

# INPLASY

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## Combination of Qi benefiting and blood circulation promoting herbs with Dapagliflozin in the treatment of type 2 diabetes mellitus combined with chronic heart failure: a systematic evaluation and meta-analysis based on a randomized controlled trial

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## ADMINISTRATIVE INFORMATION

**Support** - No funding was provided for this study.

**Review Stage at time of this submission** - Completed but not published.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY2023120120

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 December 2023 and was last updated on 31 December 2023.

## INTRODUCTION

**Review question / Objective** A systematic review of the efficacy of Combination of Qi benefiting and blood circulation promoting herbs with Dapagliflozin in the treatment of type 2 diabetes mellitus (T2DM) combined with chronic heart failure(CHF).

**Condition being studied** Type 2 diabetes mellitus (T2DM) and heart failure (HF) have become global epidemics in the 21st century, and their prevalence and incidence are increasing year by year, constituting a major health burden and public health problem worldwide[1]. The prevalence of cardiovascular disease in China is increasing year by year, with a projected 330 million people currently suffering from cardiovascular disease, of which 8.9 million are HF, and the prevalence of HF in people over 35 years of age is 1.3% [2], an

increase of about 44% compared to the epidemiological report in 2000.HF is characterised by a high rate of short-term rehospitalisation and long-term chronic treatment, thus imposing a huge economic burden on the healthcare system [3]. The global prevalence of diabetes mellitus (DM) is substantial, as evidenced by epidemiological data from 2021 indicating that over 500 million individuals are affected by the condition. Projections suggest that this number is set to increase to more than 780 million by the year 2045 [4]. HF and T2DM are often combined clinically, increasing each other's risk of disease and death, and patients with co-morbid HF and T2DM have more severe clinical symptoms and a poorer prognosis than those with the disease alone [5]. As the duration of DM increases, the risk of HF increases. Studies have shown that the risk of HF increases by 17% for every 5-year increase in the duration of DM [6-7]. Therefore, how to conduct

effective intervention in the early stage of the development of diabetes to prevent the transformation and further progress of the disease has attracted more and more attention from medical staff, diabetic patients and their families.

## METHODS

**Search strategy** China Knowledge Network (CNKI), Wanfang Database, VIP Database, PubMed, Embase, Cochrane Library, and China Biology Medicine disc(CBMD) were searched until June 2023.

**Participant or population** All included patients' diagnostic criteria were formulated with reference to the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018 [13] on acute heart failure and the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 Edition) [14] on T2DM.

**Intervention** Intervention: the control group was the addition of Dapagliflozin to the conventional treatment of diabetes, and the experimental group was the addition of Yiqi and blood activating herbs to the control group.

**Comparator** Qi benefiting and blood circulation promoting herbs.

**Study designs to be included** Randomised controlled trial(RCT), whether blinded or not, language limited to Chinese and English.

**Eligibility criteria** (1) duplicate publications, reviews, and conference papers; (2) animal experiments or individual case reports; (3) literature with incomplete data or unavailable outcome metrics; (4) literature with interventions that did not meet inclusion criteria.

**Information sources** Chinese search terms included "diabetes mellitus", "diabetes mellitus combined with heart failure", "diabetes mellitus combined with cardiac insufficiency", "Chinese medicine Chinese search terms include "Diabetes Mellitus with Heart Failure", "Diabetes mellitus with cardiac insufficiency", "Chinese medicine", "Chinese patent medicine", while English search terms include "Diabetes Mellitus with Heart Failure", "Diabetes mellitus with Cardiac insufficiency", "Chinese Medicine", "Chinese Herbal Compound", all using Subject plus free word search. The detailed search strategy is presented in Supplementary Tables S1–S7.

**Main outcome(s)** Outcome indicators: at least one of the indicators including total clinical efficiency, blood glucose, inflammatory factors, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), 6-minute walk test (6MWT), Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the incidence of adverse reactions.

**Data management** A data extraction form was created and data were extracted by two trained researchers and another researcher was added to discuss and resolve any differences of opinion. The original indicators of the relevant literature were verified and validated, and the original authors were contacted by mail if there were any errors or ambiguous information. If the valid original data could not be obtained, the literature with problems was discarded, and the quality of the original literature was strictly controlled before being included in this Meta-analysis.

**Quality assessment / Risk of bias analysis** The extracted methodological features were assessed by two evaluators with reference to the Cochrane Risk of Bias Assessment Tool [15] for the following areas of included studies: randomisation methods, allocation concealment methods, blinding, completeness of results, selective reporting of results and other sources of bias. Each was categorised as low risk, uncertain and high risk. If the literature was controversial, it was screened by a third researcher, who then read the full text and re-screened it, and those that ultimately met the criteria were included in the analysis to map the literature search and screening process.

**Strategy of data synthesis** The meta-analysis was performed using RevMan 5.4 software. Effect indicators: Ratio ratio (OR) or risk ratio (RR) was used for count data, and mean difference (MD) or standardized mean difference (SMD) was used for measurement data, and their 95% confidence intervals (CI) were calculated. Heterogeneity analysis needed to be determined according to the size of  $I^2$ ; if  $P > 0.10$  and  $I^2 \leq 50\%$ , a fixed-effects model was used; if  $P \leq 0.10$ ,  $I^2 > 50\%$ , a random-effects model was used, and subgroup analysis or sensitivity analysis was performed.

### Subgroup analysis HbA1c

A total of 5 studies were included in the literature [16, 17, 20, 21, 26], and heterogeneity tests indicated high overall heterogeneity. Sensitivity analyses by excluding literature on a case-by-case basis revealed no significant change in effect sizes. To further analyse the source of heterogeneity, we

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performed subgroup analyses based on treatment duration. The subgroup with treatment duration  $\leq 4$  weeks consisted of three RCT studies [16,17,21], which were suggested to be homogeneous by the heterogeneity test, as shown by Meta-analysis [MD=-1.46, 95% CI (-1.57,-1.35), P=0.0001], and the results of Meta-analysis using a random-effects model showed [MD=-1.30, 95% CI (-1.45,-1.15), P<0.0001]. This indicated that the combination of qi and blood promoting herbs with dapagliflozin was superior to the control group in reducing HbA1c. As shown in Figure 7.

**Sensitivity analysis** Sensitivity analysis by excluding the literature one by one revealed no significant change in effect values.

**Country(ies) involved** China.

**Keywords** type 2 diabetes mellitus; chronic heart failure; traditional Chinese medicine; systematic review; meta-analysis.

#### **Contributions of each author**

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