INPLASY PROTOCOL

To cite: Guan et al. Efficacy and Safety of Qishen Yiqi Dripping pills as a complementary treatment for Heart Failure A protocol of Updated systematic review and meta-analysis. Inplasy protocol 2020120106. doi: 10.37766/inplasy2020.12.0106

Received: 21 December 2020

Published: 22 December 2020

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Support: **The National Key R&D Program.**

Review Stage at time of this submission: **The review has not yet started**

Conflicts of interest:
None.

Efficacy and Safety of Qishen Yiqi Dripping pills as a complementary treatment for Heart Failure A protocol of Updated systematic review and meta-analysis

Guan, H[1]; Ren, L[2]; Dai, G[3]; Gao, W[4]; Fu, H[5]; Zhao, Z[6]; Liu, X[7]; Li, J[8].

Review question / Objective: **1. Study of type This study only includes the published or ongoing RCTs of QSYQ for HF. These studies will be excluded: 1) those that can not reflect the clinical efficacy of QSYQ; 2) The sample size of the QSYQ group/control group is less than 40 cases. If the studies are similar, only the studies with the highest quality or the largest sample size will be retained. 2. Participants Patients diagnosed with HF and NYHA classification II-IV will be included in the study according to any diagnostic criteria. Patients undergoing cardiac resynchronization therapy, coronary artery bypass surgery, or non-cardiovascular events (such as malignant tumors, mental illness, or severe liver and kidney insufficiency) will be excluded. 3. Interventions and comparators Both the QSYQ and control groups receive routine western medicine treatment recommended by the guidelines, including diuretics, ACEI/ARB, digitalis drugs, beta-blockers, aldosterone receptor antagonists, nitrate drugs, etc. The QSYQ group is treated with QSYQ based on the control group. The routine treatment in each RCT does not need to be consistent, but the only difference between the QSYQ and control groups should be whether to apply QSYQ. Besides, neither group takes any drugs that may interfere with the evaluation indicators.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 December 2020 and was last updated on 21 December 2020 (registration number INPLASY2020120106).

INTRODUCTION

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Condition being studied: Heart failure (HF) has become a serious global public health issue due to its high incidence, high mortality and extremely low quality of life. According to several clinical trials, Qishen Yiqi Dripping pills (QSYQ) combined with routine western medicine treatment can further enhance the curative effect of HF patients. However, most of the trials are small in sample size and poor in quality, which can only provide limited evidence-based medicine. The existing systematic reviews (SRs) of effectiveness and safety has provided evidence for the clinical application of QSYQ to a certain extent, but there are still three major defects. First, it did not deal with clinical multiple confounding factors; Second, all-cause death and readmission rates which reflect long-term prognosis, are not included in efficacy evaluation; Third, the latest high-quality clinical study was not included. Here, we will perform a systematic review and meta-analysis that include the randomized clinical trial (RCT) of CACT-IHF, apply meta-regression and subgroup analysis to cope with multiple confounding factors, and add the clinical efficacy standards, all-cause death and readmission rates as reliable efficacy evaluation indicators. The purpose of this study was to rigorous evaluate the clinical efficacy and safety of QSYQ in the complementary treatment of.

METHODS

Participant or population: Patients diagnosed with HF and NYHA classification II-IV will be included in the study according to any diagnostic criteria. Patients undergoing cardiac resynchronization therapy, coronary artery bypass surgery, or non-cardiovascular events (such as malignant tumors, mental illness, or severe liver and kidney insufficiency) will be excluded.

Intervention: Both the QSYQ and control groups receive routine western medicine treatment recommended by the guidelines, including diuretics, ACEI/ARB, digitalis drugs, beta-blockers, aldosterone receptor antagonists, nitrate drugs, etc. The QSYQ group is treated with QSYQ based on the control group. The routine treatment in each RCT does not need to be consistent, but the only difference between the QSYQ and control groups should be whether to apply QSYQ.

Comparator: The control group only receives routine western medicine treatment recommended by the guidelines.

Study designs to be included: This study only includes the published or ongoing RCTs of QSYQ for HF. These studies will be excluded: 1) those that can not reflect the clinical efficacy of QSYQ; 2) The sample size of the QSYQ group/control group is less than 40 cases. If the studies are similar, only the studies with the highest quality or the largest sample size will be retained.

Eligibility criteria: Eligibility criteria will follow the principles of the PICOS, including the following: 1.Study of type This study only includes the published or

ongoing RCTs of QSYQ for HF. These studies will be excluded: 1) those that can not reflect the clinical efficacy of QSYQ; 2) The sample size of the QSYQ group/control group is less than 40 cases. If the studies are similar, only the studies with the highest quality or the largest sample size will be retained. 2. Participants Patients diagnosed with HF and NYHA classification II-IV will be included in the study according to any diagnostic criteria. Patients undergoing cardiac resynchronization therapy, coronary artery bypass surgery, or non-cardiovascular events (such as malignant tumors, mental illness, or severe liver and kidney insufficiency) will be excluded. 3. Interventions and comparators Both the QSYQ and control groups receive routine western medicine treatment recommended by the guidelines, including diuretics, ACEI/ARB, digitalis drugs, beta-blockers, aldosterone receptor antagonists, nitrate drugs, etc. The QSYQ group is treated with QSYQ based on the control group. The routine treatment in each RCT does not need to be consistent, but the only difference between the QSYQ and control groups should be whether to apply QSYQ. Besides, neither group takes any drugs that may interfere with the evaluation indicators. 4. Outcomes Primary efficacy evaluation indicators contain effective rate, a.ll-cause mortality, emergency treatment/readmission due to HF, and other cardiovascular outcomes. Secondary efficacy evaluation indicators contain the clinical efficacy standards of TCM, 6-minute walk test, New York Heart Association classification, left ventricular ejection fraction, brain natriuretic peptide / N-terminal pro-brain natriuretic peptide, and other alternative indicators. Safety indicators include skin itching or rash, nausea, vomiting, dizziness and other adverse events.

Information sources: We will search PubMed/ MEDLINE, Web of Science, EMBASE, Cochrane Library, CNKI, Wanfang Database, VIP Database, Chinese Scientific Journal Database, Chinese Biomedical Literature Database. The search time is from the database establishment until November 30, 2020. We will also search for ongoing RCTs, such as trials registered and conducted on the WHO International Clinical Trial Registration Platform or Chinese Clinical Trial Registry. Besides searching the electronic database, we also perform the manual search, reference tracking and retrieval by the search engine. If necessary, we will contact the author of the original study by e-mail or telephone to obtain missing but essential information for this study.

Main outcome(s): Primary efficacy evaluation indicators contain effective rate, all-cause mortality, emergency treatment/ readmission due to HF, and other cardiovascular outcomes. Secondary efficacy evaluation indicators contain the clinical efficacy standards of TCM, 6-minute walk test, New York Heart Association classification, left ventricular ejection fraction, brain natriuretic peptide / N-terminal pro-brain natriuretic peptide, and other alternative indicators. Safety indicators include skin itching or rash, nausea, vomiting, dizziness and other adverse events.

Quality assessment / Risk of bias analysis: Seven items are evaluated by the Cochrane Collaboration's bias risk evaluation tool.The items are divided into three evaluation grades: low risk of bias (Grade-A), high risk of bias (Grade-C) and uncertain whether there is bias (Grade-B). All seven items are Grade-A means the risk of bias is very low. If there are Grade-B items and no Grade-C item, it demonstrates that the study has a moderate risk of bias. The existence of Grade-C item indicates that the study has a high risk of bias.

Strategy of data synthesis: Different effect indicators are chosen according to the data types of evaluation indicators. For binary variables, we will calculate using the odds ratio (OR) or relative risk (RR) and its 95% confidence interval (CI). For continuous variables, we will calculate by the mean difference (MD) or standardized mean difference (SMD) and its CI. The statistical analysis is performed with the help of stata16.0 software.

Subgroup analysis: The heterogeneity test adopts the I2 test and quantitative analysis. When I2<50%, the heterogeneity is not obvious, we will use the fixed effects model; when I2≥50%, the heterogeneity is significant, and the random effects model is used. Meta-regression and subgroup analysis are applied to discover the source of heterogeneity and deal with it. First of all, a meta-regression model is established to screen the influencing factors of heterogeneity. Then a subgroup analysis considering this influencing factor is carried out to compare the changes of heterogeneity before and after.

Sensibility analysis: The sensitivity analysis is carried out by excluding study one by one. If no significant change exists in the results before and after the exclusion, it indicates that the sensitivity is low and the results are of stability and reliability; otherwise, it means a high sensitivity, and unstable results.

Country(ies) involved: China, USA.

Keywords: heart failure, Qishen Yiqi Dripping pills, complementary treatment, meta-analysis.

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