Imaging and Physiologic Evaluation of Coronary Artery Disease: a Prospective Registry Study

(IP-CAD)

Chonnam National University Hospital,
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Research Summary	
Study Title	**Imaging and Physiologic Evaluation of Coronary Artery Disease: a Prospective Registry Study (IP-CAD)**
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Countries Involved	**Republic of Korea**

Purpose / Objectives:

To evaluate the long-term clinical outcomes and prognostic factors in patients with coronary artery disease (CAD) undergoing invasive coronary angiography (ICA), intravascular imaging, or invasive physiologic assessment.

Study Design

(1) Trial Design
A prospective observational study

(2) Cohorts
Patients with CAD who undergoing ICA, intravascular imaging (including intravascular ultrasound [IVUS] or optical coherence tomography [OCT]), or invasive physiologic assessment (including fractional flow reserve [FFR], resting indexes, coronary flow reserve [CFR], or index of microcirculatory resistance [IMR])

(3) Study Population
About 2,000 patients with suspected ischemic heart disease and underwent ICA, intravascular imaging, or invasive physiologic assessment

(4) Entry criteria
1) Inclusion criteria

① Subject must be at least 18 years of age
② Subjects who suspected ischemic heart disease and underwent ICA.
③ Subjects who were performed intravascular imaging or invasive physiologic assessment

2) Exclusion criteria

① Subject with Age <18 years
② Pregnant women

(5) Outcome Measures
1) Primary end point:
A composite of all-cause death, myocardial infarction, or any revascularization

2) Secondary end points:

① All-cause death at 3 years
② Cardiac death at 3 years
③ Myocardial infarction at 3 years
④ Target lesion revascularization at 3 years
⑤ Target vessel revascularization at 3 years
⑥ Any revascularization at 3 years
⑦ Stent thrombosis (definite or probable) at 3 years
⑧ Cerebrovascular accident 3 years
⑨ Bleeding (BARC type 2,3 or 5) at 3 years
⑩ MACCE (major adverse cardiac and cerebrovascular accident), a composite of all-cause death, myocardial infarction, any revascularization, and cerebrovascular events

1. Title of Study

Imaging and Physiologic Evaluation of Coronary Artery Disease: a Prospective Registry Study (IP-CAD)

2. Clinical Research Center

(1) 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
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Co-researchers	Myung Ho Jeong	Chonnam National University Hospital, Chonnam National University Medical School	Professor
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	Min Chul Kim	Chonnam National University Hospital, Chonnam National University Medical School	Associate Professor
	Seung Hun Lee	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor
	Kyung Hoon Cho	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor
	Jun Ho Ahn	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor
	Dae Young Hyun	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor
	Seok Oh	Chonnam National University Hospital, Chonnam National University Medical School	Clinical Professor
	Yongwhan Lim	Chonnam National University Hospital, Chonnam National University Medical School	Clinical Fellow

4. Background

The traditional standard method for evaluating coronary artery disease (CAD) is invasive coronary angiography (ICA). ICA enables the assessment of anatomic severity of the epicardial artery and the severity of diameter stenosis can be closely associated with myocardial ischemia. However, there remains concern that anatomical severity is not always identical with functional significance.

Actually, even the patients showed positive non-invasive tests including treadmill test, stress echocardiography, coronary computed tomography angiography, or nuclear imaging, less than half of the patients showed significant stenosis on ICA.[1] Therefore, we need further investigation to overcome the limitations of ICA.

In this regard, intravascular imaging, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), is a useful tool for assessing the anatomical severity in more detail. Those imaging modalities produce cross-sectional images of CAD and they are allowing to assess lesion characteristics, plaque morphology, treatment planning, and optimization of the implanted stent.[2] Furthermore, imaging-guided percutaneous coronary intervention (PCI) has been shown favorable outcomes, compared with angiography only-guided PCI, especially in complex lesions.[3–5] Meanwhile, there has been an ample body of evidence that invasive coronary physiology assessment, such as fractional flow reserve (FFR), also can be useful for assessing the functional significance.[6,7] Therefore, the current guidelines have continuously recommended intracoronary imaging and invasive physiologic assessment for guiding the treatment of CAD.[8–10]

The aim of the IP-CAD (Imaging and Physiologic Evaluation of Coronary Artery Disease: a Prospective Registry Study) is to evaluate the long-term clinical outcomes according to the imaging-guided or physiology-guided PCI in real-world practice.

5. Study design

5.1 Study design

A prospective observational study.

5.2 Patients enrollment

A total of 2,000 patients will be enrolled at single center in South Korea. Patients with CAD and underwent ICA with intravascular imaging or invasive physiologic assessment will be consecutive enrolled.

5.3 Patient follow-up

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

6. End points

6.1. Primary end point

A composite of all-cause death, myocardial infarction, or any revascularization

6.2. Secondary end point

① All-cause death at 3 years

② Cardiac death at 3 years

③ Myocardial infarction at 3 years

④ Target lesion revascularization at 3 years

⑤ Target vessel revascularization at 3 years

⑥ Any revascularization at 3 years

⑦ Stent thrombosis (definite or probable) at 3 years

⑧ Cerebrovascular accident 3 years

⑨ Bleeding (BARC type 2,3 or 5) at 3 years

⑩ MACCE (major adverse cardiac and cerebrovascular accident), a composite of all-cause death, myocardial infarction, any revascularization, and cerebrovascular events

6.3 Study timeline

Overall study will require 6~6.5 years to complete, including 3-year of recruitment and 3-year of follow-up followed by close out and reporting of final results.

IRB approval date ~ 2027.12.31
Subject enrollment: 2021.11.01 ~ 2024.12. (roughly 3 years of enrollment)
End of follow-up period: 2027.12. (3 years after the end of recruitment)
Analysis and report: ~2028.06.30

7. Patient enrollment and withdrawal

7.1 Patient population

A total of 2,000 patients derived from a population of Korean patients with CAD and underwent ICA with intravascular imaging (IVUS or OCT) and invasive physiologic assessment (FFR, resting indexes, coronary flow reserve [CFR], or index of microcirculatory resistance [IMR]).

7.2 Eligibility Criteria

7.2.1 Inclusion Criteria

① Subject must be at least 18 years of age

② Subjects who suspected ischemic heart disease and underwent ICA.

③ Subjects who were performed intravascular imaging or invasive physiologic assessment

7.2.2 Exclusion criteria

① Subject with Age <18 years

② Pregnant women

7.3 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.

7.3.1 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.

8. Protocol procedures

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 8.1 Schedule of Events. The treatment strategy will be determined by the study-certified cardiologists. During the index procedure and appropriate medical follow up, it is recommended that enrolling investigators try to adhere to current ACC/AHA/SCAI or ESC/EACTS guidelines.

8.1 Schedule of measurements

Visit	Screening & Baseline	Follow-Up				
		1-month ±14days	6-month ±30days	12-month ±30days	24-month ±30days	36-month ±30days
Medical/Clinical/History (age, sex, risk factors, clinical Dx, angina status)	×					
Informed Consent	×					
Inclusion/Exclusion Criteria	×					
Brief Physical Examination	×					
Vital status	×	×	×	×	×	×
Weight, height	×					
12 lead ECG	×	×[6)]	×[6)]	×[6)]	×[6)]	×[6)]
Coronary angiography[2)]	×					
IVUS/OCT	×					
Invasive physiologic assessment	×					
CBC	×					
Electrolytes, LFT	×					
Creatinine, BUN	×					
Fasting plasma TG, LDL, HDL, total cholesterol	×					
Fasting glucose level	×					
$HbA1_C$	×					
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. Stratified randomization according to participating center, clinical diagnosis, and complex lesion PCI will be performed.

2) The data of pre- and post-PCI angiography will be collected including lesion location, the number of diseased vessels, and the type, number, length, and diameter of DESs.

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, myocardial infarction, stent thrombosis, TLR, RVR, any revascularization, stroke, systemic embolism, bleeding [ISTH major or clinically relevant non-major bleeding]) will be collected.

6) 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.

9. Measurement of study outcome variables

9.1 Visit 1 Screening & Baseline

① 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.

② Inclusion/Exclusion Criteria

Review of subject eligibility

③ Medical/Clinical/ History

Demographic information (age, sex, risk factors, angina status, 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.

④ Brief Physical Examination, Height and Weight, Vital signs

Height, weight, blood pressure and pulse will be measured

⑤ 12 lead electrocardiogram, angiogram

Angiographic data will be obtained at Screening & baseline visits. 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 Intravascular imaging (IVUS/OCT), invasive physiologic assessment

IVUS, OCT, or invasive physiologic assessment data will be obtained at Screening & baseline visits.

⑦ Laboratory data

Complete blood count, liver function test, renal function test, electrolytes, fasting plasma glucose, and lipid profile will be obtained.

⑧ 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.

9.2 Follow-up

Follow-up will occur at 1-month, 6-month, 12-month, 24-month, and 36-month. Investigator or designee may conduct follow-up as office visits.

① Vital signs
Blood pressure and pulse will be performed

② 12 lead electrocardiogram
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 Concomitant medications

④ Clinical Event
Information regarding occurrence of clinical events (any death, any myocardial infarction or any revascularization etc.) will be captured throughout the study.

10. Ethical Considerations and Confidentiality

10.1 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.

10.2 Participant Safety

10.2.1 Elements of Informed Consent

This study will involve patients with CAD and underwent ICA with intravascular imaging or invasive physiologic assessment. We anticipate enrolling 2,000 patients with a mean age in the 60s. Patients under the age of 18 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 1-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.

10.2.2 Potential Risks

Risks of PCI with Stent Implantation

Stents are metallic foreign bodies, which remain in the artery indefinitely. Complications that may be associated with stenting include but are not limited to thrombosis with reinfarction and even death, intramural hematoma, side branch occlusion, stroke, stent migration, arterial rupture/perforation, dissection, embolization, and stent deformability. The risk of stent thrombosis is amplified by early discontinuation of antiplatelet therapy post procedure. Evidence suggests that the incidence of these complications after coronary stenting is low. Stent thrombosis is a complication that is well described in the coronary and peripheral interventional literature. Several causes of stent thrombosis have been documented and there are effective strategies for minimizing this complication. Stent delivery by the operator to the target site is an important determinant of thrombosis. Proper apposition of the stent to the arterial wall with minimal residual narrowing reduces the risk of thrombosis. Treatment with aspirin and P2Y12 inhibitor also reduces the incidence of stent thrombosis. As a result, thrombosis is distinctly uncommon with proper operator technique and use of antiplatelet medication. Stent migration may occur but is uncommon. Endovascular snares have been developed to deal with this problem. In the majority of cases, experienced operators can retrieve stents that have migrated, without permanent complications. Arterial rupture is rare. Proper device selection as well as the choice of inflation pressure effectively minimizes this complication. Stenting has been successfully performed for over 20 years.

Pharmacological Risks

Patients treated with stents will be given aspirin and P2Y12 inhibitor to minimize the likelihood of thrombus formation at the stent site. Aspirin, however, may increase the likelihood of gastrointestinal adverse effects and bleeding. Clopidogrel is uncommonly associated with rash, headache, dizziness, stomach pain, nausea, diarrhea, indigestion, increase in cholesterol levels, leucopenia, or thrombocytopenia. The anticoagulation medication used also involves additional risks.

10.2.3 Adequacy of Protection against Risks

The Data Coordinating Center (DCC), CEAC, and the DSMB play key roles in detecting any hazards the study may pose for its participants. Data are routinely collected and regularly monitored to document morbidity or mortality associated with study-related procedures. Timely reports will be made to the DSMB. In addition, the DCC is responsible for calling the Board’s attention to significant interim safety concerns.

The DSMB is responsible for advising early termination of the trial in the event if there are non-rectifiable, serious safety concerns in any groups. It will be the responsibility of the DSMB to review the data and establish limits of safety for the trial, as well as its termination, however, the final decision on the early termination of the study will be made by the executive committee upon the recommendations of the DSMB.

10.3 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.

11. Study Organization

11.1 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.

11.2 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.

11.3 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.

12. Statistical Analysis

12.1. Primary End point Analysis

Primary end points (the composite rate of all-cause death, myocardial infarction, or any

revascularization) will be analyzed with Kaplan-Meier survival with log-rank test.

12.2. Secondary End point Analysis

The individual components of ischemic and bleeding events will be with Kaplan-Meier survival with log-rank test at 3 years after enrollment.

Primary End point	Statistical methods	Time point of analysis
MACE (a composite of death, any MI, or any revascularization)	Kaplan-Meier survival estimates and log-rank tests	3 year 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	3 year after enrollment
Any myocardial infarction	χ^2-test Kaplan-Meier survival estimates and log-rank tests	3 year after enrollment
Target-lesion revascularization (clinically driven revascularization)	χ^2-test Kaplan-Meier survival estimates and log-rank tests	3 year after enrollment
Target-vessel revascularization (clinically driven revascularization)	χ^2-test Kaplan-Meier survival estimates and log-rank tests	3 year after enrollment
Any revascularization (clinically driven revascularization)	χ^2-test Kaplan-Meier survival estimates and log-rank tests	3 year after enrollment
Stent thrombosis	χ^2-test Kaplan-Meier survival estimates and log-rank tests	3 year after enrollment
Cerebrovascular accident (CVA)	χ^2-test Kaplan-Meier survival estimates and log-rank tests	3 year after enrollment
Bleeding (BARC type 2, 3 or 5)	χ^2-test Kaplan-Meier survival estimates and log-rank tests	3 year after enrollment

12.3. Multivariable Analyses

Multivariable predictors of all primary and secondary end points will be determined using multivariable 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 demographic and clinical variables that are predictive at the 0.1 level will be included in the models. The purpose of this is two-fold: to do a covariate adjusted analysis of treatment for all primary and secondary end points and to identify the risk factors which are associated with the study end points.

12.4. Survival Analyses

All time-to-event outcomes will be summarized using Kaplan-Meier survival estimates and comp

ared between groups using log-rank tests.

13. 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.

13.1 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.

13.2 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.

13.3 Authorship: Primary Outcome Paper

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

13.4 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.

14. 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.

14.1 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.

14.2 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

15. Event Adjudication and Reporting

15.1 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.

16. Regulatory Responsibilities

16.1 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,

16.2 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.

16.3 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.

16.4 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.

17. 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.

17.1 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.

17.2 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)

18. 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

19. Appendix. Definitions

Angina

Canadian Cardiovascular Society Classification of Stable Angina

I. Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.

II. Slight. Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, in wind, under emotional stress or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.

III. Marked. Marked limitation of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

IV. Inability. Inability to carry on any physical activity without discomfort. angina symptoms may be present at rest.

Braunwald Classification of Unstable Angina

I. New onset of severe or accelerated angina: Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

II. Angina at rest, subacute: Patients with 1 or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

III. Angina at rest, acute: Patients with 1 or more episodes of angina at rest within the preceding 48 hours.

Complex lesions

Defined as

1. True bifurcation lesion (Medina 1,1,1/1,0,1/0,1,1) with side branch ≥2.5mm size
2. Chronic total occlusion (≥3 months) as target lesion
3. Unprotected LM disease PCI (LM ostium, body, distal LM bifurcation including non-true bifurcation)
4. Lesion needed ≥2 more overlapping stents or lesion length ≥30mm by visual estimation
5. Multivessel PCI (≥2 vessels treated at one PCI session)
6. Multiple stent needed (≥3 more stent per patient)
7. In-stent restenosis lesion as target lesion
8. Severely calcified lesion (encircling calcium in angiography)

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 [23] 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

Restenosis

Re-narrowing of the artery following the removal or reduction of a previous narrowing.

Binary restenosis: Percent diameter stenosis > 50% at angiographic follow-up

Revascularization

Revascularization is defined by the Academic Research Consortium as follows:

Target lesion revascularization: TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs should be classified prospectively as clinically indicated* or not clinically indicated by the investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

Target vessel Revascularization: TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.

Non Target Lesion Revascularization (non-TLR): Any revascularization in a lesion other than the target lesion is considered a non-target lesion revascularization.

Non Target Vessel Revascularization (non-TVR): Any revascularization in a vessel other than the target vessel is considered a non-target vessel revascularization.

*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);

(4) A TLR or TVR with a diameter stenosis ≥ 70% even in the absence of the above-mentioned ischemic signs or symptoms.

Stent Thrombosis

Stent thrombosis is defined and discussed by the Academic Research Consortium as follows:

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the subject left the catheterization laboratory.

Timing

Acute stent thrombosis*	0-24 hours post stent implantation
Subacute stent thrombosis*:	> 24 hours-30 days post stent implantation
Late stent thrombosis†:	> 30 days-1 year post stent implantation
Very late stent thrombosis†:	> 1 year post stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0-30 days) is currently used in the community.

† Including "primary" as well as "secondary" late stent thrombosis; "secondary" late stent thrombosis is a stent thrombosis after a target segment revascularization.

Stent Thrombosis Categories: a) Definite b) Probable, and c) Possible

a) Definite stent thrombosis: Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

Angiographic confirmation of stent thrombosis [*The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).]: The presence of a thrombus [†Intracoronary thrombus] that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

. Acute onset of ischemic symptoms at rest

. New ischemic ECG changes that suggest acute ischemia

. Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)

. Nonocclusive thrombus: Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified

filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

. Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

Pathological confirmation of stent thrombosis: Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

b) Probable stent thrombosis: Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

. Any unexplained death within the first 30 days [‡ For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.]

. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

c) Possible stent thrombosis: Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Target Lesion

A lesion to be treated during the index procedure

Target Vessel

The entire epicardial vessel containing the treated lesion

Thrombosis in Myocardial Infarction (TIMI) Flow Grades

Definitions of perfusion in the TIMI Trial

Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion.

Grade 1 (penetration with minimal perfusion): The contrast material passes beyond the area of obstruction, but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for duration of the cine run.

Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.

Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

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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