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ORIGINAL ARTICLE

# Effects of multifaceted optimization management for chronic heart failure: a multicentre, randomized controlled study

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## Abstract

**Aims** In recent years, we have developed the concept of 'clinical pathway based on integrated traditional Chinese and western medicine for the management of Chronic heart failure (CHF)'. The purpose of this study was to assess the implementation effects of multifaceted optimization management of chronic heart failure.

**Methods** A total of nine physicians in optimization group from nine research sites received multifaceted intervention (a 1-day training session on how to implement the optimization programme, a written optimization programme for CHF management, supervision from daily quality coordinator, and 1-monthly monitoring and feedback of performance measure) with respect to the management of CHF, comparing to nine physicians in control group who did not receive the aforementioned multifaceted intervention and diagnosed and treated CHF patients with conventional programme (usual care). After that, a total of 256 patients with CHF were enrolled and randomly assigned to receive optimization programme [integration of usual care and traditional Chinese medicine (TCM) treatment] or conventional programme (usual care) for the treatment of CHF. The primary outcome was the change in New York Heart Association (NYHA) functional classification during 24 weeks of treatment.

**Results** When compared with usual care, multifaceted optimization management resulted in superior improvements in NYHA functional classification at the 12-week visit ($P = 0.023$), the 16-week, 20-week, and 24-week visits ($P < 0.001$). It also demonstrated superior performance in comparison with the conventional programme with respect to readmission rate for major adverse cardiovascular events (MACEs), readmission rate for worsening heart failure, plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, left ventricular ejection fraction (LVEF), patient TCM syndrome scores, quality of life, and patients with heart failure with reduced ejection fraction (HFrEF) in optimization group more likely received beta-blockers and ACE inhibitors or ARBs than those in control group ($P = 0.038$ and $P = 0.013$, respectively).

**Conclusions** It is likely that the multifaceted optimization programme used in this study is feasible would benefit patients with CHF in NYHA functional classification, readmission for worsening heart failure, plasma NT-proBNP level, LVEF, patient TCM syndrome scores, and quality of life. Additionally, it would improve hospital personnel adherence to evidence-based performance measures for HFrEF.

**Keywords** Chronic heart failure; Optimization; Implementation; Traditional Chinese medicine; Randomized controlled trial

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## Introduction

Chronic heart failure (CHF) is one of major medical and public problems throughout the world. An estimated 64.3 million people are living with heart failure (HF) worldwide.[1] In developed countries, the prevalence of known HF is generally estimated at 1–2% of the general adult population.[2] In China, the prevalence of HF after weighting was 1.3% in adults ≥35 years old,[3] and 32.8% of hospitalized patients with HF had a history of admission for the disease within the previous 12 months.[4] According to the guidelines for CHF treatment, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitor, beta-blockers, aldosterone receptor antagonists, ivabradine, and digitalis should be used as standard treatments for HF.[5–7] Although there have been modest improvements in survival rates for people with CHF over the past 70 years, the 5-year survival rate is close to 50%, and many people will die directly from HF or from related cardiovascular disease.[8]

From the perspective of traditional Chinese medicine (TCM), the primary causes of HF are qi deficiency and blood stasis, qi-yin deficiency and blood stasis, qi-yang deficiency and blood stasis, water retention and blood stasis due to Qi deficiency, and water overflowing due to yang deficiency and static blood blocking collaterals.[9–11] Recently, some Chinese herbs and Chinese patent medicine have been evaluated in several prospective studies, which were associated with significant safety and efficacy.[12–18] In recent years, we have developed the concept of 'clinical pathway based on integrated traditional Chinese and western medicine for the management of CHF', which resulted in significant reductions in length and costs of hospitalization, improvements in New York Heart Association (NYHA) functional class, and quality of life. And it also facilitates hospital personnel adherence to evidence-based performance measures in patients with CHF.[19] However, the previous study was a non-randomized control trial, and the evidence seemed not very strong.

Therefore, in the present study, we conducted a prospective randomized clinical trial of multifaceted optimization management of CHF, including 'optimized programme based on integrated traditional Chinese and western medicine for the management of CHF' (optimization programme), a 1-day training session, quality coordinator supervision, and performance measure monitoring and feedback. The aim was to optimize the management of CHF; patients treated in this manner were compared with those receiving conventional programme model. The primary outcome was the NYHA functional classification, and the secondary outcomes consisted of readmission and mortality rates for major adverse cardiac events (MACEs), plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, echocardiographic measures, patient TCM syndrome scores, quality of life, and adherence to evidence-based performance measures for HFrEF.

## Methods

## Design, setting, and eligibility

The primary aim of this study was to assess whether multifaceted optimization management was superior to the conventional programme for CHF treatment. This study was designed as a prospective, multicentre, randomized, and controlled study (TIDieR checklist and CONSORT checklist can be found in Data S1 and Data S2, respectively). The target enrolment was 294 patients at the Departments of Cardiovascular Diseases of 10 clinical research centres (seven at Guangzhou, one at Qingyuan, one at Yangjiang, and one at Jiangmen) in Guangdong Province, China. These sites are all tertiary and teaching hospitals serving more than 10 000 inpatient patients in its own region per year. Primary and secondary hospitals, private hospitals, and hospitals in rural regions were excluded. All of physicians enrolled in this trial had worked at their own hospital for more than 5 years, being familiar with the management of CHF. The enrolment criteria consisted of patients with CHF based on the inclusion and exclusion criteria. CHF was diagnosed according to the Framingham criteria of HF[20] and the Chinese guidelines published in 2014 for the diagnosis and management of HF.[21] Inclusion criteria included male and female patients aged 40–85 years with CHF; NYHA functional classification II–IV; the condition of patients remained stable or unstable; and submission of informed consent. Exclusion criteria included the patients with acute myocardial infarction, unstable angina pectoris in the past 2 weeks, severe heart valve disease prepared for cardiac surgery, end-stage HF, and other kinds of serious diseases such as hepatic, renal, or haematologic disease. In addition, patients were excluded if they were pregnant or lactating; were known or suspected to be allergic to the study drugs; or were unwilling or unable to provide written consent.

## Study protocol

In this study, 20 eligible physicians from 10 sites (two physicians per site) are randomized to optimization group or control group (in a 1:1 ratio). All participating physicians were TCM cardiologists, and participating patients were recruited from the outpatient department or after a hospital admission in each centre. The physicians in optimization group received a multifaceted implementation strategy intervention provided by the designer of this study, which included a 1-day training session on how to implement the optimization programme, a written optimization programme for CHF management, daily quality coordinator supervision, and 1-monthly performance measure monitoring and feedback (details are shown in *Table 1*). The physicians in control group did not receive the aforementioned multifaceted implementation

strategy intervention, and they diagnosed and treated CHF patients with conventional programme (usual care).

In this trial, medical history of each patient was recorded; physical examinations, laboratory screening, and transthoracic Doppler echocardiography were performed to evaluate the patients. Eligible ones were randomly assigned to two groups (in a 1:1 ratio) that received either optimization programme (optimization group) or conventional programme (control group) for CHF treatment implemented by the attending physicians. The corresponding randomization code was generated by IBM SPSS Statistics for Windows, version 23.0 (IBM Corporation, New York, NY, USA) according to the number of enrolled patients in each centre and was held centrally by Guangdong Provincial Hospital of Chinese Medicine. The optimization programme and conventional programme were displayed in *Figure 1* and *Table S2*. According to the same guideline, conventional HF medications were used in both groups, and there was not more optimization in one group vs. the other. There was not equal use in both treatment arms in other Eastern medicine modalities, such as acupuncture. Aside from addition of TCM, the intervention group had no other treatment components that were missing from the control group. Patients attended follow-up appointments every 4 weeks during the treatment. At each visit, the occurrence of any clinical event or adverse effect was recorded; in addition, symptoms were reviewed, vital signs were measured, and NYHA functional classification and the doses and kinds of the study medications were written down. NYHA functional class assessments were completed by the independent researcher blinded for group allocation. At the 12th and 24th weeks, the participants were required to complete the TCM syndrome score and Minnesota Living with Heart Failure Questionnaire (MLHFQ).(Content of TCM syndrome score is provided at *Table S3*.)

Echocardiography was performed at baseline and at the last visit. LVEF was estimated using the biplane Simpson method. The entire study period lasted 24 weeks. The study protocol was reviewed and approved by Ethics Committee of Guangdong Provincial Hospital (Approval number: B2017-080-01). All participants provided written informed consent, and the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The trial was registered with Chinese Clinical Trial Registry ChiCTR2000031456.

## Laboratory tests

Routine laboratory tests, which included complete blood count, urinalysis, serum chemistry profile, and liver and renal function, were performed in the local laboratories of the participating centres at baseline and the last visit. So were plasma NT-proBNP levels.

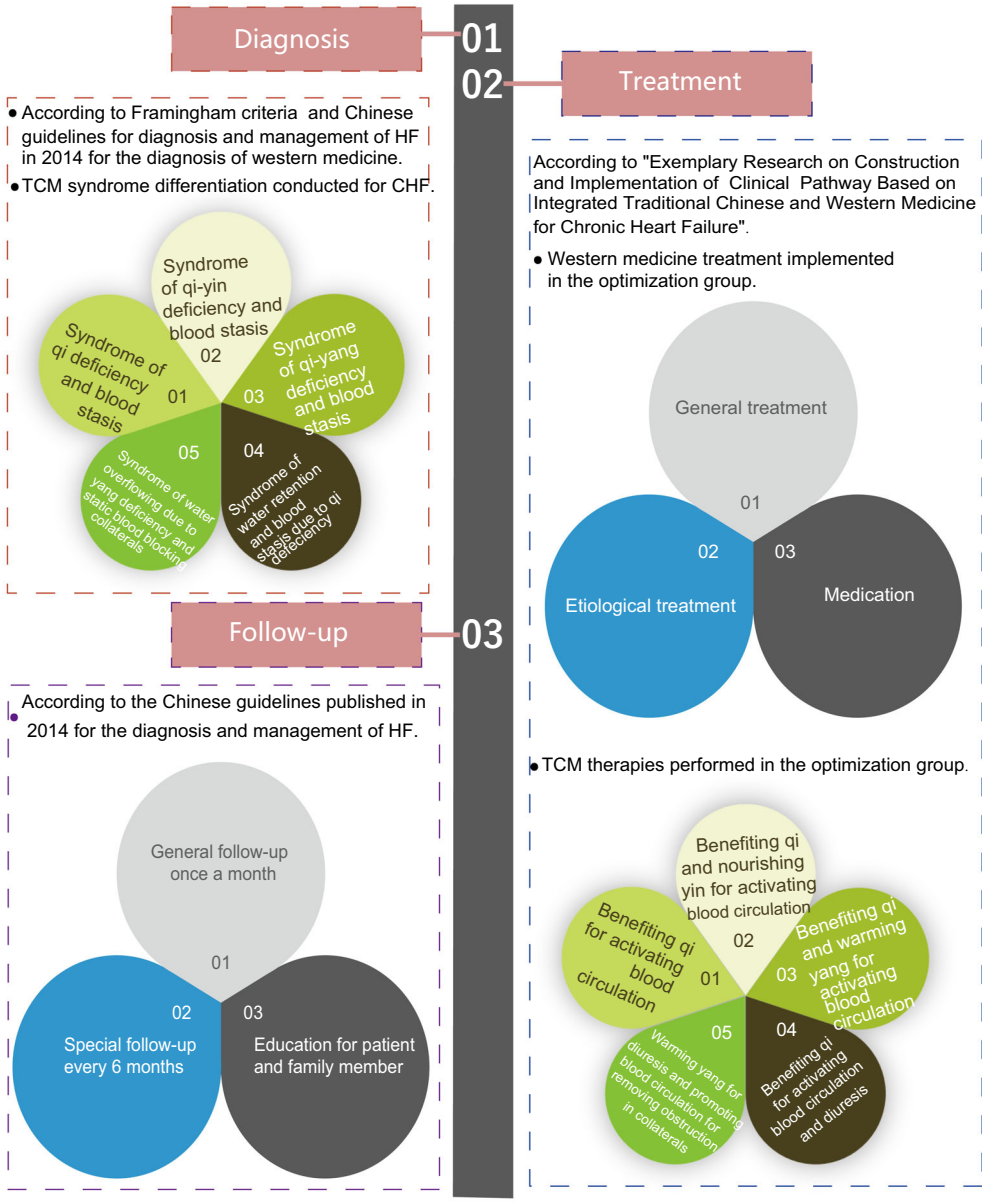
## Outcomes

The primary outcome was the change in NYHA functional classification. It could be considered to be clinically meaningful change if there were one to three reductions in NYHA functional classification scores from baseline. The secondary outcomes included readmission and mortality rates for MACEs, NT-proBNP levels, echocardiographic measures, TCM syndrome, and MLHFQ scores and adherence to four evidence-based performance measures among eligible patients with HFrEF. MACEs were defined as a composite of worsening heart failure, unstable angina pectoris, myocardial infarction, serious arrhythmia, stroke, and cardiovascular death. The components included in the MACEs were selected, because those may increase the readmission and mortality rates of patients with CHF. The assessments of safety were based on self-reports of adverse events, vital signs, and laboratory tests. The four evidence-based perfor-

**Table 1** Final components of optimization and control arms for physicians

| Optimization group | Control group |
|---|---|
| Multifaceted implementation strategy intervention<br>• A 1-day training session on how to implement the optimization programme (one-time in-person training at the session centre in Guangdong Provincial Hospital of Chinese Medicine during the weekends)<br>• A written optimization programme for CHF management (one-time printed material, the content of which is shown in *Figure 1* and *Tables S1*, *S2*, and *S4*)<br>• Daily quality coordinator supervision (one physician assigned by the director of the department of cardiovascular disease acting as a full-time quality coordinator throughout trial, and his or her responsibilities included interacting with providers once gaps in the implementation of optimization programme were identified, ensuring that all components of optimization programme were implemented for patients with CHF, identifying barriers to the application)<br>• One-monthly performance measure monitoring and feedback (quality coordinator was required to check their level of adherence to the predefined performance measures by checking their routine electronic medical records at least once a month, and feed information back to the independent researcher who was responsible for supporting the providers on how to implement the optimization programme more efficiently and more effectively via conference calls and e-mail exchanges once a month) | Usual care |

**Figure 1** Core components of optimization programme of chronic heart failure. HF, heart failure; TCM, traditional Chinese medicine.




mance measures for HFrEF included prescribing beta-blockers, ACE inhibitors or ARBs, aldosterone antagonists, and diuretics at the beginning of enrolment. Detailed performance measure specifications and contraindications are shown in *Table S4*. Adherence was expressed as an all-or-none measure or a composite measure if either one was statistically significant, the study was to be interpreted as 'positive'. The all-or-none measure was defined as the proportion of patients who received all of the performance measures for which the patient was eligible. The composite measure was defined as the total number of eligible performance measures performed divided by the total number of performance measures for which a given patient was eligible. The composite measure was calculated for each patient and then averaged.[22]

## Sample size calculation

The sample size was estimated based on the expected improvement in the primary outcome (NYHA functional classification) of optimization group through the previous clinic trials,

from which the mean percentage of patients with improve NYHA function was 96.80% and 86.10% in optimization group and control group, respectively. Therefore, assuming an additional 10% improvement in NYHA function following treatment with optimization group and given a power ($1 - \beta$) of 85% and two-tail Type I error $\alpha$ of 5%, the sample size for one arm needed to be 122, resulting in $n = 2 \times 122 = 244$ patients. Moreover, considering the dropout rate was approximately 20%, a total of 294 patients (147 per treatment group) were needed to be randomized to achieve the required number of patients for the efficacy analysis.

## Statistical analysis

Statistical analyses were performed by the primary investigator and the statistician blinded for group allocation, using IBM SPSS Statistics for Windows, version 23.0 (IBM Corporation, New York, NY, USA). The analysis for the primary endpoint was based on the intention-to-treat. Continuous variables were presented as mean ± SD. Generally, the comparability of the characteristics between the two study groups was assessed using a two-sample Student *t*-test for continuous variables and the chi-square test or Wilcoxon test, when appropriate, for categorical variables. When appropriated, the Fisher exact test was used to analysis the rates of readmission and mortality for MACEs and other adverse events between groups. For NYHA functional classification, TCM syndrome score, and MLHFQ score, the missing data were estimated by the last observed carried forward (LOCF) with at least one post-treatment evaluation.[23] Significance was attributed when a two-tail $P < 0.05$.

## Results

From July 2017 to June 2019, 18 physicians and 256 patients underwent randomization at nine sites (six at Guangzhou, one at Qingyuan, one at Yangjiang, and one at Jiangmen) in Guangdong Province, China; the flow diagram of physicians and patients through the study is presented in *Figure 2*. The baseline characteristics of the study groups are shown in *Table 2*. The details of TCM treatment in optimization group are exhibited at *Table S5*. The mean age of the total population was 69.10 years, and 61.72% were male. The CHF aetiologies included ischaemic heart disease (51.95%), hypertension (28.91%), cardiomyopathy (12.11%), rheumatic heart disease (6.64%), congenital heart disease (0.78%), viral myocarditis (0.39%), and other conditions (6.64%). The percentages of patients with HFrEF, HFmrEF, and HFpEF were 31.64%, 22.66%, and 45.31%, respectively. The distributions of the demographic and clinical characteristics between two groups were well balanced and homogeneous.

### NYHA functional classification

The NYHA class was determined at each visit. As shown in *Figure 3*, there was no difference between the two groups at baseline. The frequency of NYHA I patients gradually increased, whereas the frequency of NYHA III–IV patients gradually decreased after treatment with either optimization group or control group accompanied by background treatment. In this analysis, there were no significant differences between the optimization group and the control group at 4-week and 8-week visits ($P = 0.747$ and $P = 0.416$, respectively), but when compared with the control group, optimization treatment resulted in superior improvements at the 12-week visit ($P = 0.023$) and the 16-week, 20-week, and 24-week visits ($P < 0.001$ for all). And there were significant differences between two groups in the estimated marginal means of NYHA functional class from 4-week visit to 24-week visit ($P < 0.001$).

### Readmission and mortality rates for MACEs

*Table 3* shows the rates of readmission and mortality rates for both groups. Overall, 9.38% and 21.88% of patients in the optimization and control groups experienced readmission events for MACEs, respectively ($P = 0.006$). The number of patients with worsening HF in the optimization group was less than that in the control group (7.03% vs. 17.19%, $P = 0.013$). One patient in control group was dead and none in optimization group ($P = 1.000$).

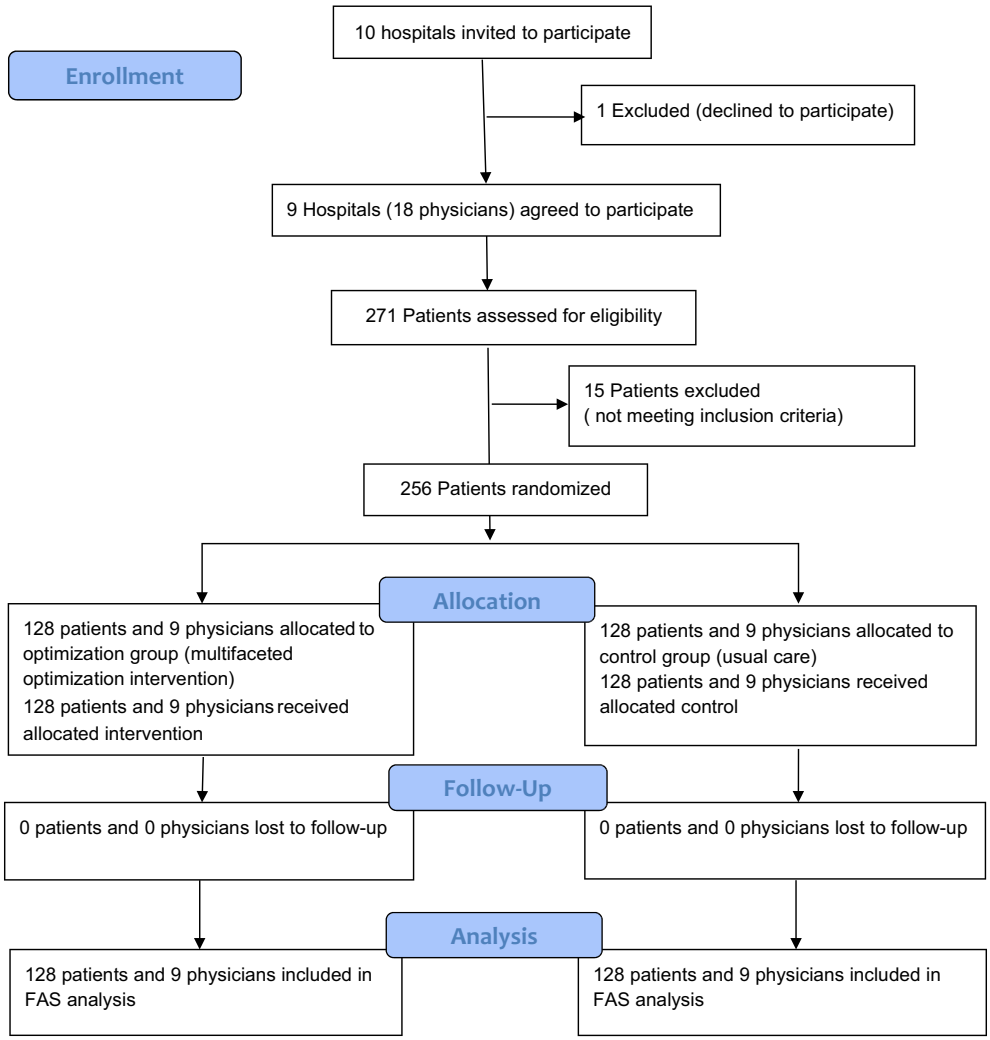
### Changes in plasma NT-proBNP level

A favourable effect of optimization group was observed on the plasma NT-proBNP level (*Table 4*). After 24 weeks of treatment, both groups showed a significant decrease in NT-proBNP levels from baseline, but treatment in optimization group led to a significantly greater reduction in NT-proBNP level than that in control group ($-0.85 \pm 1.01$ vs. -0.35 ± 1.08; $P < 0.001$). The mean percent changes in NT-proBNP level for the optimization and control groups were $-9.96\% \pm 11.91\%$ vs. $-3.42\% \pm 13.34\%$ ($P < 0.001$), respectively.

### Echocardiography measurements

Echocardiography was performed at baseline and at the 24-week visit. As shown in *Table 2*, the parameters of the echocardiography measurements did not differ between the two groups at baseline. Improvements in LVEF and reductions

**Figure 2** Flow diagram of physicians and patients throughout the study. FAS, full analysis set.




in LVED can be observed after treatment in both two groups at the 24-week visit (*Table 4*). Compared with patients randomized to the control group, patients receiving optimized treatment displayed greater improvement in LVEF ($P < 0.001$) but not in LVED ($P = 0.324$).

## TCM syndrome and MLHFQ scores

The TCM syndrome and MLHFQ scores were completed at each visit, and the two groups exhibited similar mean TCM syndrome and MLHFQ scores at baseline (*Table 2*). Interestingly, there were gradual improvements in both the mean TCM syndrome and MLHFQ scores during the whole treatment period. As for TCM syndrome scores, significant effects of optimized treatment compared with control group were observed at 24-week visit ($P = 0.002$). After treatment, more significant reduction in MLHFQ scores was observed in treatment group than in control group at 12 and 24 weeks ($P = 0.006$, $P < 0.001$), as displayed in *Figure 4*.

## Adherence to evidence-based performance measures

Adherence to evidence-based performance measures among eligible patients with HFrEF is summarized in *Table 5*. There were no statistically significant differences at the individual measure level after adjusting for patient baseline characteristics (age, sex, history of coronary heart disease, hypertension,

**Table 2** Baseline characteristics of patients in optimization group or control group

| Characteristic | Optimization group ($n$ = 128) | Control group ($n$ = 128) | All ($N$ = 256) | $P$ value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, y | 69.24 ± 9.82 | 68.95 ± 9.45 | 69.10 ± 9.62 | 0.566 |
| Male | 82 (64.06) | 76 (59.38) | 158 (61.72) | 0.440 |
| Race | | | | |
| Han | 128 (100.00) | 127 (99.22) | 255 (99.61) | 1.000 |
| Other | 0 (0.00) | 1 (0.78) | 1 (0.39) | |
| Measurements | | | | |
| Height, cm | 164.99 ± 7.93 (n = 126) | 164.19 ± 7.06 | 164.59 ± 7.50 | 0.268 |
| Weight, kg | 62.01 ± 11.88 (n = 127) | 61.54 ± 10.69 | 61.77 ± 11.28 | 0.850 |
| Systolic BP, mmHg | 134.82 ± 21.24 | 134.55 ± 20.91 | 134.69 ± 21.04 | 0.920 |
| Diastolic BP, mmHg | 79.42 ± 13.66 | 78.79 ± 14.03 | 79.11 ± 13.82 | 0.715 |
| Heart rate, beats/min | 87.61 ± 19.70 | 88.54 ± 19.53 | 88.07 ± 19.58 | 0.545 |
| Signs of HF | | | | |
| Rales | 68 (53.13) | 70 (54.69) | 138 (53.91) | 0.802 |
| Lower limb oedema | 75 (58.59) | 76 (59.84) | 151 (59.22) | 0.839 |
| Medical history | | | | |
| Coronary heart disease | 66 (51.56) | 71 (55.47) | 137 (53.52) | 0.531 |
| Hypertension | 77 (60.16) | 89 (69.53) | 166 (64.84) | 0.116 |
| Diabetes | 34 (26.56) | 41 (32.03) | 75 (29.30) | 0.336 |
| Arrhythmia | 57 (44.53) | 39 (30.47) | 96 (37.50) | 0.020 |
| Hyperlipidaemia | 19 (14.84) | 24 (18.75) | 43 (16.80) | 0.403 |
| Other | 43 (33.59) | 52 (40.63) | 95 (37.11) | 0.244 |
| Family history of cardiovascular disease | 6 (4.69) | 10 (7.81) | 16 (6.25) | 0.302 |
| Aetiology of CHF | | | | |
| Coronary heart disease | 64 (50.00) | 69 (53.91) | 133 (51.95) | 0.532 |
| Hypertension | 45 (35.16) | 29 (22.66) | 74 (28.91) | 0.027 |
| Rheumatic heart disease | 8 (6.25) | 9 (7.03) | 17 (6.64) | 0.802 |
| Cardiomyopathy | 14 (10.94) | 17 (13.28) | 31 (12.11) | 0.565 |
| Viral myocarditis | 0 (0.00) | 1 (0.78) | 1 (1.89) | 1.000 |
| Congenital heart disease | 2 (1.56) | 0 (0.00) | 2 (0.78) | 0.498 |
| Other | 6 (4.69) | 11 (8.59) | 17 (6.64) | 0.209 |
| NYHA functional class | | | | |
| I | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1.000 |
| II | 30 (23.44) | 30 (23.44) | 60 (23.44) | |
| III | 58 (45.31) | 58 (45.31) | 116 (45.31) | |
| IV | 40 (31.25) | 40 (31.25) | 80 (31.25) | |
| LVEF classification | | | | |
| HFrEF (LVEF ≤40%) | 41 (32.03) | 40 (31.25) | 81 (31.64) | 0.873 |
| HFmrEF (40% < LVEF <50%) | 31 (24.22) | 27 (21.09) | 58 (22.66) | |
| HFpEF (LVEF ≥50%) | 56 (43.75) | 60 (46.88) | 116 (45.31) | |
| Echocardiography measurements | | | | |
| LVEF (%) | 48.41 ± 13.37 | 49.35 ± 14.94 | 48.88 ± 14.15 | 0.561 |
| LVEF (%; HFrEF) | 33.80 ± 4.96 | 31.94 ± 6.03 | 32.88 ± 5.56 | 0.192 |
| LVEF (%; HFmrEF) | 44.67 ± 2.86 | 45.16 ± 2.26 | 44.90 ± 2.59 | 0.475 |
| LVEF (%; HFpEF) | 61.18 ± 7.59 | 62.84 ± 7.18 | 62.04 ± 7.40 | 0.227 |
| LVED (mm) | 53.94 ± 9.36 | 53.84 ± 9.61 | 53.89 ± 9.46 | 0.933 |
| LVED (mm; HFrEF) | 61.77 ± 8.25 | 62.86 ± 6.82 | 62.30 ± 7.56 | 0.285 |
| LVED (mm; HFmrEF) | 54.29 ± 5.36 | 56.06 ± 6.7 | 55.12 ± 6.07 | 0.273 |
| LVED (mm; HFpEF) | 48.01 ± 7.45 | 46.98 ± 6.44 | 47.48 ± 6.93 | 0.424 |
| Laboratory measurements | | | | |
| Na+ (mmol/L) | 141.16 ± 3.83 | 140.74 ± 4.35 | 140.95 ± 4.10 | 0.440 |
| K+ (mmol/L) | 4.14 ± 0.50 | 4.12 ± 0.48 | 4.13 ± 0.49 | 0.949 |
| Cr (μmol/L) | 119.09 ± 53.51 | 108.21 ± 58.98 | 113.65 ± 56.47 | 0.004 |
| ALT(U/L) | 27.49 ± 19.83 | 27.50 ± 19.33 | 27.50 ± 19.54 | 0.820 |
| HGB(g/L) | 129.35 ± 21.51 | 120.62 ± 22.51 | 124.98 ± 22.40 | 0.002 |
| Plasma NT-ProBNP (pg/mL)[a] | 8.00 ± 1.17 | 8.10 ± 1.26 | 8.05 ± 1.22 | 0.511 |
| Chest X-ray | | | | |
| Pulmonary congestion | 21 (16.41) | 32 (25.00) | 53 (20.70) | 0.09 |
| Pulmonary interstitial oedema | 15 (11.72) | 15 (11.72) | 30 (11.72) | 1.000 |
| Pleural effusion | 21 (16.41) | 29 (22.66) | 50 (19.53) | 0.207 |

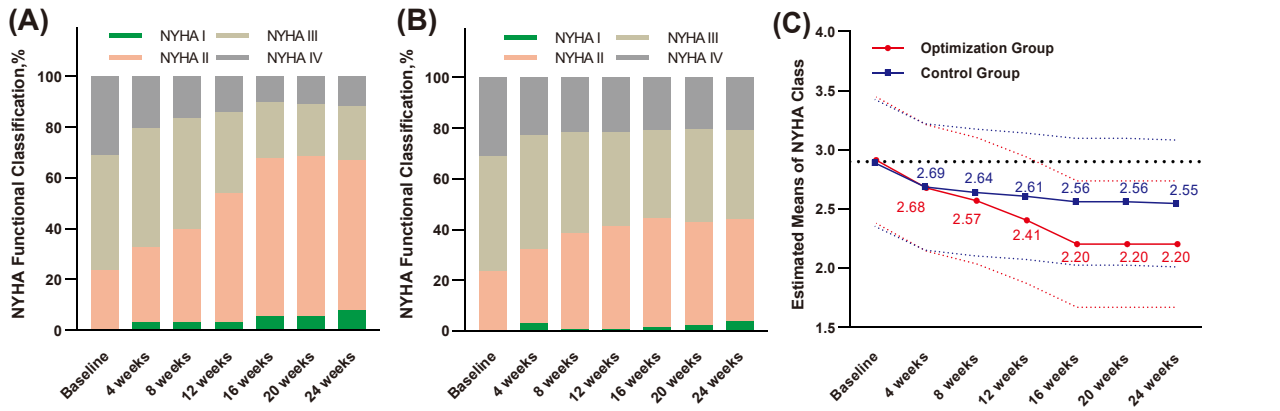
(*Continues*)

**Table 2** (continued)

| Characteristic | Optimization group ($n$ = 128) | Control group ($n$ = 128) | All ($N$ = 256) | $P$ value |
|---|---|---|---|---|
| TCM syndrome differentiation for CHF | | | | |
| Qi deficiency and blood stasis | 39 (30.47) | 50 (39.06) | 89 (34.77) | 0.542 |
| Qi-yin deficiency and blood stasis | 22 (17.19) | 8 (6.25) | 30 (11.72) | |
| Qi-yang deficiency and blood stasis | 6 (4.69) | 2 (1.56) | 8 (3.13) | |
| Water retention and blood stasis due to qi deficiency | 46 (35.94) | 38 (29.69) | 84 (32.81) | |
| Water overflowing due to yang deficiency and static blood blocking collaterals | 15 (11.72) | 30 (23.44) | 45 (17.58) | |
| TCM syndrome scores | 28.75 ± 9.44 | 28.52 ± 11.04 | 28.63 ± 10.25 | 0.744 |
| MLHFQ | 46.80 ± 17.87 | 46.64 ± 20.16 | 46.72 ± 19.01 | 0.809 |

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BNP, B-type natriuretic peptide; BP, blood pressure; CHF, chronic heart failure; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TCM, traditional Chinese medicine.
Values are mean ± SD, *n* (%), or median (Q1, Q3).
[a]NT-ProBNP level is natural logarithm-transformed before analysis.

**Figure 3** NYHA functional classification results. (A) Optimization group. (B) Control group. (C) Estimated means of NYHA functional class. NYHA, New York Heart Association.




| Time point | Optimization Group NYHA I | NYHA II | NYHA III | NYHA IV | Control Group NYHA I | NYHA II | NYHA III | NYHA IV | $P$ Value | Optimization Group Estimated Means of NYHA Class[a] | Standard Deviation | 95% CI | Control Group Estimated Means of NYHA Class[a] | Standard Deviation | 95% CI | $P$ Value[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 0.00% | 23.44% | 45.31% | 31.25% | 0.00% | 23.44% | 45.31% | 31.25% | 1.000 | 2.91 | 0.53 | 1.87 to 3.96 | 2.89 | 0.54 | 1.84 to 3.94 | 0.794 |
| 4 weeks | 3.13% | 29.69% | 46.88% | 20.31% | 3.13% | 28.91% | 45.31% | 22.66% | 0.747 | 2.68 | 0.53 | 1.63 to 3.73 | 2.69 | 0.54 | 1.64 to 3.74 | 0.928 |
| 8 weeks | 3.13% | 36.72% | 43.75% | 16.41% | 0.78% | 37.50% | 39.84% | 21.88% | 0.416 | 2.57 | 0.53 | 1.52 to 3.62 | 2.64 | 0.54 | 1.59 to 3.69 | 0.428 |
| 12 weeks | 3.13% | 50.78% | 32.03% | 14.06% | 0.78% | 40.63% | 36.72% | 21.88% | 0.023 | 2.41 | 0.53 | 1.36 to 3.45 | 2.61 | 0.54 | 1.56 to 3.66 | 0.022 |
| 16 weeks | 5.47% | 62.50% | 21.88% | 10.16% | 1.56% | 42.97% | 34.38% | 21.09% | < 0.001 | 2.20 | 0.53 | 1.16 to 3.25 | 2.56 | 0.54 | 1.51 to 3.61 | < 0.001 |
| 20 weeks | 5.47% | 63.28% | 20.31% | 10.94% | 2.34% | 40.63% | 36.72% | 20.31% | < 0.001 | 2.20 | 0.53 | 1.16 to 3.25 | 2.56 | 0.54 | 1.51 to 3.61 | < 0.001 |
| 24 weeks | 7.81% | 59.38% | 21.09% | 11.72% | 3.91% | 39.84% | 35.16% | 21.09% | < 0.001 | 2.20 | 0.53 | 1.16 to 3.25 | 2.55 | 0.54 | 1.50 to 3.60 | < 0.001 |

[a]The generalized linear mixed model (GLMM) was used to compare the change in NYHA values between the patient groups, with baseline adjustment of all the following covariates: age, male, race, height, weight, systolic BP, diastolic BP, heart rate, medical history,family history of cardiovascular disease, etiology of CHF, LVEF classification, TCM syndrome scores, MLHFQ scores, NTproBNP level, TCM syndrome differentiation, echocardiography measurements and other laboratory measurements.

NYHA functional class, scores of TCM syndrome, and MLHFQ) except for two performance measures: beta-blockers and ACE inhibitors or ARBs. Patients in optimization group more likely received beta-blockers and ACE inhibitors or ARBs than those in control group ($P$ = 0.038 and $P$ = 0.013, respectively).

## Adverse events

A total of 256 patients in two groups were included in the safety set analyses (*Table 6*). The total number of adverse events was 14 in the optimization group vs. 35 in the con-

**Table 3** Readmission and mortality for MACEs

| | Optimization group ($n$ = 128) | | Control group ($n$ = 128) | | |
|---|---|---|---|---|---|
| | $n$ (case) | % | $n$ (case) | % | $P$ value |
| Readmission | 12 (13) | 9.38 | 28 (34) | 21.88 | 0.006 |
| Worsening heart failure | 9(10) | 7.03 | 22(28) | 17.19 | 0.013 |
| Unstable angina pectoris | 1 | 0.78 | 6 | 4.69 | 0.120 |
| Myocardial infarction | 1 | 0.78 | 0 | 0 | 1.000 |
| Atrial fibrillation | 1 | 0.78 | 0 | 0 | 1.000 |
| Death | 0 | 0 | 1 | 0.78 | 1.000 |

MACEs, major adverse cardiovascular events.
Values are $n$, %. Some patients reported more than one event.

**Table 4** Changes in NT-ProBNP, LVEF, and LVED from baseline to after 24 weeks of follow-up

| | Optimization group | Control group | $P$ value (95% CI) |
|---|---|---|---|
| Mean change in NT-proBNP[a], pg/mL (95% CI) | −0.85 ± 1.01 ($n$ = 125) (−1.03 to −0.68) | −0.35 ± 1.08 ($n$ = 120) (−0.55 to −0.16) | <0.001 (−0.77 to −0.24) |
| Mean per cent reduction in NT-proBNP[a], % (95% CI) | −9.96 ± 11.91 ($n$ = 125) (−12.07 to −7.85) | −3.42 ± 13.34 ($n$ = 120) (−5.84 to −1.01) | <0.001 (−9.72 to −3.36) |
| Mean change in LVEF in HFrEF, % (95% CI) | 6.87 ± 10.22 ($n$ = 39) (3.55 to 10.18) | 1.25 ± 9.98 ($n$ = 37) (−2.08 to 4.57) | <0.001 (1.01–10.25) |
| Mean change in LVED in HFrEF, mm (95% CI) | −1.56 ± 4.49 ($n$ = 39) (−3.01 to −0.11) | −1.84 ± 4.17 ($n$ = 37) (−3.23 to −0.44) | 0.324 (−1.74 to 2.18) |

Values are mean ± SD. Difference in NT-proBNP, LVEF, or LVED = 24-week level − baseline level. Abbreviation as in *Table 2*.
[a]NT-ProBNP level is natural logarithm-transformed before analysis.

trol group ($P$ = 0.007), and the same result for serious adverse events. More than one event was reported in some patients. There was no report of adverse events related to the drugs during this study.

# Discussion

## Basis and roles of multifaceted optimization programme

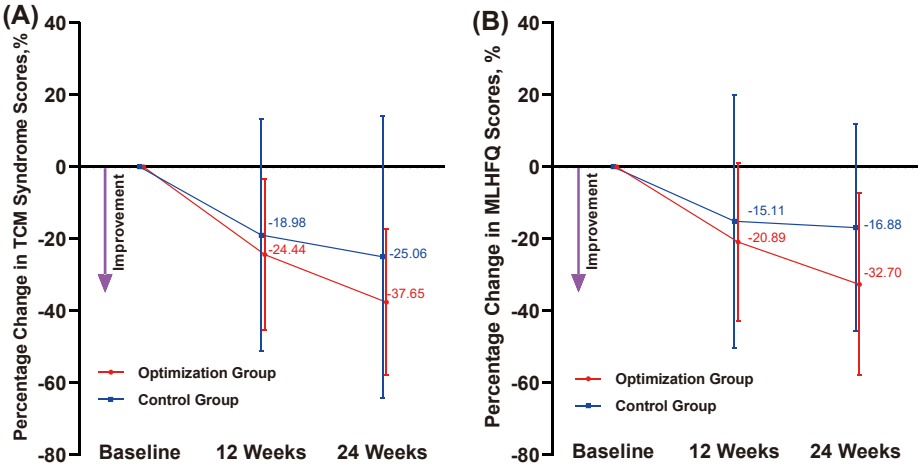
The optimization package was designed following the 'Exemplary Research on the Construction and Implementation of Clinical Pathway Based on Integrated Traditional Chinese and Western Medicine for Chronic Heart Failure'. It was also following literature reviews and expert recommendations and comprised 11 individual parameters, each of which has been shown to improve patient outcome or symptoms. General and aetiological treatments have formed integral parts of previous guidelines, which are important for the management for CHF.[5–7] Optimization programme provides a focused differential diagnosis and optimal therapeutic option based on individual patient presentation to improve cardiac function and outcomes in patients with CHF. The multifaceted intervention for physicians had been proved to improve the implementation quality of clinical guidelines for some diseases.[24] Physicians may improve their behaviour in response to their awareness of being observed, a phenomenon known as the Hawthorne effect,[25] which may be a part of the quality improvement initiative intervention. Some of the patients in the study had either HFmrEF or HFpEF based on their baseline LVEF scores. We clarify that there are well-accepted treatment guidelines for HFrEF, but not necessarily for HFmrEF or HFpEF. Medications such as ACEI, ARB, beta-blockers, and aldosterone receptor antagonists have been shown to improve survival in patients with HF; diuretics have been shown to reduce the signs and symptoms of congestion in patients with HFrEF.[5–7]

## Roles and mechanisms of TCM

TCM has been used for the treatment of HF in China since nearly two thousand years ago. TCM emphasizes the concept of holism and syndrome differentiation. The double diagnosis and treatment through Chinese and Western medicine was implemented in this study, that is, it was clearly diagnosed as CHF with the diagnostic method of modern medicine, and then TCM syndrome differentiation of CHF was carried out; we integrated the respective advantages of Chinese and Western medicine to treat eligible patients with CHF, which could cause better effects than simply implemented Western medicine or TCM.

From the perspective of TCM, there are mainly five TCM syndrome types of CHF in clinical practice, including syndrome of qi deficiency and blood stasis, syndrome of qi-yin deficiency and blood stasis, syndrome of qi-yang deficiency and blood stasis, syndrome of water retention and blood stasis due to

**Figure 4** Percent change in TCM syndrome and MLHFQ scores from baseline through 24 weeks of follow-up. MLHFQ, Minnesota Living with Heart Failure Questionnaire; TCM, traditional Chinese medicine. Values are expressed as mean ± SD. The mean rate of change ([12-week or 24-week level - baseline level]/baseline level) of (A) TCM syndrome scores and (B) MLHFQ scores.




| Group | Mean change rate in TCM Syndrome Scores,% | | Mean change rate in MLHFQ Scores,% | |
|---|---|---|---|---|
| | 12 Weeks | 24 Weeks | 12 Weeks | 24 Weeks |
| Control | -18.98±32.24 | -25.06±39.29 | -15.11±35.11 | -16.88±28.81 |
| Optimization | -24.44±20.92 | -37.65±20.26 | -20.89±21.98 | -32.70±25.34 |
| *P* Value | 0.058 | 0.002 | 0.006 | 0.001 |
| (95% CI) | (-12.16 to 1.23) | (-20.30 to -4.88) | (-13.00 to 1.43) | (-22.50 to -9.15) |

**Table 5** Adherence to evidence-based performance measures among eligible patients with HFrEF in optimization group or control group

| | Optimization group ($n$ = 41), no. of events/total patients (%) | Control group ($n$ = 40), no. of events/total patients (%) | Absolute difference (95% CI), % | *P* value | Population average odds ratio (95% CI)[a] | *P* value |
|---|---|---|---|---|---|---|
| Composite measure, mean (SD) | 86.59 (21.72) | 77.50 (28.52) | 9.09 (−1.46 to 19.63) | 0.068 | 0.36 (0.14 to 0.92) | 0.032 |
| All-or-none measure | 26/41 (63.41) | 18/40 (45.00) | 18.41 (−3.51 to 40.34) | 0.096 | 2.53 (0.95 to 6.76) | 0.063 |
| Performance measures at the beginning of enrolment | | | | | | |
| Beta-blockers | 36/41 (87.80) | 27/40 (67.50) | 20.30 (2.13 to 38.48) | 0.028 | 4.16 (1.08 to15.98) | 0.038 |
| ACE inhibitors or ARBs | 34/41 (82.93) | 26/40 (65.00) | 17.93 (−1.36 to 37.22) | 0.066 | 5.46 (1.43 to 20.78) | 0.013 |
| Aldosterone antagonists | 35/41 (85.37) | 34/40 (85.00) | 0.37(−15.55 to 16.28) | 0.963 | 1.89 (0.43 to 8.23) | 0.398 |
| Diuretics | 37/41 (92.24) | 37/40 (92.50) | −2.26 (−14.83 to 10.32) | 1.000 | 1.56 (0.15 to 16.46) | 0.712 |

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.
[a]Positive values favour the optimization group. Adjusted for patient characteristics, including age, sex, history of coronary heart disease, hypertension, NYHA functional class, scores of TCM syndrome, and MLHFQ.

qi deficiency, and syndrome of water overflowing due to yang deficiency and static blood blocking collaterals.[9–11] As for syndrome of qi deficiency and blood stasis of CHF, TCM therapies or herbs of benefiting qi for activating the blood circulation such as Huangqi injection can be implemented to balance qi and blood. Huangqi injection can improve LVEF and 6-min walking test.[16] TCM decoction or Chinese herb injections of benefiting qi and nourishing yin for activating the blood circulation such as Shengmai injection or Shenmai injection can be used to treat the syndrome of qi-yin deficiency and blood stasis of CHF because these two herb injections can significantly improve LVEF in patients with HF.[13] As to syndrome of qi-yang deficiency and blood stasis of CHF, we should prescribe these CHF patients herbs of benefiting qi and warming yang for activating blood circulation such as Nuanxin capsule to equilibrate qi, yang and blood. When Nuanxin capsule was used to treat CHF, it can increase walking distance, reduce mortality and readmission rate, and significantly improve cardiac function.[12] With regard to syndrome of water retention and blood stasis due to qi deficiency of CHF, TCM therapies or herb medicine about benefiting qi for activating blood circulation and diuresis such as Xinmailong injection can be used to make qi, blood, and body fluid balance. Xinmailong injection can alle-

**Table 6** Summary of adverse events

| | Optimization group ($n$ = 128) | | Control group ($n$ = 128) | | |
|---|---|---|---|---|---|
| | $n$ (case) | % | $n$ (case) | % | $P$ value |
| AEs | 13(14) | 10.16 | 29 (35) | 22.66 | 0.007 |
| AEs related to the drugs | 0 | 0 | 0 | 0 | 1.000 |
| SAEs | 13(14) | 10.16 | 29 (35) | 22.66 | 0.007 |
| Hospitalization | | | | | |
| Worsening heart failure | 9(10) | 7.03 | 22(28) | 17.19 | 0.013 |
| Unstable angina pectoris | 1 | 0.78 | 6 | 4.69 | 0.120 |
| Myocardial infarction | 1 | 0.78 | 0 | 0 | 1.000 |
| Atrial fibrillation | 1 | 0.78 | 0 | 0 | 1.000 |
| Arterial occlusive diseases | 1 | 0.78 | 0 | 0 | 1.000 |
| Death | 0 | 0 | 1 | 0.78 | 1.000 |

AE, adverse event(s); SAE, serious adverse event(s).
Values are $n$, %. The analysis included all patients who received at least one dose of the study medication. Some patients reported more than one event.

viate symptoms of CHF patients, improve cardiac function, and increase exercise tolerance.[17] At last, as for the syndrome of water overflowing due to yang deficiency and static blood blocking collaterals of CHF, herbs or Chinese patent medicine of warming yang and promoting blood circulation such as qili qiangxin capsules can be implemented for diuresis and removing obstruction in collaterals. One study suggests that qili qiangxin capsules can markedly reduce 24.7% NT-proBNP levels after 12-week treatment.[18] The implementation of TCM can balance the yin, yang, qi, blood, and body fluid of patients with CHF, so as to better improve cardiac function and quality of life and enhance the body's resistance to disease to reduce the readmission for worsening HF. Establishing a causal relationship between the observed cellular or molecular actions of TCM and their overall beneficial effects on HF from current published reports is difficult, especially in the context of the single compound–single target paradigm.[26] However, recently, one systematic review composed of 61 studies has shown that at least 13 pharmacological active components were found in traditional Chinese herbs or Chinese patent medicines against HF.[27] These components are flavonoids (puerarin, icariin, luteolin), saponins (ginsenosides, *Panax notoginseng* saponins, astragaloside IV), phenolic acids (salvianolic acid A, salvianolic acid B, curcumin), alkaloids (berberine, ligustrazine), polysaccharides (astragalus polysaccharide, wolfberry polysaccharide), etc. (A mini-review about effects and potential mechanisms of TCM for CHF is provided in *Appendix S1*.)

## Roles of follow-up programme

More attention should be paid to the follow-up programme due to improvement in quality of life and reduction of readmission for CHF.[5–7] The aim of education for patients and family members is to improve their self-care abilities. Recent studies have shown that self-management interventions had a beneficial effect on time to HF-related hospitalization or all-cause death.[28,29]

## Study limitations and future directions

This trial was of a prospective, randomized, and controlled design. Owing to the nature of multifaceted optimization programme, no attempt was made to blind subjects or providers except the investigators and statisticians in this study. To achieve NYHA functional classification, readmission, adherence to evidence-based performance measures, TCM syndrome scores, and quality of life targets, the motivation was required from both physicians and patients, all of whom needed to be fully informed of the expected management course. We accept that this may have introduced observer bias, but this is unavoidable in such a study. In addition, although the use of intention-to-treat principles prompted to minimize the risk of biased selection of reporting of the outcomes, this non-cluster-randomized design increased the likelihood of contamination between intervention and control groups of the trial.

The results of this study indicate that multifaceted optimization programme is superior to conventional programme for patients with CHF, especially in improvements of NYHA functional classification, readmission rate for worsening HF, plasma NT-proBNP level, LVEF, patient TCM syndrome scores, and quality of life. It also favoured the physicians at the adherence to evidence-based performance measures for HFrEF. In addition, we have found that there was less mortality rate for MACEs in optimization group than in control group, but the differences were not significant. There may be some potential challenges in implementing an integrated optimization program for CHF such as the current one long term, in a broader scale for routine clinical care. The physicians should know the double diagnosis and treatment through Chinese and Western medicine well to implement this integrated optimization programme in the long term. The basic concepts of TCM may need to be introduced to some patients with CHF who know little about TCM. In future, a cluster-randomized controlled trial should be needed to increase the follow-up time in order to assess the effects of this multifaceted optimization programme for the improvements in hard end points

of CHF and hospital personnel adherence to evidence-based performance measures in patients with HFrEF.

## Conclusions

It is likely that the multifaceted optimization programme used in this study is feasible and would benefit patients with CHF in NYHA functional classification, readmission for worsening heart failure, plasma NTproBNP level, LVEF, patient TCM syndrome scores, and quality of life. Additionally, it would improve hospital personnel adherence to evidence-based performance measures for HFrEF.

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## Conflict of interest

The authors declare that they have no competing interests.

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## Supporting information

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

**Data S1.** Supporting Information.
**Data S2.** Supporting Information.
**Appendix S1.** Effects and Potential Mechanisms of Traditional Chinese Medicine for Chronic Heart failure: A Review.
**Table S1.** Optimization syndrome differentiation with TCM for CHF.
**Table S2.** Optimization and conventional treatment and follow-up programmes for patients.
**Table S3.** TCM Syndrome Score for CHF.
**Table S4.** Specifications of guideline-recommended performance measures for HFrEF.
**Table S5.** Details of TCM treatment in Optimization Group.

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