (0.71 to 1.07)		
Deteriorated	3 (2.1)	5 (3.5)	0.59 (0.04 to 9.08)		

Notes: a: In the QSYQ group, 173 patients undergone revascularization while 146 patients did not; In the placebo group, 175 patients undergone revascularization while 144 patients did not. b: The difference compared to baseline is statistically significant. c: The difference compared to baseline is not statistically significant.

Abbreviations: BNP, brain-type natriuretic peptide; CI, confidence interval; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; QSYQ, Qishen Yiqi Dripping Pills; RR, relative risk; 6MWD, six minute walking distance.

Safety Outcomes

In the safety analysis set, the number of patients experiencing any adverse event during follow-up was 10 (5.8%) in the QSYQ group and 12 (6.9%) in the placebo group among those who undergone revascularization, and 6 (4.1%) in the QSYQ group and 6 (4.2%) in the placebo group among those who did not undergo revascularization. Regardless of whether revascularization was performed, QSYQ treatment did not increase the risk of adverse events (P>0.05) (eTable 4 in Supplement 1), indicating that QSYQ exhibits reliable safety in both patient population.

Discussion

A systematic review incorporating 59 RCT studies indicates that QSYQ demonstrates good efficacy in improving exercise tolerance, enhancing quality of life, and enhancing cardiac function in patients with IHF.[20] However, the overall quality of the included literature is poor. Based on multiple reports of patients benefiting from QSYQ treatment after revascularization, we assume that QSYQ may exhibit more significant clinical benefits in IHF patients who had undergone revascularization.[16,17] Therefore, we hope to preliminarily confirm the above hypothesis through post-hoc analyses of the CACT-IHF trial.

In this study, after a median follow-up period of 12.3 months (IQR, 12.1–18.2), it was found that QSYQ had a significant interaction with whether patients had undergone revascularization in intervening the clinical outcomes of patients with chronic IHF. Specifically, among patients who had undergone revascularization, QSYQ significantly reduced the risk of MACEs, composite endpoints, and HHF compared to placebo. However, no statistically significant differences were observed in these outcomes between the QSYQ group and the placebo group among patients who had not undergone revascularization. Regardless of whether patients had undergone revascularization therapy, QSYQ improved exercise tolerance, quality of life, and NYHA functional class in patients, with no interaction with revascularization. Furthermore, the safety outcomes were similar between the QSYQ group and the placebo group in both populations. This study provides supportive evidence and research reference for the application of QSYQ in reducing clinical outcomes in chronic IHF patients who have undergone revascularization.

QSYQ is a formula consisting of traditional Chinese medicine herbs and its main active ingredients include organic acids, flavonoids, quinones, saponins, and others.[21] The results of this study reveal the beneficial effects of QSYQ on the clinical outcomes of patients with chronic IHF who have undergone revascularization, suggesting that QSYQ may be involved in cardiac recovery after coronary recanalization in patients with IHD. A previous randomized, double-blind,

double-dummy, non-inferiority, randomized trials involving 3,505 patients found that QSYQ was no less effective than aspirin in preventing the occurrence of clinical endpoint events after myocardial infarction during an 18-month follow-up, demonstrating the protective effect of QSYQ on the long-term prognosis of IHD patients.[22] Revascularization is an important strategy for improving clinical outcomes in patients with severe IHD.[23,24] Previous studies have shown that revascularization can reduce the incidence of composite endpoint events in patients.[25,26] However, myocardial injury and ventricular remodeling following revascularization due to ischemia-reperfusion limit further patient benefits.[27] Preclinical studies have shown that QSYQ can improve the structural and functional abnormalities of myocardial cell mitochondria in rats with myocardial ischemia after reperfusion, while also enhancing cardiac function and ventricular remodeling in rats.[28] Furthermore, QSYQ can alleviate the process of myocardial fibrosis after myocardial ischemia-reperfusion by inhibiting the TGFβ1/Smad signaling pathway.[10] A comparison of the active ingredients of QSYQ in vivo and in vitro using liquid/gas chromatography-mass spectrometry methods revealed that the effective components of QSYQ for improving myocardial ischemia mainly include astragaloside IV, ononin, calycosin, formononetin, tanshinol, salvianolic acid A, rosmarinic acid, cryptotanshinone, ginsenoside Rg1, ginsenoside Rb1, Nerolidol, and santalol, suggesting that QSYQ may improve ischemic myocardial injury through multiple pathways.[29] Astragaloside IV, as a potential drug for the treatment of heart failure, has received widespread attention. Studies have found that HHQ16, a derivative of astragaloside IV, can downregulate Lnc9456 (a long non-coding RNA) to reverse myocardial hypertrophy induced by myocardial ischemia and protect cardiac function.[30] Salvianolic acid A can inhibit myocardial hypertrophy and myocardial fibrosis and reduce myocardial inflammatory damage.[31] Ginsenoside Rg1 can upregulate mitochondrial autophagy in myocardial cells, alleviate oxidative stress damage, and protect mitochondrial function in myocardial cells.[32] In conclusion, the positive effects of QSYQ on the clinical outcomes of patients with chronic IHF after revascularization observed in this study may be attributed to the synergistic protective effects of its various active ingredients on the myocardium after reperfusion.

Limitations

This study has some limitations. Firstly, the study intended to include patients with chronic IHF classified as NYHA functional class II–IV, but most of the successfully enrolled patients were class II–III, which may not fully capture the clinical effects of QSYQ. Secondly, the conclusions of this study are based on an exploratory post-hoc analysis of an RCT, the P value for an interaction alone may not sufficient to draw a conclusion. However, we attempted to minimize these risks by conducting sensitivity analyses on the PPS. In addition, considering the insufficient testing power caused by the sample size, we did not conduct further comparative analysis on the revascularization procedures (PCI and CABG). Lastly, the CACT-IHF trial was completed before the availability of angiotensin receptor-neprilysin inhibition (ARNI) and sodium-glucose cotransporter 2 inhibitor (SGLT2i) in China. The enrolled patients did not receive these two drugs currently recommended for heart failure treatment, thus limiting the generalizability of the results of this study. Therefore, it is necessary to conduct a pre-designed, multi-population, large-sample study in the future to confirm the effect of QSYQ in combination with current guideline-directed medical therapy (GDMT) on the clinical outcomes of patients with chronic IHF after revascularization.

Conclusion

In summary, this study found that QSYQ can reduce the MACEs in chronic IHF patients who have undergone revascularization, but has no significant effect on MACEs in those who have not undergone revascularization. In addition, regardless of whether patients have undergone revascularization, QSYQ is associated with improved exercise tolerance, quality of life, and cardiac function, without increasing the incidence of safety events. These results suggest that QSYQ may be an effective and safe alternative therapy for improving the long-term prognosis and clinical symptoms of chronic IHF patients after revascularization.

Data Sharing Statement

The statistical results and study protocol will be made available with publication. The deidentified participant data and data dictionary will be made available by sending a formal request with methodologically sound proposal to Dr. Jingyuan Mao (E-mail, jymao@126.com).

Acknowledgments

We thank all patients and their families for participating in this study and all of the centers and investigators who devoted their effort and time to this study.

Funding

This work was supported by the Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No. ZYYCXTD-C-202203), the Ministry of Education of the People's Republic of China "Program for Innovative Research Team in University" (No. IRT_16R54), the Clinical Collaboration Project between TCM and Western medicine for Major Complex Diseases (No. ZDYN-2024-A-066), the Special Research Project for TCM Industry of the National Administration of Traditional Chinese Medicine (No. 201007001-02), the TUTCM Graduate Research Innovation Project (No. YJSKC-20232002) and the Tianjin Key Research Areas Program for Traditional Chinese Medicine (No. 2022009). The funders had no role in the design, conduct, data collection, management, analysis, and interpretation of the data; in the preparation, review, and approval of the manuscript; or in the decision to submit the manuscript for publication.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Khan MS, Shahid I, Bennis A, et al. Global epidemiology of heart failure. *Nat Rev Cardiol*. 2024;21(10):717–734. doi:10.1038/s41569-024-01046-6
2. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118(17):3272–3287. doi:10.1093/cvr/cvac013
3. Docherty KF, Vaduganathan M, Solomon SD, et al. Sacubitril/valsartan: neprilysin inhibition 5 years after PARADIGM-HF. *JACC Heart Fail*. 2020;8(10):800–810. doi:10.1016/j.jchf.2020.06.020
4. Tromp J, Ouwerkerk W, van Veldhuisen DJ, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail*. 2022;10(2):73–84. doi:10.1016/j.jchf.2021.09.004
5. Hao G, Wang X, Chen Z, et al. Prevalence of heart failure and left ventricular dysfunction in China: the China hypertension survey, 2012-2015. *Eur J Heart Fail*. 2019;21(11):1329–1337. doi:10.1002/ejhf.1629
6. Hao P, Jiang F, Cheng J, et al. Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. *J Am Coll Cardiol*. 2017;69(24):2952–2966. doi:10.1016/j.jacc.2017.04.041
7. Cheang I, Yao W, Zhou Y, et al. The traditional Chinese medicine Qiliqiangxin in heart failure with reduced ejection fraction: a randomized, double-blind, placebo-controlled trial. *Nat Med*. 2024;30(8):2295–2302. doi:10.1038/s41591-024-03169-2
8. Zhang S, Han Y, Xu D. Chinese guidelines for the diagnosis and treatment of heart failure 2024. *Chin J Cardiol*. 2024;52:235–275.
9. Zhang J, Zhang Y, Huang J, et al. China national heart failure guideline 2023. *Chin J Heart Fail Cardiomyopathy*. 2023;7:215–311.
10. Zheng QN, Wei XH, Pan CS, et al. QiShenYiQi pills(®) ameliorates ischemia/reperfusion-induced myocardial fibrosis involving RP S19-mediated TGFβ1/smads signaling pathway. *Pharmacol Res*. 2019;146. doi:10.1016/j.phrs.2019.104272
11. Wu L, Fan Z, Gu L, et al. QiShenYiQi dripping pill alleviates myocardial ischemia-induced ferroptosis via improving mitochondrial dynamical homeostasis and biogenesis. *J Ethnopharmacol*. 2023;308:116282. doi:10.1016/j.jep.2023.116282
12. Huang Y, Zhang K, Liu M, et al. An herbal preparation ameliorates heart failure with preserved ejection fraction by alleviating microvascular endothelial inflammation and activating NO-cGMP-PKG pathway. *Phytomedicine*. 2021;91:153633. doi:10.1016/j.phymed.2021.153633
13. Wang S, Zhao Z, Wang X, et al. Qishen Yiqi dripping pill for ischemic heart failure: a multicenter prospective cohort study. *J Traditional Chin Med*. 2022;63:635–643.
14. Mao J, Zhang J, Lam CSP, et al. Qishen Yiqi dripping pills for chronic ischaemic heart failure: results of the CACT-IHF randomized clinical trial. *ESC Heart Fail*. 2020;7(6):3881–3890. doi:10.1002/ehf2.12980
15. Shah P, Pellicori P, Cuthbert J, et al. Pharmacological and non-pharmacological treatment for decompensated heart failure: what is new? *Curr Heart Fail Rep*. 2017;14(3):147–157. doi:10.1007/s11897-017-0328-x
16. He GX, Xie J, Jiang H, et al. Effects of Qishen Yiqi Dripping Pills () in reducing myocardial injury and preserving microvascular function in patients undergoing elective percutaneous coronary intervention: a pilot randomized study. *Chin J Integr Med*. 2018;24(3):193–199. doi:10.1007/s11655-017-2955-1
17. Bai RN, Gu F, Che QZ, et al. Effectiveness and Safety of Qishen Yiqi Dripping Pill in patients with acute coronary syndrome after percutaneous coronary intervention: 3-year results from a multicentre cohort study. *Chin J Integr Med*. 2024;30(10):877–885. doi:10.1007/s11655-024-3664-1
18. Hou YZ, Wang S, Zhao ZQ, et al. Clinical assessment of complementary treatment with Qishen Yiqi dripping pills on ischemic heart failure: study protocol for a randomized, double-blind, multicenter, placebo-controlled trial (CACT-IHF). *Trials*. 2013;14(1):138. doi:10.1186/1745-6215-14-138
19. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.
20. Wang XM, Dai GH, Guan H, et al. Clinical efficacy and safety of adjunctive treatment of chronic ischemic heart failure with Qishen Yiqi dropping pills: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2023;10:1271608. doi:10.3389/fcvm.2023.1271608

21. Liu L, Zhou L, Sun Z, et al. Main chemical constituents research of Qishen Yiqi Dropping Pills based on UHPLC-Q-Orbitrap HRMS. *Chinese Traditional and Herbal Drugs*. 2018;49:5761–5771.
22. Shang H, Zhang J, Yao C, et al. Qi-shen-yi-qi dripping pills for the secondary prevention of myocardial infarction: a randomised clinical trial. *Evid Based Complement Alternat Med*. 2013;2013:738391. doi:10.1155/2013/738391
23. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45 (36):3415–3537. doi:10.1093/eurheartj/ehae177
24. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289–1367. doi:10.1093/eurheartj/ehaa575
25. Zimmermann FM, Omerovic E, Fournier S, et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. *Eur Heart J*. 2019;40(2):180–186. doi:10.1093/eurheartj/ehy812
26. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391(10124):939–948. doi:10.1016/S0140-6736(18)30423-9
27. Algoet M, Janssens S, Himmelreich U, et al. Myocardial ischemia-reperfusion injury and the influence of inflammation. *Trends Cardiovasc Med*. 2023;33(6):357–366. doi:10.1016/j.tcm.2022.02.005
28. Chen JR, Wei J, Wang LY, et al. Cardioprotection against ischemia/reperfusion injury by QiShenYiQi Pill® via ameliorate of multiple mitochondrial dysfunctions. *Drug Des Devel Ther*. 2015;9:3051–3066. doi:10.2147/DDDT.S82146
29. Liu LW, Tang M, Zhang ZB, et al. A stepwise integrated strategy to explore quality markers of Qishen Yiqi dripping pills against myocardial ischemia. *Phytomedicine*. 2024;135:156182. doi:10.1016/j.phymed.2024.156182
30. Wan J, Zhang Z, Wu C, et al. Astragaloside IV derivative HHQ16 ameliorates infarction-induced hypertrophy and heart failure through degradation of lncRNA4012/9456. *Signal Transduct Target Ther*. 2023;8(1):414. doi:10.1038/s41392-023-01660-9
31. Dawuti A, Sun S, Wang R, et al. Salvianolic acid A alleviates heart failure with preserved ejection fraction via regulating TLR/Myd88/TRAF/NF-κB and p38MAPK/CREB signaling pathways. *Biomed Pharmacother*. 2023;168:115837. doi:10.1016/j.biopha.2023.115837
32. Guan S, Xin Y, Ding Y, et al. Ginsenoside Rg1 protects against cardiac remodeling in heart failure via SIRT1/PINK1/parkin-mediated mitophagy. *Chem Biodivers*. 2023;20:e202200730.