

# BMJ Open Comparison of the efficacy and acceptability of Chinese herbal medicine in adult patients with heart failure and reduced ejection fraction: study protocol for a systematic review and network meta-analysis

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## ABSTRACT

**Introduction** Heart failure with reduced ejection fraction (HFrEF) is defined as the clinical diagnosis of heart failure (HF) and ejection fraction (EF)  $\leq 40\%$ , which is a severe public healthcare issue and brings a heavy social and economic burden for patients with HFrEF. Chinese herbal medicine (CHM) has a long history in treating HF. Questions concerning the efficacy and acceptability of CHM-related interventions in adult patients with HFrEF led us to use the method of systematic review and network meta-analysis to integrate direct and indirect evidence to create hierarchies for all CHM.

**Methods and analysis** Nine medical databases, including PubMed, EMBASE (OVID), the Cochrane Library, Google Scholar, Web of Science, CNKI, VIP, Wanfang Database and CBM will be searched from the date of database inception to June 2015 (updated to March 2017) without language and publication status restriction. Completely randomised controlled trials (RCTs) comparing CHM or CHM plus routine treatment with CHM, CHM plus routine treatment, routine treatment, no treatment or placebo for adults with HFrEF will be examined. Our primary outcomes will include all-cause mortality, HF-related death, all-cause rehospitalisation, HF-related rehospitalisation and acceptability (discontinuation due to any adverse events during treatment). Secondary outcomes will include response rate, mean value or mean difference from baseline of surrogate indexes. We will perform the Bayesian network meta-analyses (NMA) for the most frequently reported primary or secondary outcome and the acceptability outcome, if available. Meta-regression, subgroup analyses and sensitivity analyses will be conducted based on prespecified effect modifiers to assess the robustness of the findings.

**Dissemination** The results of this NMA will provide useful information about the effectiveness and acceptability of CHM in adults with HFrEF, which will also have implications for clinical practice and further research. Findings will be disseminated through peer-reviewed journal publication and conference presentations.

**PROSPERO registration number** CRD42016053854.

## Strengths and limitations of this study

- As far as we know, this will be the first network meta-analysis to evaluate the effectiveness and acceptability of Chinese herbal medicine in adults with heart failure and reduced ejection fraction. Network meta-analysis based on Bayesian theory can integrate direct evidence and indirect evidence from all alternative treatment options for the same condition to estimate the effect size of all treatments and to rank them.
- Well established eligible criteria, rigorous quality assessment and data collection, standardised statistical analysis, subgroup and sensitivity analyses may increase study strength and reduce heterogeneity.
- The drawbacks of this study may potentially reside in low quality of evidence, publication bias, heterogeneity across studies and inconsistency between direct and indirect evidence, which will decrease the robustness of the results.

## BACKGROUND

Heart failure with reduced ejection fraction (HFrEF) is a clinical syndrome characterised by abnormal systolic function with or without abnormal diastolic function, reduced ejection fraction, and the symptoms and signs of heart failure (HF). According to present guidelines, HFrEF is defined as the clinical diagnosis of HF and ejection fraction (EF)  $\leq 40\%$ .<sup>1</sup> HF incidence has largely remained stable over the past several decades, with >650 000 new HF cases diagnosed annually in the United States.<sup>1</sup> Approximately 9 per 1000 individuals among those aged 35–74 years in China<sup>2</sup> and 10 per 1000 of the population over 65 years of age in the United States

have clinically manifest HF, and the prevalence continues to rise.<sup>1</sup> Being the severe and terminal phase of many cardiovascular diseases, such as hypertension, arrhythmia and coronary heart diseases, HF is a leading cause of death, hospitalisation and rehospitalisation worldwide.<sup>3</sup> Despite acquired advancements in HF treatments, including guideline-directed medicine therapies (GDMTs), implanted devices and even heart transplantation, still approximately 50% of people diagnosed with HF will die within 5 years<sup>1 4</sup> and the number of deaths with HF was as high in 2011 as it was in 1995,<sup>4</sup> not to mention the high cost of HF-related hospitalisation (about \$23 077 per patient in the United States).<sup>5</sup> HFrEF makes up about half of the overall HF burden.<sup>6</sup>

In China, Chinese herbal medicine (CHM) has been used to treat symptoms of HF for more than 2500 years, which includes oedema, shortness of breath, dizziness, exercise intolerance, palpitations and so on. The manifestations, pathogeneses and treatments of HF have been discussed and summarised in traditional Chinese medicine (TCM) theory, and CHM used alone or integrated with routine treatments has been widely accepted as an effective method in the treatment of HFrEF in China. In the early 21st century, along with the introduction of evidence-based medical conception and practical methods, many TCM doctors carried out controlled clinical trials to explore the efficacy and safety of diverse CHM on HFrEF, and relevant results were promising. However, various characteristics of these trials yielded different results, which demands further comprehensive evidence.<sup>7-9</sup> Most trials have focused on comparing CHM alone or CHM plus routine treatments versus placebo or routine treatments, but failed to compare CHM with another CHM. Currently, no published meta-analysis has combined direct and indirect evidence for the use of CHM on HFrEF, though it is important to inform both the physician and the patient which CHM or CHM plus routine treatment may be the most effective and acceptable treatment.

For the above reasons, we will use network meta-analysis (NMA), a methodological approach that allows simultaneous comparison of multiple interventions within a single analysis. Based on the transitivity and similarity between included studies, and preserving randomisation, this NMA will bring improved precision of the estimated effect size and the ability to compare treatments that have not been directly compared in any trial.<sup>10 11</sup> To be specific, this approach will be used to integrate direct evidence (from studies directly comparing interventions) with indirect evidence (from information comparing two interventions via the same comparator) to estimate and rank the effectiveness and acceptability of CHM or CHM plus routine treatment on HFrEF by comparing them with routine treatment, placebo or CHM.<sup>12</sup>

## METHODS

### Eligible criteria

#### Types of studies

All peer-reviewed, full-reported prospective parallel randomised controlled trials (RCTs) irrespective of blinding will be assessed, but non-RCTs, small sample studies (less than 20 cases), duplicate reports and pilot studies will be excluded. In addition, the first phase data of randomised crossover trials and cluster RCTs will also be included for analysis.

#### Types of participants

Patients diagnosed with HFrEF (New York Heart Association (NYHA) class II or IV) and aged over 18 years old but with no limitations on gender, course and comorbidity will be eligible. Both acute HFrEF and chronic HFrEF will be included, but patients waiting for or having accepted heart transplantation, or suffering heart shock or heart arrest will be excluded. The diagnosis criteria adopted by the included studies should be identical to at least two major criteria or one major criterion in conjunction with two minor criteria of the Framingham standard,<sup>13</sup> and must fulfil a EF  $\leq 40\%$  (online supplementary appendix 1). For those trials including patients with HFrEF and HFpEF (heart failure with preserved ejection fraction), we will contact the author to obtain data for HFrEF participants. If there is no response, this study will be discarded. Furthermore, to assure transitivity within the network, trials in a single node, for example AC and BC, should be systematically or proportionally similar in critical baseline characteristics, such as gender, age, comorbidity, combined medication and HFrEF severity.<sup>14</sup>

#### Types of interventions

The experimental interventions should be combinations of herbs or Chinese proprietary medicines but with a single herb. RCTs comparing CHM or CHM plus routine treatment with CHM, CHM plus routine treatment, routine treatment, no treatment or placebo will be included. Trials comparing the same CHM (sharing the same single herbs) but at different doses and different treatment durations will be treated as one node in the network. We define routine treatment as GDMT (eg, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker,  $\beta$  blocker, aldosterone antagonist and hydralazine/nitrate) or inotropic drugs (eg, digoxin),<sup>1</sup> which refer to only one GDMT. In addition, we will exclude trials involving a combination of more than two kinds of CHM. Furthermore, distribution with respect to potential effect modifiers (eg, administration route, dose, frequency) among trials in one single node should be similar.<sup>14</sup>

#### Types of outcome measures

We will exclude trials with treatment duration of less than 2 weeks. Our primary outcomes will include all-cause mortality, HF-related death, all-cause rehospitalisation, HF-related rehospitalisation and acceptability

(discontinuation due to any adverse events during treatment). Secondary outcomes will include response rate, mean value or mean difference from baseline of ultrasonic cardiograph indexes (eg, left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI)), NYHA grade, b-type natriuretic peptide (BNP), n-terminal pro-b-type natriuretic peptide (NT-proBNP), blood pressure (BP), weight or quality-of-life score. Only a percentage of improvement of secondary outcomes equal to or more than 50% will be considered as a response. When a 'response' is not reported, we will use 'remission', if available. Remission is defined as the proportion of patients who do not improve or even worsened.<sup>15</sup> We will only conduct NMA for two outcomes, including the most frequently reported primary or secondary outcome and the acceptability outcome, if available.

### Data sources and search strategy

A comprehensive search of nine medical databases, including PubMed, EMBASE (OVID), the Cochrane Library, Google Scholar, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), Wanfang Database and Chinese Biomedical Database (CBM) will be conducted from the date of database inception to June 2015 (updated to March 2017) without language and publication status restriction. We will search individually or combined mesh with title/abstract terms relating to the intervention of interest (complementary medicine, complementary medicine, oriental medicine, traditional medicine, Chinese medicine, Chinese herbal medicine, Chinese proprietary medicine\*, Chinese herbal drug\*, Chinese herbal preparation\*, herb\*, medicinal plant\*, plant\*, phytomedicine\*, botanical) and those relating to the patients of interest (heart failure, cardiac compensation, cardiac insufficiency, ventricular dysfunction). The above terms in Chinese will be searched in Chinese databases. Also, we will search relevant references of obtained studies and review articles by hand to identify eligible resources. In addition, Chinese Clinical Trial Registry (ChCTR), ClinicalTrials.gov, International Clinical Trials Registry Platform (WHO-ICTRP) will be reviewed for unpublished studies. All relevant authors and manufacturers will be contacted to supplement data for published papers or to provide data for unpublished trials, if available. The search strategy of EMBASE and CENTRAL is available (online supplementary appendix 2).

### Study selection

Four reviewers (JL, YL, JJJL and XYC) will independently scan the title and abstract of studies obtained through the search strategy and exclude those failing to meet the eligible criteria. They will then get the full text for potentially relevant trials to further determine whether they fulfil the same eligible criteria. These four reviewers will act as two pairs of reviewers. Reasons for trial exclusion will be documented in detail at full-text level and any

disagreement will be resolved by census or consultation with a fifth reviewer (JW).

### Data extraction

Four reviewers (JL, QG, JJJL and YCH) will extract data independently using a standardised extraction form. The following items will be extracted: article name, first author or corresponding author, publication year, journal, country, institution and sponsor, trial setting, inclusion criteria, exclusion criteria, details of trial design (ie, randomisation, allocation concealment, blinding), general characteristics of patients (ie, gender, age, HFrEF course and severity, comorbidities), details of intervention and control therapy (ie, components of CHM, CHM type, dosage, intervention duration, co-intervention), sample size, details of outcomes (ie, measuring means, time points, mean value, mean difference, response event, non-response event), and other information that may help detect bias (ie, register ID, data for analysis, termination time). Similarly, division of labour is the same as that in the 'Study selection' section and the fifth reviewer (JW) will be available for consultation regarding controversial issues.

### Risk of bias assessment

The methodological quality of the included studies will be assessed by two reviewers (SNL and JW) using the Cochrane Collaboration's tool,<sup>16</sup> which is a domain-based evaluation tool to generate a 'Risk of bias' table for each study. The domains for assessment include sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias (eg, early termination, conflict of interest). As CHM is difficult to blind participants, performance bias will likely be present in all trials. When it comes to objective outcomes such as all-cause mortality, performance bias and detection bias might not be so important so that we can summarise this trial as low risk if bias of other remaining domains is also ranked as low. However, for highly subjective outcomes such as quality-of-life score, we may decide that both blinding of participants and outcome assessment are critical, and high risk of bias for one or more key domains within a study will be evaluated as high risk of bias. In addition, regarding selective outcome, this domain will be ranked as 'low risk' unless the outcomes are critical for our issue, such as all-cause mortality, all-cause rehospitalisation and acceptability.<sup>17</sup> Also, a third reviewer (KZ) will take charge of any disagreement solution.

### Data synthesis and analysis

First, we will perform pairwise analysis for trials including same experimental intervention using a random-effect model in Stata (version 13.1). Dichotomous data will be calculated as odds ratio (OR) and continuous data as



weighted mean difference (WMD) or standardised mean difference (SMD), both with corresponding 95% confidence intervals (CIs). If mean and SD are not provided, we will calculate them from the *p* value, *t* value, CI or other statistical indices as described in the Cochrane Handbook (version 5.1.0).<sup>17</sup> Heterogeneity across trials of each pairwise comparison will be assessed by the Cochran *Q* test and presented as *I*<sup>2</sup> statistics.<sup>17</sup> Funnel plot and Egger's test will be performed to detect publication bias, if at least 10 studies are available.<sup>17</sup>

Second, we will do NMA to combine all direct and indirect evidence to compare the relative effect size of different CHM treatments, CHM plus routine treatment, routine treatment, placebo, no treatment with each other from the median of the posterior distribution.<sup>10 12</sup> OR, SMD or WMD will be calculated with corresponding 95% credible interval (CrI)<sup>10</sup> and reported in a league table. We will fit the model within a Bayesian framework by using WinBUGS (version 1.4.3) or GeMTC (version 0.14.3) software to perform random-effect multitreatment meta-analysis and Stata or R (version 3.3.0) software to plot and analyse further.

To pool estimate effects, two Markov chains will be run simultaneously by choosing different initial values. Trace plots and the Brooks-Gelman-Rubin statistic will be generated to assess convergence.<sup>18</sup> To ensure convergence, the previous 50 000 samples will be abandoned and described as 'burn in', and posterior summaries will be based on 100 000 subsequent simulations. To assess global heterogeneity in the network, we will calculate the *I*<sup>2</sup> statistic using the GeMTC R package (version 3.2.2), which is based on the magnitude of the heterogeneity variance parameter estimated from the NMA models.<sup>19</sup> To measure inconsistency between direct and indirect evidence, three methods will be used, including the node-splitting method (by separating evidence of one particular comparison into direct and indirect evidence to find inconsistency between them),<sup>20</sup> the local (loop-specific approach, evaluating inconsistency in each closed loop by generating an inconsistency factor and CI shown in a forest plot) and global (by using the 'design-by-treatment' model to compare the difference between consistency and inconsistency models based on a  $\chi^2$  test) method.<sup>21</sup> All these methods will serve to produce a more robust conclusion. If there are controversial results among different methods, we will make a comprehensive conclusion based on the ratio of results, heterogeneity and overall risk of bias. To provide a hierarchy of interventions, ranking probability will be calculated and shown as a surface under the cumulative ranking curve (SUCRA) and rankograms.<sup>12</sup> Also, to detect publication bias in each NMA, comparison-adjusted funnel plots will be drawn, if enough trials are available.<sup>22</sup>

In addition, to eliminate or explore sources of heterogeneity or inconsistency, meta-regression, subgroup or sensitivity analysis for primary outcome will be performed based on prespecified effect modifiers as follows: year of publication, study quality, trial publishing status,

sample size, NYHA grade, EF value, comorbidity, age, gender, CHM type, treatment duration, etc. Furthermore, we will use a grade framework to assess the quality of evidence attributed to each primary outcome in one network, with quality-assessment domains including study limitations, imprecision, inconsistency, indirectness and publication bias.<sup>23</sup>

### Ethics and dissemination

As no individual patient data will be used in this NMA, it is not necessary to declare ethics here. The protocol of this NMA has been drawn up in compliance with items recommended by the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Healthcare Interventions<sup>24</sup> and registered at PROSPERO with the number-CRD42016053854 (available from [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42016053854](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016053854)).

The results of this NMA will provide a more comprehensive and more reliable overview of efficacy and acceptability of CHM for adults with HF<sub>r</sub>EF by drawing on available direct and indirect evidence and a series of critical appraisal procedures, which will also have implications for clinical practice and further research. Once completed, the findings of this NMA will be published in a peer-reviewed journal and presented at conferences.

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**Contributors** QL and JL conceived the NMA. JL and JLL drafted and revised this protocol. JL, JLL, JW, YL, XYC, QG, YCH and SNL established the Data Management Committee and are separately responsible for study selection, data extraction and risk of bias assessment procedures. JW and KZ took charge in coordinating every piece of work together, disagreement settlement and data safety. QL and JL contributed to the design of statistical analysis. JL and JLL are responsible for overall data synthesis and analysis. QZD contributed to language polishing. QL is responsible for the overall quality of the NMA. All authors read this manuscript and approved the publication of this protocol.

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