Comparison of long-term clopidogrel versus aspirin monotherapy beyond dual antiplatelet therapy after drug-eluting coronary stent implantation: Harmonizing Optimal Strategy for Treatment of coronary artery diseases – EXtended Antiplatelet Monotherapy (HOST-EXAM RCT)

Version No: 4.5.3

Clinical research center: Cardiovascular Center & Clinical Research Center, Seoul National University Hospital

Principle investigator: Hyo-Soo Kim

Research Summary

Trial name and number	**H**armonizing **O**ptimal **S**trategy for **T**reatment of coronary artery stenosis – **EX**tended **A**ntiplatelet **M**onotherapy (HOST-EXAM RCT)
Principle investigator	Hyo-Soo Kim, Seoul National University Hospital, Seoul, Korea
Objectives	1) To compare the efficacy and safety of antiplatelet monotherapy with aspirin or clopidogrel for 2 years in patients who have not experienced MACE including all-cause death, acute coronary syndrome (ACS) including nonfatal MI, or urgent revascularization or bleeding under combined antiplatelet therapy for 12 ± 6 months after PCI with DES 2) The trial tests the hypothesis that clopidogrel is superior to aspirin in preventing clinical events and device-oriented outcomes
Study design	A prospective, randomized, open-labeled, multicenter, comparative effectiveness trial
Patient enrollment	5,530 patients enrolled at 37 centers in Republic of Korea
Patient follow-up	A clinical follow-up is planned at 12 and 24 months, and additional visits are at the discretion of attending physicians. The investigators will be urged to follow up the patients by office visits or telephone contacts
Primary endpoint	A composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or major bleeding at 24 months after randomization
Secondary endpoint	- Target lesion revascularization : defined as any repeat revascularization procedure at the original lesion of the index procedure any time during the follow-up period - Target vessel revascularization : defined as any repeat revascularization procedure involving at least one of the target vessels that were treated in the index procedure - Stent thrombosis : defined according to the Academic Research Consortium (ARC) - Minor GI complications : assessed on the basis of newly added GI medications (including H2-blockers and PPIs documented for each patient), or symptom-driven GI endoscopy (type of endoscopy, test results, and further interventions) - Cost-effectiveness : Additional medical costs related to these minor GI complications (South Korean won/year) will be calculated to assess the cost-effectiveness of each drug based on average Korean expenses

Research Proposal

1. Title of Study

Comparison of long-term clopidogrel versus aspirin monotherapy beyond dual antiplatelet therapy after drug-eluting coronary stent implantation: **H**armonizing **O**ptimal **S**trategy for **T**reatment of coronary artery diseases – **EX**tended **A**ntiplatelet **M**onotherapy (**HOST-EXAM RCT**)

2. Clinical Research Center

Medical Research Collaborating Center or Cardiovascular Center & Clinical Research Center, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea

3. Funding Agencies

* Chong Kun Dang Pharmaceutical Corp
* Samjin Pharmaceutical Co, Ltd
* HANMI PHARMA Co, Ltd
* Daewoong Pharmaceutical Co, Ltd.

4. Background and hypothesis

1) Background

Coronary artery disease (CAD) is the leading cause of mortality and morbidity worldwide, and numerous studies have investigated its proper management and prevention. The advent of percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) after antiplatelet therapy was an important advance in CAD management. Previous studies proposed different antiplatelet regimens to protect against thrombotic/ischemic events and minimize bleeding complications after stent implantation. However, the optimal regimen after PCI with DES is still a subject of debate. Several randomized trials including the RESET, OPTIMIZE, and PRODIGY have compared dual antiplatelet therapy (DAPT) for durations of 3-6 or 12-24 months and consistently showed no benefit with respect to thrombotic/ischemic events and a higher risk of bleeding complications for longer therapy. The recent DAPT, PEGASUS-TIMI, and OPTIDUAL trials reported a better efficacy of extended duration of DAPT over 12 months in common, whereas the ARCTIC-Interruption trial suggested no apparent benefit but instead harm with extended duration of DAPT.

Current guidelines recommend at least 6- to 12 months of DAPT with aspirin and a P2Y12

receptor inhibitor, such as clopidogrel, after DES implantation, according to clinical event leading to PCI. Therefore, in real-world practice, clinicians usually switch from DAPT to a single agent beyond 1 year after PCI with DES. The currently preferred choice for antiplatelet monotherapy tends to be aspirin, because low-dose aspirin has known efficacy for occlusive vascular disease and the issue of clopidogrel resistance is considered as an obstacle for effective post-PCI management. However, routine screening for clopidogrel responsiveness has not been shown to improve clinical outcomes, and guidelines do not recommend a platelet function test for all patients undergoing PCI with DES, implying clopidogrel monotherapy may also be beneficial for patients with DES implantation. It remains uncertain whether aspirin monotherapy is superior to clopidogrel monotherapy in the stable phase after PCI with DES for reducing the risk of thrombotic/ischemic events and bleeding complications, although the CAPRIE trial demonstrated the superiority of clopidogrel to aspirin in patients with vascular disease including myocardial infarction (MI). To our knowledge, there have been no large-scale randomized controlled trials comparing antiplatelet monotherapies for patients in the chronic phase after PCI with DES. For now, there is only one single-center observational study directly comparing aspirin and clopidogrel monotherapies in the chronic phase beyond DAPT after PCI with DES.

To present a new direction of long-term medical therapy after DES implantation, we designed this study entitled "**H**armonizing **O**ptimal **S**trategy for **T**reatment of coronary artery stenosis-**EX**tended **A**ntiplatelet **M**onotherapy (**HOST-EXAM**)." This randomized trial will compare the incidence of major adverse cardiovascular events (MACEs) and bleeding complications during clopidogrel or aspirin monotherapy for 2 years. We hypothesize that long-term maintenance with clopidogrel will have better outcomes than those of aspirin in patients with PCI with DES.

2) Hypothesis

Clopidogrel is superior to aspirin in preventing clinical events and device-oriented outcomes

5. Research Materials

Clopidogrel 75mg qd p.o. monotherapy, Aspirin 100mg qd p.o. monotherapy

6. Study Population

5,530 patients derived from a population of Korean patients that received PCI with DES without events for 12 ± 6 months under maintenance of dual or triple antiplatelet therapy will be enrolled in the present trial.

7. Study Period

IRB approval date ~ December 2028

8. Eligible criteria, Sample size calculation

1) Inclusion Criteria:

- Male and female aged ≥20 years
- Maintenance of dual or triple antiplatelet therapy at least 12 ± 6 months after PCI with DES
- No history of further clinical event after PCI with DES
- Plan to change to antiplatelet monotherapy
- Agreement to give written informed consent

2) Exclusion Criteria:

- History of hypersensitivity to aspirin or clopidogrel
- History of contraindication to aspirin or clopidogrel
- Active pathologic bleeding, such as peptic ulcer, tumor bleeding or intracranial haemorrhage
- History of major bleeding, BARC class ≥3, resulting in stop of antiplatelet agents within 3 months
- Bleeding diathesis
- Known coagulopathy or refusal of blood transfusion
- Presence of non-cardiac comorbidity with life expectancy ≤2 years from randomization
- Plan to surgery or intervention which needs to stop antiplatelet agents ≥3 months
- Females with childbearing potential or breast-feeding
- Conditions that may result in protocol non-compliance by the committees
- Co-administration of contraindicated medications as follows: other P2Y12 inhibitors (prasugrel or ticagrelor); anticoagulants (warfarin, new oral anticoagulants, or chronic therapy of heparin); cytochrome P450 2C19 inhibitors (fluoxetine, moclobemid or voriconazole); probenecid; high dose of methotrexate (≥15 mg/week); lithium
- Refusal to give written informed consent

3) Sample size calculation

Hypothesis: Clopidogrel is superior to aspirin in preventing clinical events, defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or major bleeding at 24 months after randomization. Based on the event rates of a previous trials performed in various populations including Korean, we predicted clinical event rate of clopidogrel and aspirin to be 9.6% and 12.0%, respectively.

- Primary endpoint: clinical events defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or major bleeding at 24 months after randomization.
- Design: superiority
- Sampling ratio: Clopidogrel versus Aspirin = 1:1
- Type I error (α): two-sided 5%
- Accrual time : 4 years

- Total time : 6 years (accrual year + follow-up 2 years)
- Assumption: Clinical event rate 9.6% in clopidogrel vs. 12.0% in aspirin group
- Statistical power (1- β): 80%
- Potential withdrawal rates : 5% in each groups

Based on the above assumption, expected number of events in each test drug group is 567. We would need total 5,530 patients (2,765 patients in each group) with consideration of withdrawal rates.

Final Sample Size

5,530 patients (Clopidogrel group : 2,765 patients, Aspirin group : 2,765 patients)

9. Methods

1) Study design

The HOST-EXAM is designed as a prospective, randomized, open-labeled, multicenter, comparative effectiveness trial. The study algorithm is shown in Figure below. This trial is investigator-initiated with grant support from the 4 Korean pharmaceutical firms: Chong Kun Dang Pharmaceutical Corp; Samjin Pharmaceutical Co, Ltd; HANMI PHARMA Co, Ltd; and Daewoong Pharmaceutical Co, Ltd. Other than financial support, the companies will not be involved in protocol development or the study process, including site selection, implementation, management, data collection, or data analysis. We are responsible for the design and implementation of the trial, related statistical analyses, and all aspects of manuscript preparation including drafting, editing, and approving final content. This study is based on principles outlined in the Declaration of Helsinki. All patients will be required to provide written informed consent at the time of enrollment. The study will be conducted by the independent Seoul National University Hospital Clinical Trial Center, which includes 2 managing clinical research associates who are independent from the study and have no conflicts of interest. The Medical Research Collaborating Center will help the Clinical Trial Center conduct the study.

2) Randomization, blinding, and interventions with study drugs

Once all eligible criteria are satisfied and written informed consent is obtained by the investigators, patients will be randomized to aspirin or clopidogrel monotherapy in a 1:1 ratio. The randomization will be balanced, stratified by the center, and independently conducted online via Interactive Web Response Service, a Web-based application by the Seoul National University Hospital Medical Research Collaborating Center. A total of 5,530 patients will be enrolled from 37 high-volume PCI centers in Korea. The study participants will be randomized to the experimental (clopidogrel 75 mg) or control (aspirin 100 mg) group. The medication is maintained for up to 24 months after randomization. A clinical follow-up is planned at 12 and 24 months, and additional visits are at the discretion

of attending physicians. The investigators will be urged to follow up the patients by office visits or telephone contacts as necessary. When a patient does not appear at the scheduled time, an investigator or research coordinator checks his/her status via telephone visits to minimize the risk of underreporting clinical events. On each visit, patient adherence to the study drug will be assessed, and discontinuation of the allocated drug will always be discussed and checked based on the physician's recommendation.

Drug adherence will be evaluated by the indirect method, which includes patient self-reporting, pill counts, and pharmacy refills. These parameters have been established as good tools for assessing drug adherence. It is allowed to interrupt antiplatelet therapy within consecutive 14 days, regardless of type of allocated drug or the reason leading to temporary cessation (invasive procedures, medical condition requiring a fast, deficiency of pills, or etc). During the study, some medications should not be administered simultaneously as mentioned above. For example, when the enrolled patients get to initiate anticoagulation treatment during the study, their attending physicians will stop the study progression, assess ischemic and bleeding risk, prescribe oral anticoagulant (warfarin with lower INR or new oral anticoagulants) and 1 antiplatelet (clopidogrel or low-dose aspirin), and consider adding proton pump inhibitors. Although, each will be followed up till the study completes.

3) Permitted/prohibited concomitant medications

If the drug is not prohibited for concomitant use, it can be allowed if necessary. For concomitant drugs during the clinical trial period, the drug name, dosage, and duration of use must be recorded in the case report.

The following medications can be registered as subjects after discontinuation.

- CYP2C19 inhibitors: fluvoxamine, fluoxetine, moclobemid, voriconazole
- Long-term warfarin treatment
- Probenecid (stimulating uric acid excretion)
- High dose methotrexate (15 mg/week or more)
- Lithium preparations: Lithium preparations, lithium carbonate

4) Study flow

	Screening ~ Day 0	**Baseline Day 0**	**Visit at 1 year ± 30days**	**Visit at 2 years ± 90days**
Informed Consent	●			
Allocation of Subject Number (SN)	●			
Medical and Clinical History (clinical diagnosis, risk factors, angina status, cardiac history)	●			
Demographic Characteristics (age, sex, familial history, social history)	●			
Vital Signs and	●		●	●

Anthropometric Data				
Laboratory Results	●		●	●
Brief Physical Examination	●			
Evaluation of inclusion and exclusion criteria	●			
Allocation of Randomization Number (RN)		●		
Baseline Angiographic and Procedural Data	●			
Previous and Concomitant Medications	●	●	●	●
Clinical Outcomes	●	●	●	●
Minor GI Complications			●	●

(1) Screening (Visit 1, ~ Day 0)

*Informed consent

*Subject number allocation

*History taking

Silent Ischemia/Stable Angina/Unstable Angina/NSTEMI/STEMI, Previous CABG, Previous MI, Heart Failure, Valvular Heart Disease, Previous Heart Transplantation, Diabetes Mellitus, Renal Failure, Stroke, Hypertension, Peripheral Vascular Disease, Dyslipidemia, Chronic Lung Disease, Family History of Coronary Artery Disease, Gastrointestinal Bleeding

*Demographics: sex, birth date, smoking history, alcohol intake history

*Vital signs and physical examinations: blood pressure, pulse rate, body weight, height, BSA, BMI

*Laboratory results

*Evaluation for inclusion and exclusion criteria

*Information of PCI procedure: stenosis site, number of implanted stents, type of implanted stents

*Clinical Outcomes l: All cause death, non-fatal MI, stroke, major bleeding, readmission due to ACS

*Clinical Outcomes II: TVR, TLR, Stent thrombosis

*Prior medication history

(2) Baseline data (Visit 2, Day 0)

*Evaluation for inclusion and exclusion criteria

*Clinical Outcomes l: All cause death, non-fatal MI, stroke, major bleeding, readmission due to ACS

*Clinical Outcomes II: TVR, TLR, Stent thrombosis
*Concomitant medications

(3) Week 48 ± 90 days (Visit 3)
*Vital signs and physical examinations: blood pressure, pulse rate
*Laboratory results
*Angiographic results
*Clinical Outcomes l: All cause death, non-fatal MI, stroke, major bleeding, readmission due to ACS
*Clinical Outcomes II: TVR, TLR, Stent thrombosis, minor GI complications
*Concomitant medications
*Adverse events: UGI endoscopy due to GI symptoms

(4) Week 96 ± 90 days (Visit 4)
*Vital signs and physical examinations: blood pressure, pulse rate
*Laboratory results
*Angiographic results
*Clinical Outcomes l: All cause death, non-fatal MI, stroke, major bleeding, readmission due to ACS
*Clinical Outcomes II: TVR, TLR, Stent thrombosis, minor GI complications
*Concomitant medications
*Adverse events: UGI endoscopy due to GI symptoms

5) Study endpoints

(1) Primary endpoint

[1] A composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or major bleeding at 24 months after randomization

- Detailed definition of each clinical events was determined by the third universal definition of MI, the American College of Cardiology Foundation and the American Heart Association, or objective evidence

(2) Secondary endpoints

[1] Target lesion revascularization : defined as any repeat revascularization procedure at the original lesion of the index procedure any time during the follow-up period

[2] Target vessel revascularization : defined as any repeat revascularization procedure involving at least one of the target vessels that were treated in the index procedure

[3] Stent thrombosis : defined according to the Academic Research Consortium (ARC)

[4] Minor GI complications : assessed on the basis of newly added GI medications (including H2-blockers and PPIs documented for each patient), or symptom-driven GI endoscopy (type of endoscopy, test results, and further interventions)

[5] Cost-effectiveness : Additional medical costs related to these minor GI complications (South Korean won/year) will be calculated to assess the cost-effectiveness of each drug based on average Korean expenses

6) Protocol violation

The followings will be recorded as protocol violation and the reason will be recorded and the data coordinating center must be notified promptly.

- Patients who will be lost to follow-up before 2 years, excluding patient withdrawal.
- Patients who are enrolled, but does not met inclusion/exclusion criteria.
- Patients who are not treated with allocated antiplatelet agent

In order not to miss out on the occurrence of an adverse reaction that the investigator cannot identify, a clinical subject who refuses to visit should be directly contacted by phone, letter, or in person. The reason for drop-out should be recorded in the case report form. Since the final analysis should be performed with both intention-to-treat (ITT) and per-protocol (PP) methods, follow-up should be maintained for all subjects except for the case of dropout due to the subject's withdrawal of consent. Clinical trial subjects who have been eliminated cannot be re-enrolled.

7) Trial organization and data management

(1) Executive committee

The executive committee, which consists of the study chairperson and principal investigators of the primary investigating centers, oversees the administrative progress of the study and approves the study design, protocol, and amendment to the data safety and monitoring board (DSMB) and the participating centers. The executive committee is in charge of reviewing the results, determining the adjudication of the publication, and selecting secondary projects. The executive committee also has the final decision to modify or stop the study prematurely based on DSMB recommendations.

(2) Data safety and monitoring board (DSMB)

An independent DSMB, which consists of cardiologists and biostatisticians, reviews safety data from the study and constructs recommendations for adverse events/serious adverse events, protocol deviations, and follow-up case reports. Regular DSMB meetings are held before the start of the study to establish the study policies; review the raw data; discuss the issue of patient safety, compliance, and treatment efficacy; and advise the executive committee to modify or stop the study if there are any important issues such as significant harm or benefit to the experimental group. According to the DSMB report, the executive committee decides whether the study should be continued or stopped. Because there are no formal guidelines to guide the DSMB with regard to the level of significance needed to prematurely stop the trial

for either efficacy or safety, a type I error, α will not be changed. The DSMB helps conduct the trial appropriately by reviewing the cumulative investigational data for accuracy and completeness and by ensuring protocol compliance. The independent clinical research associates will regularly check compliance with good clinical practice and protocol, dropouts, systematic deficiency, and quality of data. The risk-based source data verification will be applied to eliminate risk and improve the data quality by cross-referencing data recorded in a case report form to the original source information. The DSMB develops a consensus understanding of all trial endpoints and definitions used in the event adjudication process. All DSMB reports remain strictly confidential but are available to regulatory authorities on request.

(3) Clinical event adjudication committee

The centralized clinical event adjudication committee (CEAC), which consists of independent cardiologists, also helps execute the trial properly and reduces potential bias. The CEAC is responsible for all aspects of reviewing the results, determining the adjudication of the publication, and selecting secondary projects. In particular, the CEAC develops specific criteria for categorizing clinical events and endpoints based on the protocol. At the study onset, the CEAC will establish clear rules outlining the minimum amount of data required and the algorithm followed to classify the clinical events. To maximize the procedural justice of our study and guarantee CEAC independence, all CEAC members are masked to the assigned study arm when performing their assessment of clinical events.

(4) Data coordination and site management

Data collection, coordination, and site monitoring will be performed by a research coordinator of the Clinical Trials Center at Seoul National University Hospital, the main investigating center.

(5) Minimizing sources of bias

The following methods will be performed to minimize potential sources of bias

- Enrollment of subjects is limited by inclusion and exclusion criteria
- Subjects will be systematically randomized with blinding procedures implemented.
- An external, independent Clinical Events Committee (CEC) blinded to treatment assignment will review and adjudicate, at minimum, all deaths and safety-endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- An external, independent Data Monitoring Committee (DMC) will evaluate safety data and advise the Sponsor in regard to continued safety of the study, to ensure the well-being of the subjects.
- An independent Angiographic Core Lab will evaluate all event angiograms.
- Statistical analyses will be independently validated

- Study sites should follow their institutional procedures for maintenance of angiography and laboratory equipment used for assessing the study variables.

Study monitors will verify subject data and ensure compliance with this Clinical Investigational Plan and other study requirements, i.e., blinding and informed consenting processes

10. Statistical analysis plan

(1) Timing of analyses

- The primary outcome and its individual components will be analyzed on both intention-to-treat basis and per-protocol basis at 2 years after randomization.
- All secondary outcomes will be analyzed on both intention-to-treat basis and per-protocol basis at 2 years after randomization.

(2) Analysis populations

[1] Intention-to-treat population

- All patients who sign the written informed consent and randomized in this study will be included in the analysis regardless of their adherence to the entry criteria, the treatment they actually received, deviation from the prescribed protocol, or withdrawal from the study. Despite discontinuation of the allocated study drug in patients with protocol violation, they will be followed up till the study completes and analyzed for the primary endpoint.

[2] Per-protocol population

- The per-protocol set will be supportive to minimize unanticipated problems that could dilute treatment differences of interest.

(3) Missing data

The primary analysis of the study endpoints will not be covariate-adjusted. No imputation methods will be used to infer missing values of baseline variables. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates. As a secondary analysis, we will also examine the patients who have been lost to follow-up. We will perform a comparison of baseline characteristics in patients with vs. without 2-year follow up. The baseline characteristics will include as followed Table 1. In addition, a sensitivity analysis will be performed to assess the impact of these patients on the study outcomes. For patients lost to follow-up, multiple imputation techniques will be used to calculate pooled estimates of the treatment effect and confidence intervals which will then be compared to the primary statistical analysis.

(4) General principles of statistical analysis

In this clinical trial, unless otherwise specified, the significance level of the statistical test is

set to 0.05, and a two-sided test is a principle. In addition, the number of observational objects, mean, standard deviation, median, minimum, and maximum values are presented for continuous variables, and frequencies and ratios are presented for categorical data.

[1] Demographic information and clinical history data

- This is a process to confirm that there is no difference between each administration group by comparing the characteristics of clinical subjects in the treatment group and the control group before enrollment in the clinical trial.
- Demographic information such as gender and age is evaluated in ITT. For continuous data, the mean, standard deviation, median, minimum, and maximum value are presented and compared using a two-sample t-test or Wilcoxon's rank sum test depending on whether the normality assumption is satisfied. In the case of categorical data, frequency and ratio are presented and compared using Pearson's chi-square test or Fisher's exact test.

[2] Analysis of the primary endpoint

- Incidence of all-cause death, non-fatal MI, stroke, major bleeding, readmission due to ACS up to 2 years after antiplatelet therapy

  : The incidence of all-cause death, non-fatal MI, stroke, major bleeding, and readmission due to ACS up to 2 years after antiplatelet therapy will be estimated by Kaplan-Meier method, and the difference between the two groups will be compared using a log-rank test. Subjects who do not have all-cause death, non-fatal MI, stroke, major bleeding, or readmission due to ACS will be censored at the time of their last visit.

[3] Analysis of the secondary endpoints

- Incidence of TVR & TLR (target vessel/lesion revascularization) up to 2 years after antiplatelet therapy

  : The incidence of TVR and TLR up to 2 years after antiplatelet therapy will be estimated by Kaplan-Meier method, and the difference between the two groups will be compared using a log-rank test. Subjects who do not have TVR or TLR will be censored at the time of their last visit.
- Incidence of stent thrombosis up to 2 years after antiplatelet therapy

  : The incidence of stent thrombosis up to 2 years after antiplatelet therapy will be estimated by the Kaplan-Meier method, and the difference between the two groups will be compared using a log-rank. Subjects who do not have stent thrombosis will be censored at the time of their last visit.
- Incidence of minor GI complications up to 2 years after antiplatelet therapy

  : The incidence of minor GI complications up to 2 years after antiplatelet therapy will be estimated by the Kaplan-Meier method, and the difference between the two groups will be compared using a log-rank. Subjects who do not have minor GI complications will be censored at the time of their last visit.

[4] Cost-effectiveness analysis

i. In this analysis, we will compare Clopidogrel and Aspirin to estimate cost-effectiveness patients who underwent antiplatelet therapy after drug-eluting stent implantation for coronary artery disease.

ii. Analysis will be performed from the perspective of the health care system, and accordingly, the cost is directly calculated based on the medical cost.

- If necessary, further analysis will be performed from a social point of view. In this case, in addition to direct medical expenses, the patient's time expenses, transportation expenses, nursing expenses, and productivity loss expenses will be estimated.

iii. Effectiveness endpoint will be presented in Quality-adjusted life years (QALYs).

- Clinical events (all cause death, non-fatal MI, stroke, major bleeding, readmission due to ACS, etc.) are reported as each health status, and the corresponding quality of life life) will be applied to estimate the effect.
- To estimate the effect, the use of the EuroQol five-dimensional questionnaire (EQ-5D), a health-related quality of life measurement tool, will be utilized.

iv. Cost estimation basically utilizes micro-costing, which calculates the total cost value by grasping information on the amount of medical resources used and the unit cost used throughout the analysis period, and ischemia and bleeding. For medical expenses according to clinical cases, macro-costing is used through analysis of health insurance claim data.

- For health insurance claim data, customized health information data provided by the National Health Insurance Corporation (hereinafter, customized research DB) will be used. After approval of the IRB, an application for the use of customized research DB will be made at NHISS (http://nhiss.nhis.or.kr), a data providing site operated by the Korean National Health Insurance Service, and the research plan and IRB approval results from the National Health Insurance Service. Data is provided after deliberation based on the notice.
- All data is provided in the form of an alternative identification number of the resident registration number to ensure anonymity, and the alternative identification number is not used in presenting the analysis results.

v. Cost-effectiveness will be calculated in the form of an incremental cost-effectiveness ratio (ICER) representing the additional cost versus the additional effect between monotherapy.

vi. One-way sensitivity analysis and probabilistic sensitivity analysis will be performed on uncertainty.

11. Care for the safety of the subjects

1) For conducting institution

The head of the conducting institution should be equipped with clinical laboratories, facilities, prepare experts necessary for conducting the relevant clinical trial step by step,

and make adequate preparations so that the clinical trial can be properly conducted.

2) For principal investigator

The principal investigator must be fully aware of the adverse reactions and cautions specified in this clinical trial protocol in advance, and if any serious adverse reactions occur during the clinical trial, they must immediately report it to the Institutional Review Board.

3) For clinical trial managers

Predicted adverse reactions and precautions for use specified in the protocol should be fully understood, and if any serious adverse reactions occur during clinical trials, they must be reported to the supervisor immediately.

12. Additional statements

1) Pharmaceutical Clinical Trials Management Standards (KGCP) and Helsinki Declaration

- The procedures stipulated in this protocol are designed to ensure that clinical trial investigators comply with the standards for management of pharmaceutical clinical trials and the basic spirit of the Helsinki Declaration in conducting, evaluating and recording the results of this study. This clinical trial will also be conducted in accordance with national regulations.

2) Clinical trial subject consent

- Investigators should give patients and their caregivers ample opportunity to elaborate on all aspects of the study and to know all predictable outcomes. The patient's consent must be documented.
- The investigator must sign and confirm the clinical subject consent form. Investigators should not perform specific tests for the sole purpose of clinical trials until consent is obtained from the patient.

3) Approval of clinical trial protocol

Before starting a clinical trial, submit the clinical trial protocol and related documents to the clinical trial review committee in accordance with local regulations. Investigators must inform each other in writing that all ethical and legal requirements have been met prior to enrollment of the first subject.

4) Case Report Form

- Patient's source documents refer to the patient records of the doctor in charge that are kept in the laboratory. Most of the supporting documents are charts from the hospital or the attending physician, and all information recorded in the patient's case report should be consistent with the supporting documents.
- It is the investigator's job to record, review and sign the case record. After filling out the case record, the examiner certifies that the information recorded in the case record is true by signing each case record. In all cases, the investigator is ultimately responsible

for the accuracy and reliability of all clinical and laboratory values recorded in the case report.

5) Confidentiality Guarantee

All names of clinical subjects shall be kept confidential, and subjects shall be identified at the time of recording and evaluation by the number given in the clinical study. Inform the subject that all clinical trial data are stored on a computer and treated strictly confidentially. The signed automated clinical trial subject will be kept by the investigator. By signing this protocol, the investigator agreed to obtain the correct consent from the clinical trial subjects participating in the clinical trial, and also agreed to undergo due diligence upon request. The person in charge of the clinical trial shall have a list of the subject number and subject name recorded so that the record can be retrieved later. The consent of the clinical subject and the list of subjects are kept for 3 years from the date of approval of the item (the date of completion of the clinical trial if the product is not approved).

6) Understanding the clinical trial plan

Investigators and managers accurately analyze and understand the clinical trial plan, and conduct the clinical trial.

7) Clinical trial monitoring and inspection

In order to ensure that clinical trials are conducted in accordance with KGCP and that test data can be recognized at home and abroad, monitoring and inspection can be carried out when necessary. When monitoring this test, it is necessary to check whether the case record is complete and clear, and to review the record with the examiner in the presence of the investigator, and the investigator must cooperate with the monitor or inspector at any time.

8) Record and use of clinical test results

- Record of clinical trial results

- All data collected during this clinical trial should be recorded by the investigator in the supporting document and the original should be kept.
- In case of missing data, the tester must attach a reasonable explanation.
- When revising the contents entered in the case record, the original record must be recognizable and the revised clinical trial officer's signature must be signed.

- Use of clinical trial results

By signing this clinical trial protocol, the investigator has agreed to use the results of this trial for the purposes of registration, presentation, and information provision for medical experts.

9) Clinical test result data management

- Record of data

All data entered in the electronic case record (e-CRF) should be verifiable by each laboratory against appropriate supporting documents. The laboratory should cooperate with the clinical trial coordinator to carry out this process if necessary. In the case of monitoring, each agency's supporting document check list will be used to verify the supporting documents for all collected data.

- Data management

Data for this clinical trial is collected using the electronic (e-CRF). Management of clinical data will be performed in accordance with relevant guidelines. This process also applies to data entered into the e-CRF and other supporting documents (eg blood pressure, laboratory test data, etc.). Internationally certified and used dictionaries will be used for data coding (adverse reactions, concomitant drugs, etc.).

- Storage of data

All essential documents will be safely stored in a form that can be used/verified upon request by a person with the appropriate authority. In addition, the electronic case record (e-CRF) must be kept in the form of an electronic document at each laboratory.

10) Modification of clinical trial protocol

The contents of this protocol cannot be changed during the trial without the consent of the clinical trial director. Once the test has begun, modifications should only be made in exceptional cases. Any changes to the plan must be signed and agreed in writing by all parties involved. The revised content must be approved by the Institutional Review Board.

13. References

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