FEND II: Fexofenadine Hydrochloride Study Protocol for MI Prognosis

Study Protocol

The Impact of Fexofenadine Hydrochloride on the Prognosis of Patients Post-Acute Myocardial Infarction: A Randomized Clinical Trial (FEND II)

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Principal Investigator:

Hu Xinyang, PhD

Department of Cardiovascular Medicine,

The Second Affiliated Hospital of Zhejiang University School of Medicine

National Key Laboratory of Transvascular Implantable Devices

88 Jiefang Road, Hangzhou 310009, China

E-mail: hxy0507@zju.edu.cn

1. Study Background

Myocardial infarction (MI) and subsequent heart failure are among the leading causes of death in patients with cardiovascular diseases in China. Myocardial cell death following MI triggers the activation of fibroblasts. Although fibroblasts play a reparative role, their excessive activation and the overdeposition of extracellular matrix can form fibrotic tissue, ultimately leading to heart failure. Currently, while a series of measures can reduce early mortality after MI, there is a lack of effective therapeutic approaches targeting pathological fibrosis post-MI. Therefore, inhibiting the excessive activation of cardiac fibroblasts and reducing cardiac fibrosis after MI are crucial scientific issues and clinical needs that urgently require resolution.

Although the mechanisms driving organ-specific fibrosis have not been fully elucidated, fibrosis in different tissues and organs is characterized by the persistent abnormal activation of myofibroblasts mediated by multiple signals such as transforming growth factor (TGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). Drugs targeting these abnormal signals have achieved certain efficacy in clinical trials, such as nintedanib and pirfenidone. Our preliminary work found that the expression of flavin-containing

monooxygenase 2 (FMO2) in cardiac tissue is significantly reduced after MI. Downregulation of FMO2 in cardiac fibroblasts leads to impaired cardiac function, increased collagen deposition, and aggravated fibrosis, suggesting that FMO2 can also serve as a therapeutic target for cardiac fibrosis.

Through high-throughput screening of the FDA drug library, we previously identified that fexofenadine hydrochloride significantly promotes FMO2 expression. Fexofenadine hydrochloride is a third-generation H1 receptor antagonist primarily used for the treatment of allergic diseases such as seasonal allergic rhinitis and chronic idiopathic urticaria[10]. However, the efficacy and safety of fexofenadine hydrochloride in the treatment of acute myocardial infarction remain unclear. Our preliminary mouse studies demonstrated that fexofenadine hydrochloride can significantly improve cardiac function and reduce fibrosis after MI in mice, with no significant adverse effects on liver and kidney function within the effective dose range. We also verified the safety of this drug in human cardiac organoids. Furthermore, we initiated a prospective, multicenter, randomized controlled clinical trial to evaluate the efficacy and safety of fexofenadine hydrochloride in patients with acute ST-segment elevation myocardial infarction (STEMI). Based on this, the present clinical study aims to assess the efficacy and safety of fexofenadine hydrochloride in improving the prognosis of acute MI.

2. Study Objectives

To evaluate the prognostic effect of fexofenadine hydrochloride in patients with MI through a large-sample, multicenter randomized controlled study.

3. Study Design and Methods

3.1 Study Design

An investigator-initiated, multicenter, double-blind, placebo-controlled, superiority randomized controlled clinical trial. Participating centers include: The Second Affiliated Hospital of Zhejiang University School of Medicine, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Fuwai Central China Cardiovascular Hospital, West China Hospital of Sichuan University, The First Affiliated Hospital of Wenzhou Medical University, The Second Affiliated Hospital of Wenzhou Medical University, The First Affiliated Hospital of Harbin Medical University, The Second Affiliated Hospital of Chongqing Medical University, etc.

Additional study sites may be added subsequently.

3.2 Patient Enrollment

Patients with acute ST-segment elevation myocardial infarction (STEMI) will be enrolled from multiple centers and randomly assigned to the fexofenadine treatment group or the placebo group.

3.3 Study Period

Recruitment period: 24 months. Follow-up time points: 6th, 12th, 24th, and 60th months after enrollment.

3.4 Inclusion Criteria

1. Age ≥ 18 years old.
2. Able to verbally confirm understanding of the trial risks, benefits, and treatment options of fexofenadine hydrochloride therapy. He/she or his/her legal representative must provide written informed consent prior to participating in the clinical trial.
3. Acute ST-segment elevation myocardial infarction (STEMI) occurring within 7 days, with diagnostic criteria including:

i) Typical clinical symptoms: such as severe crushing pain in the retrosternal or precordial area, usually lasting more than 10-20 minutes, which may radiate to the left upper arm, jaw, neck, back, or shoulders, etc.;

ii) Elevated serum cardiac troponin (cTn): at least one measurement above the upper limit of normal (99th percentile of the reference upper limit);

iii) ST-segment elevation: new ST-segment elevation at the J point in 2 adjacent leads.

4. Echocardiography indicating segmental wall motion abnormalities.

3.5 Exclusion Criteria

1. Need for long-term use of fexofenadine hydrochloride or other H1 receptor inhibitors.
2. Previous coronary artery bypass grafting (CABG) surgery.
3. History of severe renal failure with estimated glomerular filtration rate (eGFR) < 30 ml/min.
4. History of severe liver dysfunction.
5. History of concurrent severe infection, hepatobiliary obstruction, or malignant tumor.
6. Expected life expectancy of less than 2 years due to non-cardiac diseases.
7. Currently receiving immunosuppressive therapy.
8. Pregnant, potentially pregnant, or lactating women.
9. Contraindication to the study drug or examinations.
10. Failure to provide written informed consent.
11. Presence of mechanical complications (ventricular septal defect, papillary muscle dysfunction, acute mitral regurgitation), refractory cardiogenic shock unresponsive to vasopressors, acute left heart failure or pulmonary edema, or malignant arrhythmias uncontrolled by antiarrhythmic drugs at enrollment.

3.6 Patient Follow-up

Clinical follow-up will be conducted via telephone or outpatient visits at 6th, 12th, 24th, and

60th months after enrollment.

3.7 Primary Endpoint

Incidence of major adverse cardiovascular and cerebrovascular events (MACCE) within 24 months after randomization, including all-cause death, recurrent myocardial infarction, stroke, hospitalization for heart failure, outpatient or emergency visits due to worsening heart failure, and repeat revascularization driven by angina pectoris.

3.8 Secondary Endpoints

1. All-cause death at 24 and 60 months after randomization.
2. Recurrent myocardial infarction at 24 and 60 months after randomization.
3. Stroke at 24 and 60 months after randomization.
4. Hospitalization for heart failure or outpatient/emergency visits due to worsening heart failure at 24 and 60 months after randomization.
5. Repeat revascularization driven by angina pectoris at 24 and 60 months after randomization.
6. Comparison of the difference in left ventricular ejection fraction (LVEF%) measured by echocardiography between the two groups at 24 months after randomization compared to baseline.
7. Comparison of the difference in left ventricular end-systolic diameter (LVIDs) measured by echocardiography between the two groups at 24 months after randomization compared to baseline.
8. Comparison of the difference in left ventricular end-diastolic diameter (LVIDd) measured by echocardiography between the two groups at 24 months after randomization compared to baseline.
9. Comparison of New York Heart Association (NYHA) functional classification between the two groups at 24 months after randomization.
10. Comparison of Kansas City Cardiomyopathy Questionnaire (KCCQ) scores between the two groups at 24 months after randomization.
11. Incidence of adverse events related to fexofenadine.

3.9 Safety Assessment

Incidence of serious and non-serious adverse events within 24 months of fexofenadine hydrochloride administration.

Adverse events (AE) include:

1. Cardiac adverse reactions (including tachycardia, palpitations).
2. Nervous system reactions (including headache, somnolence, dizziness).
3. Psychiatric reactions (including sleep disorders, anxiety).

4. Gastrointestinal reactions (including diarrhea, nausea).
5. Immune-related skin reactions (including rash, urticaria, pruritus).

Serious adverse events (SAE) include:

Severe allergic/hypersensitivity reactions (including angioedema, chest tightness, dyspnea, other systemic immediate allergic reactions).

3.10 Enrollment

All patients with acute ST-segment elevation myocardial infarction will be screened for eligibility to participate in this study. Members of each study team will review the patient's medical history to determine compliance with inclusion and exclusion criteria. If eligible, the patient can be registered and enrolled in the study after signing the written informed consent form. Prior to collecting study data, participants will be informed of study details, including: (1) this is an investigator-initiated clinical study; (2) participation is voluntary, and there will be no penalty for withdrawal; (3) potential risks and benefits of participation. Vulnerable populations will be excluded in accordance with the inclusion and exclusion criteria.

3.11 Study Methods

3.11.1 Study Design

Patients with acute ST-segment elevation myocardial infarction will be randomly assigned in a 1:1 ratio to the placebo group or the fexofenadine hydrochloride group for efficacy and safety assessment.

3.11.2 Randomization Method

Eligible patients will be randomly assigned to the placebo group or the fexofenadine hydrochloride treatment group in a 1:1 ratio after recruitment, with the randomization process conducted via an online system by the research institution.

3.11.3 Study Blinding

Drugs in the placebo group and the treatment group are identical in appearance and packaging, and participants are unaware of their group assignment. Throughout the study, blinding will be maintained during the generation of the randomization code, drug coding, patient medication administration, data monitoring, data management, and statistical analysis, and investigators are unaware of the patients' group assignments and medication status.

3.11.4 Drug Treatment

Patients in both groups will receive current standard drug therapy in accordance with the 2023 European Society of Cardiology (ESC) Guidelines for the Management of Acute Coronary Syndromes, including dual antiplatelet therapy with aspirin/indobufen + ticagrelor/clopidogrel, statins for lipid-lowering, metoprolol, ACEI/ARB drugs for anti-cardiac remodeling, etc., with updates in line with guideline revisions. On this basis, additional treatments are as

follows:

Fexofenadine hydrochloride group: Fexofenadine hydrochloride tablets, 60 mg, twice daily, orally for 24 months.

Placebo group: White starch tablets identical in appearance and packaging, twice daily, orally for 24 months.

Treatment initiation time: Immediately after randomization.

After providing informed consent, enrolled patients will be randomly assigned to receive fexofenadine hydrochloride or placebo. The fexofenadine hydrochloride group will receive 60 mg BID orally for 24 months. Patients assigned to the placebo group will receive identically appearing starch tablets orally for 24 months.

Note: The usual dose of fexofenadine hydrochloride for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria is 60 mg bid. Large-scale randomized controlled clinical studies have shown that long-term use (1 year) of different doses of fexofenadine hydrochloride (20-240 mg QD) has no significant safety impact on healthy volunteers.

3.11.5 Study Content

(1) In-hospital Management

1. Signing of Informed Consent

Each participant or their legal representative must provide informed consent before initiating any study-related procedures.

2. Physical Examination

Complete and document a physical examination, including heart rate, blood pressure, height, and weight.

3. Medical History

Complete a detailed medical history record, including age, gender, NYHA functional status, risk factors (hypertension, smoking, diabetes, etc.), and previous cardiovascular diseases (including myocardial infarction, percutaneous coronary intervention, etc.).

4. Laboratory Examinations

Including routine blood test + C-reactive protein (CRP), liver function, renal function, and routine lipid profile.

5. Electrocardiogram (ECG)

Record a 12-lead ECG at baseline. Document cardiovascular events such as severe arrhythmias occurring during hospitalization.

6. Echocardiography

Complete at least one echocardiographic examination within 3 days after MI.

(2) Post-discharge Follow-up (6th, 12th, 24th, and 60th months)

Laboratory Examinations

Including routine blood test + CRP, liver function, renal function, and routine lipid profile.

Safety and the patient's clinical status will be assessed at each follow-up time point after drug administration.

1. Medical History

Complete a detailed medical history record, supplementing any medical events occurring after enrollment in the trial (including symptoms, potential drug side effects, physical status, recurrence of MI/interventional events/hospitalization, death, etc.), as well as patient medication adherence.

2. Physical Examination

Complete and document a physical examination, including heart rate and blood pressure.

3. Electrocardiogram (ECG)

Routinely record a 12-lead ECG at 6th, 12th, and 24th months after MI.

4. Echocardiography

Complete an echocardiographic examination at 6th, 12th, 24th, and 60th months after MI.

3.11.6 Data Collection

Items	Baseline (Before Discharge, ≤3 days)	Follow-up (3 months ±14 days)	Follow-up (6 months ±30 days)	Follow-up (12 months ±30 days)	Follow-up (24 months ±90 days)	Follow-up (60 months ±90 days)
Inclusion/ Exclusion Criteria	O					
Signing of Informed Consent	O					
Medical History Information (Age, gender, height, weight, risk factors, clinical past	O					

history, NYHA functional status, previous history of heart disease)						
Medical History Information (Any medical events after enrollment in the trial)		O	O	O	O	O
Medication History*	O	O	O	O	O	O
Physical Examination	O	Δ	Δ	Δ	Δ	Δ
Vital Signs	O	Δ	Δ	Δ	Δ	Δ
Coronary Angiography Images#	O					
Laboratory Examinations (Routine blood test + CRP, liver function, renal	O		Δ	Δ	Δ	Δ

function, routine lipid profile)						
12-lead ECG	O		△	△	△	△
Echocardiographic Results (LVEF%, LVIDd, LVIDs) and Original Images	O		O	O	O	O
NYHA Functional Classification	O				O	O
KCCQ Score					O	O
MACE Events		O	O	O	O	O
Drug Distribution	O	O	O	O	O	
Drug-related Adverse Reactions		O	O	O	O	
Medication Adherence		O	O	O	O	

The timeline for data collection is shown in the table above:

Compulsory coronary angiography or laboratory blood tests during follow-up are prohibited. If a participant experiences an endpoint event, it is recommended to collect ECG and coronary angiography data.

*Medication-related information includes the patient's medication status before admission and after discharge.

O: Mandatory item.

△: Non-mandatory but recommended.

3.12 Statistical Methods

Primary Endpoint	Statistical Methods	Analysis Time Point
Incidence of major adverse cardiovascular events (MACE, including cardiac death, non-fatal MI, non-fatal stroke, readmission for heart failure, etc.) within 24 months after randomization	Survival analysis, Kaplan-Meier survival curve, Log-rank test	24th month after randomization
Secondary Endpoints	Statistical Methods	Analysis Time Point
All-cause death at 24 and 60 months after randomization	Survival analysis, Kaplan-Meier survival curve, Log-rank test	24th and 60th months after randomization
Recurrent myocardial infarction at 24 and 60 months after randomization	Survival analysis, Kaplan-Meier survival curve, Log-rank test	24th and 60th months after randomization
Stroke at 24 and 60 months after randomization	Survival analysis, Kaplan-Meier survival curve, Log-rank test	24th and 60th months after randomization
Hospitalization for heart failure or outpatient/emergency visits due to worsening heart	Survival analysis, Kaplan-Meier survival curve, Log-rank test	24th and 60th months after randomization

failure at 24 and 60 months after randomization		
Repeat revascularization driven by angina pectoris at 24 and 60 months after randomization	Survival analysis, Kaplan-Meier survival curve, Log-rank test	24th and 60th months after randomization
Difference in left ventricular ejection fraction (LVEF%) measured by echocardiography compared to baseline after randomization	T-test, Wilcoxon rank-sum test	24th month after randomization
Difference in left ventricular end-systolic diameter/body surface area% measured by echocardiography compared to baseline after randomization	T-test, Wilcoxon rank-sum test	24th month after randomization
Difference in left ventricular end-diastolic diameter/body surface area% measured by echocardiography compared to baseline after randomization	T-test, Wilcoxon rank-sum test	24th month after randomization
NYHA functional classification at 12 and 24 months after randomization	Wilcoxon rank-sum test, Chi-square test	24th month after randomization
KCCQ score at 12 and 24 months after randomization	T-test, Wilcoxon rank-sum test	24th month after randomization
Incidence of drug-related adverse events	Chi-square test	1st, 3rd, 6th, 12th, and 24th months after randomization

4. Sample Size Calculation

This study adopts a 1:1 sample size ratio between the experimental group and the control group, with a one-sided α value set at 0.025 and a power (1-β) of 0.8. Based on preliminary study results and relevant clinical data (referring to PARADISE-MI, EMPACT-MI, COLCOT,

FLAVOUR series studies), event rate estimation will be performed using Kaplan-Meier survival analysis. Assuming an event rate of 16.5% in the control group and 13.2% in the experimental group, the expected enrollment period is 2 years. The sample size will be calculated using PASS software. Considering a 10% dropout rate, 1402 patients will need to be enrolled in each group, totaling 2804 patients.

5. Data Management and Confidentiality

5.1 Data Management

Study data will be retained for at least 3 years after the completion of study outcomes (including relevant papers, research reports, etc.). Unauthorized processing of study data without patient authorization or research institution approval is prohibited. If study data is stored electronically, it is recommended to back up the data to optical discs regularly, especially for important data which requires multiple backups. Relevant software should be used to ensure timely data storage, and special attention should be paid to the security of electronic data storage.

The review committee or ethics committee will conduct regular audits or inspections of data security. Its main responsibility is to systematically and independently verify all study-related processes and documents to determine whether the implementation of the study process, the accuracy of data recording, analysis, and reporting comply with the study protocol, good clinical practice (GCP), International Council for Harmonisation (ICH) guidelines, and any regulatory requirements.

5.2 Data Confidentiality

Throughout the study, the health information of all patients must be kept confidential, and unauthorized access to data is prohibited. Each patient will be assigned a unique identification number, and patient data will be stored in locked cabinets at the clinical center with data encryption to restrict data access. Relevant regulations on the confidentiality of patient information should be roughly informed to patients in the informed consent form. In accordance with relevant regulations on the protection of patient health information, relevant health personnel are entitled to access study data.

6. Informed Consent

This study intends to recruit patients with acute ST-segment elevation myocardial infarction. To protect vulnerable populations, pregnant women, minor patients, patients with mental illness or cognitive impairment, and staff and students of the research center will be excluded.

Prior to collecting study data, the following details of the study must be informed to patients: 1. This is a Phase IV clinical study; 2. Patient participation is strictly voluntary, and no compensation is required for withdrawing from the study; 3. Patients can withdraw from the study at any time; 4. Potential risks and benefits are disclosed; 5. Necessary communication and contact will be maintained.

Participants will have sufficient time to understand the study and ask questions before

participating. They will be informed of the study purpose, available treatments, randomization assignment, the need to cooperate with outpatient follow-up and complete some auxiliary examinations. The patient's decision to accept or refuse to participate in the study will not affect clinical diagnosis and treatment.

All patients or their legal representatives must sign the informed consent form after fully understanding the study before conducting any study-related activities and treatments. Those who do not sign the informed consent form are not eligible to participate in the study. A copy of the signed informed consent form will be made, with the original retained in the patient's medical record and the copy provided to the patient or their legal representative for safekeeping. All study-related data must be supported by medical records, cardiovascular angiography images, blood test results, ECG, echocardiography, and cardiac magnetic resonance results. The acquisition of these data is mainly to support routine medical care and basic research.

7. Reporting and Management of Adverse Events

7.1 Reporting of Adverse Events

All adverse events: Timely measures should be taken for management, and events should be recorded in the case report form (CRF).

Serious adverse events (SAE): Timely measures should be taken for management, and events should be recorded in the CRF. The investigator will decide whether to discontinue or reduce the drug dosage. The ethics committee, drug clinical trial institution, and sponsor should be immediately notified, and the national and provincial drug regulatory authorities should be reported within 24 hours. SAEs must be reported through the "Hospital Intranet Adverse Event and Near-Miss Non-Punitive Reporting System". Specific procedures: see the figure below.

- No emergency treatment required
- Emergency treatment required, immediate reporting
- Report within 24 hours
- Hospital Medical Affairs Department: 3880, 3881
- Note: For night-time reports, please call the general duty room: 660000
- Responsible for proper handling
- State Drug Administration Safety Supervision Department Pharmaceutical Research Supervision Office: 010-88363228
- Provincial Food and Drug Administration Registration Office: 88903275
- Ethics Committee: 87783969

- Sponsor/CRO
- Report to the Adverse Event and Near-Miss Non-Punitive Reporting System via the hospital intranet
- Conduct follow-up and summarize handling opinions
- Report to the hospital leadership in charge)

7.2 Management of Adverse Events

1. Cardiac adverse reactions (including tachycardia, palpitations): Complete laboratory biochemical examinations, ECG, echocardiography, etc. If necessary, perform cardiac electrophysiological examinations to clarify the cause. For patients with severe symptoms, discontinue fexofenadine hydrochloride and administer antiarrhythmic drugs if necessary.

2. Nervous system reactions (including headache, somnolence, dizziness, etc.): Consult a neurologist for auxiliary diagnosis, complete neurological physical examinations and imaging examinations to rule out emergency conditions such as intracranial hemorrhage and infection. Administer analgesic drugs and physical therapy if necessary.

3. Psychiatric reactions (including sleep disorders, anxiety, etc.): Consult a psychiatrist for auxiliary diagnosis, complete relevant scales to assess the patient's emotional and sleep status. Administer hypnotic drugs or anti-anxiety medications if necessary.

4. Gastrointestinal reactions (including diarrhea, nausea, etc.): Consult a gastroenterologist for auxiliary diagnosis, supplement body fluids via oral or intravenous infusion, and administer antidiarrheal, antiemetic, and other symptomatic drugs if necessary.

5. Immune-related skin reactions (including rash, urticaria, pruritus, etc.): Consult a dermatologist for auxiliary diagnosis. Perform histopathological examination if diagnosis is difficult. Apply topical moisturizers or hormonal ointments locally. For patients with severe skin lesions, administer oral/intravenous hormones and immunosuppressive therapy.

Management of serious adverse events:

Severe allergic/hypersensitivity reactions (including angioedema, chest tightness, dyspnea, flushing, other systemic immediate allergic reactions, etc.): During the treatment of severe allergic reactions, close monitoring of cardiac function, blood pressure, respiration, and blood oxygen saturation should be performed. If severe dyspnea occurs due to laryngeal edema or bronchospasm, tracheal intubation or tracheotomy should be considered, and cricothyrotomy may be performed in emergency situations. For patients with grade II or above severe allergic reactions, epinephrine intramuscular injection is the first choice, administered at a dose of 0.01 mg/kg body weight, with a maximum single dose not exceeding 0.5 mg, at a concentration of 1 mg/ml (1:1000). If the effect is unsatisfactory after 5-15 minutes, repeat the administration. For patients with grade IV reactions who have experienced or are about to experience cardiac or respiratory arrest, epinephrine should be administered intravenously at a single dose of 0.5-1 mg, at a concentration of 0.1 mg/ml (1:10000). For patients with grade III reactions who have established venous access and are under monitoring, epinephrine can be administered intravenously at a single dose of 0.1-0.2 mg, at a concentration of 0.1 mg/ml (1:10000). If the effect is unsatisfactory after 3-5 minutes, repeat the administration. H1

receptor antagonists, β2 receptor agonists, and glucocorticoids can be used as second-line medications. Fluid resuscitation can be used for patients with severe allergic reactions accompanied by circulatory instability, with a usual fluid volume of 20 ml/kg, adjusted according to the patient's condition. After the patient is rescued from danger, monitoring should be continued for at least 12 hours, including monitoring of heart rate, rhythm, blood pressure, respiration, blood oxygen saturation, and urine output.

8. Protection Measures for Vulnerable Populations

Patients with acute MI are critically ill and clinically considered a vulnerable population. This study will take all necessary measures to fully protect the privacy rights, right to life and health, right to informed consent, and other rights and interests of vulnerable participants.

8.1 Right to Privacy

High attention should be paid to and protection provided for the privacy of vulnerable participants. Investigators will assume confidentiality responsibilities, using de-identified data instead of the participants' personal information to ensure the anonymity of participants. In addition, during the recruitment and informed consent process, investigators are obligated to inform patients of the study's confidentiality system, and participants can only participate in the trial after understanding and agreeing.

8.2 Right to Life and Health

The right to life and health of vulnerable participants should be protected as the most important and fundamental right. The drugs used in this study are all marketed drugs, and their safety has been confirmed in previous clinical trials. The dosage and administration are in accordance with drug instructions and clinical practice. In addition, participants will receive regular follow-up during the study period, and adverse events will be promptly managed and reported. The clinical event committee will assess whether participants can continue to participate in the trial. Furthermore, during the informed consent process, the risks, benefits, and compensation for damages associated with participating in the trial will be fully informed to participants, who can only participate after understanding and accepting them.

8.3 Right to Informed Consent

Informed consent is a prerequisite for vulnerable participants to participate in clinical trials. Investigators will fully inform participants of the study content, risks, benefits, rights protection, compensation for damages, etc., and answer participants' questions. Participants must sign the informed consent form after fully understanding the study before participating. For participants who lack the capacity for independent decision-making, verbal consent should be obtained from the participants themselves, and their legal representatives should sign the informed consent form.

9. References

1. Lindstrom, M. et al. Global Burden of Cardiovascular Diseases and Risks Collaboration,

1990-2021. Journal of the American College of Cardiology 80, 2372-2425, doi:10.1016/j.jacc.2022.11.001 (2022).

2. Zhang, Q. et al. Signaling pathways and targeted therapy for myocardial infarction. Signal transduction and targeted therapy 7, 78, doi:10.1038/s41392-022-00925-z (2022).

3. González, A., Schelbert, E. B., Díez, J. & Butler, J. Myocardial Interstitial Fibrosis in Heart Failure: Biological and Translational Perspectives. Journal of the American College of Cardiology 71, 1696-1706, doi:10.1016/j.jacc.2018.02.021 (2018).

4. Graziani, F., Varone, F., Crea, F. & Richeldi, L. Treating heart failure with preserved ejection fraction: learning from pulmonary fibrosis. European journal of heart failure 20, 1385-1391, doi:10.1002/ejhf.1286 (2018).

5. Zhao, M. et al. Targeting fibrosis, mechanisms and clinical trials. Signal transduction and targeted therapy 7, 206, doi:10.1038/s41392-022-01070-3 (2022).

6. Wynn, T. A. & Ramalingam, T. R. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nature medicine 18, 1028-1040, doi:10.1038/nm.2807 (2012).

7. King, T. E., Jr. et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. The New England journal of medicine 370, 2083-2092, doi:10.1056/NEJMoa1402582 (2014).

8. Richeldi, L. et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. The New England journal of medicine 370, 2071-2082, doi:10.1056/NEJMoa1402584 (2014).

9. Ni, C. et al. Flavin Containing Monooxygenase 2 Prevents Cardiac Fibrosis via CYP2J3-SMURF2 Axis. Circulation research, 101161circresaha122320538, doi:10.1161/circresaha.122.320538 (2022).

10. Axelrod, D. & Bielory, L. Fexofenadine hydrochloride in the treatment of allergic disease: a review. Journal of asthma and allergy 1, 19-29, doi:10.2147/jaa.s3092 (2008).

11. Meltzer, E. O., Rosario, N. A., Van Bever, H. & Lucio, L. Fexofenadine: review of safety, efficacy and unmet needs in children with allergic rhinitis. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 17, 113, doi:10.1186/s13223-021-00614-6 (2021).

12. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-2264. doi:10.1016/j.jacc.2018.08.1038

13. Empagliflozin after Acute Myocardial Infarction. NEJM. April 6, 2024. DOI: 10.1056/NEJMoa2314051