

Efficacy and safety of dapagliflozin for treating heart failure in China: A meta-analysis

Wanshi Wu, Shang Yao*, Qing Xu, Hui Cheng and Qing Jiang

Department of Internal Medicine-Cardiovascular, Anqing First People's Hospital of Anhui Province, China

Abstract: This study assesses the efficacy and safety of dapagliflozin in Chinese patients with heart failure through a systematic review of randomized controlled trials from PubMed and the China National Knowledge Infrastructure databases. Focusing on 977 patients across eight trials, the meta-analysis used Review Manager 5.4.1 for data analysis. Key findings include a significant reduction in N-terminal pro-B-type natriuretic peptide levels (standardized mean difference: -2.88, 95% CI: -4.31 to -1.44, $p < 0.001$) and an increase in left ventricular ejection fraction (weighted mean difference: 5.10, 95% CI: 2.32 to 10.32, $p < 0.001$). However, changes in left ventricular end-diastolic diameter were not significant (weighted mean difference: -1.33, 95% CI: -2.80 to 0.15, $p = 0.08$), and the relative risk of adverse reactions was comparable between the control and observation groups (RR: 1.17, 95% CI: 0.82 to 1.68, $p = 0.38$). Overall, dapagliflozin demonstrates good efficacy and safety in treating heart failure in this population.

Keywords: Dapagliflozin, heart failure, efficacy, safety, China.

INTRODUCTION

Heart failure (HF) constitutes a cardiovascular epidemic, and most chronic cardiovascular diseases develop into HF at a later stage (Chen *et al.*, 2023). The main symptoms of HF are dyspnoea, limitation of physical activity and/or congestion of systemic circulation, which may be accompanied by the elevation of jugular vein pressure, pulmonary oedema and systemic congestion due to structural and/or functional abnormalities of the heart, which leads to reduced cardiac output and/or increased intracardiac pressure at rest or under pressure (Ji *et al.*, 2023). When there is venous reflux, the cardiac output cannot meet the metabolic needs of the body due to primary cardiac ejection or filling disorders. Heart failure can be divided into acute HF and chronic HF (CHF). Worldwide, the incidence of HF in adults is approximately 1%-2% (Metra *et al.*, 2017). The 3-month hospitalisation rate of patients with HF is 32% (Gheorghiadu *et al.*, 2012) and the mortality of hospitalised patients is 31.7% (Givi *et al.*, 2018). Heart failure seriously endangers people's health and increases the burden of other diseases. Presently, the intervention measures for HF focus on diet, drugs, behaviour, equipment and heart transplantations. However, for a large number of patients, these measures have a poor impact on factors such as shortness of breath and disease progression. Better treatment schemes are expected in the future that will benefit more patients (Willerson, 2019). Diabetes raises the probability of death and is an important factor for HF (Sun *et al.*, 2015). A brand-new class of sodium/glucose cotransporter-2 inhibitors (SGLT-2i) called dapagliflozin is a hypoglycaemic drug (Packer *et al.*, 2017). Unlike traditional hypoglycaemic drugs, SGLT-2i reduces heart damage, hypertrophy, fibrosis,

remodelling and contraction dysfunction. These inhibitors can also reduce ejection fraction, which reduces blood pressure, body weight and fluid retention and improves renal function, which in turn may alleviate HF (Packer *et al.*, 2017). In February 2021, the indication of dapagliflozin for CHF treatment was approved in China, and national recommendations advise using it as the first line of treatment for CHF patients, delaying the onset of HF and lowering the rate of patient admissions (The working group on Chinese expert recommendations for the clinical application of new anti hyperglycemic drugs to improve cardiovascular and renal outcomes, 2020; ACC/AHA Joint Committee Members, 2022).

Dapagliflozin for patients with HF and diabetes has been studied extensively abroad, but systematic reviews are rare in China. Therefore, the authors aimed to thoroughly assess the effectiveness and safety of dapagliflozin for the treatment of HF and offer proof of these attributes together with innovative therapeutic approaches.

MATERIALS AND METHODS

Retrieval strategy

This study searched the China National Knowledge Infrastructure and PubMed database and searched for relevant literature that met the following three conditions: (1) the participant was HF patients, (2) the intervention was treated with dapagliflozin or a combination of conventional and dapagliflozin therapy and (3) the control was treated with conventional or placebo therapy. The retrieval period covered the period between the database's creation until November 21, 2021.

The text and medical subject headings (MeSH) used in this search including dapagliflozin, farxiga and (congestive/left sided/right sided) heart failure. According

*Corresponding author: e-mail: yaoshang00921@21cn.com

to different database search rules to adjust the keyword search.

The guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement were followed in the reporting of this network meta-analysis and systematic review. Additionally, the study protocol was duly recorded with the International Prospective Register of Systematic Reviews, indicated by the assigned registration number CRD4201811373.

Inclusion and exclusion criteria

Inclusion criteria: (1) clinical RCT; (2) patients meeting the grade I-IV standards of the New York Heart Association; (3) a control group treated through routine treatment measures, including β -receptor blockers such as sarkubatroxartan and Rehmannia glutinosa, physical therapy and placebos and an experimental group treated with dapagliflozin or conventional treatment plus dapagliflozin; (4) results related to efficacy and safety; and (5) a Chinese first author or publisher.

Exclusion criteria: (1) non RCT; (2) inconsistent research objects and intervention measures or an unclear outcome and/or judgement; (3) systematic evaluation, animal research; (4) obvious data loss or logical error and (5) a follow-up time <3 months.

Literature screening

Two reviewers went over the titles and abstracts of the papers they had retrieved, eliminating any study that didn't fit the criteria for inclusion. After this first step, they read the full text to determine whether the prospective literature should be included in the study. If there was a disagreement between the two reviewers, a third reviewer resolved the issue.

Quality assessment

The Cochrane Review Manual was used to evaluate the RCTs' quality and determine their bias risk, including assessing any selection bias caused by random sequence generation and allocation hiding, experimental bias resulting from blindness, reporting bias because of selective reporting and bias from other sources.

Study indicators

The study indicators were divided into efficacy and safety evaluations. The efficacy evaluation measured N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) were measured through echocardiography after follow-up; the safety criteria included all adverse reactions or complications during follow-up.

STATISTICAL ANALYSIS

The Review Manager 5.4.1(Cochrane, UK) program was used to conduct the meta-analysis. To evaluate the risk of unfavorable events, the standardized mean difference

(SMD) with a 95% confidence interval (CI) was used. The weighted mean difference was used when the difference in curative effect outcomes was small, and the SMD was used when the difference was large. Utilizing the Q test and I² statistical techniques, heterogeneity among the included literature was evaluated. A Q statistic corresponding to $p \leq 0.10$ or $I^2 > 50\%$ indicates heterogeneity among the contained literature and assesses the effect size with a random effect; otherwise, a fixed effect model is used.

RESULTS

Literature screening and quality assessment

Through the retrieval strategy, 387 studies were retrieved, including 154 Chinese-language and 233 English-language studies. After reading the titles and abstracts, 207 inconsistent research objects and intervention measures, 78 secondary research articles, 51 animal experiments or theoretical studies and 26 repeated articles were excluded. After further reading of the entire article, eight articles (Qiao *et al.*, 2021; Zhang *et al.*, 2021; Song *et al.*, 2021; Xu, 2021; He *et al.*, 2021; Zheng HS and Zhou 2021; Chen *et al.*, 2020; Dai *et al.*, 2020) were included. The general literature information is summarised in table 1.

The quality of the RCT was evaluated according to the Cochrane Review Manual, including selection bias, performance bias, detection bias, attrition bias and reporting bias. Among the eight articles included in this study, five had attrition bias, selection bias, and reporting bias and three had attrition bias and reporting bias (fig. 1).

The therapeutic effect of dapagliflozin in treating heart failure

Relationship between treatment with NT-proBNP levels

Five studies were included, but one had no standard deviation and was excluded from the calculation. The results showed significant heterogeneity among the studies ($I^2 = 98\%$, $p < 0.0001$) and the mean difference was large. Therefore, using the SMD random effect model and calculating the combined statistics (SMD: -2.88, 95% CI: -4.31, -1.44), the amount of combined effect of the control group was significantly higher than that of the observation group ($p < 0.001$). The NT-proBNP level in the dapagliflozin group was lower, as shown in fig. 2.

Relationship between treatment with dapagliflozin and the LVEF

Five studies were included, but one had no standard deviation and was excluded from the calculation. The results showed obvious heterogeneity among the studies ($I^2 = 83\%$, $p < 0.0001$). Using the random effect model and calculating the combined statistics (SMD: -5.10, 95% CI: 2.32, 7.89), the LVEF level in the observation group was significantly higher than that in the control group ($p = 0.0003$). The LVEF level was higher in dapagliflozin group, as shown in fig. 3.

Study	Chen Jiao 2020	Dai Rixin 2020	He Hongxiang 2021	Qiao Chenchen 2021	Song Qingqing 2021	Xu Zhaoxia 2021	Zhang Linchuan 2021	Zheng Huangsheng 2021
Random 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 reporting (reporting bias)	+	+	+	+	+	+	+	+
Other bias								

Fig. 1: Literature quality evaluation

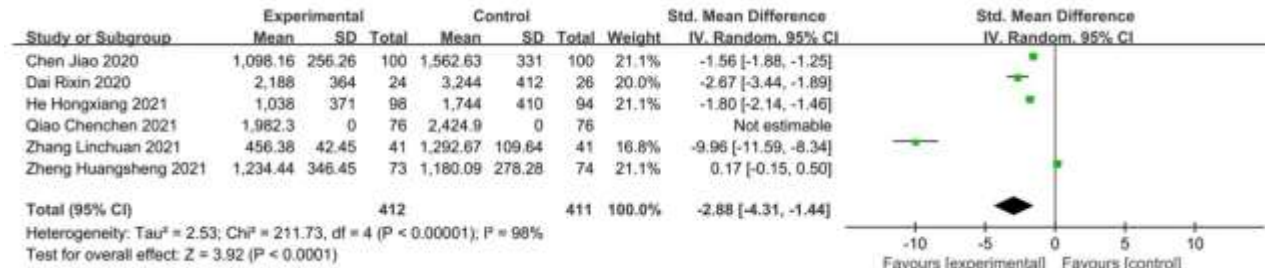


Fig. 2: Forest plot of the effect of dapagliflozin on NT-proBNP levels

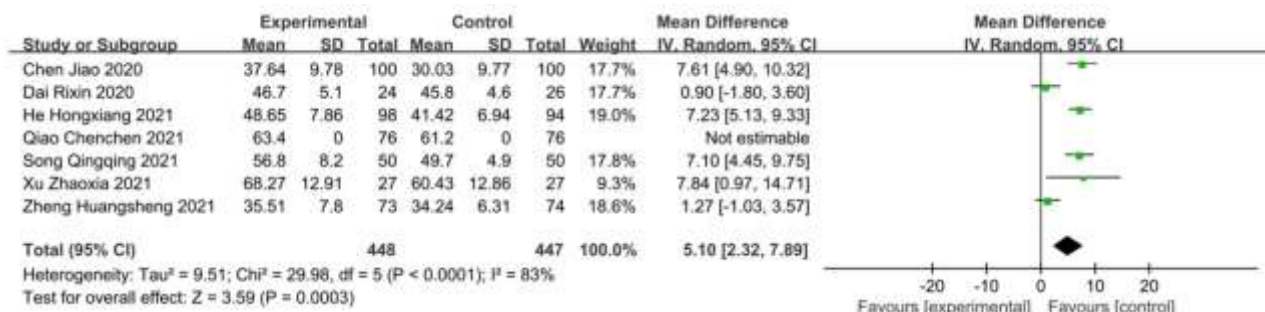


Fig. 3: Forest plot of the effect of dapagliflozin on LVEF levels

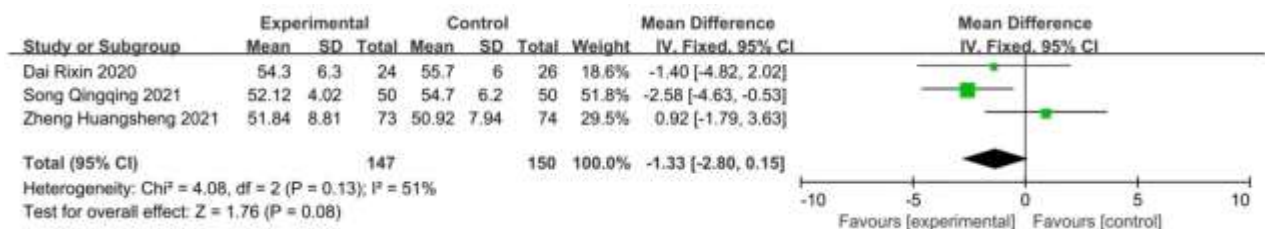


Fig. 4: Forest plot of the effect of dapagliflozin on LVEDD levels

Table 1: General information of included literature

ID	researcher	Year	Age (control/ Dapagliflozin)	Heart function	Dapagliflozin (mg/d)	control group	Follow-up (month)	Observation group	control group
1	Qiao.	2021	62.29±5.65/ 62.11±5.25	II~IV	5	Standard treatment	6	76	76
2	Zhang.	2021	67.85±10.01/ 68.20.10.10	II~IV	Initial 5, No improvement 10	Basic treatment +Other hypoglycemic drugs	6	41	41
3	Song.	2021	57.14±8.56/ 58.12±8.21	II~III	10	Basic treatment + Insulin	6	50	50
4	Xu.	2021	45.21±2.64/ 45.23±2.61	II~IV	10	Basic treatment + Metformin	3	27	27
5	He.	2021	67.9±6.7/ 68.2±7.3	II~IV	10	Basic treatment+ Sacubitril Vasartan	6	98	94
6	Zheng.	2021	62.41±10.80/ 61.43±12.34	II~IV	10	Standard treatment	12	73	74
7	Chen.	2020	65.14±9.24/ 66.37±10.04	II~IV	Initial 5, blood glucose control Poor to 10	Basic treatment+ Other hypoglycemic drugs	6	100	100
8	Dai.	2020	66±7.1/ 67±6.8	II~III	5	Standard treatment	6	24	26

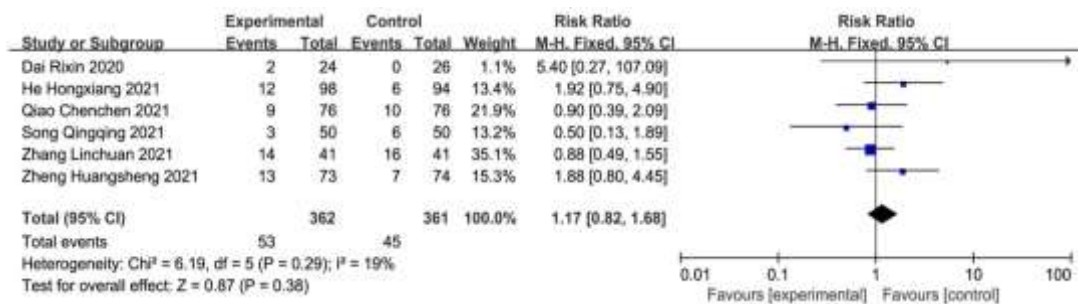


Fig. 5: Forest plot of the safety of dapagliflozin treatment

Relationship between dapagliflozin treatment and the LVEDD

Three studies were included. The data demonstrated no discernible heterogeneity among the studies ($I^2=51%$, $p=0.13$). Using the fixed effect model and calculating the combined statistics (SMD: -21.33, 95% CI: -2.80, 0.15), the difference of LVEDD level between two groups was not statistically significant ($p=0.008$). The relationship between dapagliflozin treatment and the LVEDD was shown in fig. 4.

Adverse reactions of dapagliflozin treatment

Six studies reported the occurrence of adverse reactions. The results showed no obvious heterogeneity among the studies ($I^2=19%$, $p=0.29$). No significant difference was seen in the relative risk of adverse events between two groups using the fixed effect model and the combined data (SMD: 1.17, 95% CI: 0.82, 1.68). The adverse reactions in each group mainly included hypotension, hyperkalaemia, acute renal injury and ketoacidosis, as shown in fig. 5.

DISCUSSION

The Food and Drug Administration has approved dapagliflozin to treat high-frequency HF in adults in an

effort to lower the risk of cardiovascular death and HF-related hospitalization. However, its efficacy and clinical application remain controversial and there are no standardised clinical guidelines for reference (Cai *et al.*, 2021). This study is a systematic review to assess the effects of dapagliflozin on the safety and prognosis of HF patients and to give evidence-based medical support for novel HF medications.

The primary mechanism by which dapagliflozin lowers blood sugar is by inhibiting the activity of the proximal renal tubule SGLT-2 and this reduces the reabsorption of glucose by the renal tubules (Gao *et al.*, 2020). Another benefit of using dapagliflozin in patients with HF is that it reduces the toxic effect of glucose on heart cells; it reduces glucose reabsorption, reduces the pre- and post-loads of the heart and reduces cardiac remodelling. Researchers have proposed that SGLT-2i can change myocardial metabolism and improve antioxidant and anti-inflammatory effects (Lytvyn *et al.*, 2017; Packer, 2020).

The first clinical trial to use the hypoglycaemic medication dapagliflozin in patients with HF and a low ejection fraction was the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure clinical study (McMurray *et al.*, 2019). It was a sizable, double-blind

clinical RCT and the trial's findings demonstrated that dapagliflozin treatment reduced the risk of HF worsening or death from cardiovascular causes by 26% in patients with reduced ejection fraction, independent of whether they had diabetes (McMurray *et al.*, 2019).

A multicentre, randomised, double-blind clinical trial showed that dapagliflozin could reduce the mortality of cardiac failure (hazard ratio (HR) = 0.82), worsening risk (HR = 0.70) and all-cause mortality (17%) in patients with HF (McMurray *et al.*, 2021). Vaduganathan *et al.* (Vaduganathan *et al.*, 2022) also noted that 10mg/d⁻¹ can reduce the total risk of HF deterioration or death from cardiovascular causes in HF patients who had ejection fraction retention.

The purpose of this study is to assess the effectiveness and security of treating HF in people with diabetes mellitus. The release of NT-proBNP is regulated by left ventricular diastolic and ventricular wall tension and the release of NT-proBNP is increased when ventricular wall pressure or volume load is increased. The concentration of NT-proBNP is rapidly elevated when atrial fibrillation occurs and therefore, NT-proBNP is often used in the diagnosis of atrial fibrillation, depending on the severity of atrial fibrillation, prognosis and evaluation of efficacy (Sanchez *et al.*, 2014; Welsh *et al.*, 2014). Research has reported that NT-proBNP is more accurate and objective in predicting the degree of HF and is significant in guiding the classification of HF (Pizzolo *et al.*, 2014). Therefore, this article proposes NT-proBNP detection as one of the curative effects of dapagliflozin in patients with diabetes. Clinically, the study focuses mainly on the left ventricular systolic and diastolic functions of HF patients. The LVEF refers to the percentage of stroke output in ventricular end-diastolic volume and reflects the ejection function of the heart from the perspective of volume (normally, >50%). The stroke volume and ejection fraction also decrease with the decrease in myocardial contractility. The LVEDD reaches a high abnormal range, suggesting impaired cardiac function. Although it is a direct observation of the patient's ventricular function, LVEDD is easily affected by other subjective factors. This study introduced these three indicators, hoping to comprehensively evaluate the efficacy of dapagliflozin in treating HF patients from three factors: Cardiac structure, ejection energy and biochemical level.

The dapagliflozin and control groups showed a statistically significant difference in NT-proBNP and LVEF following treatment. There was no change in the levels of LVEDD or the frequency of adverse events between the two groups, however the dapagliflozin group's NT-proBNP level was lower and its LVEF level was higher. This indicates that after treatment with dapagliflozin, the ventricular wall pressure or volume load of patients with HF is reduced in terms of biochemical level and ejection fraction, and myocardial

function is improved. Furthermore, it is safe, which is in line with the theory that hypoglycaemic drugs cannot increase the risk of cardiovascular disease and the effect on ventricular structure reconstruction is not significant. This is consistent with the results of another study reporting that SGLT-2i can improve the safety and key outcomes of patients with HF (Chambergo-Michilot *et al.*, 2020). Patients receiving dapagliflozin had a lower chance of passing away from cardiovascular causes or needing hospitalization for HF, as well as a longer survival time, according to Heerspink *et al.* (Heerspink *et al.*, 2020).

This study further demonstrates the effectiveness and security of dapagliflozin in China for HF patients with diabetes mellitus, possibly due to the reduction in blood glucose in myocardial cells or the change in myocardial metabolism, as well as the enhancement of anti-inflammatory and antioxidant capacity. The results reveal that NT-proBNP levels and LVEF are heterogeneous.

This study belongs to the secondary study. The continuous variables included in the literature did not use paired *t*-tests to analyse the changes in NT-proBNP levels, LVEF and LVEDD before and after treatment. Moreover, the difference analysis could not be used, and no explanation was given on whether a blind method should be used; there may have been biases.

Limitations

The limitations of this study are as follows: (1) there are differences in test conditions and there are differences in the dosages, measurement tools and researchers of dapagliflozin in each study; (2) the methodological heterogeneity, the length of time included in the study is inconsistent and the methods of randomisation are also different; (3) all the selected studies were single-centre or single-department studies and the sample sizes were limited; (4) the observation and follow-up times were relatively short and the safety of long-term medication needs to be further clarified. More articles should be included in the future to analyse the sources of heterogeneity through subgroup analysis and reduce heterogeneity.

CONCLUSION

In summary, dapagliflozin has the advantages of good efficacy and high levels of safety in its clinical application to HF. The drug is effective, safe and worthy of promotion in China.

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