SMart Angioplasty Research Team: Comparison between P2Y12 Antagonist MonotHerapy and Dual Antiplatelet Therapy in Patients UndergOing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) Trial

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PROTOCOL SUMMARY

Trial Name and Number	Smart Angioplasty Research Team: Comparison between P2Y12 Antagonist MonotHerapy and Dual Antiplatelet Therapy in Patients UndergOing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) Trial
Objectives	To compare the efficacy and safety of P2Y12 antagonist monotherapy versus aspirin plus P2Y12 antagonist following 3-month of dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES)
Study Design	Prospective, open label, two-arm, randomized multi-center trial to test the noninferiority of P2Y12 antagonist monotherapy compared with aspirin plus P2Y12 antagonist following 3-month of DAPT after DES implantation. Patients will be stratified by stent types (cobalt-chrome everolimus-eluting stents, platinum-chrome everolimus-eluting stents, and sirolimus-eluting stents with bioresorbable polymer) only for descriptive subgroup analysis. Patients will be further stratified by P2Y12 antagonist (clopidogrel, prasugrel, or ticagrelor), clinical presentation (acute coronary syndrome) and investigational center.
Patient Enrollment	3,000 patients will be enrolled at 33 centers in South Korea.
Patient Follow-Up	Clinical follow-up will occur at 3, 6 and 12 months, and at 2 and 3 years. Investigator or designee may conduct follow-up as telephone contacts or office visits.
Primary Endpoint	A composite of death, myocardial infarction, or cerebrovascular events at 12 months after the index procedure
Secondary Endpoints	1) Each component of primary endpoint at 12-month 2) Cardiac death at 12-month 3) Target lesion revascularization (TLR) at 12-month 4) Target vessel revascularization (TVR) at 12-month 5) Any revascularization at 12-month 6) Stent thrombosis at 12-month: definite or probable stent thrombosis by ARC definition 7) BARC bleeding ≥3 at 12-month 8) BARC bleeding ≥2 at 12-month 9) Major adverse cardiac and cerebrovascular events (death, MI, cerebrovascular event, or any revascularization [MACCE]) at 12-month 10) Each component of primary and secondary endpoints at 2- and 3-year

1 Background

Current guidelines recommend 6 to 12 months of dual antiplatelet therapy (DAPT; aspirin plus P2Y12 antagonist) in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES).[1,2] However, these recommendations are not based on randomized studies, but data from several registries with the 1st generation DES.[3,4] In randomized studies, prolonged DAPT longer than 12 months did not improve clinical outcomes compared with aspirin monotherapy,[5] and 6-month DAPT was noninferior to 12-month or longer DAPT in reducing adverse cardiac events.[6,7] Considering improved safety of the currently used 2nd generation DES compared with the 1st generation DES,[8,9] the minimum required duration of DAPT can be shortened. A recent large randomized study reported that shorter duration (3 months) of DAPT is noninferior to prolonged duration (12 months) of DAPT.[10] Prolonged DAPT increases bleeding risk[11,12] and cost. Endoscopic, dental, and surgical procedures are often delayed due to prolonged DAPT, which may affect the patient's quality of life.[13] Therefore, to determine the optimal or minimal necessary duration of DAPT is very important.

The other important issue is that which antiplatelet agent is more appropriate after DAPT. Aspirin monotherapy has been recommended traditionally.[1,2] However, there is no randomized comparison study between aspirin monotherapy versus clopidogrel monotherapy after DAPT in patients undergoing PCI with DES. In CAPRIE trial, clopidogrel showed a superior efficacy in preventing ischemic events compared with aspirin.[14] Moreover, the incidence of gastrointestinal bleeding was significantly lower with clopidogrel than with aspirin. Clopidogrel monotherapy can reduce ischemic events and bleeding risk compared with aspirin monotherapy.

Therefore, in the SMART-CHOICE trial we will test noninferiority of P2Y12 antagonist monotherapy compared with aspirin plus P2Y12 antagonist after 3-month of DAPT.

2 Study Objectives and Hypotheses

2.1 Objective

To compare the efficacy and safety of P2Y12 antagonist versus aspirin plus P2Y12 antagonist following 3-month of dual antiplatelet therapy (DAPT) in patients undergoing PCI with DES

2.2 Hypothesis

P2Y12 antagonist monotherapy is noninferior to aspirin plus P2Y12 antagonist in reducing ischemic events and bleeding risk after 3-month DAPT.

3 Study Design

3.1 Study Design

Prospective, open label, two-arm, randomized multi-center trial to test the noninferiority of P2Y12 antagonist monotherapy compared with aspirin plus P2Y12 antagonist following 3-month of DAPT after DES implantation. Patients will be stratified by stent types (cobalt-chrome everolimus-eluting stents, platinum-chrome everolimus-eluting stents, and sirolimus-eluting stents with bioresorbable polymer) only for descriptive subgroup analysis. Patients will also be stratified by P2Y12 antagonist (clopidogrel, prasugrel, or ticagrelor), clinical presentation (acute coronary syndrome) and investigational center.

3.2 Patient Enrollment

A total of 3,000 patients will be enrolled at 33 centers in South Korea. Patients undergoing PCI with DES will be eligible. After successful PCI with DES, all eligible patients will be randomized either to P2Y12 antagonist monotherapy or to aspirin plus P2Y12 antagonist following 3-month of DAPT.

3.3 Patient Follow-up

Clinical follow-up will occur at 3, 6 and 12 months, and at 2 and 3 years after intervention. The investigator may conduct follow-up as telephone contacts or office visits.

3.4 Early Study Termination

No statistical rule for early trial termination is defined and this study will not be stopped early based on efficacy results. An independent Data Safety Monitoring Board (DSMB) will review the safety data including death, MI, stroke or other serious adverse events. The DSMB will be powered to recommend suspension of enrollment or termination of the study based on safety concerns (refer to section 10.3 Data Safety Monitoring Board). The Executive Committee will make the final decision for early study termination based on DSMB recommendations.

3.5 Measures to Avoid/Minimize Bias

In order to minimize bias in assessing clinical events, an independent Clinical Event Adjudication Committee (CEAC) (refer to section 10.4 Clinical Event Adjudication Committee) and DSMB (refer to section 10.3 Data Safety Monitoring Board) will be established. In addition, all angiographic analysis data will be obtained from an independent core laboratory in South Korea. Data management will be performed by an independent data management core center, and a web based electronic case report form (eCRF) and a web-based online randomization program will be utilized. Restricted access to the data management system will be maintained throughout the trial period.

4 Endpoints

4.1 Primary Endpoint:

A composite of death, myocardial infarction [MI], or cerebrovascular events at 12 months after index procedure for comparison of P2Y12 antagonist monotherapy vs. aspirin plus P2Y12 antagonist therapy

4.2 Secondary Endpoints:

1) Each component of primary endpoint at 12-month
2) Cardiac death at 12-month
3) Target lesion revascularization (TLR) at 12-month
4) Target vessel revascularization (TVR) at 12-month
5) Any revascularization at 12-month
6) Stent thrombosis at 12-month: definite or probable stent thrombosis by ARC definition
7) BARC bleeding ≥3 at 12-month
8) BARC bleeding ≥2 at 12-month
9) Major adverse cardiac and cerebrovascular events (death, MI, cerebrovascular event, or any revascularization [MACCE]) at 12-month
10) Each component of primary and secondary endpoints at 2- and 3-year

4.3 Study Timeline:

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

5 Randomization

5.1 Randomization

Patients will be randomized according to the type of antiplatelet therapy.

Randomization of the type of antiplatelet therapy will be done 1:1:

a) P2Y12 antagonist monotherapy
b) Aspirin plus P2Y12 antagonist therapy

5.2 Stratification

To ensure balance among the strata, randomization will be stratified by the following factors:

a) Acute coronary syndrome
b) Enrolling sites
c) Stent types : cobalt-chrome everolimus-eluting stents (Xience PrimeTM stents, Xience ExpeditionTM stents, or Xience AlpineTM stents), platinum-chrome everolimus-eluting stents (PromusTM ElementTM stents, PromusTM PremierTM stents, or Synergy stents), or sirolimus-eluting stents with bioresorbable polymer (Orsiro, Biotronik)
d) P2Y12 antagonist :clopidogrel, prasugrel, or ticagrelor

6 PATIENT ENROLLMENT AND WITHDRAWAL

6.1 Patient Population

A total of 3,000 patients derived from a population of Korean patients receiving PCI for coronary artery disease will be enrolled in the present trial. It is recommended that each enrolling investigator review the most recent instructions for use (IFU) and assess the contraindications, warnings, and precaution sections for treating potential patients.

6.2 Patient Screening

Consecutive patients presenting at participating centers will be evaluated for the entry into the study. All consecutive patients undergoing PCI with DES should be invited to participate in the study. A member of each research team should review the patients′ medical history for eligibility. If all eligibility criteria are met and written informed consent is provided, the patient may be enrolled in the study. In all cases, the final decision regarding eligibility for randomization in the trial of all target vessels will be the responsibility of the interventional investigator based upon clinical factors and review of the initial angiogram. Patients will be entered into the electronic Case Report Form (eCRF) only after informed consent has been obtained.

6.3 Eligibility Criteria

6.3.1 General Inclusion Criteria

a) Subject must be at least 20 years of age.

b) Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving P2Y12 antagonist monotherapy or aspirin plus P2Y12 antagonist and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.

c) Patients should have undergone successful percutaneous coronary intervention with drug-eluting stent for stable ischemic heart disease or acute coronary syndrome

d) Patients must have one or more coronary stenosis of 50% or more in a native coronary artery with visually estimated diameter of ≥2.25 mm and ≤4.25 mm eligible for stent implantation.

e) Target lesion(s) must be amenable for percutaneous coronary intervention

6.3.2 General Exclusion Criteria

a) Hemodynamic instability or cardiogenic shock
b) Active bleeding
c) Known hypersensitivity or contraindication to study medications
d) Female of childbearing potential, unless a recent pregnancy test is negative, who possibly plan to become pregnant any time after enrollment into this study
e) Non-cardiac co-morbid conditions are present with life expectancy <2 year or that may result in protocol non-compliance (per site investigator's medical judgment).
f) DES implantation within 12 months before index procedure

6.4 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 death
- Patient voluntary withdrawal
- Patient withdrawn by investigator as clinically indicated
- Patient lost to follow-up (unofficial withdrawal)

It is imperative to obtain complete follow-up data for all patients, whether or not they receive their assigned treatment. 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, whether or not a patient continues to receive treatment according to the protocol. Patients will not be replaced in this trial.

6.4.1 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.

7 Interventions/ 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 7.1 Schedule of Events. The treatment strategy will be determined by the study-certified interventional operator. It is recommended that each enrolling investigator review the most recently updated instructions for use (IFU) and assess the contraindications, warnings, and precaution sections for treating potential patients. During the index procedure and appropriate medical follow up, it is recommended that enrolling investigators try to adhere to the following guidelines when applicable:

- 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions[15]
- 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention.[16]
- AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update. A Guideline From the American Heart Association and American College of Cardiology Foundation *Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association*.[17]
- Third Report National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III Guidelines)[18]
- The Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[19]
- 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update) A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.[20]
- 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.[21]

7.1 Schedule of Events

	Screening &	Post-Procedure	Follow up				
			3M	6M	12M	2Y	3Y

	Baseline		3 Months ±30 days	6 Months ±30 days	12 Months ±30 days	2 Years ±30 days	3 Years ±30 days
Informed consent	X[1]						
Inclusion/Exclusion Criteria	X						
Demography/ Medical History	X[2]						
Randomization	X						
Prescription for antiplatelet	X	X	X	X	X	X	
Drug Compliance			X	X	X	X	X
Adverse events[4]			X	X	X	X	X
Serious Adverse Event			X	X	X	X	X
12 lead ECG	X[5]						
Coronary angiogram	X						
CBC	X		X				
Creatinine, BUN	X		X				
hs-CRP	X		X				
Total cholesterol, LDL cholesterol	X		X				
Fasting glucose level	X[6]						
Pregnancy test, Urine (if applicable)	X						
CPK, CK-MB, Troponin I	X	X[7]					
VeryfyNow-PRU/ARU			X				
Echocardiogram		X					

[1] The informed consent should be signed prior to the diagnostic angiogram, but is can be signed after the diagnostic angiogram in the urgent situation.
[2] Assessment of Age, Sex, Risk factors, Clinical diagnosis, Angina status, Cardiac history, Cardiocerebral event and bleeding
[3] For patients undergoing stent implantation
[4] Assessment of Cardiocerebral event and bleeding, especially
[5] ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, or significant arrhythmias, heart failure or other signs or symptoms of clinical instability.
[6] It may be done later, before discharge when the patient is in a fasting state
[7] Optional in selected centers and if baseline lab is done, enzymes must be followed every 8-hours for 24 hours post-index procedure

7.2 Index PCI Procedure

7.2.1 Index PCI

PCI will be performed according to standard procedure. After successful PCI, all eligible patients will be randomized either to P2Y12 antagonist monotherapy group or to aspirin plus P2Y12 antagonist group. Randomization will be performed with a Web-based response system and stratified per hospital, stent types, and clinical presentation (acute coronary syndrome or not). All patients will receive cobalt-chrome everolimus-eluting stents (Xience PrimeTM stents, Xience ExpeditionTM stents, or Xience AlpineTM stents), platinum-chrome everolimus-eluting stents (PromusTM ElementTM stents, PromusTM PremierTM stents, or Synergy stents), or sirolimus-eluting stents with bioresorbable polymer (Orsiro, Biotronik).

7.2.2 Adjunctive Pharmacological Therapy

Pre-procedure:

Aspirin: Aspirin in dose 300 mg po must be administered at least 24 hours before the index PCI, whether or not patient was taking Aspirin at home. Aspirin will be further continued at 100-325 mg PO indefinitely.

P2Y12 antagonist: It will be recommended that patients receive oral 300 mg or 600 mg loading dose of clopidogrel at least 12 hours before the index PCI if the patient was not taking clopidogrel prior to admission. However, if the administration of a loading dose was not possible 12 hours in advance, a 600mg loading dose of clopidogrel will be acceptable given in the catheterization lab prior to intervention. Post-procedure, the treatment should be continued 75 mg PO per day for the designated period of either 6-month or 12-month or longer. The use of additional antiplatelet combination (i.e., cilostazol) will not be allowed. If patients present with acute coronary syndromes, prasugrel 60 mg or ticagrelor 180 mg can be used instead of clopidogrel.

In the cardiac catheterization laboratory:

Unfractionated heparin, dosage per label instructions and local standard of care (target ACT 250sec) will be administered. The use of combination with the glycoprotein GPIIb/IIIa inhibitor abciximab will be left to discretion of the operator. The standard dose of abciximab (0.25 mg/kg initial bolus 15 minutes pre-PCI, followed by infusion of 0.125 mcg/kg/minute at a maximum of 10 mcg/minute) will be prescribed. Post procedure, no more heparin is recommended, and abciximab should be continued for 12 hours.

Post procedure and after discharge

Aspirin 100mg plus P2Y12 antagonist daily or P2Y12 antagonist daily following 3-month DAPT will be given according to the randomization. For patients with stents requiring anticoagulation (chronic atrial fibrillation, deep vein thrombosis, left ventricular thrombi for example) it is recommended that investigators follow the ACC/AHA STEMI guidelines for triple therapy after stenting, which include ASA, Clopidogrel, and Warfarin. The goal of Warfarin therapy should be an INR of 2.0-2.5. Patients, who prematurely discontinue antiplatelet therapy secondary to significant active bleeding or for other procedures, should be monitored carefully for cardiac events and, once stabilized, their antiplatelet therapy should be restarted as soon as possible.

7.2.3 Post-PCI

The patient may be monitored in the coronary care unit or angioplasty unit as per institutional routine.

Sheath removal and ambulation.

Any non-investigational closure devices may be used at operator discretion, in which case sheaths may be removed immediately following the procedure and the patient ambulated as per standard of care. If closure devices are not used, sheath(s) should be removed and manual compression applied: In patients receiving to heparin ± GP IIb/IIIa inhibitors: when the ACT falls below 170 seconds. As protracted sheath dwell times are a major risk for bleeding, sheath removal should not be prolonged beyond these guidelines, especially in the presence of GP IIb/IIIa infusion.

Patients receiving GP IIb/IIIa inhibitors should be at strict bed rest until the infusion is complete. Two hours post-infusion discontinuation (and at least 6 hours after sheath removal), the patient may be mobilized and ambulated progressively as per standard of care. For patients not receiving GP IIb/IIIa inhibitors, slow progressive mobilization and ambulation may begin within 4 hours after hemostasis, as per usual standard of care.

7.2.4 Staged PCI Procedures

Either in the planning stages or during the course of multivessel angioplasty it may be advantageous to perform a "staged procedure" defined as serial interventional procedures either during the same hospitalization or during different hospitalizations to achieve complete revascularization. Staged PCI may be required due to renal insufficiency precluding excessive radiocontrast agent use, intra-procedural complications obviating continuation of the complete planned PCI, or other patient related factors limiting single procedure time. A staged procedure may be either planned (declared prior to the procedure as a component of declared PCI strategy) or provisional (declared during procedure due to operator discretion and for specific reasons), but must be declared prior to finishing the initial index procedure. Staged procedure should not be confused with clinically-driven repeat revascularization procedures on index target lesions during or after the initial hospitalization, and should not be counted as part of the primary outcome endpoint. After the first staged procedure, the next planned staged procedure should be completed within 4 weeks of randomization. In the next stage procedure, the same allocated stent should be used. The 30-day follow-up visit should be performed 30 ± 7 days following the day of the final stage of a staged index PCI.

7.3 Lab tests, ECGs and additional hospital procedures

Cardiac enzymes:

In selected participating centers, in addition to the baseline measures, samples for CK, CK-MB and Troponin I/T analyses should be obtained at 8 ± 2 hours, 16 ± 2 hours, and at 24 ± 2 hours post-index procedure, and post any additional PCI or CABG procedures. The peak CPK, CPK-MB and TroponinI/T will be recorded. If the patient develops recurrent chest pain, ischemia, significant arrhythmias, heart failure or other signs or symptoms of clinical instability, additional cardiac enzymes, including CPK, CK-MB and Troponins, should be obtained.

Serum creatinine:

In addition to the baseline value, samples for serum creatinine will be obtained daily post-procedure for two days (minimum) if the baseline calculated creatinine clearance < 60ml/min using the MDRD formula. It is recommended that if the serum creatinine is elevated by ≥0.3 mg/dl from baseline, daily creatinine levels should be measured until renal function is improving.

ECGs:

In addition to the baseline ECG, additional ECGs will be performed at 60±30 minutes post-procedure. An ECG will be obtained at follow-up visits only if clinically indicated.

7.4 Timing of Discharge

Patients may be considered stable for discharge if all of the following are present:

- They have had no chest pain consistent with ischemia
- They have had no signs or symptoms of congestive heart failure
- They have had no significant ventricular arrhythmias (ventricular tachycardia or symptomatic ectopy)
- They are ambulating without limitation, and
- Heparin and GP IIb/IIIa inhibitors have been discontinued for at least 12 hours.

8 Post Index Procedure Management: Follow-up phase

8.1 Clinical follow-up

Clinical follow-up will occur at the following time points:

Follow-up time point	± days
3 months	30
6 months	30
12 months	30
2 years	30
3 years	30

Follow-ups should be office visits but telephone contact will be allowed. Data collected during all follow-up visits will include angina class and major adverse ischemic, neurologic and bleeding events, including re-hospitalization and re-catheterization and Adverse Events/ Serious Adverse Events. Original source documents must be submitted for any clinical events (death, reinfarction, stent thrombosis, revascularization, bleeding, stroke, or any other SAE within 1 year). If the patient is readmitted to a non-study hospital, all possible efforts should be made to obtain original source documents from that hospital. For all reinfarctions, ECGs and cardiac enzymes (CPK, CK-MB, troponin) must be obtained and recorded.

8.2 Additional Event-Driven Visits

Additional event-driven visits may occur as clinically warranted. The following data should be collected at these visits:

- Clinical events including death, MI, revascularization, bleeding, cerebrovascular events, and stent thrombosis. Also, AE related data including laboratory test results, ECG, details, and subsequent coronary angiography results
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and major bleeding complications
- Chronic concomitant medication

8.3 Pharmacological Management and Risk Factors Interventions

Optimal pharmacological management will be given to all patients enrolled the study. In particular, it will be advised to each investigator to emphasize the importance of cardiovascular risk-factor modification.

Applicable investigators should try to follow the most up to date guidelines in pharmacologic management and secondary prevention.

• AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update. A Guideline From the American Heart Association and American College of Cardiology Foundation *Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association*.[17]

• Third Report National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III Guidelines)[18]

• The Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[19]

9 Ethical Considerations and Confidentiality

9.1 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.

9.2 Participant Safety

9.2.1 Elements of Informed Consent

This trial will involve patients with significant coronary artery disease who have been deemed eligible for coronary revascularization. We anticipate enrolling 3,000 patients with a mean age in the 60s. Pregnant women and patients under the age of 20 will be excluded from the trial 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 phase IV clinical trial, (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 random manner of assignment to treatment, 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 obtained both for routine medical care as well as for research purposes.

9.2.2 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 clopidogrel 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 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 clopidogrel to try 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. Hemorrhage (at any site) is the chief complication associated with heparin therapy. A higher incidence of bleeding has reported in patients, particularly women, over 60 years of age. It has also been reported that that patients on heparin may develop new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets induced by Heparin, the so called ″white clot syndrome″. The process may lead to severe thrombo-embolic complications, like skin necrosis, gangrene of the extremities that may lead to amputations, pulmonary embolism, stroke, and possibly death. Therefore heparin administration should be promptly discontinued if a patient develops new thrombosis associated with a reduction in low platelet count.

9.2.3 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 in each clinic. Serious adverse events must be reported to the DCC within 24 hours. 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. Results for the different clinics are compared to identify the sources and causes of any trends deviating from the average performance.

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. This study will not be stopped early based on efficacy results.

9.3 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.

10 Study Organization

10.1 Steering Committee and DSMB

The executive steering committee,committee comprised of the chairperson and the principal investigators of the main participating centers, approved the study design, protocol, and amendments issued to the Data and Safety Monitoring Board (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 executivesteering 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 endpoints and definitions used in the event adjudication process.

10.2 Clinical Event Adjudication Committee

The Clinical Events Committee (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 endpoints 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.

10.5 Data Coordination and Site Management

Data coordination and site management services will be performed at the Cardiovascular Center and Clinical Research Center of Samsung Medical Center.

11 Statistical Analysis

11.1 Statistical Overview

This trial is a prospective, open label, two-arm, randomized multi-center trial to test the noninferiority of P2Y12 antagonist monotherapy compared with aspirin plus P2Y12 antagonist following 3-month of DAPT after DES implantation.

11.2 Sample Size

Hypothesis: P2Y12 antagonist monotherapy is noninferior to aspirin plus P2Y12 antagonist therapy in reducing ischemic events and bleeding risk after 3-month DAPT.

The study is a noninferiority trial. For the primary endpoint, we assume the incremental rate of composite events at 12-month follow-up will be 4.0% in both groups based on the results from previous studies.[6,7] The non-inferiority margin of 1.8 percentage points is chosen.

Sampling ratio is 1:1 = P2Y12 antagonist monotherapy : aspirin plus P2Y12 antagonist therapy

With a total of 3,000 patients (1,500 per group), the power of the study will be at least 80% with a 1-sided type I error rate of 0.05 and a loss to follow-up rate of 2%.

11.3 Randomization

Randomization will be performed 1:1 between P2Y12 antagonist and aspirin plus P2Y12 antagonist stratified by stent type, acute coronary syndrome, and enrolling sites. A written informed consent will be obtained from all patients. After obtaining informed consent, patients will be screened for eligibility and, if qualified, will be randomly assigned to a treatment group using a web-based response system (http://www.ecrf.kr/smartchoice) by computer-generated block randomization, and was stratified by clinical presentation (stable ischemic heart disease or acute coronary syndrome), enrolling center, type of P2Y12 receptor antagonist (clopidogrel, prasugrel, or ticagrelor), and type of stents used.

11.4 Analysis

General

Continuous variables will be presented as mean ± SD and compared with the Student t test. Categorical variables will be presented as counts and percentages and compared with the $\chi 2$ or Fisher exact test as appropriate. End points will be analyzed with the use of time-to-event methods. Cumulative event rates will be estimated with the Kaplan–Meier method and compared using log-rank tests. Hazard ratios with 95% confidence interval (CI) will be estimated by the Cox proportional-hazards method. Landmark analysis at 3 months from the index procedure will be separately performed as major secondary analysis. Patients who are lost to follow-up will be censored at the time of the last known contact.

Analysis Populations

All primary and secondary endpoints will be analyzed both on an intention-to-treat basis (all patients analyzed as part of their assigned treatment group) and on a per protocol basis (patients analyzed as part of their assigned treatment group only if they actually received their assigned treatment. For a intention-to-treat analysis, all patients who signed the written informed consent form and are randomized in the study will be included in the analysis sample, regardless of whether or not the correct treatment was administered, or whether crossover occurred. For the per protocol analysis, only enrolled patients who actually received the assigned treatment will be included in the analysis sample.

Primary Endpoint Analysis

The primary endpoint will be analyzed on an intention-to-treat and per protocol basis. The null hypothesis will be evaluated on the intention-to-treat population using an inferiority statistic. If the upper limit of the 1-sided 95% CI of the difference is less than that of the prespecified non-inferiority margin, P2Y12 inhibitor monotherapy will be considered to be noninferior to conventional 12-month duration of DAPT.

Subgroup Analyses

1. Major subgroup analyses of the primary and major secondary endpoints will be performed:
   (1) ACS
   (2) Diabetes mellitus
   (3) Implanted stent type
   (4) Type of P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor)
   (5) Chronic kidney disease, defined as estimated glomerular filtration rate <60 ml/min/m^2
   (6) Multivessel PCI
   → The consistency of treatment effects in prespecified subgroups will be assessed using Cox regression models with tests for interaction.

Treatment of missing values

The primary analysis of the study end points will not be covariate adjusted. No imputation methods will be used to infer missing values of baseline variables. For the study end points, we will censor patients lost to follow-up and regard them as not having the primary end point when estimating Kaplan–Meier event rates.

12 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. The presentation and/or publication of results from a single study site cannot precede presentation and/or publication of the multi-center results.

12.1 Data Analysis and Release of Results

No results will be released publicly before completion of the final analysis regarding the primary endpoint 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.

12.2 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.

12.3 Authorship: Primary Outcome Paper

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

12.4 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. The first priority of authorship on subset studies will be given to the PI or an investigator designated by the PI. The investigators with the priority of authorship should be one of members in the major institutions which will include more than 50 study patients. Each presentation of results on behalf of the investigators should have the approval of the Executive Committee.

13 Quality Assurances, Quality Control and Clinical Monitoring

The purposes are:

- To ensure accuracy of study data;
- To ensure that data collection at multiple sites meets pre-specified criteria to ensure standard implementation;
- To provide constructive feedback to site and core laboratory staff to improve and/or maintain high performance; and
- 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.

13.1 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 (absence of crossovers, unblinding etc.), 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, Dr. Hyeon-Cheol Gwon. 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:

Protocol Violations:

- Eligibility not confirmed, or subject found to be ineligible;
- Informed consent not obtained (or not obtained in a timely manner); and
- Randomized therapy not implemented per protocol (crossover to other treatment, use of other stents with PCI, excessive delay following randomization, non-certified operator performing procedure).
- Failure to conduct protocol required clinical follow-ups and within time windows
- Failure to report serious adverse events according to protocol requirements

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 PI 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. Poor performance at a site with respect to data entry and edit resolution will, in general, be remediated via conference calls and site visits initiated by the DCC.

13.2 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 documentably 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 CRC as an online electronic form where investigators from individual site can access and input the data via the internet.

13.3 Training/Certification and Retraining

The DCC will be responsible for providing training to the investigator and appropriate clinical site personnel. It is recommended that investigators review the IFU. Designated monitors will be trained appropriately to monitor study progress including but not limited to the protocol and eCRFs. The DCC will support trainings over a 1 month period, to ensure standard protocol implementation, data collection and management across sites. These training sessions will be carried out on-site or at the conference meeting. Clinical staff training components include (1) The Trial and Registry Protocols; (2) DATABASE SYSTEMS and eCRF for local web-based data entry; 3) medical record abstraction; 4) specimen/media collection and handling; 5) data handling; 6) interview techniques and 7) quality control expectations.

13.4 Site monitoring

The DCC will monitor the trial over its duration. A designated trial monitor, at appropriate intervals, will review investigational data for accuracy and completeness and to ensure compliance with the protocol. This trial monitor may inspect all documents and required records that are maintained by the Investigator/site, including medical records (office, clinic, or hospital) for the subjects in this trial. The Investigator/site will permit access to such records.

14 Core Labs

14.1. Angiographic Core Lab Measurements

The central angiographic core laboratory (Samsung Medical Center, Seoul, South Korea) will have the following main functions: (1) to oversee major angiographic inclusion and exclusion criteria, and confirm the eligibility of the patient, (2) to quantify the disease burden and severity at baseline, before revascularization, (3) to assess the success of percutaneous interventional procedure for each lesion treated, (4) to independently review all revascularization procedures during the follow-up phase and determine whether revascularizations are due to treatment failure or are due to progression of disease at remote sites, which will then be adjudicated by the Clinical Events Adjudication Committee (CEAC). (5) To perform qualitative and quantitative analysis of all baseline and follow-up films. All baseline angiograms of patients entered in the trial will be reviewed. A comprehensive analysis of all major epicardial coronary arteries and side branches (>2.0mm) will be assessed quantitatively to define the extent of coronary disease severity (% diameter stenosis) for each coronary segment. The percent diameter stenosis will be assessed for each coronary segment and will be identified by the Coronary Artery Surgery Study (CASS) lesion number. In

addition, patients randomized to percutaneous intervention will undergo a sequential qualitative and quantitative analysis using computerized quantitative angiographic software (CASS, PIE MEDICAL, The Netherlands) to determine lesion specific procedure success. Any angiogram performed during the follow-up phase of the trial will be sent to the angiographic core laboratory. Revascularization procedures will be adjudicated as resulting from a target revascularization or disease progression if revascularization results from a new obstruction at a remote site. This information will be provided to CEAC for final adjudication. All data will be collected on individual case report forms identified by clinical site, patient identification and procedure date. Appendix B contains more details on the Angiographic Core Laboratory.

15. Adverse Events/Serious Adverse Events/Unexpected Adverse Device Effects

Definitions

15. 1 Adverse Event

For the purpose of this trial, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject enrolled in a device clinical study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the study procedures, whether or not considered related to the investigational device or procedure.

15. 2 Serious Adverse Event

An adverse event is considered serious for this trial if it meets one or more of the following criteria and is device-related:

- Results in death
- Is life-threatening, *i.e.*, the patient was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred *(It does not include an event that, had it occurred in a more severe form, might have caused death.)*
- Results in persistent or significant disability or incapacity (significant, persistent or permanent change or disruption in patient′s body function/structure, physical activity or quality of life
- Requires in-patient hospitalization or prolongs hospitalization
- Results in a congenital anomaly/birth defect or,
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient and/or may require intervention to prevent one of the outcomes listed in this definition and/or necessitates immediate medical or surgical intervention to prevent permanent impairment of a body function/structure or to relieve unanticipated temporary impairment or damage. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A distinction is to be drawn between serious and severe adverse events. A severe adverse event may not be serious and a serious adverse event need not be considered severe. The term ″severe″ is used to describe the intensity of a specific event (as in mild, moderate, severe). However, the event itself may be of minor medical significance (e.g., severe headache). This is not the same as ″serious″, which is based on

patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Note: All events included in the endpoint events are considered SAEs (the cause for an unscheduled revascularization will represent the SAE).

15. 3 Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was:

- Not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Note: The term "effect" implies causal relationship with the device

16 Event Adjudication and Reporting

16.1 Investigator Responsibilities:

16.1.1 Adverse Events

The investigator will assess all adverse events for the severity, seriousness, and the causal relationship to study device and procedures. All non-serious adverse events are to be reported in detail and in a timely manner to DCC, on appropriate Case Report Form pages, whether or not they are believed to be serious or related to the investigational device.

16.1.2 Serious Adverse Events (SAE)/Unanticipated Adverse Device Effects

All events meeting the SAE/UADE criteria must be reported to the DCC within 24 hours of becoming aware of the events, which will be notified promptly to the DSMB and CEAC. To be noted that all endpoint events fall into this category, and must be reported within the above timeframe.

The Investigator must complete the Case Report Form for each serious adverse event, whether related or not to study device or procedure. The information provided must be sufficient to allow for independent medical assessment of the event. The Safety Officer will contact the Investigator should it be necessary to clarify any information. The Investigator should provide any additional follow-up information regarding the event to DCC as soon as it becomes available. All adverse events should be followed until resolution or stabilization

The site IRB/EC must be notified by the Investigators within the timeframe specified by their local standard operating procedures (SOPs) and the applicable regulations. Complications associated with PCI, such as abrupt closure, dissection, no reflow, thrombosis, dissection, embolism, stroke, perforation and/or extravascular staining, will be recorded on the Case Report Form as such, and will be recorded specifically as an adverse event/SAE.

Planned hospital admissions and/or planned surgical operations for an illness or disease which existed before the device was deployed or the patient was randomized in a clinical study are not to be considered adverse events. However, baseline conditions which deteriorate during a clinical study may be considered adverse events.

It should be noted here that all clinical endpoints, including MI/Stroke, unscheduled revascularization and death will require central adjudication and are included here, even though they contribute to trial outcomes. The study investigators will be responsible to provide all applicable and

available source documentation to the Data Coordinating Center (DCC) in order to allow an independent assessment of these events by the CEAC members.

Periodically, the database will be queried for cardiac enzyme triggers/ECG triggers or QCA triggers. Copies of original lab reports all required source documentation for these triggers must be submitted by the investigators to the CEAC for adjudication.

16. 2 Designee's responsibilities

16.2.1. Reporting responsibilities

All UADEs will be reported to the all participating Investigators and all reviewing IRBs/ECs within 10 working days of being notified by the event. All non-serious and serious adverse events (not UADEs) will also be provided to CEAC.

16. 2. 2. Endpoint and SAE/UADE Adjudication.

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

16.2.3 Device Failures and Malfunctions

Device malfunctions, device-related adverse events and product nonconformities will be reported to the appropriate manufacturers following the local product complaint procedures by all participating site(s). Complaints will also be reported to regulatory authorities as per local requirements.

17 Regulatory Responsibilities

17.1 Investigator Responsibilities

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

- Sign and adhere to the Investigator Agreement
- Participate in Investigator meetings and training sessions as scheduled by Sponsor
- Maintain up-to-date angiographic and IVUS equipment (if applicable)
- Be willing to provide original cine films/CD ROMs/IVUS 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 (i.e., TVF, SAE/UADE, TVR) prior to scheduled monitoring visits
- Be willing to change hospital routine if required by protocol (as long as patient safety and well-being is not compromised)
- Adhere to all relevant Core Laboratory requirements and,

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

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

17.3 Informed Consent

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

17.4 Study Coordinator

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

18 Protocol Deviations and Amendments

18.1 Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the patient require immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the executive committee at the earliest possible time by telephone. This will allow an early joint decision regarding the patient′s continuation in the study. The investigator will document this decision. The IRB or EC will be informed of all protocol changes by the investigator in accordance with the IRB or EC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB or EC established procedures.

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that due to the study observations, some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report. Furthermore, any additional analyses performed beyond those specified in this protocol will be descriptive in nature and will not include hypothesis testing for the purposes of inferential conclusions.

18.2 Protocol Amendments

In case any revisions to the protocol are required, protocol amendments will be provided to investigators by the executive committee prior to implementation. The Primary Investigator(s) will be responsible for notifying the IRB of the protocol amendment with administrative changes or obtaining IRB approval of the protocol amendment with changes in patient care or safety. Institutional Review Board acknowledgements/approvals must be documented in writing prior to implementing protocol amendments.

19 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.

19.1 Records

Each 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 receipt, use, or disposition of the study device, including receipt dates, serial and lot numbers, names of all persons who received or used the device, why and how many devices were disposed.
- Records of each subject's case history, including study-required Case Report Forms, evidence of informed consent, all relevant observations of adverse device or drug effects, 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.

19.2 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**
Serious adverse event	IRB/EC	Per local regulations.
	DCC	Within 24 hours
Patient withdrawal	DCC	Notify within 7 days.
Annual progress report	EC DCC	Submitted per 6 months.
Deviations from investigational plan	IRB/EC	Per local standard.
	DCC	Notify within 7 days.
Informed consent not obtained	DCC IRB	Notify within 7 days.

Final summary report	DCC	Within 1 month.

20. 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 devices 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 device and 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 or randomized 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

Appendix A. Definitions

ACC/AHA Classification Scheme of Coronary Lesions: Lesion-Specific Characteristics

Type A Lesions (High Success, >85%; Low Risk)
. Discrete (< 10 mm length)
. Little or no calcification
. Concentric
. Less than totally occlusive
. Readily accessible
. Not ostial in location
. Nonangulated segment, < 45°
. No major branch involvement
. Smooth contour
. Absence of thrombus

Type B Lesions* (Moderate Success, 60-85%; Moderate risk)
. Tubular (10-20 mm length)
. Moderate-to-heavy calcification
. Eccentric
. Total occlusions < 3 mo old
. Moderate tortuosity of proximal segment
. Ostial in location
. Moderately angulated segment, > 45°, < 90°
. Bifurcation lesions requiring double guide wires
. Irregular contour
. Some thrombus present
* Type B1 lesions: One adverse characteristic
* Type B2 lesions: ≥ two adverse characteristics

Type C Lesions (Low Success, <60%; High Risk)
. Diffuse (> 2 cm length)
. Total occlusions > 3 mo old
. Excessive tortuosity of proximal segment
. Inability to protect major side branches
. Extremely angulated segments > 90°
. Degenerated vein grafts with friable lesions

Acute closure (abrupt closure)

Occurrence of new severely reduced flow Thrombosis In Myocardial Infarction (TIMI) grade 0 or 1 within the target vessel during the index procedure that persists and requires rescue by a non-assigned treatment strategy (including emergency surgery), or results in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment lesion or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" (due to microvascular flow limitation), in which the vessel is patent but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application reversed the closure.

Subabrupt Closure: abrupt closure that occurs after the index procedure is completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.

Threatened Abrupt Closure: Grade B dissection and ≥ 50% diameter stenosis or any dissection of grade C or higher.

Acute coronary syndrome

* ST-segment elevation MI (STEMI)
: elevation of ST-segment more than 0.1 mV in 2 or more contiguous ECG leads or new left bundle-branch block with elevated biomarkers of myocardial necrosis

* Non-ST-segment elevation MI (NSTEMI)

: Elevated biomarkers of myocardial necrosis (troponin or CK-MB > X1 URL) with one of the following
(a) Transient ST-segment elevation or depression, or T-wave changes consistent with myocardial ischemia
(b) Identification of a culprit lesion at coronary angiography

* Unstable angina
An accelerating pattern or recurrent episodes of chest pain at rest or with minimal effort AND new ST-segment depression of at least 0.05 mV, or T wave inversion of at least 0.3 mV in at least 2 leads

Anticipated Adverse Event

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a patient, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or IFU, that is identified or worsens or occurs in frequency that is not considered normal during a clinical trial. See also: Adverse Event (AE), Serious Adverse Event (SAE), Unanticipated Adverse Device Effect (UADE)

Adverse Device Effect

Any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use or the deployment of the device. It also includes any event that is a result of a user error.

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation when the patient was administered a study product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the study product. See also: Anticipated Adverse Event, Serious Adverse Event (SAE), Unanticipated Adverse Device Effect (UADE)

Aneurysm

An abnormal expansion or protrusion of a coronary blood vessel resulting from a disease or weakening of the vessel wall (all 3 layers) that exceeds the reference vessel diameter by 1.5 times

Angina

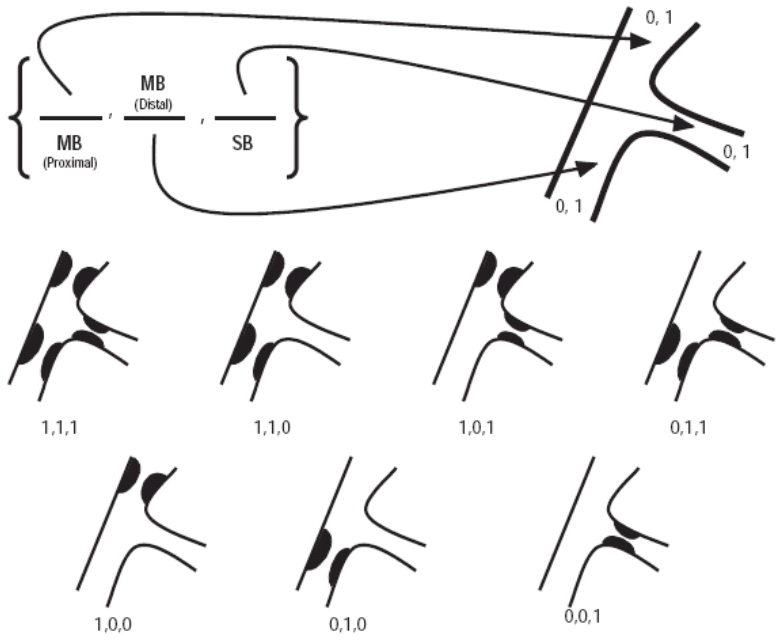
Canadian Cardiovascular Society Classification of Stable Angina
I. Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.
II. Slight. Slight limitation of ordinary activity. Angina occurs on 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.

Bifurcation Lesion

A lesion located at both the main vessel and a side branch of that main vessel.

Indicate if the lesion is at a bifurcation/trifurcation. A bifurcation/trifurcation is a division of a vessel into at least two branches, each of which is >2 mm or greater in diameter. [Medina classification]



Bleeding/Hemorrhagic Complications

An episode of bleeding is defined by the BARC[22] criteria as:

Table 3. Bleeding Academic Research Consortium Definition for Bleeding

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

- Type 3a
  - Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding
- Type 3b
  - Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  - Bleeding requiring intravenous vasoactive agents
- Type 3c
  - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
  - Subcategories confirmed by autopsy or imaging or lumbar puncture
  - Intraocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

- Type 5a
  - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- Type 5b
  - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood−1 g/dL hemoglobin).

†Cell saver products are not counted.

Chronic Concomitant Medication

Chronic concomitant medication refers to the following:
a) medication that has been prescribed or is over the counter, that has been taken or will continue to be taken regularly for at least a period of 6 months; or
b) medication that is required to be taken indefinitely by the patient; or
c) medication that has been prescribed or taken multiple times (each time for at least 6 months).

Chronic Occlusion

Chronic total occlusion: Total occlusion (TIMI 0 and 1) with either: (1) known duration ≥ 3 mo, or (2) bridging collaterals

Clinical Device Failure

A device is said to have failed if it did not meet the requirements of the definition for clinical device success. See also: Clinical Device Success and Clinical Procedure Success

Clinical Device Success

Achievement of a final in-stent residual diameter stenosis of < 20% assessed by online quantitative angiography or visual estimation, without device failure or malfunction. A device is considered to have failed if it did not meet the requirements of the definition for clinical device success. See also: Clinical Procedure Success and Device Failure and malfunction.

Clinical Procedure Success

Achievement of a final in-stent diameter stenosis of < 20% by online QCA or visual estimation with or without any adjunctive devices, and without the occurrence of cardiac death, target vessel MI (Q-wave and non Q-wave MI), or repeat revascularization of the target lesion during the health care facility stay. See also: Clinical Device Success

Composite Endpoint

Composite endpoint is defined by the Academic Research Consortium as follows:

Device-oriented composite includes cardiac death, myocardial infarction attributed to the target vessel, and target lesion revascularization

Patient-oriented composite includes all-cause mortality, any myocardial infarction, and any repeat revascularization (includes all target and non-target vessel)

Coronary Artery Bypass Graft (CABG) Surgery

Acute CABG surgery is defined as immediate transfer from the catheterization laboratory to the operative room for emergent bypass surgery during the initial treatment phase. Coronary artery bypass graft surgery during follow-up is only considered as a target vessel revascularization and major adverse coronary event if coronary angiography indicates a diameter of stenosis >50% of the stented coronary segment associated with one of the following conditions:

A positive history of recurrent angina pectoris presumably related to the target vessel

Objective signs of ischemia (exercise test or equivalent) presumably related to the target vessel

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

Cerebrovascular accident (CVA)

Sudden onset of vertigo, numbness, sphasia, 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.

Device Failure

Defined when the following occur:

1. Failure to cross lesion due to limitations in delivery system flexibility or profile
2. Poor or otherwise inaccurately placed stent due to poor sheath movement (possible if angulation of

anatomy is high), inadequate fluoro angle, poor dye flow/visibility due to device profile or guide size, or other equipment related limitation

3. Inability to cross previously implanted stent (again for profile/flexibility reasons)

Device Malfunction

Failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

1. Break/inoperable delivery mechanism (handle apparatus)
2. Kink/break in delivery system shaft
3. Stent not retained within sheath
4. Stent moves after placement
5. Stent lost at any point during procedure

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)

Dissection

Defined according to the National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System

E031 Dissection NHLBI classification

Dissection type	Diescription	Angiographic Apparence
A	Minor radiolucencies within the coronary lumen during contrast injection with minimal or no persistence after dye clearance.	
B	Parallel tracts or double lumen separated by a radiolucent area during contrast injection with minimal or no persistence after dye clearence.	
C	Extraluminal cap with persistence of contrast after dye clearence from the coronary lumen.	
D	Spiral luminal filling defects.	
E +	New persistent filling defects.	
F +	Those non-A-E types that lead to impaired flow or total occlusion.	

+ May represent thrombus

- Type A, B: minor dissection, type C-F: major dissection

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

In-stent

Within the stent margins

In-segment

Within the stent margins and 5 mm proximal and 5 mm distal to the stent

Late Loss (LL)

Late loss is calculated as follows:

[Minimum lumen diameter (MLD) post-procedure] − [MLD at follow-up]

In-segment Late Loss: [in-segment MLD post-procedure] − [in segment MLD at follow-up]

In-stent Late Loss: [in-stent MLD post-procedure] − [in-stent MLD at follow-up]

Minimum Lumen Diameter (MLD)

The average of 2 orthogonal views (when possible) of the narrowest point within the area of assessment in lesion, in stent, or in segment.

MLD is measured during QCA by the angiographic core laboratory

Myocardial Infarction (MI)

Myocardial Infarction Classification and Criteria for Diagnosis is defined by the Academic Research Consortium as follows:

Classification	Biomarker Criteria*	Additional Criteria
Periprocedural PCI	Troponin > 3 x URL or CK-MB > 3 x URL	Baseline value <URL
Periprocedural CABG	Troponin > 5 x URL or CK-MB > 5 x URL	Baseline value <URL and any of the following: new pathologic Q waves or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium
Spontaneous	Troponin > URL or CK-MB > URL	
Sudden death	Death before biomarkers obtained or before expected to be elevated	Symptoms suggestive of ischemia and any of the following: new ST elevation or LBBB, documented thrombus by angiography or autopsy
Reinfarction	Stable or decreasing values on 2 samples and 20% increase 3 to 6 hours after second sample diagnose recurrent MI	If biomarkers increasing or peak not reached then insufficient data to diagnose recurrent MI

URL = Upper Reference Limit (defined 99th percentile of normal reference range); LBBB = Left Bundle-branch Block
* Baseline biomarker value requiring before study procedure and presumes a typical rise and fall

Periprocedural MI After PCI: The periprocedural period includes the first 48 hours after percutaneous coronary intervention.

Periprocedural MI After CABG: The periprocedural period includes the first 72 hours after coronary artery bypass grafting.

Spontaneous MI: MI after the periprocedural period may be secondary to late stent complications or progression of native disease. Performance of ECG and angiography supports adjudication to either a target or non-target vessel in most cases.

With the unique issues and pathophysiological mechanisms associated with these later events as well as the documented adverse impact on short-and long-term prognosis, a more sensitive definition than for periprocedural MI of any elevation of troponin above the upper range limit is used. All late events that are not associated with a revascularization procedure should be classified as spontaneous.

Electrocardiographic Classification: Within this category Q-wave MI and Non Q-wave MI are distinguished as follows:

- Q-wave MI: Development of new pathologicals in 2 or more contiguous leads (according to the Minnesota code as assessed by the ECG core laboratory) with or without post-procedure CK or CK-MB levels elevated above normal.
- Non Q-wave MI: All MIs not classified as Q-wave.

Relation to the Target Vessel: All infarcts that cannot be clearly attributed to a vessel other than the target vessel will be considered related to the target vessel.

No-Reflow

An acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion. See also Abrupt Closure (Acute Closure)

Percent Diameter Stenosis (% DS)

Calculated by the following:

100 * {1 – (minimum lumen diameter / reference vessel diameter)}

using the mean values from 2 orthogonal views (when possible) determined by quantitative coronary angiography.

Permanent Impairment

Permanent impairment means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Principal Investigator

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

Primary Investigator

A physician responsible for conducting the study at each investigational site

Reference Vessel Diameter (RVD)

The diameter of and adjacent reference segment that is presumed to be free of disease representing an approximation of the target lesion vessel diameter. The reference vessel diameter is visually estimated during angiography by the investigator and it is measured using quantitative coronary angiography by the angiographic core laboratory.

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 [ǂ 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.

Stroke

See Cerebrovascular Accident

Suboptimal result

Residual stenosis > 10% within the stented segment

Any peri-stent dissection ≥ NHLMI type B.

Lucency or filling defect consistent with thrombus.

No reflow or TIMI 2 flow.

Unstented inflow or outflow stenosis ≥60% diameter stenosis (visually assessed).

Successful Stent Implantation

10% or less residual stenosis by visual assessment over the entire stent length, with TIMI − 3 flow and no more than an NHLBI type A peri-stent dissection.

Target Lesion

A lesion to be treated during the index procedure

Target Vessel

The entire epicardial vessel containing the treated lesion

Thrombocytopenia

Thrombocytopenia: Nadir platelet count <100,000 cells/mm^3 in a patient with a baseline platelet count >100,000 cells/mm^3. Further divided into mild (50,000 - <100,000 cells/mm^3), moderate (20,000 - <50,000 cells/mm^3), or severe (<20,000 cells/mm^3, or requiring platelet transfusion).

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

Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Appendix B: Angiographic Core Lab Guidelines

To improve accuracy and reproducibility in off-line QCA measurements, the following guidelines should be respected.

• Use a fixed table system
Use a CD-ROM at a minimum speed of preferably 25-30 frames/ second; Cinefilms are not allowed
The image mode of the image intensifier should b 5 inch (13 cm) or 7 inch (18 cm);
It is mandatory to use catheters of 6 French or larger;
The catheter tip must be clearly visible in each projection, preferably near the center of the screen (essential for calibration). With tapered catheter, an even larger portion of the catheter must be present;
Flush the catheter tip after each contrast infection; Contrast can be cleared from the catheter tip by back bleeding (e.g., by briefly opening the Y-connector or the pressure line to air)l
Pre-procedural and final angiograms must be obtained, during breath hold, without a guidewire in the coronary artery;
At least 2 different projections, for the right coronary artery and at least 3 different projections for the loft coronary artery must be filmed, with at least 30° difference before the PCI/Stent. These same projections must be repeated after PCI/Stent and at follow-up angiography, preferably without a guidewire in place;
There should be no overlap of the lesion to be dilated with other vessels, catheters or electrodes;
Foreshortening of the segment should be avoided and stenosis should be viewed in their maximal severity;
The segment to be dilated should preferably be located near the center of the screen;
Each angiogram has to be preceded by intra-coronary injection of nitrates and repeated if necessary, this must appear on the film (use plates);
The balloon of the delivery system or any subsequent balloon inflated within a stent must be filmed at maximum inflation pressure. The pressure applied must also be visible on the film (use plates);
(Record the complete filming sequence for each site to be dilated in the ″Technician Work Sheet″(TWS) sections of the Case Report Form;
(N.B. In case the angulations of all angiographic projections are displayed in the Dicom image of the CD-ROM, the listing of the filming sequence (columns 1 and 2 of T.W.S.) may be skipped. However, The information in the 3rd column (i.e. field size, catheter number etc.) is mandatory.

(The procedure is completed when the guiding catheter is removed and the patient is off the table. If the guiding catheter is reinserted, this should be considered as a repeat intervention;
(If there is a long lesion covering more than one segment, always identify the site by the segment number in which the lesion begins;
(It is important to use same type of contrast material for baseline and follow-up angiograms.
In addition, it is of key importance to
- film all balloon dilatations
- film deflated balloon while it remains at site of inflation
- film any stent placement.

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Statistical Analysis Plan for SMART-CHOICE Trial

1.1 Statistical Overview

This trial is a prospective, open label, two-arm, randomized multi-center trial to test the noninferiority of P2Y12 antagonist monotherapy compared with aspirin plus P2Y12 antagonist following 3-month of DAPT after DES implantation.

1.2 Sample Size

Hypothesis: P2Y12 antagonist monotherapy is noninferior to aspirin plus P2Y12 antagonist therapy in reducing ischemic events and bleeding risk after 3-month DAPT.

The study is a noninferiority trial. For the primary endpoint, we assume the incremental rate of composite events at 12-month follow-up will be 4.0% in both groups based on the results from previous studies.[6,7] The non-inferiority margin of 1.8 percentage points is chosen.

Sampling ratio is 1:1 = P2Y12 antagonist monotherapy : aspirin plus P2Y12 antagonist therapy

With a total of 3,000 patients (1,500 per group), the power of the study will be at least 80% with a 1-sided type I error rate of 0.05 and a loss to follow-up rate of 2%.

1.3 Randomization

Randomization will be performed 1:1 between P2Y12 antagonist and aspirin plus P2Y12 antagonist stratified by stent type, acute coronary syndrome, and enrolling sites. A written informed consent will be obtained from all patients. After obtaining informed consent, patients will be screened for eligibility and, if qualified, will be randomly assigned to a treatment group using a web-based response system (http://www.ecrf.kr/smartchoice) by computer-generated block randomization, and was stratified by clinical presentation (stable ischemic heart disease or acute coronary syndrome), enrolling center, type of P2Y12 receptor antagonist (clopidogrel, prasugrel, or ticagrelor), and type of stents used.

1.4 Analysis

General

Continuous variables will be presented as mean ± SD and compared with the Student t test. Categorical variables will be presented as counts and percentages and compared with the $\chi 2$ or Fisher exact test as appropriate. End points will be analyzed with the use of time-to-event methods. Cumulative event rates will be estimated with the Kaplan–Meier method and compared using log-rank tests. Hazard ratios with 95% confidence interval (CI) will be estimated by the Cox proportional-hazards method. Landmark analysis at 3 months from the index procedure will be separately performed as major secondary analysis. Patients who are lost to follow-up will be censored at the time of the last known contact.

Analysis Populations

All primary and secondary endpoints will be analyzed both on an intention-to-treat basis (all patients analyzed as part of their assigned treatment group) and on a per protocol basis (patients

analyzed as part of their assigned treatment group only if they actually received their assigned treatment. For an intention-to-treat analysis, all patients who signed the written informed consent form and are randomized in the study will be included in the analysis sample, regardless of whether or not the correct treatment was administered, or whether crossover occurred. For the per protocol analysis, only enrolled patients who actually received the assigned treatment will be included in the analysis sample.

Primary Endpoint Analysis

The primary endpoint will be analyzed on an intention-to-treat and per protocol basis. The null hypothesis will be evaluated on the intention-to-treat population using an inferiority statistic. If the upper limit of the 1-sided 95% CI of the difference is less than that of the prespecified non-inferiority margin, P2Y12 inhibitor monotherapy will be considered to be noninferior to conventional 12-month duration of DAPT.

Subgroup Analyses

1. Major subgroup analyses of the primary and major secondary endpoints will be performed:

(1) ACS

(2) Diabetes mellitus

(3) Implanted stent type

(4) Type of P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor)

(5) Chronic kidney disease, defined as estimated glomerular filtration rate <60 ml/min/m^2

(6) Multivessel PCI

→ The consistency of treatment effects in prespecified subgroups will be assessed using Cox regression models with tests for interaction.

Treatment of missing values

The primary analysis of the study end points will not be covariate adjusted. No imputation methods will be used to infer missing values of baseline variables. For the study end points, we will censor patients lost to follow-up and regard them as not having the primary end point when estimating Kaplan–Meier event rates.