INPLASY PROTOCOL

To cite: Dong et al. Efficacy and safety of dapagliflozin in the treatment of chronic heart failure: A protocol for systematic review and meta-analysis. Inplasy protocol 202150046. doi: 10.37766/inplasy2021.5.0046

Received: 12 May 2021

Published: 13 May 2021

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Support: **2018WS184, 202003040045.**

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

Conflicts of interest:
None declared.

Efficacy and safety of dapagliflozin in the treatment of chronic heart failure: A protocol for systematic review and meta-analysis

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Review question / Objective: **As the last link in the chain of cardiovascular events, chronic heart failure (CHF) has high morbidity, high mortality, and poor prognosis. It is one of the main causes of death and disability worldwide. As a new drug for the treatment of chronic cardiovascular disease, dapagliflozin, the efficacy and safety issues are still the focus of attention. Therefore, we conducted a meta-analysis to evaluate the efficacy and safety of dapagliflozin in the treatment of CHF.**
Information sources: **We will conduct a literature search from the following electronic databases: PubMed, EMBASE, the Cochrane Library, Web of Science, CNKI, Wan-fang Data, Chinses Biomedical Literature Database, Chinese Scientific Journal Database. There are no restrictions on publication date and language. In addition, the references listed in each included article are also manually searched.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 May 2021 and was last updated on 13 May 2021 (registration number INPLASY202150046).

INTRODUCTION

Review question / Objective: **As the last link in the chain of cardiovascular events, chronic heart failure (CHF) has high morbidity, high mortality, and poor prognosis. It is one of the main causes of death and disability worldwide. As a new drug for the treatment of chronic cardiovascular disease, dapagliflozin, the**

efficacy and safety issues are still the focus of attention. Therefore, we conducted a meta-analysis to evaluate the efficacy and safety of dapagliflozin in the treatment of CHF.

Condition being studied: Chronic heart failure(CHF) is a group of complex clinical syndromes caused by abnormal changes in cardiac structure and (or) function caused by various reasons, which make ventricular contraction and (or) diastolic dysfunction occur. The main manifestations are dyspnea, fatigue and fluid retention, etc. CHF is the end-stage manifestation of cardiovascular disease and the main cause of death. It has a high recurrence rate and a poor prognosis, which seriously threatens people's physical and mental health. In developed countries, the prevalence of HF in adults is about 1-2%, and it gradually increases with age, and exceeds 10% in people over 80. After being diagnosed with chronic heart failure (CHF), the rehospitalization rate was as high as 83.1%, and 42.6% were hospitalized more than 4 times. The Framingham Heart Study in the United States shows that within 5 years of the initial diagnosis of CHF, the mortality rate of patients is about 50%. In patients with acute myocardial infarction with CHF, the 1-year mortality rate is more than 50%. Therefore, extending the survival period of patients with CHF, reducing the mortality rate, and improving the prognosis are key issues that need to be resolved. Dapagliflozin is a new type of hypoglycemic agent belonging to the Sodium-Glucose Transporter 2 Inhibitors (SGLT-2i) class. Its effect of lowering blood sugar does not depend on improving insulin secretion and peripheral tissue resistance to insulin. It mainly inhibits the activity of proximal renal tubules SGLT-2, reduces the reabsorption of glucose by the renal tubules, thereby increasing the excretion of glucose in the urine, lower blood sugar. In addition, SGLT-2i drugs also have unique effects other than hypoglycemic effects. For example, Empagliflozin and Canagliflozin have been proven to have additional cardiovascular protection and can reduce the occurrence of cardiovascular events. As a similar drug, dapagliflozin has also been proven to benefit cardiovascular disease in some studies, and this effect is independent of the hypoglycemic effect. In Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) Trial, dapagliflozin can reduce hospitalization rates and mortality from cardiovascular events in patients with and without Type 2 Diabetes Mellitus (T2DM) who had HF with reduced ejection fraction (EF). However, some studies found that dapagliflozin can reduce the hospitalization rate of patients with CHF in the analysis of the baseline data and EF value of the DECLARE-TIMI 58 trial, regardless of whether the ejection fraction is normal or not. In addition, people may worry about the potential safety issues of this new drug in the treatment of CHF. Therefore, this study proposes a systematic review program to evaluate the efficacy and safety of dapagliflozin on CHF, and to provide sufficient basis for further guidance of clinical medication, so as to avoid unnecessary traps.

METHODS

Participant or population: Patients with CHF, whether diagnosed by a clinician, or by any recognized criteria diagnosis of CHF, will be included. There are no restrictions on nationality, age, gender, or race. Patients who have received acute heart failure, or patients with severe liver and kidney, or blood diseases, or malignant tumors, or other uncontrolled systemic diseases are excluded.

Intervention: The treatment group was given Dapagliflozin (5-10mg) on the basis of routine western medicine of CHF.

Comparator: The control group was only given routine western medicine, or the same dose of placebo was given on the basis of routine western medicine. Routine western medicine mainly includes diuretics, ACEI, ARB, β-receptor blockers, ivabradine, digitalis and inotropic drugs, vasodilators, anticoagulants, etc.

Study designs to be included: Randomized controlled trials (RCTs) will be included in

this study irrespective of language or publication category. Animal trials, review article and studies with incorrect RCT designs will be excluded.

Eligibility criteria: We will formulate the inclusion and exclusion criteria for this study based on the PICOS principles.

Information sources: We will conduct a literature search from the following electronic databases: PubMed, EMBASE, the Cochrane Library, Web of Science, CNKI, Wan-fang Data, Chinses Biomedical Literature Database, Chinese Scientific Journal Database. There are no restrictions on publication date and language. In addition, the references listed in each included article are also manually searched.

Main outcome(s): The primary outcomes include mortality and HF rehospitalization rate.

Additional outcome(s): The secondary outcomes include New York Heart Association classification (NYHA classification), EF, N terminal pro B type natriuretic peptide (NT-proBNP), quality of life (QOL), etc; the safety indicators include hypovolemia, hypoglycemia, kidney damage, infections of the genitourinary system and other adverse reactions.

Quality assessment / Risk of bias analysis: Two reviewers will independently assess the quality of the included literature according to the Cochrane Collaboration's tool for randomized controlled trials. If there is a disagreement between two reviewers, the third reviewer resolves the issue. According to Cochrane Handbook V.5.2.0, Characteristics of each item will be evaluated in three categories: low, unclear and high. The results of the quality assessment will be completed using software Review Manager 5.3.

Strategy of data synthesis: We will execute Rev Man 5.3 and STATA 14.2 software for traditional meta-analysis. For dichotomous data, we will calculate a summary estimate with 95% confidence interval (CI) odds ratio (OR) value; for continuous data, we will calculate a summary estimate of standardized mean difference (SMD) with 95% CI, and P50%, it indicates that there is heterogeneity among the included literature, and assess the effect size by the random effect; on the contrary, a fixed effect model is used.

Subgroup analysis: Taking into account the issue of heterogeneity, we will conduct a subgroup analysis based on the specific circumstances of the included literature. If there is a problem of heterogeneity, we will conduct a subgroup analysis of age, gender, and interventions. In addition, in order to understand whether the LVEF will affect the efficacy of dapagliflozin, it will be used for CHF patients with LVEF<40% and CHF with unknown LVEF the mortality rate and rehospitalization rate are analyzed by subgroups. In order to understand whether patients with CHF and T2DM affect the efficacy of dapagliflozin, the mortality rate and rehospitalization rate will be subgroups-analyzed on whether patients with CHF have T2DM.

Sensitivity analysis: This systematic review will use the method of eliminating each study one by one for sensitivity analysis. If the effective indicators (e.g., the mortality rate and rehospitalization rate) of dapagliflozin in the treatment of CHF have not changed significantly, it indicates that the study is robustness. On the contrary, it is not robustness. According to the specific situation, low-quality research is excluded.

Language: Randomized controlled trials (RCTs) will be included in this study irrespective of language or publication category. Animal trials, review article and studies with incorrect RCT designs will be excluded.

Country(ies) involved: China.

Keywords: Chronic heart failure; dapagliflozin; systematic review; meta-analysis.

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