A randomized, double-blind, controlled clinical study of SGLT-2i combined with probiotic preparations in the treatment of elderly patients with HFpEF Informed Consent Form

Research Institution: The First Affiliated Hospital of Air Force Military Medical University

Project Leader: Su Hui / Ji Chenyang

Research Period: May 1, 2026 to November 30, 2027

Version Number: V2.0

Version Date: May 7, 2026

Informed Consent - Informed Disclosure Page

Dear Patient:

The doctor has diagnosed you with reduced ejection fraction heart failure (HFpEF). We will invite you to participate in a randomized, double-blind, controlled clinical study on the treatment of elderly HFpEF patients with SGLT-2i combined with probiotic preparations. This study aims to compare the changes in heart and kidney functions, intestinal barrier function, quality of life, and physical function of elderly HFpEF patients after treatment when combined with iciglarestat and probiotic preparations on the basis of conventional anti-heart failure therapy. We aim to explore the effects and mechanisms of SGLT-2 inhibitors and probiotic preparations on elderly HFpEF patients, thereby providing new ideas for the prevention and treatment of elderly HFpEF. The study protocol has been reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Air Force Military Medical University (Xijing Hospital), and clinical research is permitted.

Before you decide whether to participate in this clinical study, please carefully read the following content. It can help you fully understand why this study is being conducted, the procedures and duration of the study, the potential benefits you may receive after participating in the study, risks, and discomforts. You can discuss with your relatives and friends and ask the doctor in charge of the study, who will explain any questions you have about this study and help you make a final decision.

1. Research Background

Reduced ejection fraction heart failure (HFpEF) is a group of highly heterogeneous clinical syndromes, mainly characterized by left ventricular diastolic dysfunction. The prevalence of HFpEF accounts for approximately 40% - 71% of heart failure. With the intensification of population aging, its prevalence and mortality rates continue to rise. Currently, there is no effective therapy that can significantly reduce the mortality rate of HFpEF.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors exert cardiovascular protective effects through mechanisms such as diuresis, improving myocardial energy metabolism, and inhibiting inflammation. The 2023 ESC Heart Failure Guidelines update lists SGLT2 inhibitors (dapagliflozin or empagliflozin) as Class I recommended drugs for HFpEF. Iciglarestat is China's first domestically developed SGLT2 inhibitor, which is targeted at type 2 diabetes. Early clinical trials have shown that its hypoglycemic effect and safety are good. A multicenter, randomized, double-blind, placebo-controlled trial (HELD-HF study) of iciglarestat in HFpEF patients with dialysis included 112 patients. The results showed that the left ventricular mass index (LVMI) in the iciglarestat group decreased significantly by 3.38 g/m^2 compared to the baseline, while the placebo group increased by 2.08 g/m^2 (group difference -5.38 g/m^2, P = 0.026). In terms of safety, the incidence of drug-related adverse events in the iciglarestat group was lower than that in the placebo group (1.79% vs. 3.57%), suggesting good tolerance of the drug in HFpEF patients with dialysis. However, the efficacy of iciglarestat in non-dialysis HFpEF patients is not yet clear, especially in the elderly population, where there is a lack of data. It is worth noting that SGLT-2 inhibitors-induced weight loss may lead to fat and skeletal muscle loss, increasing the risk of sarcopenia and frailty in elderly patients, which may partially offset their cardiovascular benefits.

Gut microbiota disorder is closely related to systemic inflammation in HFpEF. The diversity of gut microbiota in HFpEF patients is reduced, and the intestinal mucosal barrier is damaged. Bacterial metabolites enter the bloodstream and activate systemic inflammatory responses, exacerbating

myocardial remodeling and diastolic dysfunction.

Probiotics, as a core intervention method for regulating the gut microbiota, can exert cardiac protective effects through mechanisms such as inhibiting inflammation and slowing adverse cardiac remodeling, and have potential in improving muscle health and preventing sarcopenia. The triple live probiotic preparation of Lactobacillus acidophilus, Clostridium butyricum, and Saccharomyces cerevisiae is composed of Saccharomyces cerevisiae, Lactobacillus acidophilus, and Saccharomyces cerevisiae. Among them, Enterococcus produces lactic acid to inhibit harmful bacteria; Clostridium butyricum produces organic acids mainly composed of butyric acid, providing energy for intestinal epithelial cells and repairing the intestinal mucosal barrier; the glycation bacteria secrete digestive enzymes to promote nutrient absorption and activate the proliferation of beneficial bacteria. The three work together to achieve multi-target regulation of the intestinal microecology. Clinical studies have shown that this preparation has good efficacy and safety in the elderly population, significantly improving the effective rate of functional constipation treatment in the elderly, and reducing the incidence of antibiotic-associated diarrhea in patients over 80 years old. Our research group's previous studies have further discovered that on the basis of conventional anti-heart failure treatment for elderly HFpEF patients, giving the triple live bacteria tablet of Clostridium butyricum and Enterococcus for 12 weeks can significantly improve the symptoms, cardiac function and quality of life of the patients, suggesting that regulating the intestinal flora can be an effective strategy for the auxiliary treatment of HFpEF.

SGLT-2 inhibitors and probiotics act from multiple targets such as metabolism, inflammation, and intestinal flora, and the combination of the two may have synergistic therapeutic potential. The addition of probiotics may also alleviate the weight loss and risk of sarcopenia caused by SGLT-2 inhibitors. Currently, this combined strategy has not been verified in clinical trials. Therefore, this research group intends to conduct a randomized double-blind controlled trial to explore the effects of icigelnetin combined with probiotic preparations on the cardiac and renal functions, intestinal barrier function, quality of life and physical function of elderly HFpEF patients, and detect the inflammatory levels to explore its potential mechanism, aiming to provide a new combined treatment strategy that can effectively improve the cardiac and renal outcomes of elderly HFpEF patients while minimizing the exacerbation of frailty.

2.Research objective

To explore the effects of icigelnetin combined with probiotic preparations on the cardiac and renal functions, intestinal barrier function, quality of life and physical function of elderly HFpEF patients, and to detect the inflammatory levels to explore its potential mechanism, in order to provide a new treatment strategy for elderly HFpEF patients.

3. Research design

3.1. Before the inclusion of the study, you can voluntarily sign the informed consent form. Then, the doctor will ask and record your medical history, previous drug treatment situation and auxiliary examination data, such as cardiac ultrasound examination, blood biochemical indicators, etc. If you meet the inclusion and exclusion criteria, you can voluntarily participate in the study.

If you do not want to participate in the study, we will respect your will.

3.2. If you voluntarily participate in the study, you will follow the following steps:

(1) One to two weeks before the start of the trial, we will ask and record your medical history, physical examination, conduct routine laboratory tests such as blood routine, liver function, kidney function, and heart failure indicators, inflammatory indicators and other related laboratory

tests, perform 12-lead electrocardiogram, echocardiography and other auxiliary examinations, as well as assess frailty, sarcopenia, body composition analysis, nutrition, activity ability, quality of life, etc. And collect stool and blood samples for intestinal flora analysis, intestinal flora metabolite detection, intestinal barrier function detection, etc.

(2) After assessment, the researcher will free of charge intervene you with proline icigelnetin tablets (10mg, qd) combined with Clostridium butyricum Enterococcus triple live bacteria tablets (400mg, tid) or the corresponding placebo (prepared from starch, with the appearance and physical properties of proline icigelnetin tablets and Clostridium butyricum Enterococcus triple live bacteria tablets the same), for 12 weeks. At the 4th, 8th and 12th weeks of taking the medication, you need to visit our outpatient clinic for a follow-up and be fully evaluated, the content being the same as the first evaluation.

3.3. Other matters that you need to cooperate with

(1) You must take the medication according to the prescribed usage and dosage, which is very important for the authenticity of the research results;

(2) You must report your relevant clinical data to the clinical doctor who collects the data in the true situation, which is very important because the doctor will analyze the treatment effect based on this;

(3) You must follow the requirements for follow-up, which is very important for the doctor to evaluate your treatment effect and guide subsequent treatment.

4. Inclusion Criteria and Exclusion Criteria

4.1. Inclusion Criteria:

(1) Age over 60 years;

(2) Within 6 months, relevant examinations meet the diagnostic criteria for HFpEF:

1) Have the epidemiological and population characteristics of patients with HFpEF;

2) Have symptoms and/or signs of heart failure;

3) Cardiac imaging examination indicates LVEF ≥ 50%;

4) Sinus rhythm with BNP ≥ 35 pg/ml and/or NT-proBNP ≥ 125 pg/ml, atrial fibrillation with BNP ≥ 105 pg/ml and/or NT-proBNP ≥ 365 pg/ml;

5) At least one of the following conditions is met:

① LVMI ≥ 115 g/m2 (male) or 95 g/m2 (female); ② LAVI > 34 ml/m2; ③ Relative wall thickness > 0.42; or left ventricular free wall thickness > 12 mm; ④ E/e' ≥ 14; ⑤ Ventricular septal e' < 7 cm/s, or lateral wall e' < 10 cm/s, or average e' < 8 cm/s; ⑥ Tricuspid regurgitation velocity > 2.8 m/s, or pulmonary artery systolic pressure > 35 mmHg;

(3) Cardiac function NYHA classification II to III;

(4) Within 6 months before enrollment, did not take SGLT-2 inhibitors;

(5) Within 3 months before enrollment, did not take probiotic preparations;

(6) The current anti-heart failure treatment plan is well tolerated by the patient and has been stable for at least 1 month;

(7) Current heart failure condition is stable, without acute exacerbation;

(8) Cognitive function is basically normal, can understand the content of the assessment scale;

(9) Has basic behavioral ability, can independently or with assistive devices perform daily activities;

(10) Understands the purpose of the clinical trial, voluntarily participates and signs the informed consent form.

4.2. Exclusion Criteria:

(1) Symptoms of the patient are caused by non-cardiac diseases;

(2) Have contraindications to canagliflozin:

1) Allergic to canagliflozin;

2) Severe renal impairment (eGFR < 30 ml/min/1.73m2), end-stage renal disease, or requiring dialysis;

(3) Have contraindications to probiotics:

1) Patients with intestinal barrier damage due to various reasons, such as sepsis, active gastrointestinal bleeding, perforation, etc.

2) Currently diagnosed with fulminant colitis or toxic megacolon.

3) Unable to tolerate 50% calorie requirement enteral nutrition due to severe diarrhea, significant fibrotic intestinal lumen stenosis, severe gastrointestinal bleeding, high-flow intestinal fistula, etc.

4) Patients with congenital or acquired immunodeficiency diseases.

5) Recently received high-risk immunosuppressive or cytotoxic drug treatment: such as rituximab, doxorubicin or medium to high-dose corticosteroids (20 mg/d prednisone or higher dose) for 4 weeks or more.

6) Severe immunosuppressed patients: neutrophils < 1500/mm3.

(4) Had myocardial infarction within 6 months before enrollment, undergone coronary artery bypass surgery or any event that may reduce LVEF (unless confirmed LVEF ≥ 50%);

(5) Had valve replacement surgery within 6 months before enrollment;

(6) Poor blood pressure control (SBP ≥ 180 mmHg or DBP ≥ 100 mmHg);

(7) Acute decompensated heart failure requiring treatment at rest;

(8) Resting heart rate exceeds 120 beats/min, or concurrent malignant arrhythmia;

(9) Significant coronary artery lesion requiring PCI revascularization treatment;

(10) Severe renal insufficiency (serum creatinine > 442 μmol/L) or undergoing dialysis treatment;

(11) Had urinary tract infection at the time of enrollment; There are symptoms and signs of urinary tract infection, such as urinary tract irritation (urinary frequency, urinary pain, urinary urgency), pain and tenderness above the pubic bone, fever, lumbar pain or percussion pain, etc. The number of bacterial colonies in urine culture is all ≥ 105 /ml;

(12) Currently suffering from malignant tumors that need treatment;

(13) Currently having acute diseases or acute exacerbation of chronic diseases;

(14) Have participated in other interventional studies within the past 3 months.

5. Research Process

This study is a randomized, double-blind, controlled study. The total number of cases is 162 (including 3 groups, each group has 54 people, Group A receives propranolol combination with Clostridium butyricum enterococcus triple live bacteria tablets, Group B receives propranolol and placebo, Group C receives double placebo). After screening according to the inclusion and exclusion criteria, if you meet this study, the researcher will arrange you to the corresponding group according to the grouping requirements, and then will collect some information needed for the trial from you, and will free of charge distribute propranolol combination with Clostridium butyricum enterococcus triple live bacteria tablets (or corresponding placebo tablets) to you; You need to take propranolol combination with Clostridium butyricum enterococcus triple live bacteria tablets (taking method: propranolol combination once a day, 1 tablet each time; Clostridium

butyricum enterococcus triple live bacteria tablets three times a day, 2 tablets each time, for 12 consecutive weeks). Before treatment and at the 4th, 8th, and 12th weeks of treatment, we will conduct a comprehensive assessment of you. The researcher will collect relevant information for the study (including medical history, physical examination, routine laboratory tests such as blood routine, coagulation function, liver function, kidney function, heart failure indicators, inflammatory indicators, etc., auxiliary examinations such as 12-lead electrocardiogram, echocardiography, etc., and assessment of activity ability and quality of life), and collect your stool and blood samples for intestinal flora analysis, intestinal flora metabolite detection, intestinal barrier function detection, etc.

If you have any doubts about this study, please contact your researcher.

6. Risks and Adverse Reactions

This project is an additional treatment based on conventional drug anti-heart failure therapy, using propranolol combination with Clostridium butyricum enterococcus triple live bacteria tablets (or corresponding placebo tablets). The placebo tablets are made of edible starch and are the same in appearance, color, and smell as propranolol combination and Clostridium butyricum enterococcus triple live bacteria tablets, but have no active ingredients and no adverse reactions. The main adverse reaction of propranolol combination is urinary and reproductive system infection (occurrence rate about 2.6%), and a small number of severe adverse reactions may occur: ketoacidosis, acute kidney injury, etc. In the existing clinical research cases, no side effects related to this drug have been found for Clostridium butyricum enterococcus triple live bacteria tablets. After taking the medication, we will closely monitor you, promptly detect and handle possible adverse reactions to ensure your health and safety.

If during the study period you experience any discomfort, or new changes in your condition, or any unexpected situations, regardless of whether they are related to the study, you should promptly notify your study doctor, who will make a judgment and may give you appropriate medical guidance and suggestions.

7. Handling Emergencies During the Treatment

If during the treatment of this study intervention measures, adverse reactions or emergencies related to this study intervention measures occur, as well as serious adverse events caused by the development of your own disease (not related to the study intervention measures), if you are in our hospital, we will immediately provide full treatment; if you are at home, please immediately seek medical treatment nearby and contact the researcher. If conditions permit, please directly come to our hospital for treatment. Regardless of whether it is related to the experimental drug or not, you should promptly notify the researcher. The researcher will make a judgment and provide medical treatment, and report to the hospital ethics committee to ensure your health and rights.

8. Potential Benefits of Participating in the Study

8.1. Direct Benefits: Your cardiac and renal metabolic conditions may improve, and your cardiac function and quality of life may be enhanced. During the study, you can be informed of the relevant research results, which will help you have a comprehensive understanding of your own disease and enable you to make early predictions about the outcome of HFpEF development.

8.2. Indirect Benefits: ① Benefits for the subject themselves: Early prediction of the outcome of HFpEF development may reduce the burden of disease diagnosis and treatment you are bearing, improve your quality of life, and you will receive good medical services during the study. ② Benefits for the social group: It may provide assistance in finding the effects and mechanisms of

SGLT-2 inhibitors and probiotic preparations on elderly HFpEF patients, and provide clues for the prevention and treatment of elderly HFpEF. This will benefit future patients with similar diseases to obtain more scientific diagnosis and treatment methods. It may also increase the patient's dependence on treatment.

9. Costs of the Study

Routine treatment for HFpEF patients requires blood routine, liver and kidney function tests, blood lipids, blood glucose, NT-proBNP, cardiac ultrasound, and electrocardiogram examinations. The costs of these tests need to be borne by you. The costs of empagliflozin prucalopride tablets and Clostridium butyricum Enterococcus tri-enzyme tablets (or placebo) and the costs of trial-related examinations (inflammatory indicators, intestinal flora analysis, intestinal flora metabolite detection, intestinal barrier function detection) as well as comprehensive assessment scales (degeneration, sarcopenia, body composition analysis, nutrition, activity ability, quality of life, etc.) will be borne by us. In addition, participating in this study will not result in additional subsidies or rewards.

10. Compensation and Compensation for the Study

If damage occurs related to this study, Xijing Hospital will promptly provide corresponding medical treatment and compensate according to the law.

11. Confidentiality of Personal Information

The information collected in this study will be kept confidential in the hospital. To protect your identity, any information about you in the research documents will be numbered in a unified format instead of using your name. All the collected and combined information of the subjects, any information that can help identify your identity will be removed to ensure that the relevant information cannot be linked to a specific research subject.

The ethics committee and regulatory authorities, within the scope permitted by applicable laws and regulations and without infringing upon the privacy of the subjects, will directly review the original medical records of the subjects to verify the clinical trial procedures and/or data (the sponsor cannot review), and you or your legal representative have authorized such review when signing the informed consent form. Within the scope permitted by applicable laws and regulations, records that can identify you will be kept confidential and will not be made public. The results of this study may be published in medical journals or shared for scientific purposes or used by the sponsor for product research or improvement, but your identity and personal information will not be disclosed at any time.

12. Withdrawal from the Study

During the study, the study doctor will consider maximizing your interests. Your participation in this study is completely voluntary. You have the right to choose not to participate in this study and can withdraw at any time without being punished or suffering any loss. Your subsequent treatment will not be affected. If you plan to withdraw from the study, please inform your study doctor in time. To ensure your safety, he will conduct a comprehensive examination and treatment for you. The researcher will promptly inform you or your guardian of any information that may affect your continued participation in the trial.

13. Contact Person and Contact Information

You can always obtain information and progress related to this study at any time. If there is new safety information related to this study, we will also notify you promptly. If you have any questions related to this research, or if you experience any discomfort or injury during the research

process, or if you have any concerns regarding the rights and interests of the participants in this study, you can contact (researcher: Ji Chenyang) through (phone number: 15591423352).

14. Contact Information for the Ethics Committee

This trial protocol has been approved by the hospital's ethics committee for implementation. If there are any violations of the research protocol during the trial, the participants can directly file a complaint with the Ethics Committee of Xijing Hospital. The contact number is 029-84771794.

Informed Consent Form - Signature Page

Clinical Research Project Name: Randomized Double-blind Controlled Clinical Study of SGLT-2i Combined with Probiotic Preparation in Treating Elderly Patients with HFpEF

Investigator: Su Hui, Wang Lin, Liu Yan, Hou Liming, Ji Chenyang, Wang Xia

Ethical Review Approval Number:

1. Subject's Consent Statement

I have read the above information about this study and had the opportunity to discuss it with the doctor and ask questions. All the questions I raised have received satisfactory responses.

I am aware of the possible risks and benefits of participating in this study. I understand that participation in the study is voluntary, and I confirm that I have had sufficient time to consider this and understand:

I can consult the doctor for more information at any time.

I can withdraw from this study at any time without being discriminated against or retaliated against, and my medical treatment and rights will not be affected.

I am also clear that if I withdraw from the study halfway, especially due to the medication causing me to withdraw from the study, if I inform the doctor of any changes in my condition and complete the corresponding physical examinations and physical tests, it will be very beneficial for me and the entire study.

If I need to take any other medication due to changes in my condition, I will seek the doctor's advice in advance or tell the doctor the truth afterwards.

I agree that the drug regulatory authority, ethics committee, or sponsor representative can review my research materials.

Finally, I decide to agree to participate in this study and try to follow the doctor's instructions.

Subject's Signature: Date: Year Month Day

Subject's Legal Representative's Signature (if necessary): Date: Year Month Day

Subject's Contact Number:

2. Doctor's Statement

I confirm that I have explained the details of this trial to the patient, including their rights and possible benefits and risks, and have given them a signed copy of the informed consent form.

Investigator's Signature Date: Year Month Day

Investigator's Contact Number:15591423352