

Qishen Yiqi dripping pills for chronic ischaemic heart failure: results of the CACT-IHF randomized clinical trial

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Abstract

Aims Qishen Yiqi dripping pills (QSYQ) may be beneficial in patients with ischaemic heart failure (IHF). We aimed to assess the efficacy and safety of QSYQ administered together with guideline-directed medical therapy in patients with IHF.

Methods and results This prospective randomized, double-blind, multicentre placebo-controlled study enrolled 640 patients with IHF between March 2012 and August 2014. Patients were randomly assigned to receive 6 months of QSYQ or placebo in addition to standard treatment. The primary outcome was 6 min walking distance at 6 months. Among the 638 IHF patients (mean age 65 years, 72% men), the 6 min walking distance increased from 336.15 ± 100.84 to 374.47 ± 103.09 m at 6 months in the QSYQ group, compared with 334.40 ± 100.27 to 340.71 ± 104.57 m in the placebo group (mean change +38.32 vs. +6.31 m respectively; $P < 0.001$). The secondary outcomes in composite clinical events, including all-cause mortality and emergency treatment/hospitalization due to heart failure, were non-significantly lower at 6 months with QSYQ compared with placebo (13% vs. 17%; $P = 0.45$), and the change of brain natriuretic peptide was non-significantly greater with QSYQ compared with placebo (median change −14.55 vs. −12.30 pg/mL, respectively; $P = 0.21$). By contrast, the Minnesota Living with Heart Failure Questionnaire score significantly improved with QSYQ compared with placebo (−11.78 vs. −9.17; $P = 0.004$). Adverse events were minor and infrequent with QSYQ, similar to the placebo group.

Conclusions Treatment with QSYQ for 6 months in addition to standard therapy improved exercise tolerance of IHF patients and was well tolerated.

Keywords Ischemic heart failure; 6 min walking distance; Traditional Chinese medicine

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Introduction

Ischaemic heart disease has become the main cause of heart failure (HF) in China in recent decades.^{1,2} Patients with ischaemic HF (IHF) have a poorer quality of life and worse prognosis than those without IHF, even after receiving the standard international guideline-directed medical therapy. Traditional Chinese medicine may have a complementary effect in improving exercise tolerance and cardiac function among patients with HF.^{3–8} The traditional Chinese medicine Qishen Yiqi dripping pills (QSYQ) (Figure 1), produced by the Tasly Pharm. Co., Ltd (Tianjin, China), are a patented medicinal product (drug approval number: Z20030139) that is considered to have the effects of nourishing *Qi* and activating blood (i.e. promoting blood circulation). It is used for the integrative treatment of patients with ischaemic heart disease who are also diagnosed with *Qi* deficiency and blood stasis or IHF. According to the instruction, the active ingredients of QSYQ include *Astragalus mongholicus*, *Salviae miltiorrhizae radix et rhizoma*, *Panax notoginseng*, and *Dalbergia* wood oil, prepared as fine particles in the form of ‘dripping pills’ (Figure 1). A systematic review showed that QSYQ combined with standard international therapy may improve cardiac function, increase the left ventricular ejection fraction (LVEF), and reduce rehospitalization in patients with chronic IHF.⁹ However, prior studies were limited by small size, observational design, lack of a placebo control arm, or use of biomarkers as surrogate outcomes. To overcome these shortcomings, we

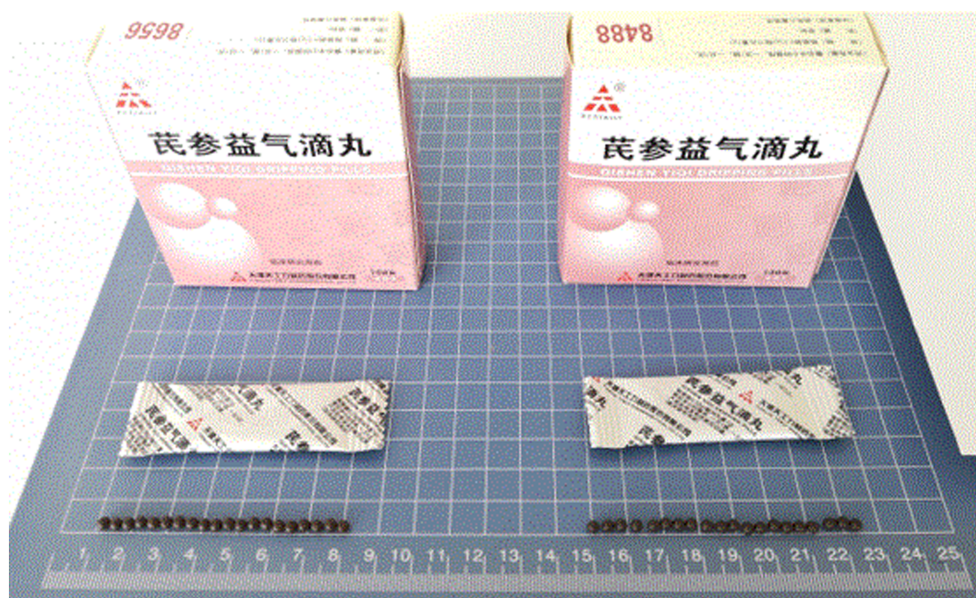
conducted a prospective randomized controlled trial with sufficient statistical power to assess the clinical efficacy [in terms of 6 min walk distance (6MWD)] and safety of QSYQ in addition to guideline-directed medical therapy in patients with IHF.

Methods

Study design and subjects

The design of the Clinical Assessment of Complementary Treatment with Qishen Yiqi dripping pills on Ischemic Heart Failure (CACT-IHF) trial has been published (ClinicalTrials.gov number: NCT01555320).¹⁰ In this randomized, double-blind, placebo-controlled multicentre study, patients with chronic IHF from 32 centres were enrolled from March 2012 to August 2014. The inclusion criteria were as follows: (i) 40–79 years of age; (ii) diagnosis of ischaemic heart disease (previous history of myocardial infarction, coronary angiography or computed tomography angiography suggesting lumen stenosis of at least one major coronary artery branch exceeding 50%, and coronary artery lesions likely closely correlated with HF); (iii) LVEF \leq 45% or a history of HF/related clinical symptoms for more than 3 months; (iv) New York Heart Association (NYHA) functional Class II–IV; and (v) signed informed consent.

Figure 1 Qishen Yiqi (QSYQ) dripping pills and the placebo.



QSYQ Dripping Pills (Placebo)[†]

QSYQ Dripping Pills[†]

The exclusion criteria were as follows: (i) acute decompensated HF or acute disease exacerbation; (ii) unstable clinical condition such as acute coronary syndrome within 30 days, revascularization within 6 months, uncontrolled hypertension despite multiple drugs, malignant arrhythmia, specific forms of cardiomyopathy (e.g. dilated cardiomyopathy, hypertrophic obstructive cardiomyopathy, and myocarditis), acute pulmonary embolism or pulmonary heart disease, severe valvular heart disease, or cerebral stroke within 6 months; (iii) cardiac resynchronization therapy; (iv) use of diuretics or intravenous cardiac and vasodilator drugs in the past 7 days; (v) alanine aminotransferase >2 times of the upper limit of the normal range; (vi) serum creatinine >256 $\mu\text{mol/L}$; (vii) severe endocrine diseases such as hyperthyroidism; (viii) haemoglobin ≤ 9 g/dL; (ix) mental illness or malignant tumours; (x) pregnancy or lactation in women; (xi) drug abuse or allergies; (xii) involvement in other studies in the previous 2 months; and (xiii) inability to perform the 6MWD test due to physical impairment or other reasons.

Randomization and registration

Randomization was performed using a centralized randomization system (IWRS/IVRS software; ClinicalSoft Co. Ltd., Beijing, China). The predefined stratification factors were NYHA status and revascularization status (percutaneous coronary intervention, coronary artery bypass graft, or percutaneous coronary intervention and coronary artery bypass graft). A total of 640 enrolled patients were randomly assigned to receive QSYQ or placebo on top of standard international medication, with 320 patients in each group. Patients, investigators, and the study statistician were all blinded to treatment allocation. To ensure masking, the taste, shape, colour, and packaging of the placebo and QSYQ were identical (*Figure 1*, provided by Tasly Pharm. Co., Ltd).

Treatment strategy, drug therapy, and follow-up

Standard international guideline-directed medications were prescribed according to the Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guideline¹¹ and the 2007 American College of Cardiology guidelines. The patients received one package (0.52 g) of QSYQ or matched placebo thrice daily for 6 months in the combined treatment period. After 6 months, standard international medication was continued, and patients were followed up for 12 months to assess late effects. Any other traditional Chinese medicine preparation was forbidden during the entire research period. NYHA functional classification and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores were assessed at baseline and at 1, 3, 6, 9, and 12 months of follow-up. LVEF was measured by independent investigators at baseline and

at the 6 month follow-up using the biplane Simpson method on standard two-dimensional echocardiography. Brain natriuretic peptide (BNP) was similarly determined at baseline and 6 months using the Biosite point-of-care test meter (Triage[®] MeterPro, Quidel Cardiovascular Inc. San Diego, CA, USA) at all sites. Other laboratory parameters (serum potassium, sodium, chlorine, alanine aminotransferase, aspartate aminotransferase, urea nitrogen, creatinine, routine blood indexes, and routine urine parameters) were measured at qualified laboratories in each centre.

Outcomes

The 6MWD at baseline and 6 months was assessed as the primary outcome following the American Thoracic Society guidelines using a 30 m straight line. Patients were verbally encouraged to continue walking every minute. Secondary outcomes included 6MWD at 3 months; changes in BNP, LVEF, NYHA functional classification, and MLHFQ score at 6 months; and composite clinical endpoints (including all-cause mortality within 12 months, emergency treatment/hospitalization due to HF, acute coronary syndrome, malignant arrhythmia, cardiogenic shock, revascularization, cerebral stroke, pulmonary embolism, and peripheral vascular events). Safety was assessed using vital signs (including the heart rate and blood pressure), laboratory tests (routine blood and urine tests, hepatic and renal function, and blood electrolyte levels), electrocardiography, and surveillance for adverse events.

Study management

This trial was designed and run by the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, which coordinated multiple centres. The study followed the ethical guidelines of the Declaration of Helsinki, and signed informed consent was provided by all subjects. The trial protocol was approved by the ethics committee of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (Approval No. TYLL2011 [K] 005). All clinical endpoints were evaluated by the clinical events committee. The data and safety monitoring board ensured the safety of the study participants, while maintaining trial integrity. All data were managed by the Evidence-based Medicine Center of Tianjin University of Traditional Chinese Medicine. Statistical analysis was conducted by the Clinical Research Institute of Peking University. The study was supported by the Special Fund for Traditional Chinese Medicine Research in the Public Interest and registered at the Chinese Clinical Trials Registry (registration number: ChiCTR-TRC-11001863) and ClinicalTrials.gov (registration number: NCT01555320).

Statistical analysis

As determined in the study protocol, the analysis of efficacy followed the modified intention-to-treat (ITT) principles. All randomized patients with at least one primary efficacy assessment were included in the ITT population. Missing data in the primary endpoint were added using the last observation carried forward (LOCF) method. In case of missing baseline, the mean of all patients was used. All patients who received any study treatment were included in the safety population.

Continuous variables were expressed as means (standard deviation) or median (inter-quartile range), depending on the variable distribution. For comparisons between groups, the *t*-test was used for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. The within-subjects *t*-test and Wilcoxon signed-rank test were performed for normally and non-normally distributed variables, respectively. Categorical variables were expressed as number (%) and analysed using the χ^2 test for between-group comparison.

For the analysis of the primary endpoint, changes in the 6MWD at 6 months were evaluated using analysis of covariance, with 6MWD changes from baseline as the dependent parameter, as well as the treatment group, baseline values, and study site as fixed effects, considering the site–treatment interaction. To assess the influence of missing data on the ITT–LOCF and analysis of covariance analysis of the primary endpoint, we fitted a mixed model for repeated measures (MMRM), with missing data assumed to be missing randomly. In the MMRM analysis, treatment group, study site, and visit were included as fixed effects, with visit by group as the interaction term and subjects as random effects.

For composite events in secondary endpoints, log-rank tests with risk curves were used for graphical description. A Cox proportional hazard model was fitted to estimate the hazard ratios for composite events of treatment groups (QSYQ vs. placebo). In the Cox model, the study site was adjusted as a covariate. The analyses of the secondary endpoints in this study should be considered exploratory as they were not adjusted for multiple testing. The restricted mean survival time and competing risk methods were applied, and the section was 0–180 days. A value of $\alpha = 0.05$ in a two-sided test was considered to indicate statistical significance. Statistical analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Minneapolis, MN, USA).

Involvement of the patients and general public

There has been no patient and public involvement as co-producers of research and the patients participated in the study starting with enrolment.

Results

Baseline characteristics

From 19 March 2012 to 21 August 2014, 640 patients with IHF were enrolled, with 320 patients randomly assigned to each treatment group. One patient in each group did not receive treatment as randomized, leaving 319 patients in the QSYQ group and 319 patients in the placebo group. The baseline characteristics were well balanced between the two groups (*Table 1*). The patients' mean age was 65 years, 72% were men, and the majority had a prior myocardial infarction with a mean history of coronary artery disease of >7.5 years. Consistently, >75% of the patients were on standard anti-ischaemic therapy including antiplatelet therapy, beta-blockers, and statins. There was a high proportion of nitrate and calcium channel blocker usage. The patients had a shorter history of HF (mean ~3.5 years), with mean LVEF ~38%, and the majority were in NYHA II–III status with corresponding moderate impairment of their quality of life (mean MLHFQ score ~35) and moderately increased BNP levels (median ~200 pg/mL). Among those receiving anti-failure therapy, ~67% were on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, ~53% were taking loop diuretics, ~45% were on aldosterone antagonists, and ~28% were on digoxin. In the QSYQ group, 319 patients were included in the safety analysis, among whom 307 (96%) completed the 6 month follow-up and 12 discontinued the trial. In the placebo group, 319 patients were included in the safety analysis, among whom 309 (97%) completed the 6 month follow-up and 10 discontinued the trial (Supporting Information, *Figure S1*).

The 6 min walking distance test

Compared with baseline values, the 6MWD increased significantly at the 3 and 6 month follow-up in both groups. The primary outcome, increase in the 6MWD at 6 months, was significantly greater in the QSYQ group than in the placebo group (38.32 vs. 6.31 m, $P < 0.001$) (*Table 2*). This difference remained significant following adjustment for baseline variables (42.07 m in the QSYQ group and 8.88 m in the placebo group at 6 months, indicating a difference of 33.19 m between the two groups, 95% confidence interval: 22.68, 43.71, $P < 0.001$). The increase in 6MWD at 3 months was also greater in the QSYQ group (21.82 vs. 6.81 m, $P < 0.001$), as was the absolute 6MWD at 3 months (357.97 vs. 341.21 m, $P = 0.032$) and 6 months (374.47 vs. 340.71 m, $P < 0.001$), compared with the placebo group (*Figure 2*). Sensitivity analysis using MMRM gave similar results.

Table 1 Baseline characteristics

Parameters	QSYQ group (n = 319)	Placebo group (n = 319)	P value
Demographic data			
Age (years)	65.0 ± 9.1	64.9 ± 8.9	0.861
Gender			
Male	223 (69.9%)	238 (74.6%)	0.185
Female	96 (30.1%)	81 (25.4%)	
Weight (kg)	67.4 ± 12.4	69.4 ± 12.3	0.049
Height (cm)	167.2 ± 7.5	167.9 ± 7.1	0.241
BMI	24.0 ± 3.6	24.5 ± 3.4	0.061
SBP (mmHg)	126.8 ± 16.9	125.6 ± 15.7	0.141
DBP (mmHg)	76.2 ± 9.7	75.0 ± 9.3	0.094
Heart rate (b.p.m.)	72.5 ± 11.3	71.6 ± 11.8	0.136
Disease history			
History of coronary heart disease (years)	7.6 ± 6.3	7.8 ± 6.4	0.680
Course of heart failure with coronary heart disease (years)	3.8 ± 3.8	3.8 ± 3.7	0.872
Coronary angiography or CTA	234 (73.4%)	237 (74.3%)	0.787
PCI	165 (52.1%)	163 (52.4%)	0.928
PTCA	15 (4.7%)	18 (5.6%)	0.592
CABG	33 (10.3%)	39 (12.3%)	0.444
History of myocardial infarction	231 (72.4%)	228 (71.5%)	0.792
History of arrhythmia	94 (29.5%)	105 (32.9%)	0.347
History of hypertension	189 (59.3%)	186 (58.3%)	0.809
History of diabetes	106 (33.2%)	91 (28.5%)	0.199
History of hyperlipidaemia	99 (31.0%)	111 (34.8%)	0.312
Smoking history	149 (46.7%)	143 (44.8%)	0.634
Drinking history	77 (24.1%)	69 (21.6%)	0.451
Medications			
Antiplatelet drugs	295 (92.5%)	307 (96.2%)	0.058
Beta-blockers	246 (77.1%)	251 (78.7%)	0.703
ACEI/ARB	213 (66.8%)	217 (68.0%)	0.800
Statins	245 (76.8%)	258 (80.9%)	0.245
Nitrates	194 (60.8%)	194 (60.8%)	1.000
Calcium antagonists	63 (19.8%)	57 (17.9%)	0.613
Aldosterone receptor antagonists	144 (45.1%)	147 (46.1%)	0.874
Diuretics	171 (53.6%)	168 (52.7%)	0.874
Digoxin	92 (28.8%)	89 (27.9%)	0.861
Clinical indicators			
6MWD (m)	336.2 ± 100.8	334.4 ± 100.3	0.849
LVEF (%)	37.5 ± 7.7	37.9 ± 6.8	0.655
BNP (pg/mL)	206.0 (52.0, 579.0)	193.0 (69.8, 467.0)	0.795
Score of MLHFQ	35.3 ± 19.8	36.2 ± 20.9	0.652
NYHA functional classification			0.145
Grade I	0 (0.0%)	0 (0.0%)	
Grade II	149 (46.7%)	133 (41.7%)	
Grade III	149 (46.7%)	167 (52.4%)	
Grade IV	21 (6.6%)	19 (6.0%)	

6MWD, 6 min walking distance; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CTA, computed tomography angiography; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure.

The values are presented as means ± standard deviations or n (%).

Brain natriuretic peptide and left ventricular ejection fraction

Compared with the baseline values, BNP decreased significantly in the QSYQ ($P < 0.001$) and placebo groups ($P = 0.007$) at 6 months, with no statistically significant difference between the two groups ($P = 0.565$) (Table 3). Similarly, LVEF increased significantly compared with the baseline values in both groups at 6 months ($P < 0.001$), with no statistically significant difference between groups ($P = 0.643$) (Table 3).

New York Heart Association and Minnesota Living with Heart Failure Questionnaire

After 6 months of treatment, more patients in the QSYQ group had no or only mild symptoms (NYHA Class I or II), compared with patients in the placebo group ($P = 0.001$; Table 3). The changes of NYHA class from baseline to 6 months in the QSYQ vs. placebo group were as follows: improved in 38.24% vs. 29.47%, unchanged in 60.50% vs. 67.40%, and deteriorated in 1.25% vs. 3.13% ($P = 0.012$) (Table 3).

The MLHFQ score decreased in both groups after 6 months, reflecting an improvement of the quality of life. The improvement was significantly greater in the QSYQ group compared with the placebo group ($P = 0.004$) (Table 3).

The changes of NYHA status and MLHFQ score over 12 months are shown in Supporting Information, Tables S2 and S3. Compared to placebo, the improvement with QSYQ in the NYHA class was evident at 3 months and was sustained until 9 months. Similarly, the improvement with QSYQ in the MLHFQ score was evident at 6 months and was sustained until 12 months.

Composite endpoints

In the QSYQ and placebo groups, the respective incidence rates of composite endpoints at 6 months were 13.17% vs. 16.61%, the incidence rates of hospitalization due to HF were 7.84% vs. 11.29%, and those cardiovascular events were 9.40% vs. 13.17%, while the death rates were 3.76% vs. 4.70% (Table 3).

Follow-up was complete at 12 months in 300 (94%) patients from the QSYQ group and 306 (96%) patients from the placebo group. At 12 months, the incidence rates of composite endpoints in the QSYQ vs. placebo group were 20.38% vs. 22.88%, those of hospitalization due to HF were 12.85% vs. 15.99%, and those of cardiovascular events were 15.67% vs. 19.12%, while the death rates were 5.33% vs. 5.64%, respectively. The Kaplan–Meier curves stratified by composite endpoints are shown in Figure 3. The incidence rates of clinical events in the QSYQ group were lower than in the placebo

Table 2 Primary outcome results: 6 min walk distance

Parameters	QSYQ group (n = 319)	Placebo group (n = 319)	Difference (95% CI)	P value
Baseline	336.15 (100.84)	334.40 (100.27)	1.76 (−13.88, 17.39)	0.849
3rd month	357.97 (99.22)	341.21 (97.97)	16.76 (1.43, 32.09)	0.032
Changes between 3rd month and baseline	21.82 (45.54)	6.81 (45.57)	15.00 (7.92, 22.09)	<0.001
6th month	374.47 (103.09)	340.71 (104.57)	33.76 (17.62, 49.91)	<0.001
Changes between 6th month and baseline	38.32 (56.10)	6.31 (61.25)	32.00 (22.87, 41.13)	<0.001

CI, confidence interval.

The values are presented as means ± standard deviations.

group, but the difference was not statistically significant. When the analysis was restricted to 180 days (duration of treatment), the restricted mean survival time of the incidence rates of hospitalization due to HF at 6 months was 176.103 vs. 171.761 ($P = 0.039$) in the QSYQ and placebo groups, respectively. After accounting for death as a competing risk in competing risk models, the HF hospitalization rate was lower in the QSYQ group than in the placebo group (hazard ratio: 0.550, 95% confidence interval: 0.334, 0.908).

Safety evaluation

The most common adverse events were minor, including cold (0.94%) and dizziness with nausea (0.94%) in the QSYQ group, as well as cold (1.57%) and hematochezia (0.94%) in the placebo group (Table 4). Serious adverse events were rare (three cases in total, none related to QSYQ treatment) and included (i) dizziness requiring in-hospital treatment at Month 3, with symptoms relieved in 2 h and not deemed to be related to treatment; (ii) oral ulcer at 1 month of treatment, cured with multivitamins in 7 days and not deemed to be related to treatment; and (iii) high fever accompanied by nausea and vomiting requiring hospitalization, with recovery in 2 days. In the QSYQ group, there were two cases of liver dysfunction

and two of vomiting, whereby one of each was deemed to be related to the drug (Table 4).

Discussion

Treatment with the traditional Chinese medicine QSYQ for 6 months combined with standard guideline-directed international medications was well tolerated by patients with stable IHF in our prospective multicentre double-blind randomized controlled trial and improved 6MWD compared with placebo. This improvement in exercise tolerance with QSYQ was associated with improvements in NYHA class and MLHFQ score at 6 months, which was sustained for 1 year, as well as a trend towards fewer HF hospitalizations over 6 months but no significant difference in composite clinical events at 1 year. While BNP decreased and LVEF increased over 6 months with QSYQ, these improvements were similar to those in the placebo group.

Despite effective guideline-directed medical therapies for ischaemic heart disease and HF, there is still a high residual risk among patients with IHF. Almost two-thirds of patients with HF with reduced ejection fraction have underlying ischaemic heart disease,^{12,13} and the presence of coronary artery disease is associated with worse outcomes among patients with HF.¹⁴ Although treatments are available, 55–68% of pa-

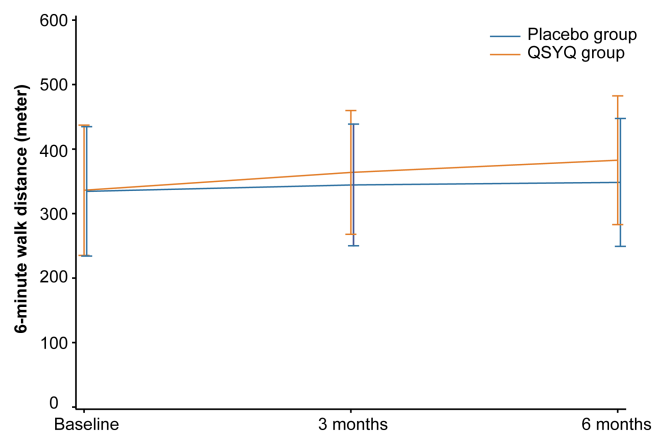
Figure 2 Figure for the main outcome.

Table 3 Secondary outcomes

Parameters	6 month			
	QSYQ	Placebo	Difference (95% CI)	P value
Composite endpoints, <i>n</i> (%)	42 (13.17%)	53 (16.61%)	0.03 (−0.09, 0.02)	0.451
Cardiovascular events, <i>n</i> (%)	30 (9.40%)	42 (13.17%)	−0.04 (−0.09, 0.01)	0.255
Hospitalization due to HF	25 (7.84%)	36 (11.29%)	−0.03 (−0.08, 0.01)	0.241
Death, <i>n</i> (%)	12 (3.76%)	15 (4.70%)	−0.01 (−0.04, 0.02)	0.689
BNP (pg/mL)	108.00 (38.30, 276.00)	114.50 (38.60, 384.00)	−6.00 (−28.00, 14.00)	0.565
Change (pg/mL)	−14.55 (−193.00, 18.50)	−12.30 (−134.00, 42.00)	7.10 (−24.20, 38.20)	0.209
LVEF (%)	43.78 ± 11.01	43.44 ± 9.56	0.34 (−1.42, 2.09)	0.643
Change (%)	6.25 ± 8.80	5.48 ± 8.73	0.77 (−0.72, 2.27)	0.196
Score of MLHFQ	23.36 ± 17.23 ^a	26.54 ± 17.67 ^a	−3.17 (−6.01, −0.34)	0.022
Change	−11.78 ± 13.66 ^a	−9.17 ± 13.25 ^a	−2.60 (−4.79, −0.42)	0.004
NYHA, <i>n</i> (%)				0.001
Change in NYHA (%)				0.012
Improved (higher to lower class)	122 (38.24%)	94 (29.47%)		
Remained the same	193 (60.50%)	215 (67.40%)		
Deteriorated (lower to higher class)	4 (1.25%)	10 (3.13%)		

BNP, brain natriuretic peptide; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association.

Values are presented as means ± standard deviations or *n* (%). The change value is corrected for the baseline.

^aIntragroup comparison of baselines ($P < 0.05$).

tients with IHF die within 5 years, while 78–84% experience the composite cardiac adverse events of death, readmissions for HF, or admission for coronary events of ischaemic stroke—all events associated with substantial healthcare resource utilization and costs.^{13,15} Furthermore, the patients' quality of life is impaired (as assessed by MLHFQ), which was demonstrated to be associated with an increased risk of mortality and hospitalization in HF (the majority of ischaemic aetiology).¹⁶ Addressing the residual risk in IHF is clearly urgent and requires additional effective therapies. Traditional Chinese medicine, a system of medical practice with a long history in China of more than 2000 years, has increasingly been adopted as a complementary approach to standard international treatments in Europe, the USA, and Australia.^{17,18} By taking a holistic approach to individual

patients, the practice of traditional Chinese medicine is based on the concept of 'Syndrome Differentiation' and basic theories derived from the Chinese philosophy of yin-yang and Five Elements. In this system, the key pathophysiological mechanisms of chronic IHF are 'Qixu' (vital energy deficiency) and 'Xueyu' (blood stasis).¹⁹ As a compound preparation, QSYQ regulates energy metabolism and inhibits oxidative stress, leucocyte adhesion to endothelial cells, plasma albumin leakage, inflammation, and apoptosis.^{20,21} In aggregate, QSYQ is believed to have an integrated effect in the treatment of IHF by regulating metabolism and promoting normalization of the metabolic phenotype, as well as by adjusting the levels of specific metabolites in the amino acid metabolism.²² As the effective components of QSYQ, *Astragalus mongholicus* (NAG, 3-hydroxybutyric acid,

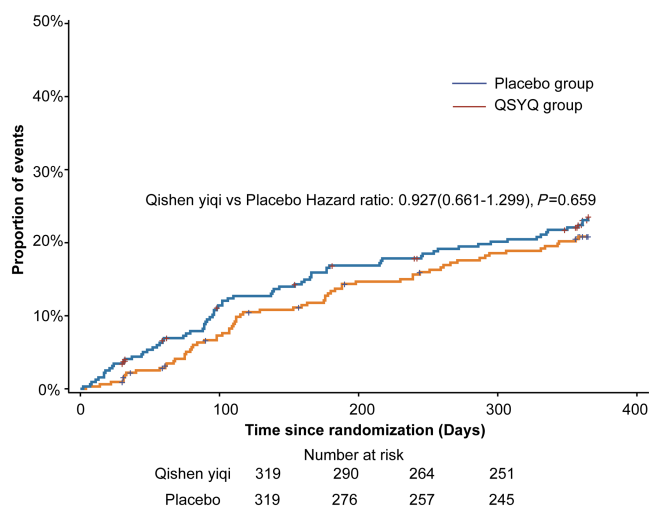
Figure 3 Kaplan–Meier curves of composite endpoints.

Table 4 Comparison of the incidence of adverse events in the two groups

Adverse events	QSYQ group (n = 319)	Placebo group (n = 319)	Total (n = 638)
Any	16 (5.01%)	18 (5.64%)	34 (5.33%)
Related to treatment	2 (0.63%)	3 (0.94%)	5 (1.57%)
Serious	2 (0.63%)	1 (0.31%)	3 (0.94%)
Related to treatment	0 (0.00%)	1 (0.31%)	1 (0.31%)
Occurring in $\geq 0.5\%$ of patients in any group			
Cold	3 (0.94%)	5 (1.57%)	8 (1.25%)
Dizziness and nausea	3 (0.94%)	1 (0.31%)	4 (0.63%)
Hematochezia	1 (0.31%)	3 (0.94%)	4 (0.63%)
Hyperkalaemia	1 (0.31%)	2 (0.63%)	3 (0.47%)
Liver dysfunction	2 (0.63%)	0 (0.00%)	2 (0.31%)
Vomiting	2 (0.63%)	0 (0.00%)	2 (0.31%)
Cough	0 (0.00%)	2 (0.63%)	2 (0.31%)
Bloating	0 (0.00%)	2 (0.63%)	2 (0.31%)
Fever	0 (0.00%)	2 (0.63%)	2 (0.31%)

The values are shown as n (%).

glutamine, succinic acid, and acetoacetate) regulates the metabolism of HF.²³ Astragalosides reduce oxidative damage by reducing MDA, maintain SOD and reduce free radical-induced myocardial cell damage, prevent cell death by blocking the influx of Ca²⁺, and open mitochondrial KATP channel to reduce apoptosis.²⁴ It is also reported that astragaloside IV has positive inotropic effect on left ventricular ejection in patients with congestive HF.²⁵ Among the components of *Salvia miltiorrhiza*, tanshinone IIA can reduce the activation of angiotensin II-induced β -catenin and IGF-2R pathways, apoptosis and Estrogen Receptors-induced cardiac remodelling in cardiac fibroblasts,²⁶ and so on. QSYQ has similar effects to aspirin in the secondary prevention of myocardial infarction.²⁷

Our study addresses an important gap in scientific evidence regarding the effects of QSYQ in addition to standard international medication in chronic IHF, by providing rigorous prospective double-blind randomized placebo-controlled data in a large group of patients and using 6MWD as an objective validated index of exercise tolerance to measure its effect. We found that 6 months of QSYQ treatment in addition to standard international medication was robustly associated with improved 6MWD. This was supported by consistent improvements in NYHA class and MLHFQ scores, evident at 3 and 6 months, which was sustained at 1 year, suggesting a slow chronic effect of the drug rather than a rapid acute action as may be expected, for instance, with diuretics or nitrates. Although LVEF and BNP improved over 6 months with QSYQ, these improvements were not significantly greater than those observed in the placebo group. This was also consistent with the lack of significant difference in composite clinical events at 6 months and 1 year, although there was a trend of reduced HF hospitalizations at 6 months.

Longer-term treatment and follow-up may be needed to fully evaluate the effects of QSYQ on clinical events in this population.

It should be noted that our study population comprised patients with chronic stable IHF rather than acute decompensated HF or acute coronary syndrome. The relatively low use of loop diuretics at baseline, only mildly reduced mean LVEF, and high proportion of patients with NYHA Class II symptoms were consistent with mild HF in a compensated state at recruitment. However, the overall raised BNP levels corroborate that the patients indeed had HF. While the majority of patients were receiving guideline-directed HF therapies at baseline (angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, beta-blockers, and aldosterone antagonists), their proportions were lower than anticipated based on global HF trials and may reflect a general gap in treatment reported among multinational Asian patients with HF.²⁸ Importantly, QSYQ was well tolerated in our population.

While we attempted to provide the best available scientific evidence for QSYQ in IHF according to international principles of evidence-based medicine, we acknowledge inherent limitations of incorporating traditional Chinese medicine principles in a randomized controlled trial. The international standardized trial approach with disease-centric randomization is somewhat in discordance with the individualized treatment approach of traditional Chinese medicine, and it is challenging to fully reconcile patient selection based on disease diagnosis using the traditional 'Syndrome Differentiation' approach.¹⁷ We did not systematically collect data on screen failures and therefore cannot fully assess whether these results can be generalized. Nonetheless, our standardization of QSYQ preparation, use of matching placebo, double-blind prospective design, and adequate sample size address some of the limitations of prior clinical studies of traditional Chinese medicine.¹⁷

Conclusions

Among patients with stable chronic IHF in our prospective multicentre double-blind randomized controlled trial, treatment with QSYQ for 6 months in addition to standard guideline-directed international medications was well tolerated and improved exercise tolerance compared with placebo. Future trials with longer duration of treatment and follow-up are warranted to assess the effects of QSYQ on left ventricular remodelling and clinical events.

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Conflict of interest

None of the listed authors have any conflicts of interest, financial or otherwise, related to the study results.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The list of participating institutions in the CACT-IHF trial.

Table S2. New York Heart Association classification in 12 months.

Table S3. Minnesota Living with heart failure questionnaire score in 12 months.

Figure S1. Flowchart of patient recruitment and retention.

Figure S2. Figure for secondary outcomes.

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