ABSTRACT

Introduction Heart failure (HF) with preserved ejection fraction (HFpEF) has become the main type of HF worldwide. Although large randomised controlled studies have demonstrated the beneficial effects of sodium–glucose cotransporter 2 inhibitors among patients with HFpEF, the mechanisms remain unclear. Basic research suggests that empagliflozin inhibits myocardial fibrosis. Myocardial extracellular volume (ECV) can be calculated using cardiac MRI (CMRI), which can reflect the degree of diffuse myocardial fibrosis. Studies show that empagliflozin can reduce ECV and left ventricular mass (LVM) assessed by CMRI in patients with diabetes with coronary heart disease and patients without diabetes with HF with reduced ejection fraction. However, whether empagliflozin reduces ECV and LVM among patients with HFpEF is unclear. This study intends to use CMRI to evaluate ECV and LVM, combined with echocardiography and an assessment of related biomarkers, to determine whether empagliflozin can improve myocardial fibrosis and left ventricular remodelling in patients with HFpEF.

Methods and analysis This report describes the study design of a prospective, multicentre, randomised, double-blind, placebo-controlled and parallel-group clinical study. A total of 180 participants with HFpEF aged 40–80 years old who meet the inclusion and exclusion criteria will be randomly divided into an empagliflozin treatment group or a placebo control group. The empagliflozin treatment group will receive 10 mg of empagliflozin per day for 6 months in addition to guideline-directed medical treatment, while the control group will receive placebo oral administration with guideline-directed medical therapy for 6 months. The primary outcomes are ECV and LVM changes measured by CMRI after 6 months of treatment.

Ethics and dissemination The study design is approved by the ethical committee of Beijing Hospital (2022BJYYEC-070-02). The trial is registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn). The trial results will be published in peer-reviewed journals and conferences.

Trial registration number Chinese Clinical Trial Registry (ChiCTR200060862).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a novel multicentre randomised controlled trial to evaluate the effects of empagliflozin on myocardial fibrosis in patients with heart failure with preserved ejection fraction.
⇒ The study uses cardiac MRI to accurately assess the degree of diffuse myocardial fibrosis.
⇒ The small sample size (180 participants) and short follow-up period in this study (about 6 months) are the main limitations.

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) is defined as HF with left ventricular ejection fraction (LVEF) ≥50% and has emerged as a critical public health problem worldwide. The prevalence of HFpEF is increasing with the ageing population and the ongoing epidemics of obesity, diabetes mellitus and hypertension. In addition, HFpEF is considered to be the greatest unmet need in cardiovascular medicine today because of a general lack of effective treatments.

Recent studies of sodium–glucose cotransporter 2 (SGLT2) inhibitors have highlighted an effective therapy for HFpEF. The Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial, Canagliflozin Cardiovascular Assessment Study (CANVAS) and Dapagliflozin Effect on Cardiovascular Events (Thrombolysis in Myocardial Infarction) (DECLARE-TIMI 58) randomised controlled trial have demonstrated that SGLT2 inhibitors reduce the risk of cardiovascular death or hospitalisation for HF in patients with
type 2 diabetes. The Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF) trial and EMPEROR-Reduced (Empagliflozin outcome trial in Patients With chronic heart Failure With Reduced Ejection Fraction) trial have demonstrated that SGLT2 inhibitors reduce the risk of cardiovascular death or hospitalisation for HF in patients with HF with reduced ejection fraction (HFrEF). The Empagliflozin outcome trial in Patients With chronic heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial further confirmed that empagliflozin reduced the risk of cardiovascular death or hospitalisation for HF by 21% in patients with HF and LVEF >40%. Recently, the Dapagliflozin Evaluation to Improve the LIVeS of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial confirmed that dapagliflozin reduced the combined risk of worsening HF or cardiovascular death by 18% among patients with HF and a mildly reduced or preserved ejection fraction. Thus, SGLT2 inhibitors are expected to become the first effective drug for patients with HFrEF, but more research is needed to confirm it and the mechanisms are still unclear.

Myocardial fibrosis, particularly diffuse interstitial fibrosis, is present in a sizeable proportion of patients with HFrEF and has been implicated in its pathophysiology. Some basic research suggests that empagliflozin can inhibit myocardial fibrosis. Cardiac MRI (CMRI) allows for the accurate assessment of the degree of diffuse myocardial fibrosis using T1 mapping after gadolinium contrast, measured as extracellular volume (ECV), which is related to a poor prognosis of HFrEF. Clinical studies show that empagliflozin can reduce ECV in patients with coronary heart disease with diabetes and patients without diabetes with HFrEF. Left ventricular mass (LVM) is derived by the summation of cardiomyocyte volume and ECV, and can also be assessed using CMRI. Studies show that empagliflozin can reduce LVM. Therefore, our study intends to use CMRI to evaluate ECV and LVM in patients with HFrEF to determine whether empagliflozin can reduce myocardial fibrosis in these patients. Echocardiography is more convenient and more commonly used in clinical practice compared with CMRI. Many new parameters such as left ventricular global longitudinal strain by speckle-tracking echocardiography can evaluate cardiac structure and function more sensitively. Our study intends to use echocardiography, as a supplement to CMRI, to find parameters more available in clinical practice to evaluate cardiac structure and function. A combination of imaging and assessment of biomarkers can help better define the effects of empagliflozin. The results of related studies are inconsistent and more studies are required to assess a broader range of biomarkers, which may help to discover the underlying mechanisms. Therefore, related biomarkers will be tested in our study, including markers involved in tissue remodelling and possible mechanisms such as oxidative stress and inflammation.

### METHODS AND ANALYSIS

#### Study design

This study is a prospective, multicentre, randomised, double-blind, placebo-controlled and parallel-group clinical study (1:1 treatment ratio). The flow chart followed Standard Protocol Items: Recommendations for Interventional Trials checklist showing enrolment, allocation, treatment and follow-up of participants and is presented in figure 1.

#### Study setting and timeline

The study will recruit participants from five hospitals in Beijing, China: Beijing Hospital, China-Japan Friendship Hospital, The Sixth Medical Center of the Chinese People’s Liberation Army General Hospital, Beijing Anzhen Hospital and Beijing Chaoyang Hospital. The trial progress and interim results will be monitored at regular intervals by us, and by professional staff with clinical and statistical expertise from a clinical trial centre in Beijing Hospital and Beijing Municipal Health Commission.

Recruitment of patients started in October 2022, and the study will be completed in December 2024.

#### Participants

Potential participants will be identified by cardiologists. The inclusion and exclusion criteria are shown in box 1. Participants who meet the criteria and provide written informed consent will be recruited.

#### Randomisation

After consent and completion of the baseline assessment, participants will be entered into the study and randomised to empagliflozin treatment or placebo control groups according to a 1:1 ratio. Stratified randomisation by centres will be used with a random number sequence generated by electronic data collection (EDC) system and each participant will be assigned a randomised number and allocated to the intervention or control group.

#### Blinding

The trial is to be designed and performed as a double-blind trial, in which participants, clinicians and nurses, as well as staff performing the outcome assessment and data analysis, will be blinded until the primary outcome occurs. Investigators will be able to perform emergency unblinding through the EDC system if necessary.

#### Intervention

Participants assigned to the placebo control group will receive guideline-directed medical therapy and placebo oral administration for 6 months. Participants assigned to the empagliflozin treatment group will receive 10 mg/day of empagliflozin for 6 months in addition to guideline-directed medical treatment. We purchased empagliflozin and placebo from Wanbang Biochemical Pharmaceutical Group, Jiangsu, China. The placebo was prepared to simulate the appearance of empagliflozin.
Data collection
Participants will undergo baseline assessment and four follow-up visits. The baseline assessment will be conducted prior to randomisation and further assessments will be conducted 14 days, 42 days, 98 days and 182 days after randomisation. Blinded cardiologists and nurses will conduct these assessments. CMRI and echocardiography will be used during the baseline assessment and after 6 months of treatment. To exclude special cardiomyopathy such as amyloidosis, CMRI must be done before randomisation. In addition, comprehensive evaluation will be conducted, including assessment of frailty, cognitive, emotional and nutritional status, exercise ability and Kansas City Cardiomyopathy Questionnaire (KCCQ), which has been authorised by Outcomes Instruments. The case report forms are available from the authors. Data will be collated on paper forms and entered into the EDC system. Paper files will be stored in a locked filing cabinet. The final trial dataset will be available to trial authors only who undertake data analysis for presentations or publications. The schedule of enrolment, interventions and assessments during the study period is shown in table 1.

Outcomes measures
The study will use parameters of CMRI and echocardiography as well as biomarkers to explore the effects of empagliflozin on cardiac structure and function in patients with HFP EF.

Primary outcomes
1. ECV changes measured by CMRI after 6 months of treatment.
2. LVM changes measured by CMRI after 6 months of treatment.

Secondary outcomes
1. Changes in cardiac structure and function measured by echocardiography after 6 months of treatment including the average septal-lateral E/e’, the average e’ (ventricular septum and lateral wall), strain, left atrial...
Box 1  Inclusion and exclusion criteria

**Inclusion criteria**

- Age ≥40 years old and ≤80 years old
- Diagnosis of chronic HF ≥3 months, and underlying disease medications have been stable for 3 months.
- New York Heart Association class II–IV
- LVEF >40% detected by echocardiography within 1 month (without LVEF <40% in case of previous stable disease)
- NT-proBNP >300 pg/mL in patients without atrial fibrillation or >900 pg/mL in patients with atrial fibrillation
- Echocardiography shows left atrial enlargement and/or left ventricular hypertrophy and/or decreased diastolic function.*
- If oral diuretic is needed, the dose is stable for 1 week (before randomisation).

**Exclusion criteria**

- Patients with acute decompensated HF using intravenous diuretic, vasodilator or inotropic agents therapy
- Diagnosis of myocardial amyloidosis, hemochromatosis, Fabry disease, cardiomyopathy with reversible causes (eg, stress cardiomyopathy), hypertrophic obstructive cardiomyopathy, constrictive pericarditis, muscular dystrophies and severe valvular heart disease (moderate or severe aortic stenosis, severe aortic regurgitation, moderate or severe mitral stenosis, severe mitral regurgitation, or expected to undergo heart valve surgery during the trial period)
- Diagnosis of acute myocardial infarction, stroke or transient ischaemic attack in the past 3 months. Coronary artery bypass grafting, aortic valve replacement or other major cardiovascular surgery has been performed.
- Patient with implantable cardioverter defibrillator or cardiac resynchronisation therapy
- Use of sodium–glucose cotransporter 2 inhibitors in the past 3 months
- Systolic blood pressure ≥180 mm Hg or <100 mm Hg or symptomatic hypotension at screening, with or without antihypertensive drugs
- Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm on ECG at screening
- Known allergy to empagliflozin
- History of ketoacidosis
- Pregnancy, current breast feeding or planning a pregnancy
- Any serious disease affecting the clinical course of the subject, such as acute exacerbation of chronic obstructive pulmonary disease, acute or chronic liver disease, severe renal impairment (eGFR <45 mL/min/1.73 m² as estimated by CKD-EPI formula or subjects on regular dialysis), severe anaemia (haemoglobin <90 g/L), gastrointestinal surgery or gastrointestinal disease that may affect the absorption of the trial drug, acute or chronic pancreatitis, current urinary or reproductive system infection, any documented active or suspected malignancy or history of malignancy within 1 year before screening
- Severe hypoglycaemia in the past year
- Presence of any disease other than HF that results in a life expectancy ≤1 year in the opinion of the investigator
- Receiving any other clinical trial of drugs other than this study drug
- Inability to comply with the schedule of study assessments for follow-up or unsuitability for trial based on the investigator’s clinical judgement

*Left atrial enlargement refers to at least one of the following indicators: left atrial width ≥4.0 cm, left atrial length ≥5.0 cm, left atrial area ≥20 cm², left atrial volume ≥55 mL or Left Atrial Volume Index ≥34 mL/m². Left ventricular hypertrophy refers to at least one of the following indicators: septal thickness ≥0.4 cm, posterior wall thickness ≥0.4 cm, left ventricular mass index ≥115 g/m² in men or ≥95 g/m² in women. Decreased ventricular diastolic function refers to at least one of the following indicators: the average septal-lateral E'/E ≥13 or the average e' (ventricular septum and lateral wall) <9 cm/s. bpm, beats per minute; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Box 1  Continued

**Sample size calculation**

There are no previous studies about the effects of empagliflozin on ECV and LVM in patients with HFpEF. In the EMPA-HEART trial, the ECV after 6 months of empagliflozin treatment was 28.7±4.3 in patients with diabetes and coronary heart disease, who share several common features with patients with HFpEF, and the ECV after 6 months in the control group was 31.1±4.3. Based on this previous study, we calculated the sample size. Based on a desired power of 0.80 and an alpha error probability of 0.05, each group needs 69 participants. In order to account for dropouts, we aim to include a total of 180 participants.

**Statistical analysis**

For continuous variables, normally distributed parameters will be expressed as mean with SD, and compared using a Student’s t-test. Non-normally distributed parameters will be expressed as medians with IQRs and compared using a Wilcoxon rank-sum test. For categorical variables, parameters will be expressed as number of cases with percentage, and compared using a χ² test and Fisher’s exact test when appropriate. The primary and secondary outcomes will be compared using analysis of covariance corrected by baseline values and a rank-sum test when appropriate. Data analysis of this trial will follow the intention-to-treat principle, in which all randomised participants will be considered in the primary comparison between treatment groups. Missing data about the efficacy-related component in this analysis will be supplemented with the method of last observation carried forward. Per-protocol analysis will be conducted as a secondary analysis in participants who complied with the protocol. Missing data in this analysis will not be carried forward and will be conducted as missing data. All tests will be two-sided, and differences with a p value of <0.05 will be considered statistically significant.
Table 1  Schedule of enrolment, interventions and assessments

<table>
<thead>
<tr>
<th>Study period</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Postallocation</th>
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<tr>
<td>Content</td>
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<td>Randomisation</td>
<td>Follow-up</td>
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*Laboratory tests include blood routine, serum biochemistry, N-terminal pro-B-type natriuretic peptide, troponin, glycated haemoglobin and urine routine.

†Frailty assessment includes the Frail Scale, the Fred Frailty Scale and Frailty Index.

‡Nutritional assessment includes the Mini Nutritional Assessment short-form and NRS2002.

§We use the 12-item short-form health survey to assess quality of life.

Patient and public involvement
This research will be conducted without patient or public involvement. Neither patients nor the public are involved in the development of the research question, study design or implementation of this trial. Patients will not be invited to develop patient relevant outcomes or interpret the results, or be involved in the writing or editing of the final manuscript for readability and accuracy.

Ethics and dissemination
This research will strictly follow the Declaration of Helsinki, the relevant laws and regulations of Chinese
ethical review, and be conducted in accordance with the research protocol. The Beijing Hospital Ethics Committee approved the study (2022BJYJYEC-070-02), and all participants will provide written informed consent prior to randomisation. During the research process, the revision of the research protocol, informed consent and other documents will be submitted to the hospital ethics committee for review and can only be implemented after approval. The identities of the participants will not be publicly available when the research information and data obtained from this study are published in scientific conferences or journals.

**DISCUSSION**

HFpEF is considered to be the greatest unmet need in cardiovascular medicine today because of a general lack of effective treatments. The current article describes the methodology of a novel trial evaluating the effects of empagliflozin on ECV and LVM in patients with HFpEF using CMRI, which will provide important information on the mechanisms underlying the protective effects of empagliflozin for HF. The upcoming results will help to broaden understanding of empagliflozin as a therapeutic, thereby potentially benefitting patients, and aiding in the decision-making process regarding treatment.

Myocardial fibrosis plays an important role in the progression of structural cardiac remodelling and HFpEF. Several studies suggest that empagliflozin may have an effect on cardiac fibrosis. Lee et al. found that empagliflozin significantly attenuated myocardial fibrosis in both atrial and ventricular tissues in hypertensive HF rats. Kang et al. found that empagliflozin significantly attenuated cell-mediated myocardial extracellular matrix (ECM) remodelling as measured by the collagen fibre alignment index in human cardiac myofibroblasts. CMRI has the potential to evaluate ECM, measured as ECV, as well as LVM, to determine the extent of myocardial fibrosis. Even though a CMRI trial in patients with type 2 diabetes showed that there were no differences in LVM measures at baseline and 6 months between the empagliflozin group and the control group, some clinical trials suggest that empagliflozin reduces ECV and LVM compared with a placebo in patients with type 2 diabetes and coronary artery disease or patients without diabetes with HFpEF. Whether empagliflozin reduces ECV or LVM in patients with HFpEF is unclear. Thus, we aim to assess the effect of empagliflozin on cardiac structure using CMRI in patients with HFpEF.

Beyond the primary outcome, this study also has secondary outcomes including relevant parameters evaluated by echocardiography and the assessment of biomarkers. The effect of empagliflozin on the circulatory levels of tissue remodelling biomarkers is still controversial. Lebedev et al. found that compared with patients without HF, patients with diabetes treated with SGLT2 inhibitors, who developed HFpEF after 3 years of follow-up, had higher markers of fibrosis. However, Mason et al. found that empagliflozin treatment for 6 months did not alter the circulating levels of tissue remodelling biomarkers. Our study aims to provide more evidence for this. Meanwhile, the possible mechanisms remain unclear. The processes of fibrosis development may be secondary to an underlying factor of inflammation or increased oxidative stress, which would be a possible antifibrotic mechanism of SGLT2 inhibitors. In a female rodent model of diabetes, empagliflozin improved cardiac diastolic function measured by echocardiography, which was accompanied by a reduction in the expression of profibrotic proteins and attenuation of interstitial fibrosis. Adding parameters evaluated by echocardiography and biomarker assessment will be an important supplement to CMRI and may shed new light on the mechanisms whereby SGLT2 inhibitors are effective in patients with HFpEF.

Improvements in exercise ability and quality of life (QoL) after treatment are quite significant for patients with HF, especially for those with HFpEF, as treatments to improve prognosis are relatively scarce. The effects of empagliflozin on QoL are not well defined. Oxygen consumption is one of the most critical factors in indexing HFpEF disease burden, measured by peak oxygen consumption in the cardiopulmonary exercise test. In the EMPA-TROPISM trial, patients without diabetes with HFpEF who received empagliflozin had significant improvements in peak oxygen consumption, 6-minute walk test distance and QoL evaluated by KCCQ-12 compared with a placebo. In the EMPEROR-Preserved trial, empagliflozin improved health-related QoL; however, in the EMPERIAL-Preserved trial, empagliflozin did not improve 6-minute walk test distance and KCCQ Total Symptom Score in patients with HFpEF. Further, in the EMPA-HEART trial, empagliflozin had a neutral impact on peak oxygen uptake in subjects with type 2 diabetes without heart disease. The assessment of frailty and emotional status in patients with HFpEF are also crucial as these conditions are associated with poor outcomes and reduced tolerance of treatments. Related studies are scarce in China; therefore, we will conduct an assessment of exercise ability, QoL, frailty, cognitive, emotional and nutritional status. However, these assessment results will not be classified as outcomes, in order to give patients a comprehensive assessment according to the guidelines, and try to explore the impact of empagliflozin.

This study has some limitations. First, the sample size is small, with a short follow-up period of 6 months. The sample size and length of the study may be insufficient to achieve the primary endpoint. Therefore, we choose some secondary endpoints including echocardiography and biomarkers. Larger studies in populations with HFpEF are required to identify the impact of empagliflozin on myocardial fibrosis. Second, some standard therapies used in patients with cardiovascular diseases such as ACE inhibitors and mineralocorticoid receptor antagonists modify collagen metabolism and have antifibrotic effects. Thus, the potential influence of previous pharmacological treatment must be carefully considered. We will choose patients on stable medications to avoid the influence. Lastly, patients with old myocardial infarction but preserved LVEF are not excluded, which may
influence the analysis of myocardial fibrosis. Patients with mild-reduced LVEF (40%–49%) are not excluded, and the effect of empagliflozin may be different in these patients. We will clarify the effects of empagliflozin on more specific populations.

Despite being a small study, our research will provide novel information in terms of pathogenesis of empagliflozin on HFpEF if this intervention is shown to be effective.

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Contributors KC and YuL contributed to drafting of the manuscript. HW obtained funding. HW and JY designed the study. HW, KC, YL, MZ and JY participated in the design of the study. KC, YL, YC, WZ and CM participated in the recruitment of participants. HW and YL participate in the assessment of clinical outcomes. WH, YL and KC will perform data analysis. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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