Effect and safety of Fexofenadine hydrochloride vs Placebo in Patients With Acute Myocardial Infarction (FEND-AMI):

A Randomized Clinical Trial

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1. Background

Myocardial infarction and its consequent heart failure are among the leading causes of cardiovascular death in China [1]. After myocardial infarction, cardiomyocyte death activates fibroblasts. Although fibroblasts play a reparative role, their excessive activation and excessive deposition of extracellular matrix lead to fibrotic tissue, ultimately resulting in heart failure [2]. While

current measures can reduce early mortality after MI, effective treatments targeting post-MI pathological fibrosis are lacking [3,4]. Therefore, inhibiting excessive cardiac fibroblast activation and reducing cardiac fibrosis after MI is a critical scientific and clinical need.

Although the mechanisms driving organ-specific fibrosis have not been fully elucidated, persistent abnormal activation of myofibroblasts mediated by multiple signals—including transforming growth factor (TGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF)—is common across different tissues and organs [5,6]. Drugs targeting these aberrant signals have shown some efficacy in clinical trials, such as nintedanib and pirfenidone [7,8]. Our previous work revealed that flavin-containing monooxygenase 2 (FMO2) levels in cardiac tissue are significantly reduced after MI. Knockdown of FMO2 in cardiac fibroblasts led to impaired cardiac function, increased collagen deposition, and aggravated fibrosis, suggesting FMO2 as a potential therapeutic target for cardiac fibrosis.

Using high-throughput screening of an FDA drug library, we identified that fexofenadine hydrochloride significantly promotes FMO2 expression. Fexofenadine hydrochloride is a third-generation H1-receptor antagonist primarily used for allergic diseases such

as seasonal allergic rhinitis and chronic idiopathic urticaria [10]. However, its efficacy and safety in treating acute myocardial infarction remain unknown. Our preclinical mouse studies demonstrated that fexofenadine hydrochloride significantly improved post-MI cardiac function and fibrosis, with no obvious effects on liver or kidney function at effective doses. We also validated its safety in human cardiac organoids. Based on these findings, this clinical trial aims to evaluate the efficacy and safety of fexofenadine hydrochloride in patients with acute myocardial infarction.

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2. Study Objective

To evaluate the efficacy and safety of fexofenadine hydrochloride in patients with acute ST-segment elevation myocardial infarction (STEMI).

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3. Study Design and Methods

3.1 Study Design

Prospective, multicentre, double-blind, placebo-controlled randomised clinical trial. Participating centres include: The Second Affiliated Hospital of Zhejiang University School of Medicine, The First Affiliated Hospital of Harbin Medical University, The First Affiliated Hospital of Wenzhou Medical University, The Second Affiliated Hospital of Wenzhou Medical University, West China Hospital of Sichuan University, and other centres.

3.2 Patient Enrolment

A total of 160 patients will be enrolled across multiple centres.

3.3 Study Duration

The total study duration is 18 months, with a recruitment period of 1 year. Follow-up visits are scheduled at 1, 3, and 6 months after drug administration.

3.4 Inclusion Criteria

1. Age ≥ 18 years.
2. Able to verbally confirm understanding of the risks, benefits, and treatment options of fexofenadine hydrochloride therapy. The patient or their legal representative must provide written informed consent before participating.
3. Acute ST-segment elevation myocardial infarction, diagnosed according to the following criteria [12]:

   i) Typical clinical symptoms: e.g., severe crushing chest pain (retrosternal or precordial) lasting >10-20 minutes, possibly radiating to the left arm, jaw, neck, back, or shoulder;

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

   iii) ST-segment elevation: new ST-segment elevation at the J-point in two adjacent leads.
4. Undergoing emergency PCI with culprit-vessel revascularisation.
5. Echocardiography showing regional wall motion abnormality, and transthoracic echocardiography within 72 hours after revascularisation showing left ventricular ejection fraction (LVEF) ≤ 50%.

3.5 Exclusion Criteria

1. Long-term use of fexofenadine hydrochloride or other H1-receptor antagonists.
2. Prior myocardial infarction or coronary artery bypass grafting.
3. History of severe renal failure with eGFR < 30 ml/min.
4. History of severe hepatic insufficiency.
5. Concurrent severe infection, hepatobiliary obstruction, or history of malignancy.
6. Currently receiving immunosuppressive therapy.
7. Pregnant, possibly pregnant, or lactating women.
8. Contraindications to the study drug or to magnetic resonance imaging (MRI).
9. Failure to provide written informed consent.
10. Haemodynamically unstable patients.

3.6 Patient Follow-up

Clinical follow-up will be conducted at 1, 3, and 6 months post-procedure through outpatient visits, including laboratory tests and imaging examinations.

3.7 Primary Endpoint

The difference from baseline in late gadolinium enhancement / left ventricular mass percentage (LGE/LV%) measured by cardiac magnetic resonance (CMR) at 6 months after administration of fexofenadine hydrochloride or placebo.

3.8 Secondary Endpoints

1. Change from baseline in CMR-derived left ventricular ejection fraction (LVEF%) at 6 months.
2. Change from baseline in CMR-derived left ventricular end-systolic volume indexed to body surface area (LVESV/BSA) at 6 months.
3. Change from baseline in CMR-derived left ventricular end-diastolic volume indexed to body surface area (LVEDV/BSA) at 6 months.
4. Change from baseline in CMR-derived extracellular volume fraction (ECV) at 6 months.

5. Change from baseline in CMR-derived intramyocardial haemorrhage (IMH) at 6 months.
6. Change from baseline in CMR-derived stroke volume at 6 months.
7. Change from baseline in CMR-derived peri-infarct zone area at 6 months.
8. Change from baseline in BNP at 6 months.
9. Maximal oxygen uptake (VO_2 max) at 6 months.
10. Quality of life assessed by the Seattle Angina Questionnaire (SAQ) score at 6 months.
11. Incidence of major adverse cardiovascular events (MACE, including cardiovascular death, recurrent acute myocardial infarction, and hospitalisation for heart failure) at 6 months.
12. Incidence of drug-related adverse events at 1, 3, and 6 months.

3.9 Safety Assessment

Incidence of serious and non-serious adverse events during the 6-month fexofenadine administration period. Adverse events include:

1. Cardiac adverse reactions (including tachycardia, palpitations);
2. Neurological reactions (including headache, somnolence, dizziness);
3. Psychiatric reactions (including sleep disorders, anxiety);
4. Gastrointestinal reactions (including diarrhoea, nausea);
5. Immune-related skin reactions (including rash, urticaria, pruritus);
6. Severe allergic/hypersensitivity reactions (including angioedema, chest tightness, dyspnoea, flushing, other systemic anaphylactic reactions).

3.10 Enrolment

All patients with acute STEMI undergoing emergency revascularisation will be screened for this study. Each study team member will review the patient's medical history against the inclusion/exclusion criteria. If eligible, patients will be enrolled after signing written informed consent. Before data collection, participants will be informed of study details, including: (1) this is an investigator-initiated

clinical trial; (2) participation is voluntary and withdrawal carries no penalty; (3) potential risks and benefits. Vulnerable subjects will be excluded according to the criteria.

3.11 Study Procedures

3.11.1 Study Design

Patients with acute STEMI (LVEF ≤ 50%) undergoing emergency revascularisation will be randomised 1:1 to the control group or fexofenadine group for efficacy and safety evaluation.

3.11.2 Study Flowchart

3.11.3 Randomization Method

Eligible patients will be randomised 1:1 to the control or fexofenadine group after enrolment. The randomisation process will be performed via a web-based system by the study institution.

3.11.4 Blinding

The control and treatment drugs will be identical in appearance; subjects will be blinded to group assignment. The entire process—from generation of the randomisation code, drug coding, drug administration, data monitoring, data management, to statistical analysis—will be conducted in a blinded manner. Investigators will be blinded to patient grouping and treatment allocation.

3.11.5 Drug Treatment

Both groups will receive standard medical therapy according to the 2023 ESC Guidelines for the management of acute coronary syndromes, including aspirin + ticagrelor/clopidogrel dual antiplatelet therapy, statins for lipid lowering, metoprolol, ACEI/ARB for anti-remodelling, etc., and will be updated as guidelines evolve. On top of this, they will receive the following:

- **Fexofenadine group:** Fexofenadine hydrochloride tablets, 60 mg twice daily, orally for 6 months.
- **Placebo group:** White starch tablets, 60 mg twice daily, orally for 6 months.

Treatment initiation: Day 3 after coronary revascularisation.

After informed consent, enrolled subjects will be randomly assigned to fexofenadine or placebo. The fexofenadine group will receive 60 mg bid orally for 6 months. The placebo group will receive identical-appearing starch tablets, 60 mg bid orally for 6 months.

Note: The current recommended dose of fexofenadine for seasonal allergic rhinitis and chronic idiopathic urticaria is 60 mg bid. Large randomised controlled trials have shown that long-term use (1 year) of various doses (20-240 mg qd) has no significant safety concerns in healthy volunteers [11].

3.11.6 Study Assessments

(1) In-hospital management

1. **Informed consent** – Obtained before any study procedures.
2. **Physical examination** – Including heart rate, blood pressure, height, and weight.
3. **Medical history** – Detailed history including age, sex, NYHA functional class, risk factors (hypertension, smoking, diabetes, etc.), prior cardiovascular disease (including MI, PCI, etc.).

4. **Laboratory analysis** – Blood samples collected on day 1 post-procedure for: complete blood count, liver and renal function, electrolytes, glucose, lipids, coagulation profile, cardiac enzyme profile, BNP, inflammatory markers (CRP, IL-6, PCT). Additionally, 2 ml of peripheral blood will be collected, appropriately labelled, and stored.
5. **Electrocardiogram** – 12-lead ECG recorded on day 1 post-procedure. In-hospital cardiovascular events (e.g., serious arrhythmias) will be recorded.
6. **Echocardiography** – At least one echocardiogram within 3 days after PCI.
7. **Contrast-enhanced cardiac MRI** – At least one CMR within 3 days after PCI.

(2) Post-discharge follow-up (1 month, 3 months, 6 months)

Safety and clinical status will be evaluated at 1, 3, and 6 months after drug initiation.

1. **Medical history** – Update with any medical events since enrolment (including symptoms, potential drug side effects, physical capacity, recurrent MI/intervention/hospitalisation, death, etc.), and medication adherence.
2. **Physical examination** – Including heart rate and blood pressure.

3. **ECG** – 12-lead ECG routinely recorded at 1, 3, and 6 months.
4. **Laboratory safety analysis** – Blood samples at 1, 3, and 6 months for: complete blood count, liver and renal function, BNP, inflammatory markers (CRP, IL-6, PCT). At 6 months, 2 ml of peripheral blood will be collected, labelled, and stored.
5. **Echocardiography** – Optional at 6 months ± 2 weeks after PCI.
6. **Contrast-enhanced cardiac MRI** – At 6 months ± 2 weeks after PCI.

3.11.7 Data Collection Schedule

Item	**Baseline** (pre-discharge, ≤3 days)	**Month 1** (±7 days)	**Month 3** (±14 days)	**Month 6** (±14 days)
Inclusion/exclusion criteria	**O**			
Informed consent	**O**			

Item	**Baseline** (pre-discharge, ≤3 days)	**Month 1** (±7 days)	**Month 3** (±14 days)	**Month 6** (±14 days)
Medical history (age, sex, height/weight, risk factors, clinical history, NYHA class, prior cardiac disease)	**O**			
Medical history (any events since enrolment)		**O**	**O**	**O**
Medication history*	**O**	**O**	**O**	**O**
Physical examination	**O**	△	△	△
Vital signs	**O**	△	△	△
Coronary angiography images#	**O**			
12-lead ECG	**O**	**O**	**O**	**O**
Echocardiography (LVEF% and raw images)	**O**			△

Item	**Baseline** (pre-discharge, ≤3 days)	**Month 1** (±7 days)	**Month 3** (±14 days)	**Month 6** (±14 days)
Contrast-enhanced CMR (LVEF%, LGE, LVEDV, LVESV, ECV, IMH, stroke volume, peri-infarct zone)	**O**			**O**
Complete blood count, liver function, renal function	**O**	**O**	**O**	**O**
Inflammatory markers (CRP, IL-6, PCT)	**O**	**O**	**O**	**O**
Triglycerides, total cholesterol, HDL, LDL	**O**			
Glucose, HbA1c	**O**			
CK, CK-MB, troponin I or T	**O**			
PT, APTT, TT, fibrinogen, FDP, D-dimer, antithrombin III	**O**			
BNP	**O**	**O**	**O**	**O**
VO_2 max				**O**

Item	**Baseline** (pre-discharge, ≤3 days)	**Month 1** (±7 days)	**Month 3** (±14 days)	**Month 6** (±14 days)
SAQ score				**O**
MACE incidence				**O**
Peripheral blood (2 ml)	**O**			**O**
Drug dispensing	**O**	**O**	**O**	
Drug-related adverse events		**O**	**O**	**O**
Medication adherence		**O**	**O**	**O**

*Routine coronary angiography or laboratory testing are not mandatory during follow-up; if a subject experiences an endpoint event, collection of ECG and coronary angiography data is recommended.

- Medication information includes drug use before admission and after discharge.

O = mandatory; ∆ = optional but recommended.

3.12 Statistical Methods

Endpoint	Statistical Method	Analysis Time Point
Primary endpoint: Change from baseline in CMR-derived LGE/LV% at 6 months	General linear model	6 months post-randomisation
Secondary endpoints:		
Change from baseline in CMR-derived LVEF% at 6 months	General linear model	6 months post-randomisation
Change from baseline in CMR-derived LVESV/BSA at 6 months	General linear model	6 months post-randomisation

Endpoint	Statistical Method	Analysis Time Point
Change from baseline in CMR-derived LVEDV/BSA at 6 months	General linear model	6 months post-randomisation
Change from baseline in CMR-derived ECV at 6 months	General linear model	6 months post-randomisation
Change from baseline in CMR-derived IMH at 6 months	General linear model	6 months post-randomisation
Change from baseline in CMR-derived stroke volume at 6 months	General linear model	6 months post-randomisation
Change from baseline in CMR-derived peri-infarct zone area at 6 months	General linear model	6 months post-randomisation
Change from baseline in BNP at 6 months	General linear model	6 months post-randomisation

Endpoint	Statistical Method	Analysis Time Point
VO_2 max at 6 months	General linear model	6 months post-randomisation
SAQ score at 6 months	General linear model	6 months post-randomisation
Incidence of MACE at 6 months	General linear model	6 months post-randomisation
Incidence of drug-related adverse events	Chi-square test	1, 3, and 6 months post-randomisation

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4. Sample Size Calculation

The sample size was estimated based on prior animal data and previous clinical studies. The allocation ratio between placebo and fexofenadine groups is 1:1. The type I error (one-sided) is set at 0.025, and power (1-β) at 0.8. The placebo group change from baseline is assumed to be -4.5% (SD 9.5%), and the fexofenadine group change from baseline -10.0% (SD 12.9%) (referencing the CARE-AMI trial [13] and our preliminary animal data). Using PASS 15 software, accounting for a 5% loss-to-follow-up rate and one interim analysis, the Pocock method will adjust the significance levels. The nominal significance levels for the interim and final analyses are one-sided 0.016 and 0.014, respectively. Therefore, 80 patients per group, i.e., 160 patients in total, are required.

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5. Interim Analysis

5.1 Purpose

A pre-specified interim analysis will be performed by an independent Data Monitoring and Safety Board (DMSB). The objectives are:

1. To assess overall subject safety, including adverse events and serious adverse events;

2. To evaluate recruitment progress, dropout/loss-to-follow-up rates, and protocol deviations;
3. To monitor efficacy for the primary endpoint and apply early stopping rules (for superiority or futility);
4. For the DMSB to provide recommendations on trial continuation, modification, or early termination.

5.2 Trigger Timing

The interim analysis will be triggered when 50% of patients have reached the primary endpoint follow-up time.

5.3 Datasets and Analysis Sets

- **Interim efficacy dataset:** The ITT set as of the data cut-off, including only primary and key secondary endpoints that occurred up to the cut-off, with statistical comparisons between fexofenadine and placebo using a general linear model.
- **Interim safety dataset:** The safety analysis set as of the cut-off, summarising all AEs and SAEs.
- Baseline characteristics and screening/enrolment summaries will also be provided to the DSMB.

5.4 Statistical Method for Interim Efficacy Monitoring

Given a 5% loss-to-follow-up rate, one interim analysis is planned. The Pocock method will be used to adjust the significance level.

The nominal significance levels for the interim and final analyses are one-sided 0.016 and 0.014, respectively. A total of 80 patients per group (160 total) are required.

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6. Data Management and Confidentiality

6.1 Data Management

Study data will be retained for at least 3 years after the production of study results (including publications, reports, etc.). Unauthorised access or processing of research data without patient consent or institutional approval is prohibited. If data are stored electronically, regular backup (e.g., CD copies) is recommended, especially for critical data, with multiple copies. Appropriate software should ensure timely storage, with special attention to the security of electronic data.

The review board or ethics committee will conduct regular audits or inspections of data security. Their primary responsibility is to systematically and independently verify all study-related processes and documents to ensure that study conduct, data recording, analysis, and reporting comply with the protocol, Good Clinical Practice, ICH guidelines, and regulatory requirements.

6.2 Confidentiality

All patient health information must be kept confidential throughout the study. Data access must not be unauthorised. Each patient will be assigned a unique identification number. Patient data will be stored in locked cabinets at clinical sites, encrypted, and with restricted access. The informed consent form will generally inform patients about confidentiality provisions. According to regulations on patient health information protection, relevant health authorities are entitled to access study data.

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7. Informed Consent

This study will enrol patients with acute STEMI undergoing emergency revascularisation and LVEF ≤ 50%. For ethical and safety reasons, pregnant women and patients under 18 years of age will be excluded.

Before data collection, patients must be informed of the following details: (1) this is a Phase 4 clinical study; (2) participation is strictly voluntary and withdrawal carries no penalty; (3) they may withdraw at any time; (4) potential risks and benefits; (5) the importance of maintaining communication.

Subjects will have adequate time to understand the study and ask questions before participation. They will be informed of the study purpose, treatment options, randomisation, the need for outpatient follow-up and examinations. Their decision to participate or not will not affect their clinical care.

All patients or legally authorised representatives must sign informed consent after full understanding of the study, before any study-related activities or treatment. Without signed consent, they are not eligible. A copy of the signed consent will be provided to the patient or their representative, and the original will be retained in the patient's medical record. All study-related data must

include medical records, angiography images, blood tests, ECGs, echocardiograms, and CMR results. These data are obtained to support routine medical care and basic research.

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8. Adverse Event Reporting and Management

8.1 Adverse Event Reporting

- **Adverse events (AEs):** Timely management and recording in the case report form (CRF).
- **Serious adverse events (SAEs):** Immediate management, recording in the CRF; the investigator will decide on dose reduction or discontinuation; report to the ethics committee, the clinical trial institution, and the sponsor within 24 hours; report to the national and provincial drug regulatory authorities within 24 hours. SAEs must be reported through the institutional adverse event reporting system. The reporting process is shown in the figure below.

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8.2 Management of Adverse Events

1. **Cardiac adverse reactions (tachycardia, palpitations):** Perform laboratory biochemical tests, ECG, echocardiography, and if necessary, electrophysiological studies to identify the cause. For severe symptoms, discontinue fexofenadine and administer antiarrhythmic drugs as needed.
2. **Neurological reactions (headache, somnolence, dizziness):** Consult neurologist for assistance; perform neurological physical examination and imaging to rule out emergencies such as intracranial haemorrhage or infection; provide analgesics or physiotherapy as needed.
3. **Psychiatric reactions (sleep disorders, anxiety):** Consult psychiatrist; administer relevant scales to assess mood and sleep; provide hypnotics or anxiolytics as needed.
4. **Gastrointestinal reactions (diarrhoea, nausea):** Consult gastroenterologist; administer oral or IV fluid replacement; provide anti-diarrhoeal or anti-emetic symptomatic treatment as needed.

5. **Immune-related skin reactions (rash, urticaria, pruritus):** Consult dermatologist; if differential diagnosis is difficult, perform biopsy. Topical moisturisers or corticosteroid ointments may be used. For severe skin lesions, administer oral/intravenous corticosteroids and immunosuppressants.
6. **Severe allergic/hypersensitivity reactions (angioedema, chest tightness, dyspnoea, flushing, other systemic anaphylactic reactions):** During management of severe allergic reactions, monitor cardiac function, blood pressure, respiration, and oxygen saturation closely. If airway oedema or bronchospasm causes severe dyspnoea, consider intubation or tracheostomy; emergency cricothyroidotomy may be performed if necessary. For grade II or above severe allergic reactions, intramuscular adrenaline is the first-line treatment: 0.01 mg/kg (maximum single dose 0.5 mg) of 1 mg/ml (1:1000) solution; may repeat after 5-15 minutes if insufficient response. For grade IV patients with cardiac/respiratory arrest or impending arrest, administer intravenous adrenaline 0.5-1 mg (0.1 mg/ml, 1:10000). For grade III patients with IV access and monitoring, intravenous adrenaline 0.1-0.2 mg (0.1 mg/ml, 1:10000) may be given; repeat after 3-5 minutes if needed. H1-antihistamines, β_2-agonists, and corticosteroids may be used as second-line agents. Fluid resuscitation (20 ml/kg, adjusted as needed) may be used for patients with circulatory instability. After emergency treatment, patients should be

monitored for at least 12 hours, including heart rate, rhythm, blood pressure, respiration, oxygen saturation, and urine output.

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