

INPLASY PROTOCOL

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Corresponding author:
Hui Guan

gh20111008@163.com

Author Affiliation:
First College of Clinical
Medicine, Shandong
University of Traditional
Chinese Medicine

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We declare no conflicts of interest.

Effect and Safety of Oral Chinese Patent Medicine for Heart Failure: A protocol for systematic review and network meta-analysis

Guan, H¹; Dai, G²; Wang, N³; Gao, W⁴; Ren, L⁵; Cai, Z⁶.

Review question / Objective: Heart failure (HF) is the terminal stage of various common cardiovascular diseases with quite frequent readmission and high mortality rate, and brings heavy financial burdens to families and society. Oral Chinese patent medicine (CPM) has been widely applied in the treatment of HF in China because of its simplicity, cheapness, convenience, and high efficiency. However, due to the large number and broad clinical selectivity of oral CPMs, there is a lack of uniformity and clinical application standardization. To choose more effective and safe medicine among so many oral CPMs is particularly essential for further improving the therapeutic effect. In this study, the efficacy and safety of different oral CPMs are compared by a network meta-analysis of (NMA), and the best CPM is selected for the treatment of HF. **Participants:** patients diagnosed with HF according to any of the diagnostic criteria are eligible to be included. **Interventions and comparators:** the treatment group is defined as treating with oral CPMs based on western medicine, and the control group is defined as treating with western therapy alone or placebo or blank. **Outcomes:** the primary efficacy outcomes, secondary efficacy outcomes, and safety indicators. **Study of type:** all published or ongoing RCTs of oral PCMs for HF will be included.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 September 2020 and was last updated on 12 September 2020 (registration number INPLASY202090053).

INTRODUCTION

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quite frequent readmission and high mortality rate, and brings heavy financial burdens to families and society. Oral Chinese patent medicine (CPM) has been widely applied in the treatment of HF in

China because of its simplicity, cheapness, convenience, and high efficiency. However, due to the large number and broad clinical selectivity of oral CPMs, there is a lack of uniformity and clinical application standardization. To choose more effective and safe medicine among so many oral CPMs is particularly essential for further improving the therapeutic effect. In this study, the efficacy and safety of different oral CPMs are compared by a network meta-analysis of (NMA), and the best CPM is selected for the treatment of HF. **Participants:** patients diagnosed with HF according to any of the diagnostic criteria are eligible to be included. **Interventions and comparators:** the treatment group is defined as treating with oral CPMs based on western medicine, and the control group is defined as treating with western therapy alone or placebo or blank. **Outcomes:** the primary efficacy outcomes, secondary efficacy outcomes, and safety indicators. **Study of type:** all published or ongoing RCTs of oral CPMs for HF will be included.

Condition being studied: Heart failure (HF) is the terminal stage of various common cardiovascular diseases with quite a frequent readmission and a high mortality rate, and brings heavy financial burdens to families and society. Oral Chinese patent medicine (CPM) has been widely applied in the treatment of HF in China because of its simplicity, cheapness, convenience, and high efficiency. However, due to the large number and broad clinical selectivity of oral CPMs, there is a lack of uniformity and clinical application standardization. To choose more effective and safe medicine among so many oral CPMs is particularly essential for further improving the therapeutic effect. In this study, the efficacy and safety of different oral CPMs are compared by a network meta-analysis of (NMA), and the best CPM is selected for the treatment of HF.

METHODS

Participant or population: Patients diagnosed with HF according to any of the diagnostic criteria are eligible to be

included, such as the 2014 "Guidelines for the Diagnosis and Treatment of Heart Failure in China," the 2014 "Expert Consensus on TCM Diagnosis and Treatment of Chronic Heart Failure." Patients who have received coronary artery bypass surgery or cardiac resynchronization therapy, or accompanied by non-cardiovascular events such as malignant tumours, mental illnesses, or severe liver and kidney dysfunction are excluded. No restrictions on nationality, age, gender, race.

Intervention: The treatment group is defined as treating with oral CPMs based on western medicine. According to the guidelines and expert consensus, oral CPMs mainly include Qili Qiangxin Capsules, Shexiang Baoxin Pills, Shengmai Capsules, Shenfu Qiangxin Pills, Tongxinluo Capsules, Xinbao Pills, Xuefu Zhuyu Capsules, Danshen Dripping Pills, Xinkeshu Pills, Zhenyuan Capsules, Qishen Yiqi Dripping Pills, etc. Western medicine mainly include Ace inhibitors/Angiotensin II receptor antagonists, β -receptor blockers, aldosterone receptor antagonists, diuretics, nitrates, antiplatelet drugs, anti-myocardial ischemia drugs, and statins, etc.

Comparator: The control group is defined as treating with western therapy alone or placebo or blank. According to the guidelines and expert consensus, western medicine mainly include Ace inhibitors/Angiotensin II receptor antagonists, β -receptor blockers, aldosterone receptor antagonists, diuretics, nitrates, antiplatelet drugs, anti-myocardial ischemia drugs, and statins, etc.

Study designs to be included: All published or ongoing RCTs of oral CPMs for HF will be included. Research sources mainly include journal papers, conference papers and graduation thesis. The self-control and review literature, case report, experience summary, and repeatedly published literature is excluded.

Eligibility criteria: Eligibility criteria under the guidance of the PICOS principle include

the followings: **Participants:** patients diagnosed with HF according to any of the diagnostic criteria are eligible to be included, such as the 2014 "Guidelines for the Diagnosis and Treatment of Heart Failure in China," the 2014 "Expert Consensus on TCM Diagnosis and Treatment of Chronic Heart Failure." Patients who have received coronary artery bypass surgery or cardiac resynchronization therapy, or accompanied by non-cardiovascular events such as malignant tumours, mental illnesses, or severe liver and kidney dysfunction are excluded. No restrictions on nationality, age, gender, race. **Interventions and comparators:** the treatment group is defined as treating with oral CPMs based on western medicine, and the control group is defined as treating with western therapy alone or placebo or blank. According to the guidelines and expert consensus, oral CPMs mainly include Qili Qiangxin Capsules, Shexiang Baoxin Pills, Shengmai Capsules, Shenfu Qiangxin Pills, Tongxinluo Capsules, Xinbao Pills, Xuefu Zhuyu Capsules, Danshen Dripping Pills, Xinkeshu Pills, Zhenyuan Capsules, Qishen Yiqi Dripping Pills, etc. Western medicine mainly include Ace inhibitors/Angiotensin II receptor antagonists, β -receptor blockers, aldosterone receptor antagonists, diuretics, nitrates, antiplatelet drugs, anti-myocardial ischemia drugs, and statins, etc. **Outcomes:** the primary efficacy outcomes contain mortality, other cardiovascular events, the secondary efficacy outcomes contain New York Heart Association classification (NYHA classification), left ventricular ejection fraction (LVEF), quality of life (QOL) scores, brain natriuretic peptide (BNP) / N-terminal pro-brain natriuretic peptide (NT-proBNP), 6-minute walk test (6-MWT), the safety indicators contain adverse events such as itchy skin or rash, nausea, vomiting, dizziness, dry cough, etc. **Study of type:** all published or ongoing RCTs of oral PCMs for HF will be included. Research sources mainly include journal papers, conference papers and graduation thesis. The self-control and review literature, case report, experience summary, and repeatedly published literature is excluded.

Information sources: Electronic search: according to the search strategy, 4 English databases include PubMed/ MEDLINE, Web of Science, EMBASE, Cochrane Library, and 4 Chinese databases include China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Scientific Journal Database, Chinses Biomedical Literature Database (CBM) will be searched. The research time is from the establishment of the database to July 31, 2020. We will also search for ongoing RCTs, such as trials registered and conducted on WHO International Clinical Trial Registration Platform. The languages are restricted to Chinese, and English. Other sources of data: in addition to a comprehensive search of the databases, manual retrieval, and tracking of references and retrieval through search engines are also carried out.

Main outcome(s): The primary efficacy outcomes contain mortality, other cardiovascular events, the secondary efficacy outcomes contain New York Heart Association classification (NYHA classification), left ventricular ejection fraction (LVEF), quality of life (QOL) scores, brain natriuretic peptide (BNP) / N-terminal pro-brain natriuretic peptide (NT-proBNP), 6-minute walk test (6-MWT), the safety indicators contain adverse events such as itchy skin or rash, nausea, vomiting, dizziness, dry cough, etc.

Quality assessment / Risk of bias analysis: The methodological quality evaluation is one of the most important parts of the NMA, and it is the judgment of the authenticity of the research. The quality evaluation is mainly carried out by evaluating the bias risk in the design and implementation of clinical trials. All included literature is evaluated by the bias risk assessment tool of the Cochrane Handbook Version 5.2.0 for Systematic Reviews of Interventions, and seven items are included in the tool. All biases are evaluated in three risk levels: low, uncertain, and high. For divergent literature evaluation results, independent evaluation and adjudication will be conducted by a third member.

Strategy of data synthesis: In this study, the Stata software (Stata for Windows 15.0, Corporation, College Station, TX) is used for pairwise meta-analysis. The odds ratio (OR) and mean difference (MD) as the effect sizes of continuous and categorical variables, respectively. The 95% confidence interval (CI) is calculated to represent the possibility of the results in this interval. The Aggregate Data Drug Information System (ADDIS) (Version for Windows 1.16.8) is used for NMA, and Markov-chain-Monte-Carlo (MCMC) is used to perform Bayesian inference. Perform iterative operations based on preset model parameters. After the statistical analysis, the convergence needs to be measured by the potential scale reduction factors (PSRE). The closer the PSRE is to 1, the better the convergence. PSRE greater than 1.1 or 1.2 means the number of simulations needs to be increased to achieve good convergence. After the consistency model analysis is completed, the rank probability and relative effects are used to compare the effects of CPMs.

Subgroup analysis: It is necessary to analyze the causes if there is heterogeneity in the research results. Subgroup analysis will be carried out according to research characteristics related to the heterogeneity source. For example, if the heterogeneity may be caused by the methodology's quality, the hierarchical analysis may be carried out according to methodology quality; if different design schemes may cause it, the hierarchical analysis will be carried out according to the design scheme.

Sensitivity analysis: In the process of effect size synthesizing, only when the included studies have the least heterogeneity, the credibility of the synthesized effect size is high. Sensitivity and subgroup analyses are the most common approaches to solve heterogeneity. Stata 15.0 software is used to analyze the sensitivity if the results of NMA are positive, and more than three studies are included. The sensitivity analysis is carried out by excluding the 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: Chinese patent medicine, heart failure, network meta-analysis.

Contributions of each author:

Author 1 - Hui Guan.

Author 2 - Guohua Dai.

Author 3 - Ning Wang.

Author 4 - Wulin Gao.

Author 5 - Lili Ren.

Author 6 - Zhenhao Cai.