COVER PAGE

Official Title:

Artificial Intelligence-Enhanced Multimodal Cardiovascular Phenotyping for Cardiac Remodeling and Risk Stratification in Ischemic and Nonischemic Acute and Chronic Heart Failure: A Prospective, Multicenter, Observational Cohort Study

NCT Number: Not available

Document Date:

October 10, 2026

Organization's Unique Protocol ID:

SWYX: NO.2025-524

Brief Title:

Multimodal Assessment of Remodeling and Stratification in Heart Failure

Acronym:

MARS-HF

Study Type:
Observational

Observational Study Model:
Cohort

Time Perspective:
Prospective

Biospecimen Retention:
None Retained

Enrollment:
Anticipated: 2000

Number of Groups/Cohorts:
2

Groups/Cohorts:

1. Patient group: Participants enrolled who meet the diagnostic criteria according to clinical guidelines and the inclusion and exclusion criteria.
2. Healthy volunteers: Healthy volunteer group matched with the patient group for age and sex.

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1. ADMINISTRATIVE INFORMATION

1.1 Study Title

Artificial Intelligence-Enhanced Multimodal Cardiovascular Phenotyping for Cardiac Remodeling and Risk Stratification in Ischemic and Nonischemic Acute and Chronic Heart Failure: A Prospective, Multicenter, Observational Cohort Study

1.2 Brief Title

Multimodal Assessment of Remodeling and Stratification in Heart Failure

1.3 Acronym

MARS-HF

1.4 Organization's Unique Protocol ID

SWYX:NO.2025-524

1.5 Registration

NCT Number: [To be assigned by ClinicalTrials.gov; insert assigned NCT number before upload]

1.6 Document Date

October 10, 2026

1.7 Study Sites

This prospective, multicenter, observational cohort study will be conducted at the following clinical sites:

- Jinan Central Hospital, Jinan, Shandong, China — Recruiting
- Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China — Recruiting
- The First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China — Recruiting

Site contact information is maintained in the ClinicalTrials.gov record. No research participant names are included in this protocol document.

1.8 Study Type

Observational

1.9 Observational Study Model

Cohort

1.10 Time Perspective

Prospective

1.11 Biospecimen Retention

None Retained. Blood samples will be collected for clinically indicated laboratory testing. Residual biospecimens will not be retained for future research.

1.12 Anticipated Enrollment

2000 participants.

1.13 Number of Groups/Cohorts

2 groups:

1. Patient group

2. Healthy volunteer group

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2. MEDICAL SUBJECT HEADINGS (MeSH) TERMS

2.1 MeSH Headings for Conditions and Interventions Studied

- Heart Failure
- Cardiomyopathy, Dilated
- Cardiomyopathy, Hypertrophic
- Myocarditis
- Coronary Artery Disease
- Ventricular Remodeling
- Cardiac Remodeling
- Magnetic Resonance Imaging, Cardiac
- Myocardial Perfusion Imaging
- Stress Perfusion
- Myocardial Microvascular Dysfunction
- Myocardial Fibrosis
- Artificial Intelligence
- Risk Stratification
- Prognosis
- Hospitalization
- Death, Sudden, Cardiac
- Heart Transplantation
- Left Ventricular Assist Device

2.2 MeSH Check Tags

- Humans
- Adult
- Middle Aged

- Aged
- Male
- Female
- Prospective Studies
- Cohort Studies
- Multicenter Studies
- Observational Studies

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3. BASIC STUDY INFORMATION

Item	Content
Study Title	Artificial Intelligence-Enhanced Multimodal Cardiovascular Phenotyping for Cardiac Rem and Risk Stratification in Ischemic and Nonischemic Acute and Chronic Heart Failure: A P Multicenter, Observational Cohort Study
Brief Title	Multimodal Assessment of Remodeling and Stratification in Heart Failure
Acronym	MARS-HF
Study Type	Observational
Study Design	Prospective, multicenter, observational cohort study with two groups: a patient group ar and sex-matched healthy volunteer group. Participants receive usual medical care. No e drug, device, or treatment will be administered.
Sample Size	Anticipated enrollment of 2000 participants across participating centers.
Study Duration	Approximately 60 months, including preparation, recruitment, baseline assessment, follo analysis, and report writing.
Follow-up	Follow-up at 3, 6, 12, 24, 36, and 48 months after baseline cardiac magnetic resonance (

Item	Content
Period	examination. Additional clinically indicated follow-up may be performed if needed.
Primary Endpoint	Heart failure-related composite endpoint: heart failure-related death, unplanned heart f hospitalization, or cardiac transplantation.
Secondary Endpoint	Sudden cardiac death (SCD)-related endpoint: SCD, appropriate implantable cardioverte defibrillator (ICD) shock, or resuscitated cardiac arrest.
Primary Analysis	Evaluation of associations between integrated multimodal cardiovascular phenotypes an primary heart failure-related composite endpoint.
Secondary Analysis	Evaluation of associations between multimodal markers and the SCD-related composite
Exploratory Analyses	Characterization of cardiac remodeling across ischemic, nonischemic, acute, and chronic failure; comparison of incremental value of advanced imaging and clinical parameters; ex of artificial intelligence and advanced statistical methods as supporting analytical approa

4. RESEARCH BACKGROUND AND SIGNIFICANCE

Heart failure is a heterogeneous clinical syndrome in which the heart cannot pump blood effectively. Patients with heart failure differ widely in cause, presentation, cardiac structure and function, and prognosis. Ischemic and nonischemic heart failure, as well as acute and chronic heart failure, may have different patterns of cardiac remodeling and different risks of adverse events.

Cardiac remodeling refers to changes in cardiac structure, function, tissue characteristics, and blood flow that occur in response to injury, hemodynamic stress, inflammation, fibrosis, microvascular dysfunction, and other pathological processes. Standard clinical assessment, laboratory tests, and single imaging methods provide important but incomplete information. Combining multiple sources of data may provide a more complete picture of the disease and may improve risk stratification.

Cardiac magnetic resonance (CMR) can assess myocardial structure, function, fibrosis, edema, perfusion, strain, extracellular volume, and flow. Stress perfusion CMR can

evaluate myocardial perfusion reserve and microvascular function. Computed tomography (CT), including high-resolution coronary CT or photon-counting CT when available, can provide complementary information on coronary anatomy and plaque. Echocardiography, electrocardiography, and blood biomarkers provide additional clinical and pathophysiological information.

Advanced statistical methods and artificial intelligence may help integrate multimodal data. However, artificial intelligence is not the main focus of this study. The study aims to integrate all data sources in a balanced way to better understand cardiac remodeling and to improve risk stratification in heart failure.

No new drug or device will be tested. Treatment decisions will remain at the discretion of the treating physicians. The results may help doctors improve how they evaluate and monitor patients with heart failure.

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5. STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the association between integrated multimodal cardiovascular phenotyping and the primary heart failure-related composite endpoint, including heart failure-related death, unplanned heart failure hospitalization, or cardiac transplantation, in adults with ischemic or nonischemic acute or chronic heart failure.

5.2 Secondary Objective

To evaluate the association between integrated multimodal cardiovascular phenotyping and the secondary SCD-related composite endpoint, including SCD, appropriate ICD shock, and resuscitated cardiac arrest.

5.3 Exploratory Objectives

1. To characterize cardiac remodeling across ischemic, nonischemic, acute, and chronic heart failure using integrated multimodal data.
2. To evaluate the associations between multimodal markers and clinical outcomes.
3. To develop and validate risk stratification models that combine information from different modalities in a balanced way.
4. To compare the incremental value of advanced imaging and clinical parameters beyond conventional assessment.

5. To explore artificial intelligence and other advanced analytical methods as part of the analysis, although artificial intelligence is not the main focus of the study.
6. To establish standardized multimodal assessment methods for clinical research in heart failure.

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6. STUDY DESIGN AND METHODS

6.1 Study Design

This is a prospective, multicenter, observational cohort study. It will enroll adults with acute or chronic heart failure, including both ischemic and nonischemic causes, as well as a healthy volunteer group matched for age and sex. Participants will receive their usual medical care. No experimental drug, device, or treatment will be administered. Treatment decisions will remain at the discretion of the treating physicians.

The study will collect clinical, electrocardiographic, laboratory, and multimodal imaging data using a standardized protocol. Multimodal assessments may include CMR, echocardiography, electrocardiography, blood tests, and CT, including high-resolution coronary CT or photon-counting CT when available.

6.2 Study Setting

The study will be conducted at participating tertiary hospitals. All participating centers will use standardized protocols for data collection, image acquisition, image analysis, endpoint adjudication, and quality control.

6.3 Study Population

6.3.1 Patient Group

Participants in the patient group must meet the diagnostic criteria according to current clinical guidelines and the inclusion and exclusion criteria. The patient group may include participants with:

- Ischemic heart failure
- Nonischemic heart failure
- Acute heart failure
- Chronic heart failure
- Dilated cardiomyopathy (DCM)
- Hypertrophic cardiomyopathy (HCM)

- Myocarditis
- Heart failure with reduced ejection fraction (HFrEF)
- Heart failure with mildly reduced ejection fraction (HFmrEF)
- Heart failure with preserved ejection fraction (HFpEF)

6.3.2 Healthy Volunteer Group

Healthy volunteers will be matched with the patient group for age and sex. Healthy volunteers must have no known history of heart failure, cardiomyopathy, coronary artery disease, myocarditis, significant valvular disease, or other clinically significant cardiovascular disease. They must be able to provide informed consent and complete scheduled assessments.

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7. PARTICIPANT ELIGIBILITY CRITERIA

7.1 General Inclusion Criteria

1. Male or female adults aged ⩾18 years.
2. Ability to understand and provide written informed consent.
3. Ability to complete scheduled follow-up assessments.
4. For the patient group, a clinical diagnosis consistent with acute or chronic heart failure, ischemic or nonischemic heart failure, DCM, HCM, myocarditis, or another eligible heart failure phenotype according to current clinical guidelines.
5. For the healthy volunteer group, no known clinically significant cardiovascular disease and age- and sex-matched to the patient group.

7.2 Disease-Specific Inclusion Criteria

7.2.1 Dilated Cardiomyopathy

Diagnosed DCM according to World Health Organization / International Society and Federation of Cardiology (WHO/ISFC) criteria, characterized by elevated body surface area-indexed left ventricular end-diastolic volume and left ventricular ejection fraction below published age- and sex-specific reference values.

7.2.2 Hypertrophic Cardiomyopathy

Diagnosis of HCM independently made by clinicians according to current guidelines, based on imaging examinations including CMR, electrocardiography, family history, and

genetic testing if available. Inclusion criterion: left ventricular wall thickness ⩾13 mm in ⩾1 myocardial segment on CMR.

7.2.3 Chronic Heart Failure

1. Age ⩾18 years.
2. Established clinical diagnosis of chronic heart failure for at least 3 months based on current guideline criteria.
3. NYHA class I–IV.
4. LVEF assessed within 12 months by echocardiography, CMR, or other validated imaging, meeting HFrEF, HFmrEF, or HFpEF criteria.
5. For HFpEF, at least one supportive finding documented within 12 months, such as elevated NT-proBNP or BNP, structural heart disease, diastolic dysfunction, or prior heart failure hospitalization.
6. Stable clinical condition with no change in NYHA class or heart failure-specific therapy within 7 days before enrollment.
7. Receiving guideline-directed medical therapy at a stable dose for at least 4 weeks unless contraindicated or not tolerated.
8. Ability to provide written informed consent.

7.2.4 Acute Decompensated Heart Failure

1. Male or female adults aged ⩾18 years.
2. Current hospitalization or unscheduled clinic/emergency department visit for a primary diagnosis of acute decompensated heart failure, de novo or decompensation of chronic heart failure, regardless of LVEF category.
3. At least one clinical sign of volume overload, such as peripheral edema, pulmonary congestion or pleural effusion, ascites, or elevated jugular venous pressure.
4. Elevated natriuretic peptides, such as NT-proBNP >1000 pg/mL or BNP >250 pg/mL.
5. Receiving or anticipated to receive intravenous diuretic therapy during the index hospitalization or acute care episode.
6. For HFpEF, diagnosis supported by structural heart disease and/or diastolic dysfunction plus elevated natriuretic peptides.

7. Ability to provide written informed consent or consent from a legally authorized representative if temporarily unable.

7.2.5 Myocarditis

1. Male or female adults aged ⩾18 years.
2. Diagnosis of myocarditis confirmed by at least one of the following:
    - Cardiac magnetic resonance fulfilling the modified Lake Louise Criteria.
    - Endomyocardial biopsy demonstrating histologic, immunologic, and immunohistochemical evidence of myocardial inflammation.
    - In patients with high clinical pretest probability, a combination of at least one clinical presentation, at least one diagnostic finding, and CMR findings consistent with myocardial inflammation.
3. Time from symptom onset classified as acute, subacute, or chronic.
4. For chronic myocarditis, persistent or recurrent symptoms or imaging evidence of ongoing myocardial inflammation for >3 months from initial onset.
5. Receiving standard clinical care, including guideline-directed medical therapy for heart failure when applicable.
6. Ability to provide written informed consent prior to any study-related assessment, or consent from a legally authorized representative if temporarily unable.

7.2.6 Coronary Artery Disease and Ischemic Heart Failure

1. Age ⩾18 years.
2. CAD diagnosed according to current guidelines, including at least 70% stenosis in one or more coronary arteries or >50% stenosis of the left main stem by percutaneous coronary intervention or computed tomography angiography; history of severe angina or myocardial infarction; or previous revascularization history, including coronary artery bypass grafting.
3. Participants with stable ischemic heart failure may be included. Participants with acute myocardial infarction at screening should generally be excluded unless the treating physician confirms clinical stability and the participant meets all other eligibility criteria.

7.3 General Exclusion Criteria

1. Age <18 years.
2. Pregnant or breastfeeding women.
3. Women of childbearing potential unwilling to use effective contraception during the study.
4. Life expectancy <12 months due to non-cardiac disease.
5. Concurrent acute coronary syndrome at screening, defined as typical chest pain with troponin above the 99th percentile and electrocardiographic changes suggestive of ischemia.
6. History of cardiac transplantation or current ventricular assist device.
7. Prior solid organ transplantation.
8. Systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg at screening.
9. Estimated glomerular filtration rate <30 mL/min/1.73 m².
10. Renal replacement therapy or ultrafiltration before enrollment.
11. Severe hepatic impairment, Child-Pugh class C.
12. Known or suspected non-cardiac cirrhosis.
13. Active malignancy or current treatment for malignancy that may affect participation or outcomes.
14. Any condition that may interfere with compliance or compromise data quality.
15. Participation in another clinical trial that may affect the results of this study.

7.4 CMR-Specific Exclusion Criteria

1. Any absolute contraindication to MRI, including non–MR-conditional pacemaker or implantable cardioverter-defibrillator, intracranial aneurysm clips, metallic intraocular foreign body, cochlear/otological/ear implant, neurostimulator, or non–MR-conditional monitoring/support devices.
2. Severe claustrophobia not manageable with preparation or mild sedation.
3. Contraindication to gadolinium-based contrast agents, including previous anaphylactic reaction, eGFR <30 mL/min/1.73 m², known nephrogenic systemic fibrosis, or pregnancy.
4. Inability to lie flat or hold breath sufficiently for image acquisition.

5. Clinically unstable condition precluding safe MRI.

7.5 Stress Perfusion-Specific Exclusion Criteria

1. Previous anaphylactic reaction to adenosine, regadenoson, or dobutamine.
2. Severe obstructive airways disease or mild-to-moderate disease with contraindication to adenosine/regadenoson.
3. High-degree atrioventricular block or symptomatic bradycardia (<40 beats per minute) without functioning pacemaker.
4. Symptomatic severe or critical aortic stenosis.
5. Known left ventricular thrombus.
6. Uncontrolled arterial hypertension or uncontrolled atrial fibrillation during imaging.
7. Acute coronary or aortic syndrome within 7 days before imaging.
8. Concomitant theophylline, dipyridamole, or caffeine within 6–12 hours before stress perfusion imaging.

7.6 Disease-Specific Exclusion Criteria

7.6.1 DCM

Severe coronary artery disease defined as >50% stenosis of a major coronary artery, infiltrative cardiomyopathy, arrhythmogenic cardiomyopathy, or other conditions that may confound the diagnosis of DCM.

7.6.2 HCM

Apical hypertrophic myocardial infarction, any contraindications to CMR, adenosine or gadolinium-based contrast agents, systemic hypertension, severe valvular disease, infiltrative cardiomyopathy, prior myocardial infarction, or coronary intervention.

7.6.3 Myocarditis

Any condition that would make CMR or stress perfusion unsafe, or any alternative diagnosis that fully explains the clinical presentation.

7.7 Withdrawal Criteria After Enrollment

1. Found not to meet inclusion criteria or to meet any exclusion criteria after enrollment.
2. Lost to follow-up for more than 3 months or failure to complete scheduled

follow-up without reasonable cause.

3. Voluntary request to withdraw from the study.
4. Occurrence of severe adverse events that make it impossible to continue participation.
5. Violation of the study protocol.

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8. STUDY PROCESS

8.1 Recruitment and Enrollment

Participants will be recruited through outpatient clinics, inpatient wards, and referrals from participating cardiology departments. Researchers will explain the purpose, process, potential risks, and benefits of the study. Written informed consent will be obtained before any study-related assessment.

After informed consent, participants will undergo baseline assessment, including clinical data collection, laboratory tests, electrocardiogram, echocardiography, and CMR when eligible and safe. Inclusion and exclusion criteria will be reviewed again before final enrollment.

8.2 Baseline Assessment

Baseline assessment will include:

1. Clinical data collection: age, sex, height, weight, body mass index, smoking history, alcohol history, family history of cardiovascular disease, medical history, medication history, and heart failure history.
2. Laboratory examinations: NT-proBNP or BNP, troponin I/T, creatinine, liver function, electrolytes, fasting blood glucose, and other clinically relevant biomarkers.
3. Electrocardiogram: resting 12-lead electrocardiogram.
4. Echocardiography: chamber size, systolic and diastolic function, strain, and valve assessment when available.
5. CMR: routine CMR sequences and stress perfusion CMR when safe and feasible.
6. CT: coronary CT angiography and, when available, photon-counting CT for high-resolution coronary imaging.
7. Clinical outcomes and symptom assessment.

8.3 CMR Examination

All eligible participants will undergo CMR using standardized protocols. CMR may include:

- Cine imaging for ventricular volumes, mass, and ejection fraction
- T1 mapping
- T2 mapping
- Late gadolinium enhancement
- Extracellular volume
- Strain imaging
- Cardiac diffusion tensor imaging
- Four-dimensional flow
- Stress perfusion imaging

For stress perfusion CMR, adenosine or another protocol-approved stress agent may be used according to local standards and safety criteria. Rest and stress myocardial blood flow will be measured, and myocardial perfusion reserve will be calculated as the ratio of stress myocardial blood flow to rest myocardial blood flow.

8.4 CT Examination

CT may include CT angiography and, when available, photon-counting CT for high-resolution coronary imaging. CT will be performed according to clinical indications and local protocols.

8.5 Echocardiography

Echocardiography may include chamber size, systolic and diastolic function, strain, and valve assessment. Echocardiographic data will be collected when clinically available.

8.6 Laboratory Tests

Laboratory tests may include natriuretic peptides, troponin, renal function, electrolytes, liver function, glucose, and other clinically relevant markers. No biospecimens will be retained for future unspecified research.

8.7 Artificial Intelligence-Assisted Analysis

Artificial intelligence and machine learning may be explored as supporting analytical methods. AI may be used for auxiliary image feature extraction, image segmentation,

and efficiency improvement in CMR analysis. AI is not the main focus of the study. The study aims to integrate all data sources in a balanced way.

8.8 Follow-up

Participants will be followed at 3, 6, 12, 24, 36, and 48 months after baseline CMR examination. Follow-up may include outpatient visits, telephone contact, medical record review, and registry review where available.

Data collected during follow-up may include:

- Occurrence of primary and secondary endpoint events
- Changes in symptoms and functional status
- Medication adjustments
- Rehospitalization
- Laboratory tests
- Electrocardiogram
- Echocardiography
- CMR re-examination if clinically indicated and feasible

8.9 Endpoint Ascertainment

An endpoint event judgment committee composed of senior cardiologists will review and confirm the occurrence of primary and secondary endpoint events. The committee will make judgments based on medical records, examination results, and follow-up records.

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9. OUTCOME MEASURES

9.1 Primary Outcome Measure

Heart failure-related composite endpoint

The prespecified primary endpoint is a composite of heart failure events, including heart failure-related death, unplanned heart failure hospitalization, or cardiac transplantation. Death is attributed to heart failure if progressive worsening of heart failure symptoms and signs occurred before death. Heart failure hospitalization is defined as admission due to new or worsening heart failure symptoms and signs requiring intensified heart failure-specific therapy.

Time Frame: At 3, 6, 12, 24, 36, and 48 months after CMR examination.

9.2 Secondary Outcome Measure

Sudden cardiac death-related endpoint

The prespecified secondary endpoint is a composite of SCD-related events, including SCD, appropriate ICD shock, and resuscitated cardiac arrest.

Time Frame: At 3, 6, 12, 24, 36, and 48 months after CMR examination.

9.3 Exploratory Outcome Measures

1. Cardiac remodeling patterns across ischemic, nonischemic, acute, and chronic heart failure.
2. Associations between multimodal markers and clinical outcomes.
3. Incremental value of advanced imaging and clinical parameters beyond conventional assessment.
4. Performance of integrated risk stratification models.
5. Exploratory AI and machine learning analyses.

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10. STATISTICAL ANALYSIS

Statistical analysis will be performed using SPSS and R or equivalent software. Measurement data will be expressed as mean ± standard deviation if normally distributed or median with interquartile range if abnormally distributed. Comparisons between groups will be performed using t-tests, non-parametric tests, chi-square tests, or Fisher's exact tests as appropriate.

The Kaplan-Meier method will be used to estimate survival curves for endpoint events. The log-rank test will be used to compare event rates between groups. Multivariate Cox proportional hazards regression models will be used to identify independent risk factors for the primary and secondary endpoints. Receiver operating characteristic curves and AUC values may be used to evaluate predictive efficacy.

Subgroup analyses may be performed for ischemic versus nonischemic heart failure, acute versus chronic heart failure, LVEF categories, age, sex, and other clinically relevant variables. Missing data will be handled using appropriate methods, such as multiple imputation, where applicable. A two-sided P value <0.05 will be considered statistically significant unless otherwise specified.

Artificial intelligence and machine learning will be explored as one of several analytical approaches, alongside conventional statistical methods. Models will be internally validated, and external validation will be performed if feasible.

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11. QUALITY CONTROL

1. Personnel training: All investigators, radiologists, data managers, and study coordinators will receive standardized training on the protocol, standard operating procedures, data collection, endpoint adjudication, CMR acquisition, and ethical requirements.
2. CMR quality control: Participating centers will use standardized CMR protocols. A quality control team will regularly review image quality. Unqualified images may be repeated if necessary.
3. Data quality control: Data will be double-entered and verified. Regular checks will be performed for completeness, accuracy, and consistency. A random sample of case report forms may be reviewed by the study leader.
4. Ethical supervision: The ethics committee at each participating center will supervise the study conduct.

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12. ETHICAL CONSIDERATIONS

1. Informed consent: All participants will provide written informed consent before any study-related assessment. Participants have the right to ask questions and withdraw at any time without affecting their medical care.
2. Confidentiality: Personal information will be encrypted and stored securely. Study data will be used for scientific research purposes only. Participant identity will be anonymized during analysis.
3. Risk management: If adverse events related to the study occur, timely medical measures will be taken. All adverse events will be recorded and reported according to local requirements.
4. Voluntary withdrawal: Participants may withdraw at any time. Data already collected may be retained and included in the final analysis unless the participant requests deletion, subject to local regulations.
5. Ethical approval: Institutional review board or ethics committee approval will be

obtained before study initiation.

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13. ADVERSE EVENT MANAGEMENT

13.1 Definition of Adverse Events

Any untoward medical occurrence in a participant during the study period, regardless of whether it is related to the study, including but not limited to adverse reactions to CMR examination, contrast agents, stress perfusion agents, or other study procedures.

13.2 Reporting of Adverse Events

Researchers will record the occurrence time, type, severity, handling measures, and outcome of adverse events. Mild and moderate adverse events will be reported to the study leader and ethics committee according to local requirements. Severe adverse events will be reported immediately.

13.3 Handling of Adverse Events

For adverse events related to the study, researchers will take timely and effective medical measures. If an adverse event is severe and cannot be controlled, the participant may be withdrawn from the study, and follow-up medical treatment will be arranged. For adverse reactions related to adenosine infusion during stress perfusion, infusion will be stopped immediately, and symptomatic treatment will be given as clinically indicated.

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14. STUDY TERMINATION

1. Voluntary termination: The study leader may terminate the study if objectives are achieved early, or if serious safety, ethical, or other unexpected issues occur.
2. Termination by the ethics committee: The ethics committee may terminate the study if it finds that the study does not comply with ethical principles or if risks exceed benefits.
3. Termination due to other reasons: The study may be terminated due to insufficient funding, difficulty in recruitment, or changes in national policies and regulations.
4. Disposal after termination: Data collected will be sorted and analyzed. A study termination report will be submitted to the ethics committee and relevant departments. Follow-up of participants will continue if necessary to ensure

safety and rights.

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15. STUDY SCHEDULE

Stage	Time Arrangement	Key Tasks
Preparation	Months 1–3	Finalize protocol, train personnel, standardize CMR protocols data management system, obtain ethical approvals.
Recruitment and Baseline Assessment	Months 4–15	Recruit participants, obtain informed consent, conduct baseli assessment, perform CMR and other multimodal assessment eligibility, complete data entry and verification.
Follow-up	Months 16–60	Conduct follow-up at 3, 6, 12, 24, 36, and 48 months after ba Record endpoint events and adverse events. Perform clinicall repeat assessments.
Data Analysis and Report Writing	Months 55–60	Conduct statistical analysis, summarize results, write study re report to ethics committee and relevant departments.

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16. STUDY TEAM AND RESPONSIBILITIES

1. Principal Investigator: Responsible for overall design, implementation, and supervision of the study.
2. Co-Investigators: Responsible for participant recruitment, baseline assessment, follow-up, and data collection at each research center.
3. Sub-Investigators: Assist with study work, including data entry, sample collection, and follow-up visits.
4. Radiologists: Responsible for CMR image acquisition, image quality control, image analysis, and review of LGE and perfusion images.
5. Data Managers: Responsible for data entry, verification, storage, and management.

6. Statisticians: Responsible for statistical analysis plan design and statistical analysis.
7. Study Coordinators: Responsible for daily management and communication.
8. Ethics Committee: Responsible for reviewing the protocol and informed consent form and supervising ethical conduct.
9. Endpoint Event Judgment Committee: Responsible for reviewing and confirming primary and secondary endpoint events.

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17. INVESTIGATOR OFFICIAL TITLES

Role	Investigator Official Title
Principal Investigator	Principal Investigator, Department of Cardiology, participating hospital; Chief Phys Professor
Co-Investigator	Co-Investigator, Department of Cardiology, participating hospital; Associate Chief
Radiologist	Radiologist, Department of Radiology, participating hospital
Statistician	Statistician, participating institution
Data Manager	Data Manager, participating institution

No research participant names are included in this document.

APPENDIX S1: DIAGNOSTIC CRITERIA FOR ENDPOINTS

1. Heart Failure-Related Composite Endpoint

The primary endpoint is a composite of:

1. Heart failure-related death
2. Unplanned heart failure hospitalization
3. Cardiac transplantation

Heart failure-related death refers to death associated with clinically worsening heart failure symptoms and signs without evidence of other causes.

Unplanned heart failure hospitalization refers to admission due to new or worsening heart failure symptoms and signs requiring intensified heart failure-specific therapy.

Cardiac transplantation refers to transplantation performed for end-stage heart failure.

2. Sudden Cardiac Death-Related Composite Endpoint

The secondary endpoint is a composite of:

1. Sudden cardiac death
2. Appropriate ICD shock
3. Resuscitated cardiac arrest

Sudden cardiac death is defined as death due to cardiac causes occurring within 1 hour of symptom onset with sudden loss of consciousness. For unwitnessed deaths with clear evidence of cardiac etiology, the event may be classified as probable SCD.

Appropriate ICD shock refers to shocks delivered by an ICD in response to hemodynamically unstable ventricular tachycardia or ventricular fibrillation without reversible causes.

Resuscitated cardiac arrest refers to a cardiac arrest event reversed by cardiopulmonary resuscitation, defibrillation, cardioversion, or cardiac pacing, with restoration of spontaneous circulation.

END OF STUDY PROTOCOL