Clinical Relevance of **C**oronary **M**icrovascular **D**ysfunction Assessments in **M**yocardial **I**nfarction with **N**on-**O**bstructive **C**oronary **A**rteries **(CMD-MINOCA)**

Chonnam National University Hospital,
Chonnam National University Medical School

Principal Investigator: Young Joon Hong

Research Manager: Seung Hun Lee

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Research Summary	
Study Title	Clinical Relevance of Coronary Microvascular Dysfunction Assessments in Myocardial Infarction with Non-Obstructive Coronary Arteries (CMD-MINOCA)
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Countries Involved	**Republic of Korea**

Purpose / Objectives:

To compare clinical outcomes of myocardial infarction with non-obstructive coronary arteries (MINOCA) according to the coronary microvascular dysfunction (CMD), evaluated by optical coherence tomography (OCT), invasive and non-invasive coronary physiologic assessment.

Study Design:

1. Trial Design
A prospective observational study

2. Target Population
Patients with MINOCA

3. Enrollment criteria
(1) Inclusion criteria

① Subject with age ≥19 years and acute myocardial infarction
- Rise and/or fall of cardiac troponin with one level >99 percentile plus ischemic signs/symptoms

② Subject with non-obstructive coronary arteries
- <50% diameter stenosis or
- fractional flow reserve (FFR) >0.80

③ Subject without previous history of coronary artery disease

④ Subject who performed invasive coronary angiography within 24 hours after presentation

⑤ Subject who eligible for invasive and non-invasive coronary physiologic assessment

(2) Exclusion criteria

① Subject with obstructive coronary arteries

② Subject with alternate diagnosis including sepsis, pulmonary embolism, myocarditis, Takotsubo syndrome, spontaneous coronary dissection, and other cardiomyopathies.

③ Subject with cardiogenic shock or cardiac arrest

④ Subject who has non-cardiac co-morbid conditions with life expectancy <2 years

⑤ Subject or lactating women

⑥ Subject unable to provide consent

4. Outcome Measures

(1) Primary end point:

Major adverse cardiovascular and cerebrovascular events (a composite of cardiac death, any MI, any revascularization, stroke, readmission due to heart failure) at 2 years

(2) Secondary end points:

① Cardiac death at 2 years

② All-cause death at 2 years

③ Any MI at 2 years

④ Any revascularization at 2 years

⑤ Stroke (ischemic or hemorrhagic) at 2 years

⑥ Readmission due to heart failure at 2 years

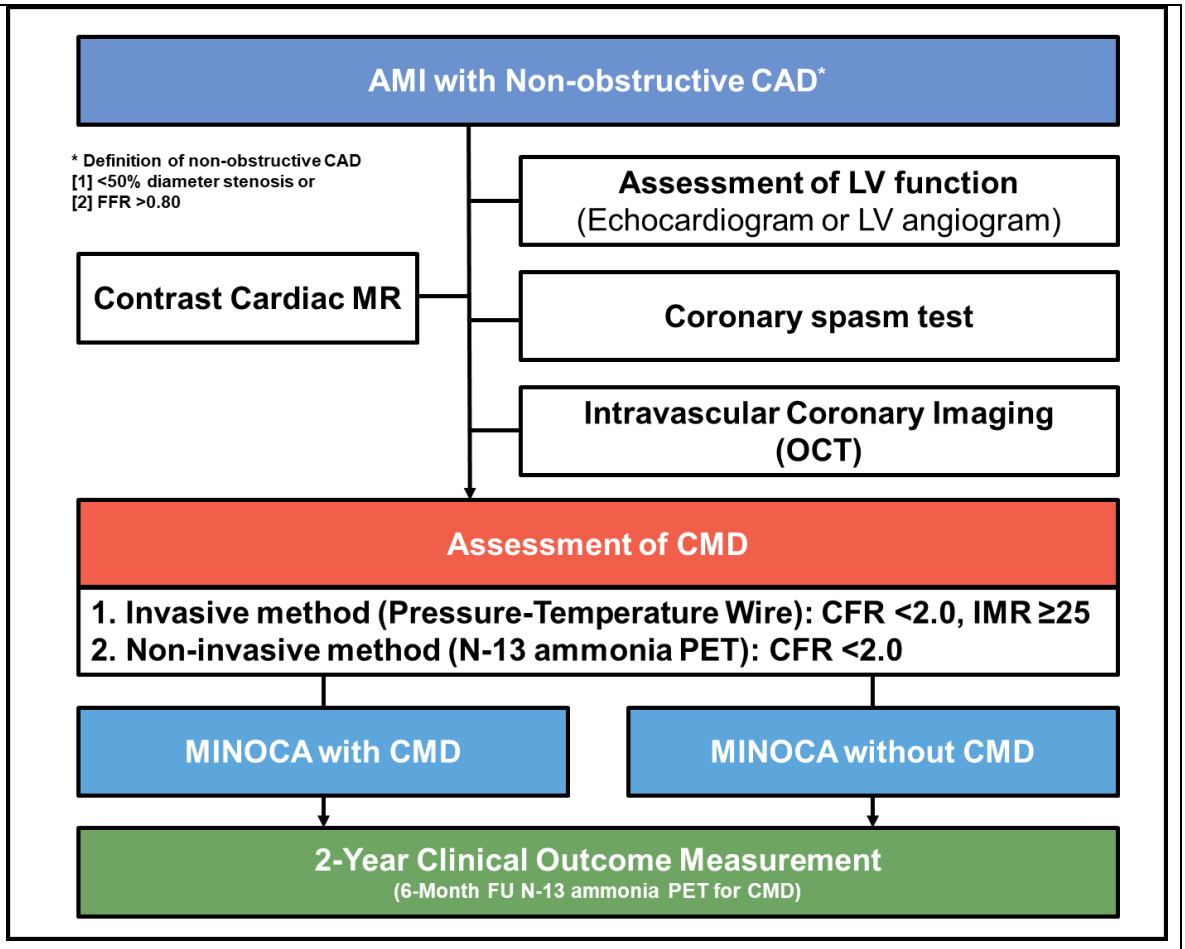
⑦ All-cause death, any MI, or any revascularization at 2 years

⑧ Left ventricular ejection fraction at 2 years

⑨ Coronary flow reserve at 6 months

5. Study Procedure

(1) Flow chart



About **150 patients** with suspected myocardial infarction underwent invasive coronary angiography, but without obstructive coronary arteries will be enrolled. These patients will be evaluated by OCT, coronary functional assessment including coronary spasm test, invasive (FFR, CFR, IMR) and non-invasive coronary physiologic assessment (N-13 ammonia positron emission tomography). Left ventricular function will be assessed using echocardiography or left ventriculogram. Cardiac magnetic resonance imaging is recommended to exclude other causes for elevating cardiac enzymes, if necessary. Patients will be managed with cardioprotective therapies and cause-targeted therapies according to the latest recommendation. MINOCA patients with CMD will be followed-up their microcirculatory function using non-invasive method.

6. Study Duration and Dates
IRB approval date ~ 2027.12.31

7. Follow-up
After the enrollment, clinical follow-up will be done at 1, 6, 12, and 24 months.

Research Grant:

The Korean Cardiac Research Foundation (Seoul, Korea)

Abbott Medical Korea (Seoul, Korea)

1. Title of Study

Clinical Relevance of Coronary Microvascular Dysfunction Assessments in Myocardial Infarction with Non-Obstructive Coronary Arteries (CMD-MINOCA)

2. Clinical Research Center

Chonnam National University Hospital, Chonnam National University Medical School

3. Principal Investigator, Staff, Co-researchers

	Name	Center	Position
Principal investigator	Young Joon Hong	Chonnam National University Hospital, Chonnam National University Medical School	Professor
Research Manager	Seung Hun Lee	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor
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	Hee-Seung Bom	Chonnam National University Hospital, Chonnam National University Medical School	Professor
	Ho-Chun Song	Chonnam National University Hospital, Chonnam National University Medical School	Professor
	Sang-Geon Cho	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor
	Yun-Hyeon Kim	Chonnam National University Hospital, Chonnam National University Medical School	Professor

	Jong Eun Lee	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor

4. Research Grant

The Korean Cardiac Research Foundation (Seoul, Korea)

Abbott Medical Korea (Seoul, Korea)

5. Background

Approximately 5~10% of patients with acute myocardial infarction (AMI) have been reported as myocardial infarction with non-obstructive coronary arteries (MINOCA) in the contemporary clinical setting.(1,2) Although those with MINOCA have a better prognosis than with obstructive coronary artery disease,(2,3) several observational studies continuously reported that patients with MINOCA showed comparable outcomes.(4,5) One plausible explanation of this discrepancy is the heterogeneous and variable definition of MINOCA. Possible causes of MINOCA include plaque erosion and/or rupture, vasospasm, and CMD. Therefore, it is natural that heterogeneous pathophysiology of MINOCA causes diagnostic challenges and proper management.(2,3)

Recently, there have been efforts for establishing the diagnosis of MINOCA and standardizing the systematic management according to the cause of MINOCA. According to the AHA scientific statement, patients who suspected MINOCA have been recommended to perform multimodality approach, including intravascular imaging (i.e., OCT). Although non-invasive methods, such as N-13 ammonia positron emission tomography (PET), can be used for evaluating the CMD, invasive coronary physiologic assessment using pressure-temperature wire has been recommended. CMD has been known as a major sub cause of MINOCA, and it may be required specific treatment.

Nevertheless, there has no data on the outcomes of MINOCA with or without CMD. Therefore, the aim of CMD-MINOCA sought to assess the MINOCA patients regarding the latest clinical pathway for diagnosis of CMD and evaluate their clinical outcomes at 2 years.

6. Study Plans

6.1. Study Design

A prospective observational study.

6.2. Study Timeline

Overall study will require 5.5~6 years to complete, including 3-year of recruitment and 2-year of follow-up followed by close out and reporting of final results.

IRB approval date ~ 2027.12.31
Subject enrollment: 2022.02.01 ~ 2024.12.31 (roughly 3 years of enrollment)
End of follow-up period: 2026.12.31 (2 years after the end of recruitment)
Analysis and report: ~2027.12.31

6.3. Study Population

About **150 patients** with suspected myocardial infarction underwent invasive coronary angiography, but without obstructive coronary arteries will be enrolled. These patients will be evaluated by OCT, coronary functional assessment including coronary spasm test, invasive (FFR, CFR, IMR) and non-invasive coronary physiologic assessment (N-13 ammonia positron emission tomography). Left ventricular function will be assessed using echocardiography or left ventriculogram. Cardiac magnetic resonance (CMR) imaging is recommended to exclude other causes for elevating cardiac enzymes, if necessary. Patients will be managed with cardioprotective therapies and cause-targeted therapies according to the latest recommendation. MINOCA patients with CMD will be followed-up their microcirculatory function using non-invasive method.

6.4. Eligibility Criteria

6.4.1. Inclusion Criteria

① Subject with age ≥19 years and acute myocardial infarction

- Rise and/or fall of cardiac troponin with one level >99 percentile plus ischemic signs/symptoms

② Subject with non-obstructive coronary arteries

- <50% diameter stenosis or
- fractional flow reserve (FFR) >0.80

③ Subject without previous history of coronary artery disease

④ Subject who performed invasive coronary angiography within 24 hours after presentation

⑤ Subject who eligible for invasive and non-invasive coronary physiologic assessment

6.4.2. Exclusion Criteria

① Subject with obstructive coronary arteries
② Subject with alternate diagnosis including sepsis, pulmonary embolism, myocarditis, Takotsubo syndrome, spontaneous coronary dissection, and other cardiomyopathies.
③ Subject with cardiogenic shock or cardiac arrest
④ Subject who has non-cardiac co-morbid conditions with life expectancy <2 years
⑤ Subject or lactating women
⑥ Subject unable to provide consent

6.5. Patient Follow-up

Clinical follow-up will occur at 1-month, 6-month and every 12-month after enrollment. The investigator may conduct follow-up as telephone contacts or office visits.

7. End Points

7.1. Primary End Point

Major adverse cardiovascular and cerebrovascular events (MACCE), a composite of cardiac death, any MI, any revascularization, stroke, readmission due to heart failure) at 2 years

7.2. Secondary End Point

① Cardiac death at 2 years
② All-cause death at 2 years
③ Any MI at 2 years
④ Any revascularization at 2 years
⑤ Stroke (ischemic or hemorrhagic) at 2 years
⑥ Readmission due to heart failure at 2 years
⑦ All-cause death, any MI, or any revascularization at 2 years
⑧ Left ventricular ejection fraction at 2 years
⑨ Coronary flow reserve at 6 months

8. Patient Enrollment and Withdrawal

8.1. Patient Enrollment

About **150 patients** with MINOCA with undergoing invasive and non-invasive coronary physiologic assessments will be enrolled in the study.

8.2. Patient Discontinuation (Withdrawal Criteria)

Once enrolled, each patient should remain in the study until the required follow-up period is complete. However, all patients have the right to withdraw at any point during the study without penalty or loss of benefit. The investigator may discontinue any patient at any time if medically necessary. Data obtained to the last follow-up will be used for the analysis. It will be documented whether or not each patient completed the clinical study. If the study treatment(s) or observations are discontinued in any patient, the reason will be recorded and the data coordinating center must be notified promptly.

The following events will result in terminating the patient's follow-up:

- Patient voluntary withdrawal
- Patient withdrawn by investigator as clinically indicated

Every attempt should be made to collect follow-up information, except for those patients who specifically withdraw consent for release of such information. All procedures and laboratory specimens or tests

requested for evaluation after enrollment in the study should be carried out when possible. Patients will not be replaced in this trial.

8.3. Lost to Follow-up

Patients that do not complete the scheduled follow-up visits and have not officially withdrawn from the study are considered lost to follow-up; this term does not apply to missed visits. Site personnel should make considerable effort to locate and communicate with the patient using all available methods (eg, telephone, emails, and postcards). The following contact procedure is recommended at each time point:

- A minimum of 2 telephone calls on different days over the specified follow-up windows should be recorded in the source documentation including date, time, and site personnel initials for staff attempting to contact the patient.
- If these attempts are unsuccessful, a certified letter should be sent to the patient.

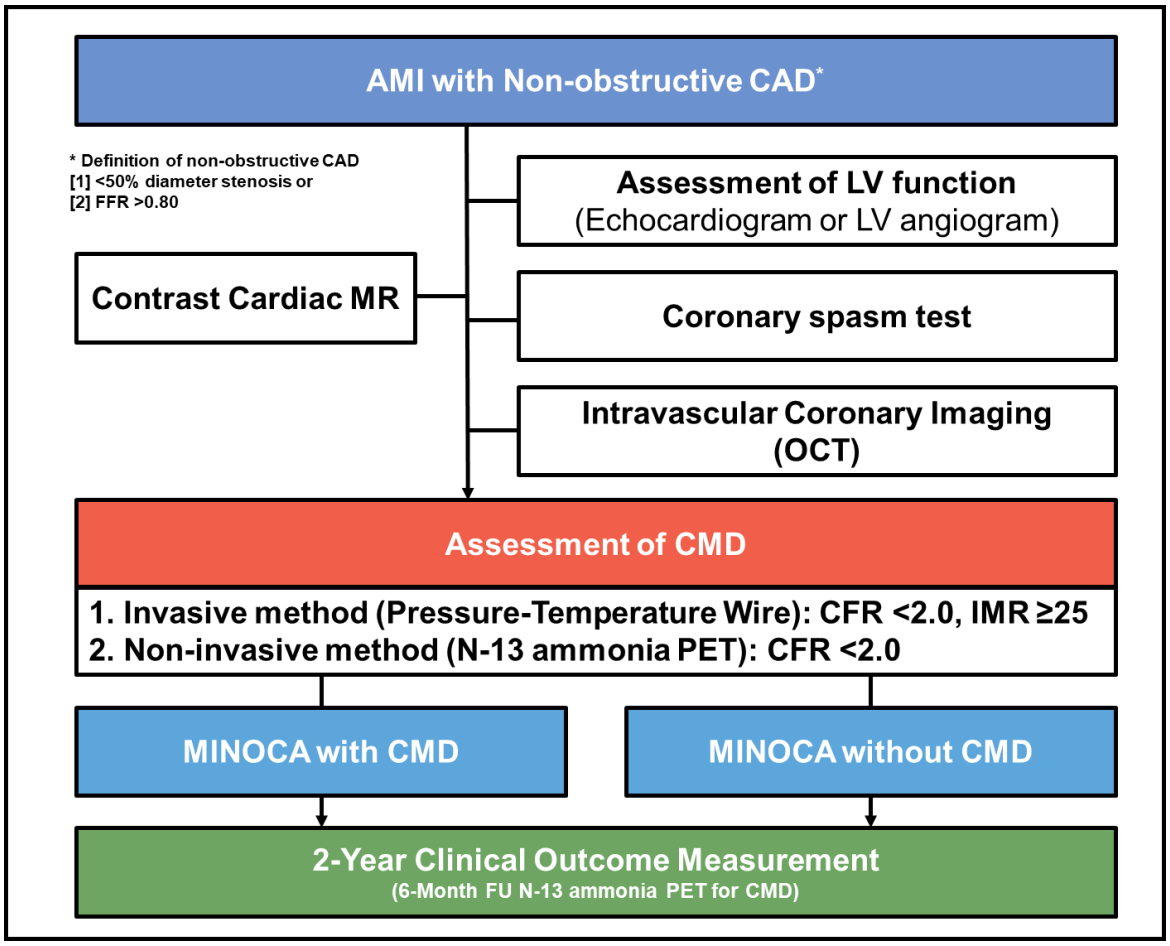
If the patient misses 2 consecutive scheduled contact time points and the above-mentioned attempts at communicating with the patient are unsuccessful, the patient will be considered lost to follow-up.

9. Study Protocol

After the patient has been enrolled in the present study, the following procedures will take place. The schedule of events for this trial is located in section 9.3. Schedule of Measurements.

During the index procedure and appropriate medical follow up, it is recommended that enrolling investigators try to adhere to current American and European recommendation for MINOCA.(2,3) Specific medical treatment is also strongly recommended according to the causes of MINOCA. The treatment strategy will be determined by the study-certified cardiologists.

9.1. Flow Chart



9.2. Study Procedure

(1) Coronary Provocative Spasm Test

Intracoronary infusion of ergonovine was used for the provocation test. Incremental doses of 20, 40, and 60 mcg were injected into the left coronary arteries and incremental doses of 10, 20, and 40 mcg were injected into the right coronary artery.(6-8) 'Definite' positive result was defined when the patient was fulfilled following criteria: 1) typical ischemic angina during provocation test, 2) transient total or subtotal coronary artery occlusion (≥90% constriction), and 3) transient ECG changes. 'Suspected (or intermediate)' result was defined as 50~90% coronary artery constriction with or without ischemic symptoms and/or ECG changes. Negative result was <50% constriction without ischemic symptoms and ECG changes.(7,8)

(2) Invasive Physiologic Assessment

All coronary physiologic measurements were performed after diagnostic angiography and provocative vasospasm test.(9) Standardized measurement protocols for resting distal coronary pressure (Pd) to aortic pressure (Pa), FFR, CFR, and IMR were adopted before the beginning of the study. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100-200 μg) was administered before each physiologic measurement. Three injections of 4mL room-temperature saline were performed to obtain resting mean transit time (Tmn) by using a

thermodilution curve. Hyperemia was induced by intravenous infusion of adenosine (140μg/kg/min) or intracoronary bolus injection of nicorandil (2mg). Hyperemic Pa, Pd, and hyperemic Tmn were measured during sustained hyperemia after the pressure curve reached a nadir point. The hyperemic period was recognized by a decreased Pd/Pa pattern and a left shift in the Tmn. After measurements were complete, the guide wire was pulled back to the guide catheter, and the presence of a pressure drift was checked. With a drift larger than >0.03 FFR unit, re-equalizations and repeated measurements were recommended. Resting Pd/Pa was calculated as the ratio of mean Pd to mean Pa. CFR was calculated as resting Tmn/hyperemic Tmn. FFR was calculated as the lowest average of 3 consecutive beats during hyperemia. IMR was calculated by Pd × Tmn during hyperemia and expressed as unit (U). All coronary physiologic data were collected and validated at a core laboratory (Chonnam National University Hospital) in a blinded fashion.

Based on the American and European consensus, which proposed definition of CMD based on 1) functionally non-obstructive coronary arteries defined by a FFR>0.80 and 2) impaired coronary microvascular function determined by abnormal CFR and/or microvascular resistance.(2,3,10) CMD was defined as having depressed CFR (<2.0) and/or elevated IMR (≥25U).

(3) N-13 Ammonia PET

All patients were performed N-13 ammonia PET according to the standardized method. The details of protocol was previously reported.(11) If the patients showed CMD at baseline, those patients were recommended 6-month follow-up PET for assessing the effect of CMD-specific medical treatment after enrollment.

9.3. Schedule of Measurements

Visit	Screening & Baseline		Follow-Up			
		1-month ±14days	6-month ±30days	12-month ±30days	24-month ±30days	SCV
Medical/Clinical/History (age, sex, risk factors)	×					
Informed Consent	×					
Enrollment[1)]						
Inclusion/Exclusion Criteria	×					
Brief Physical Examination	×					
Vital status	×	×	×	×	×	×
Weight, height	×					
12-lead ECG	×	×[2)]	×[2)]	×[2)]	×[2)]	×[2)]
Coronary angiography	×					
Coronary spasm test	×					
OCT						
Invasive physiologic assessment (FFR, CFR, IMR)	×					

Visit	Screening & Baseline		Follow-Up			
		1-month ±14days	6-month ±30days	12-month ±30days	24-month ±30days	SCV
N-13 ammonia PET	×		×			
Contrast CMR	×					
CBC	×	×	×	×	×	×
Electrolytes, LFT	×	×	×	×	×	×
Creatinine, BUN	×	×	×	×	×	×
Fasting plasma TG, LDL, HDL, total cholesterol	×	×	×	×	×	×
Fasting glucose level, HbA1c	×					
CK-MB, Troponin-I or Troponin-T, proBNP	×	×	×	×	×	×
Medications[3)]	×	×	×	×	×	×
Echocardiography[4)]	×			×	×	×
Clinical event[5)]		×	×	×	×	×

* Follow-up visits will allow telephone contact if clinic visits are unavailable.

* Because all test results are collected only when performed with clinical requirements, it will not be recorded as a protocol violence whether or not the tests are done.

* The last visit will be conducted within 1 month from the time when the participating center declares the end of follow-up.

1) The subject identification code will be assigned consecutively from CNUH-0001 by the interactive web response system of e-CRF.

2) Electrocardiogram at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, significant arrhythmias, heart failure or other signs or symptoms of clinical instability.

3) Medication data included medication at baseline (before admission) and post-discharge.

4) Echocardiography will be recorded with the closest result from the enrollment among the tests performed before and after the enrollment.

5) Only end point-related clinical events (all-cause death, cardiac death, any MI, any revascularization, stroke, readmission due to heart failure) will be collected.

10. Measurement of study outcome variables

10.1. Visit 1 Screening & Baseline

(1) Medical/Clinical/ History
Demographic information (age, sex, risk factors, cardiac history, and cardio-cerebral event) will be recorded at Screening& Baseline.

Relevant medical history, including history of current disease, other pertinent cardiac history, and information regarding underlying diseases will be recorded at Screening & Baseline.

(2) Informed consent
Before any examination, they will be informed about the study aims, procedures, and possible risks and the Investigator will ensure that the patient or the patient's legally acceptable representative has provided written informed consent. Written consent should include signature and date of legally authorized representatives and investigator.

A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

(3) Inclusion/Exclusion Criteria
Review of subject eligibility.

(4) Brief Physical Examination, Height and Weight, Vital signs
Height, weight, blood pressure and pulse will be measured

(5) 12-Lead ECG, Angiogram
Electrocardiogram at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, significant arrhythmias, heart failure or other signs or symptoms of clinical instability.

(6) Coronary Angiogram
Angiographic data will be obtained at Screening & baseline visits.

(7) Coronary Provocative Spasm Test
Coronary provocative spasm test will be performed at Screening & baseline visits.

(8) Intravascular Imaging (OCT), Invasive Physiologic Assessment
OCT and invasive physiologic assessment data will be obtained at Screening & baseline visits.

(9) N-13 Ammonia PET
N-13 Ammonia PET data will be obtained at Screening & baseline visits.

(10) Contrast Cardiac MR
Contrast cardiac MR data will be obtained at Screening & baseline visits.

(11) Laboratory data
Complete blood count, liver function test, renal function test, electrolytes, fasting plasma glucose, lipid profile, cardiac enzyme, and proBNP will be obtained.

(12) Concomitant Medication
Concomitant medication will be documented at Baseline/Screening and at follow-up. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

(13) Echocardiography
Echocardiography data will be obtained at Screening & baseline visits.

10.2. Follow-up

After enrollment, follow-up will occur at 1-month, 6-month, 12-month and 24-month. Investigator or designee may conduct follow-up as office visits.

(1) Vital Signs
Blood pressure and heart rate will be performed

(2) 12-Lead ECG
ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, significant arrhythmias, heart failure or other signs or symptoms of clinical instability
(3) Concomitant medications

(4) Clinical Event
Information regarding occurrence of clinical events (all-cause death, cardiac death, any MI, any revascularization, stroke, readmission due to heart failure etc.) will be captured throughout the study.

(5) N-13 Ammonia PET
If the patients showed CMD, follow-up N-13 Ammonia PET data will be obtained at 6-month.

11. Ethical Considerations and Confidentiality

11.1. Institutional Review Board (IRB) / Ethical Committee Approval

Institutional Review Board / Ethical Committee approval for the protocol and informed consent form will be obtained by the investigator prior to study participation. The approval letter must be signed by the IRB Chairperson or authorized representative prior to beginning the present study. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB. According to IRB requirements, the investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

11.2. Participant Safety

11.2.1 Elements of Informed Consent

This study will involve patients with MINOCA and underwent intravascular imaging, invasive, and non-invasive physiologic assessment. We anticipate enrolling 150 patients with a mean age in the 60s. Patients under the age of 19 will be excluded from the study for ethical and safety concerns. Women of child-bearing potential must have a negative serum/urine pregnancy test prior to enrollment and sexually-active females must use contraception for up to 2-year following the index procedure.

Prior to collecting study data, the details of the study will be explained to the participant including: (1) that the study represents a prospective observational study, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) anticipated costs to the patient for participation, (4) potential risks and

benefits for participation, and (5) contact information for additional concerns. Patients are informed of the purpose of the study, the treatment alternative, the need to be available for telephone follow-up and return clinic visits at regular intervals for questionnaires and/or medical tests, and of their options to accept or refuse entry into the study without affecting their clinical care.

All patients or legally authorized patient representatives must sign the current IRB approved informed consent form prior to any study-related activities and the index procedure. Failure to obtain signed informed consent will render the patient ineligible for the study. The signed informed consent will be kept in the patient's medical records and a copy given to the patient or legally authorized patient representative.

All sources of research materials will be in the form of medical records, coronary angiograms, electrocardiograms and routine blood work. This material will be obtained both for routine medical care as well as for research purposes.

11.3. Confidentiality

The confidentiality of protected health information shall be maintained by all parties involved at all times throughout the clinical trial. All data should be secured against unauthorized access. Study patients will be assigned a unique coded identifier on eCRFs. Patient data will be protected by the use of locked cabinets at the Clinical Centers and use of passwords, data encryption and secure, limited access storage of electronic data. The DCC has programs, policies and procedures in use at all times to ensure the security and confidentiality of the data. The explicit issue of privacy and confidentiality is outlined in the Informed Consent Form.

12. Study Organization

12.1. Steering Committee and Data Safety Monitoring Board (DSMB)

The executive steering committee comprised of the chairperson and the principal investigator approved the study design, protocol, and amendments issued to the DSMB and the participating centers. An independent DSMB will review the safety data from the study and construct recommendations for adverse events/serious adverse events, protocol deviation, and follow-up case reports. Scheduled DSMB meetings will discuss safety or compliance issues and will provide advice on modifying or stopping the study as needed. However, the final decisions regarding changes in the study protocol remain in the hands of the executive steering committee. In addition, the DSMB will help to conduct the trial appropriately by reviewing and reporting the cumulative investigational data for accuracy and completeness, ensuring protocol compliance. The DSMB will develop a consensus understanding of all trial end points and definitions used in the event adjudication process.

12.2. Clinical Event Adjudication Committee (CEAC)

CEAC is comprised of interventional and non-interventional cardiologists who are not participants in the study. The CEAC is charged with the development of specific criteria used for the categorization of clinical events and clinical end points in the study which are based on protocol. At the onset of the trial, the CEAC will establish explicit rules outlining the minimum amount of date required, and the algorithm

followed in order to classify a clinical event. All members of the CEAC will be blinded to the primary results of the trial.

The CEAC will meet regularly to review and adjudicate all clinical events. The Committee will also review and rule on all deaths that occur throughout the trial.

12.3. Data Coordination and Site Management

Data coordination and site management services will be performed at the Heart Center and Biomedical Research Institute of Chonnam National University Hospital.

13. Statistical Analysis

13.1. Primary End point Analysis

Primary end points (the composite rate of cardiac death, any MI, any revascularization, stroke, or readmission due to heart failure) will be analyzed with Kaplan-Meier survival with log-rank test.

13.2. Secondary End point Analysis

The individual components of events will be with Kaplan-Meier survival with log-rank test at 2 years after enrollment.

Primary End point	Statistical methods	Time point of analysis
MACCE (a composite of cardiac death, any MI, any revascularization, stroke, or readmission due to heart failure)	Kaplan-Meier survival estimates and log-rank tests	2 years after enrollment

Secondary End point	Statistical methods	Time point of analysis
All-cause and cardiac death	χ^2-test Kaplan-Meier survival estimates and log-rank tests	2 years after enrollment
Any myocardial infarction	χ^2-test Kaplan-Meier survival estimates and log-rank tests	2 years after enrollment
Any revascularization (clinically driven revascularization)	χ^2-test Kaplan-Meier survival estimates and log-rank tests	2 years after enrollment
Stroke (ischemic or hemorrhagic)	Kaplan-Meier survival estimates and log-rank tests	2 years after enrollment
Re-admission due to heart failure	Kaplan-Meier survival estimates and log-rank tests	2 years after enrollment
Composite of all-cause death, any MI, or any revascularization	Kaplan-Meier survival estimates and log-rank tests	2 years after enrollment
Left ventricular ejection fraction	Paired T-test	2 years after enrollment
Coronary flow reserve	Paired T-test	6 months after enrollment

13.3. Multivariable Analyses

Multivariable predictors of all primary and secondary end points will be determined using multiv ariable regression models, using either binary or Cox's proportional hazard method. Forward or backward stepwise selection algorithms will be used to select predictors as needed. Baseline de mographic and clinical variables that are predictive at the 0.1 level will be included in the mod els. The purpose of this is two-fold: to do a covariate adjusted analysis of treatment for all pri mary and secondary end points and to identify the risk factors which are associated with the s tudy end points.

13.4. Survival Analyses

All time-to-event outcomes will be summarized using Kaplan-Meier survival estimates and comp ared between groups using log-rank tests.

14. Publication Policy

Study derived data are the property of the participating investigators. However, individual investigators will not use study related data for any purpose other than study completion or for generating publication material as stated in the study site agreement without prior consent from the executive committee.

14.1. Data Analysis and Release of Results

No results will be released publicly before completion of the final analysis regarding the primary end point of this study. The statistical analysis will be performed according to the pre-specified analysis plan as described in this protocol. Any decisions on release of results will be undertaken by the Executive Committee after the approval of the DSMB.

14.2. Review Process

The Executive Committee will review the primary outcome data according to the pre-specified statistical analysis plan, and then will (i) decide on the early dissemination of the information at national and international scientific meetings (ii) provide the data to the publications committee which will in turn (a) first prepare a formal presentation to the Steering Committee members and (b) after taking under account the input and comments of the Steering Committee will proceed with submitting the manuscript to the Executive Committee. No study results will be released to the scientific or lay community without the approval of the Executive Committee.

14.3. Authorship: Primary Outcome Paper

Authorship of the primary outcome paper will be credited collectively to the "Investigators".

14.4. Other Study Papers, Abstracts and Presentations

Manuscripts on Ancillary Studies or Subset Analyses should be approved by the Executive Committee. The investigators significantly contributing to the study, considering both the number of patients enrolled

by the specific investigators and their contribution to the study design will have the priority in the authorships of the ancillary studies or subset analysis. Each presentation of results on behalf of the investigators should have the approval of the Executive Committee.

15. Quality Assurances, Quality Control and Clinical Monitoring

The purposes are:

- To ensure accuracy of study data;
- To provide constructive feedback to site and core laboratory staff to improve and/or maintain high performance;
- To document data quality for the study record.

This section addresses of issues with respect to protocol adherence, data collection at the clinical centers, and interpreter variability at the core laboratories.

15.1. Protocol Adherence

There are three key components, each of which is pre-specified. The DATABASE will be programmed to monitor: eligibility criteria, correct treatment administration, and completion in a timely manner of all required data collection (no missed visits, missed studies or specimens). Eligibility criteria are also checked for all or a random sample of patients at every clinic site visit by auditing the patient's record/worksheet.

It is the Investigator's responsibility to ensure that there are no deviations from the protocol except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the patient. The DCC will monitor these aspects of protocol adherence continually. In addition, clinic site personnel will have clearly specified timeframes for entry of all data and for resolution of any edit queries. All of these aspects of protocol can be monitored at the DCC via real-time reporting, in aggregate and by clinic site.

Any of the protocol violations listed below will be reviewed immediately by the DCC and communicated to the principal investigator. All remedial actions will be jointly decided and, in general, implemented by the DCC. Any clinical site being considered for temporary or permanent termination of patient recruitment may be visited administratively by the monitoring group. The major protocol violations for this study consist of, but are not limited to, the following:

<u>Protocol Violations</u>:

- Eligibility not confirmed, or subject found to be ineligible;
- Informed consent not obtained (or not obtained in a timely manner);
- Failure to conduct protocol required clinical follow-ups and within time windows;

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required if necessary. After any one violation, the DCC will work closely with the site PI to ensure further violations are avoided. Any clinic investigator, certified for the trial, who commits any two of the above violations will be immediately considered for suspension from participation in the trial and the clinic site principal investigator will also be given notice that further

violations by investigators at that site may result in site suspension (after an administrative site visit). If a site is suspended early in the trial, all patient recruitment and follow-up (except for vital status and safety) may be terminated. A site suspended later in the trial may still be required to complete follow-up on those subjects already randomized, assuming that the site's adherence to the follow-up protocol is satisfactory or can be remediated.

15.2. Data Collection: Electronic Case Report Forms (eCRF)

DCC personnel will determine form content, considering (1) Identify the minimal set of measurements for the specified variables; (2) Choose those measurements (if more than one candidate) which are valid and reliable and, other considerations being equal, are least burdensome to the subject; and (3) Develop, test and assess reliability of new measures as required. Experienced DCC staff will then order and format items to ensure clarity, smooth flow and to minimize missing information, using clear skip patterns, consistent coding for all close-ended items, and standard "footers" to identify form name, version date, and page number. Standard, modular data forms will be identified and developed to be used in both the Trial and Registry as needed.

Case report forms will be developed by the Clinical Research Center as an online electronic form where investigators from individual site can access and input the data via the internet

16. Event Adjudication and Reporting

16.1. End point Adjudication

With the exception of all-cause mortality, most end points will require clear, prespecified criteria, and centralized review. These end points will be captured during patient interview, supplemented by death certificates; hospital record abstracts and related reports (autopsy, biopsy, diagnostic output).

From extensive experience, the following approach is proposed. First, all required documents, reports, hospital records will be identified, made anonymous, and copied to the DCC by clinical staff. Second, the DCC will check to ensure confidentiality and, if required, have the records centrally abstracted onto standard forms by trained DCC staff. Central abstraction in large (>30) batches is recommended to reduce variability and secular drift and maintain adequate accuracy and completeness. Third, centrally prepared forms and documents will be circulated to CEAC members for assessment.

17. Regulatory Responsibilities

17.1. Investigator Responsibilities

The investigator is responsible for ensuring that the trial is conducted according to all signed agreements, the study protocol and good clinical practice (GCP) requirements. Also, each investigator must complete and sign the Investigator's Agreement. In signing, the investigator agrees to:

- Sign and adhere to the Investigator Agreement
- Participate in Investigator meetings and training sessions as scheduled by Sponsor
- Maintain up-to-date angiographic and intravascular ultrasound equipment (if applicable)
- Be willing to provide original cine films/CD ROMs/intravascular ultrasound videotape for analysis
- Have access to cardiac surgery

- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply angiographic material suitable for quantitative analysis
- Obtain written Informed Consent from each study participant before any study specific procedures are performed in accordance with GCP
- Complete all electronic case report forms for completed patients visits and/or applicable events prior to scheduled monitoring visits
- Adhere to all relevant Core Laboratory requirements and,

17.2. Institutional Review Board (IRB) or Ethics Committee Approval

The investigator must submit the study protocol to IRB or Ethics Committee and obtain their written approval before being allowed to conduct and participate in the study. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, etc. The investigator will provide the Sponsor with copies of such approvals and reports.

17.3. Informed Consent

Part of the IRB/Ethics Committee approval must include approval of an Informed Consent text specific to the study. The investigator must administer this approved Informed Consent text to each prospective study patient and obtain the patient's signature on the text prior to enrollment in the study. This may be modified to suit the requirements of the individual site. The investigator will provide the Sponsor with a copy of the approved Informed Consent for his/her site.

17.4. Study Coordinator

To assure proper execution of the study protocol, each investigator must identify at least one study coordinator. Working with and under the authority of the investigator, the study coordinator assures that all study requirements are fulfilled and is the contact person at the site for all aspects of study administration.

18. Records Retention and Reports

To comply with ICH guidelines, the Primary Investigator will maintain all records relevant to this study for 2 years following study completion, unless the records are archived by an external vendor. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated as required during this study. Such documentation may be subject to inspection by appropriate regulatory agencies.

18.1. Records

investigator must maintain the following accurate, complete, and current records relating to the conduct of the investigation. (The data for some of these records may be available in computerized form from

the Data Coordinating Center; however the final responsibility for maintaining remains with the investigator.)

- All correspondence with another investigator, an IRB, a Core Laboratory, the Sponsor, a monitor, Data Coordinating Center, including required reports.

- Records of each subject's case history, including study-required Case Report Forms, evidence of informed consent, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, and the date of each study treatment.

18.2. Reports

Below is a list of the reports which are the investigator's responsibility to generate. The table also shows to whom the report is to be sent and with what frequency or within what time constraints. While some of these reports will be developed by or with the assistance of the Data Coordinating Center, the final responsibility for them rests with the investigator.

Reports Required from Clinical Investigators:

Type of Report	**Prepared by Investigator For:**	**Time Constraints of Notification**
Patient withdrawal	DCC	Notify within 7 days
Annual progress report	EC/Principal investigator	Submitted per 1 year
Deviations from investigational plan	IRB	Per local standard.
	EC/Principal investigator	Notify within 7 days.
Informed consent not obtained	DCC/IRB	Notify within 7 days.
Final summary report	EC/Principal investigator	Within 1 month.

* DCC: Data Coordinating Center; DSMB; Data Safety Monitoring Board; EC: Executive Committee (Co-researchers)

19. Investigational Agreement

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial. I will personally conduct the study as described and agree to adhere strictly to the attached protocol.

I will provide copies of the protocol to all physicians, nurses and other professional personnel, who under my responsibility will participate in this study. I will discuss the protocol with them to assure that they are sufficiently informed regarding the drugs used in the study, the concurrent medications, the efficacy and safety parameters, and the overall execution of the study in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for such matters in the clinical study facility where the drug will be tested, prior to commencement of this study. I agree that clinical data entered on case report forms by the staff and I, can be utilized in various ways including, but not limited to, publication in peer journals, submission as abstracts, submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow monitors and auditors as well as inspectors from regulatory authorities, full access to all medical records at the research facility for patients screened in the study.

I agree to provide all patients with informed consent forms, as required by government and ICH regulations. I further agree to report to the DCC any adverse experiences in accordance with the terms of this protocol, KFDA regulation, and ICH guideline.

Principal Investigator (print)

Principal Investigator (signature) Date

Institution Name/Location

20. Appendix. Definitions

Cerebrovascular accident (CVA) or Stroke

Sudden onset of vertigo, numbness, dysphasia, dysarthria or central neurologic deficit secondary to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists for > 72 hours

* CVA type

1. Hemorrhagic: A stroke with documentation on imaging (e.g., CT scan or MRI of hemorrhage in the cerebral parenchyma, or a subdural or subarachnoid hemorrhage). Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.
2. Nonhemorrhagic: A focal neurological deficit that results from a thrombus or embolus (and not due to hemorrhage) that appears and is still partially evident for more than 24 hours
3. Unknown/no imaging performed: if the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy)

Death

Death defined by the Academic Research Consortium is as follows:

All death is considered to be cardiac death unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (eg, cancer, infection) should be classified as cardiac. The cause of death (cardiac vs. non-cardiac) will be adjudicated by an independent clinical event adjudication committee

Cardiac death: Any death due to proximate cardiac cause (eg, myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.

Vascular death: Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

Non-cardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Diabetes

Defined as

1. History of diabetes, regardless of duration of disease, need for antidiabetic agents, or
2. a fasting blood glucose > 126 mg/dl.

The type of diabetic control should be noted:

① None
② Diet: Diet treatment
③ Oral: Oral agent treatment
④ Insulin: Insulin treatment (includes any combination of insulin)

Enrolled Patient

The point of enrollment occurs when a patient or patient's legally authorized representative has provided written informed consent to participate in the trial

Myocardial Infarction (MI)

Myocardial Infarction Classification and Criteria for Diagnosis is defined by the Fourth Universal Definition of Myocardial Infarction (12) as follows:

Type	Biomarker criteria	Time frame	Necessary additional criteria
Type 1: Spontaneous	Rise and/or fall of cTn values with at least one value above 99th percentile URL	None	**Requiring at least one of the following:** - Symptoms of acute myocardial ischemia - New ischemic ECG changes - Development of pathological Q waves - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology - Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
Type 2: Ischemic imbalance	Rise and/or fall of cTn values with at least one value above 99th percentile URL	None	**Requiring at least one of the following:** - Symptoms of acute myocardial ischemia - New ischemic ECG changes - Development of pathological Q waves - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
Type 3: Cardiac death before biomarkers drawn	None	None	- Symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation - Myocardial infarction is detected by autopsy
Type 4a: After percutaneous coronary intervention (PCI)	One of the following: Elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values Rise of postprocedural cTn values >20% in patients with cTn level are stable or falling	Within 48 hours after PCI	**Requiring at least one of the following:** - New ischemic ECG changes - Development of new pathological Q waves - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology - Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization
Type 4b: Stent thrombosis	Rise and/or fall of cTn values with at least one value above 99th percentile URL	Acute, 0~24 hours; Subacute, >1~30 days; Late, >30 days~1 year; Very late, > 1 year	Documented by angiography or autopsy using the same criteria utilized for type 1 myocardial infarction
Type 4c: PCI restenosis	Focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL	None	Same criteria utilized for type 1 myocardial infarction

Type 5: After coronary artery bypass grafting (CABG)	Elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated preprocedure cTn in whom cTn levels are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%.	Within 48 hours after CABG	**Requiring at least one of the following:** - Development of new pathological Q waves - Angiographic documented new graft occlusion or new native coronary artery occlusion - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

cTn = cardiac troponin; ECG = electrocardiogram; URL = Upper Reference Limit (defined 99th percentile of normal reference range).

Principal Investigator

A physician-specialist responsible for overseeing trial conduct at all sites, protocol compliance, and relevant KFDA regulations

Repeat coronary revascularization

See revascularization

Revascularization

Revascularization is defined by the Academic Research Consortium as follows:

*Clinically indicated revascularization: A revascularization is considered clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥ 50% (core laboratory quantitative coronary angiography assessment) and if one of the following occurs:

(1) A positive history of recurrent angina pectoris, presumably related to the target vessel;

(2) Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel;

(3) Abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve);

Transient Ischemic Neurological Attack (TIA)

A sudden onset of reversible focal neurological deficits due to vascular lesions of the brain that lasts ≤ 24 hours

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