

## Supplementary Online Content

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### **Trial protocol**

This supplementary material has been provided by the authors to give readers additional information about their work.

# **Impact of intravascular ultrasound guidance on long-term clinical outcomes of everolimus-eluting stents in long coronary lesions**

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## Protocol Summary

<b>Title of Study</b>	Impact of intravascular ultrasound guidance on long-term clinical outcomes of everolimus-eluting stents in long coronary lesions
<b>Objective</b>	The primary purpose of this study is to investigate the impact of IVUS guidance on the clinical outcomes after implantation of DES in patients with long coronary lesions (implanted stent $\geq$ 28 mm in length)
<b>Methodology</b>	Prospective, randomized, multi-center trial
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<b>Name of Sponsor</b>	Cardiovascular Research Center
<b>Study Centers</b>	20 centers in Korea.
<b>Participating Sites</b>	<ol style="list-style-type: none"> <li>1. Yonsei University Severance Hospital, Seoul</li> <li>2. Yonsei University Gangnam Severance Hospital, Seoul</li> <li>3. Ulsan University Hospital, Ulsan</li> <li>4. Wonju Christian Hospital, Wonju</li> <li>5. Gachon Gil University Hospital, Incheon</li> <li>6. Dankook University Hospital, Cheonan</li> <li>7. NHIC Ilsan Hospital, Goyang</li> <li>8. Kwandong University Myongji Hospital, Goyang</li> <li>9. Seoul Eulji Hospital, Seoul</li> <li>10. Wonkwang University Hospital, Iksan</li> <li>11. Sejong General Hospital, Bucheon</li> <li>12. Inje University Ilsan Paik Hospital, Goyang</li> <li>13. Keimyung University Dongsan Hospital, Daegu</li> <li>14. Eulji University Hospital, Daejeon</li> <li>15. Hallym University Kangnam Sacred Heart Hospital</li> <li>16. Kangwon National University Hospital, Chuncheon</li> <li>17. Chunnam National University Hospital, Kwangju</li> <li>18. Hallym University Chunchun Sacred Hospital, Chunchun</li> <li>19. Inje University Haeundae Paik Hospital, Busan</li> <li>20. Yonsei University Yongin Severance Hospital, Yongin</li> </ol>
<b>Number of Subjects</b>	A total of 1400 patients requiring treatment with long coronary lesions (implanted stent $\geq$ 28 mm in length) will be enrolled.

<b>Product Name</b>	Long Xience Prime™ stents (length 28, 33 or 38 mm) will be primarily used for treatment of all long lesions. For additional coverage of long lesions and other lesions, Xience Prime™ stents of appropriate length will be used.
<b>Study Design</b>	<ul style="list-style-type: none"> <li>• Prospective, randomized, multi-center trial</li> <li>• A total of 1400 subjects long coronary lesions (implanted stent <math>\geq</math>28 mm in length) who meet all inclusion and exclusion criteria will be included.</li> <li>• Patients will be randomized in a two by two factorial manner according to the use of IVUS guidance (IVUS guidance vs. no IVUS guidance) and the duration of dual anti-platelet therapy (6 months vs. 12 months). Each randomization of the enrolled subjects will be done 1:1.</li> <li>• Patients will be followed clinically for 1 year after PCI.</li> </ul>
<b>Inclusion criteria</b>	<p><u>General Inclusion criteria:</u></p> <ol style="list-style-type: none"> <li>1) Age 20 years or older</li> <li>2) Patients with typical chest pain or evidences of myocardial ischemia</li> <li>3) Non-emergent conditions</li> <li>4) Patients who provide signed informed consent</li> </ol> <p><u>Angiographic inclusion criteria:</u></p> <ol style="list-style-type: none"> <li>1) Stent length <math>\geq</math>28 mm based on angiographic estimation</li> <li>2) Significant coronary artery stenosis (&gt;50% based on visual estimate) considered for coronary revascularization with stent implantation</li> <li>3) Reference vessel diameter 2.5- 4.0 mm based on operator assessment</li> </ol>
<b>Exclusion criteria</b>	<p><u>General Exclusion criteria</u></p> <ol style="list-style-type: none"> <li>1) Acute ST elevation myocardial infarction within 48 hrs</li> <li>2) Contraindication for anti-platelet agents and bleeding history within prior 3 months</li> <li>3) Known hypersensitivity, contraindication to any of the following medications: heparin, aspirin, clopidogrel</li> <li>4) Prior history of the following presentations <ul style="list-style-type: none"> <li>- Cerebral vascular accident (not including transient ischemic attack)</li> <li>- Peripheral artery occlusive disease</li> <li>- Thromboembolic disease</li> <li>- Stent thrombosis</li> </ul> </li> <li>5) Age; older than 80 years</li> <li>6) Severe hepatic dysfunction (&gt; 3 times normal reference values)</li> <li>7) Significant renal dysfunction (Serum creatinine &gt;2.0 mg/dl)</li> <li>8) Significant leucopenia, neutropenia, thrombocytopenia, anemia, or known bleeding diathesis</li> <li>9) Cardiogenic shock</li> </ol>

	<p>10) Left ventricular ejection fraction &lt;40%</p> <p>11) Pregnant women or women who might be pregnant</p> <p>12) Life expectancy ; less than 1 year</p> <p><u>Angiographic Exclusion criteria</u></p> <p>1) Left main disease requiring PCI</p> <p>2) Bifurcation lesion with 2-stent technique</p> <p>3) Chronic total occlusion</p> <p>4) Presence of previously implanted DES within 6 months</p> <p>5) In-stent restenosis lesion</p>
<b>Primary and Secondary Endpoints</b>	<p><u>Primary endpoint:</u></p> <p>Major adverse cardiac event including cardiac death, target lesion-related myocardial infarction, or ischemia-driven target lesion revascularization at 1 year post-procedure</p> <p><u>Secondary endpoints:</u></p> <p>1) Overall incidence of cardiac death, target lesion-related myocardial infarction, stent thrombosis, and ischemia-driven target lesion revascularization at 1 year post-procedure</p> <p>2) Incidence of cardiac death, myocardial infarction, stent thrombosis, or target vessel revascularization according to 6-month versus 12-month dual antiplatelet therapy</p>
<b>Sample size</b>	<p>Superiority comparison</p> <p>Type I error; Set at 0.05, Statistical power = 80%</p> <p>Sampling ratio is 1:1 = IVUS guidance : no IVUS guidance</p> <p>Adjustments; 5-10% drop out rate (for 1-year clinical follow up)</p> <p>Based on the above assumption, we will need each 700 patients in the IVUS guidance arm and in the control arm without IVUS guidance totaling 1400 patients.</p>
<b>Study Duration</b>	<p>Patient enrollment: October 01, 2010 ~ November 30, 2014 (4 years)</p> <p>Follow-up duration: 1 year</p> <p>Expected date of last patient follow-up: November 30, 2015</p> <p>Total duration of the study: December 01, 2010 ~ November 30, 2015</p>
<b>Angiographic Core Lab</b>	<p>Cardiovascular Research Institute, Severance Cardiovascular Hospital, Yonsei University Health System</p>

## 1. Background

Drug-eluting stents (DES) have shown to be highly effective in reducing restenosis compared with bare-metal stents (BMS).<sup>1,2</sup> However, restenosis still occurs after implantation of DES and stent thrombosis is considered the most feared complication of DES.<sup>3-5</sup> Clinical and procedural factors contributing to development of restenosis and stent thrombosis are similar. Especially, incomplete stent expansion, procedural and acquired stent malapposition, and smaller minimum stent area after stent implantation measured by intravascular ultrasound (IVUS) were reported to be associated with restenosis and stent thrombosis.<sup>6-10</sup> In the BMS era, two randomized, controlled studies have demonstrated that the IVUS guidance during the percutaneous coronary intervention (PCI) significantly reduced restenosis and need for repeat revascularization.<sup>11,12</sup> In the CRUISE study IVUS-guidance achieved larger stent area and a significantly lower rate of target vessel revascularization at 9 month-follow-up (8.5% versus 15.3%,  $P < 0.05$ ; relative reduction of 44%).<sup>11</sup> The TULIP study also showed that angiographic and clinical outcome up to 12 months after long stent placement guided by IVUS was superior to guidance by angiography.<sup>12</sup> At 12 months, target lesion revascularization (TLR) and the major adverse cardiac event (MACE), a composite of death, myocardial infarction (MI), and TLR, occurred in 10% and 12% of the IVUS group and 23% and 27% of the angiography group ( $P = 0.018$  and  $P = 0.026$ ), respectively. However, there are no prospective randomized trials assessing the clinical utility of routine IVUS guidance in the current era of DES. Recently, Roy et al.<sup>13</sup> investigated in a retrospective study the impact of IVUS guidance on the outcomes after implantation of DES and found no significant difference between IVUS or angiography guidance in the rates of target vessel revascularization, stent thrombosis, or MACE. However, their study was not a prospective randomized study and did not restrict the study inclusion to patients at high risk for restenosis or stent thrombosis, but included subjects at lower risk. Therefore, the primary aim of the present study is to investigate the impact of IVUS guidance on the clinical outcomes in patients with long lesions treated with implantation of DES.

Generally, implantation of DES requires prolonged dual antiplatelet therapy compared with BMS. However, how long the dual antiplatelet therapy is needed for the prevention of stent thrombosis is unclear.<sup>14,15</sup> Xience Prime<sup>TM</sup> (Abbott Vascular, Santa Clara, CA, USA), a new generation DES, is a thin strut cobalt chromium alloy metal stent, coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient) same as Xience V<sup>TM</sup>, but with improved flexibility. In the recent SPRIT III trial, Xience V achieved significantly improved event-free survival at a 2-year follow-up compared to Taxus, a first generation paclitaxel eluting DES.<sup>16</sup> Furthermore, the trial showed encouraging trends toward fewer stent thrombosis episodes after 6 months in patients treated with Xience V who discontinued a thienopyridine. Among the 360 patients who discontinued clopidogrel or ticlopidine after 6 months, stent thrombosis subsequently developed in 0.4% of EES patients versus 2.6% of PES patients ( $P = 0.10$ ). Therefore, one of secondary objectives in the present study is to investigate the safety of a 6-month dual antiplatelet therapy in patients undergoing PCI using Xience Prime<sup>TM</sup>.

## 2. Study Objectives

The primary purpose of this study is to investigate the impact of IVUS guidance on the clinical outcomes after implantation of DES in patients with long coronary lesions (implanted stent  $\geq 28$  mm in length).

## **2.1. Primary Endpoint**

The occurrence of MACE including cardiac death, target lesion-related MI, or ischemia-driven TLR at 1 year post-procedure with IVUS versus angiography guidance

## **2.2. Secondary Endpoints**

- 1) Overall incidence of cardiac death, target lesion-related MI, stent thrombosis, and ischemia-driven TLR at 1 year post-procedure
- 2) Incidence of cardiac death, MI, stent thrombosis, or target vessel revascularization according to 6-month versus 12-month dual antiplatelet therapy

The definition criteria of cardiac death, MI, stent thrombosis, TLR, and target vessel revascularization are outlined in the appendix A.

## **3. Study Design**

### **3.1. Study Design**

This trial is designed as a prospective, randomized, multi-center trial to compare the long-term clinical outcomes of IVUS-guided vs. angiography-guided everolimus-eluting stent implantation in patients with long coronary lesions (implanted stent  $\geq 28$  mm in length) at 12 months as a primary objective and safety of 6-month dual antiplatelet therapy following everolimus-eluting stent implantation in comparison with a 12-month dual antiplatelet therapy.

### **3.2. Patient Enrollment**

Patients who present to the cath lab for non-emergent PCI and stenting are eligible for the participation. A patient is considered enrolled if they meet all of the inclusion and have none of the exclusion criteria.

#### **3.2.1 Inclusion Criteria**

##### General inclusion criteria

- 1) Age 20 years or older
- 2) Patients with typical chest pain or evidences of myocardial ischemia (e.g., stable, unstable angina, silent ischemia and positive functional study or reversible changes in the electrocardiogram (ECG) consistent with ischemia)
- 3) Non-emergent conditions
- 4) Patients who provide signed informed consent

##### Angiographic inclusion criteria

- 1) Stent length  $\geq 28$  mm based on angiographic estimation
- 2) Significant coronary artery stenosis ( $>50\%$  based on visual estimate) considered for coronary revascularization with stent implantation
- 3) Reference vessel diameter 2.5- 4.0 mm based on operator assessment

#### **3.2.2 Exclusion Criteria**

##### General exclusion criteria

- 1) Acute ST elevation myocardial infarction within 48 hrs
- 2) Contraindication for anti-platelet agents and bleeding history within prior 3 months
- 3) Known hypersensitivity, contraindication to any of the following medications: heparin, aspirin, clopidogrel
- 4) Prior history of the following presentations
  - Cerebral vascular accident (not including transient ischemic attack)
  - Peripheral artery occlusive diseases
  - Thromboembolic disease
  - Stent thrombosis
- 5) Age; older than 80 years
- 6) Severe hepatic dysfunction ( $\geq 3$  times normal reference values)
- 7) Significant renal dysfunction (Serum creatinine  $> 2.0$  mg/dl)
- 8) Significant leucopenia, neutropenia, thrombocytopenia, anemia, or known bleeding diathesis
- 9) Cardiogenic shock
- 10) Left ventricular ejection fraction  $<40\%$
- 11) Pregnant women or women who might be pregnant
- 12) Life expectancy; less than 1 year

#### Angiographic exclusion criteria

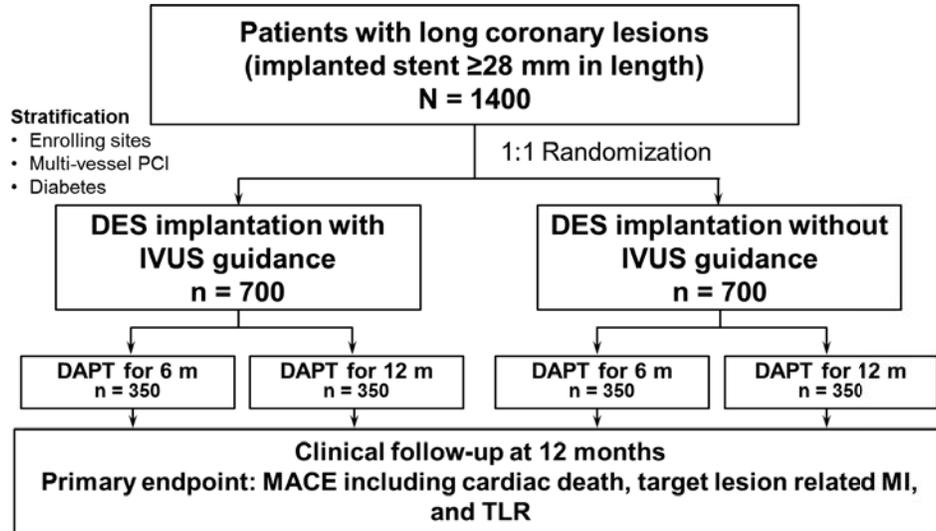
- 1) Left main disease requiring PCI
- 2) Bifurcation lesion with 2-stent technique
- 3) Chronic total occlusion
- 4) Presence of previously implanted DES within 6 months
- 5) In-stent restenosis lesion

### **3.3. Study Timeline**

- Patient enrollment: October 01, 2010 ~ November 30, 2014 (4 years)
- Follow-up duration: 1 year
- Expected date of last patient follow-up: November 30, 2015
- Total duration of the study: December 01, 2010 ~ November 30, 2015

### **3.4. Randomization**

Patients will be randomized in a two by two factorial manner according to the use of IVUS guidance (IVUS guidance vs. no IVUS guidance) and the duration of dual anti-platelet therapy (6 months vs. 12 months). Each randomization of the enrolled subjects will be done 1:1. Randomization procedure will be performed using a web-based program.



### 3.4.1. Stratification

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

- 1) Enrolling sites
- 2) Multi-vessel PCI
- 3) Diabetes

### 3.5. Study Centers

#### 3.5.1. Principal Investigator

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#### 3.5.2. Participating Centers

1. Yonsei University Severance Hospital, Seoul
2. Yonsei University Gangnam Severance Hospital, Seoul
3. Ulsan University Hospital, Ulsan
4. Wonju Christian Hospital, Wonju
5. Gachon Gil University Hospital, Incheon
6. Dankook University Hospital, Cheonan
7. NHIC Ilsan Hospital, Goyang
8. Kwandong University Myongji Hospital, Goyang
9. Seoul Eulji Hospital, Seoul
10. Wonkwang University Hospital, Iksan
11. Sejong General Hospital, Bucheon

12. Inje University Ilsan Paik Hosital, Goyang
13. Keimyung University Dongsan Hospital, Daegu
14. Eulji University Hospital, Daejeon
15. Hallym University Kangnam Sacred Heart Hospital
16. Kangwon National University Hospital, Chuncheon
17. Chunnam National University Hospital, Kwangju
18. Hallym University Chunchun Scared Hospital, Chunchun
19. Inje University Haeundae Paik Hospital, Busan
20. Yonsei University Yongin Severance Hospital, Yongin

### **3.6. Statistical Analysis**

#### **3.6.1. Sample Size**

The calculation of the sample size will be based to test the primary endpoint; the composite of cardiac death, target lesion related MI, and ischemia driven TLR

Hypothesis: The primary analysis is a superiority comparison of IVUS guidance to angiographic guidance with respect to the occurrence of the primary end point. Calculation of the sample size was based on a 2-sample and 2-sided test. From previous studies, we assume the overall incidence of MACE, including cardiac death, myocardial infarction, or TLR, to be 7% at 1-year follow-up in the angiography-guided arm.<sup>17-22</sup> We expect that IVUS guidance will reduce the MACE rate by 50%. With the superiority design, 700 patients are needed for each arm, assuming a two-sided alpha level of 0.05, statistical power of 80%, and estimated dropout rate of 5–10%.

#### **Final Sample Size**

Based on above assumptions, we will need 1400 patients (700 patients in the IVUS guidance arm and 700 in the control arm).

#### **3.6.2. Statistical Analysis**

Comparisons between patients treated with and without IVUS-guided PCI will be conducted using  $\chi^2$  test or Fisher's exact test for categorical variables and student t tests for continuous variables. We estimate cumulative incidences of MACE at 12-month. Kaplan-Meier estimates will be used to determine overall and MACE-free survival rates for both groups. Comparison between groups will be performed using log-rank test. The clinical and lesion variables of specific clinical interest will be used in subgroup analyses. Additional subgroups or covariates of clinical interest may be considered in the future. A p-value of < 0.05 is considered to be statistically significant. All analyses will be performed using Statistical Analysis System SPSS 18.0 (SPSS Inc, Chicago, Ill, USA).

### **4. Study Procedure**

Patients evaluated with coronary angiography and planned to be treated with PCI will be screened for inclusion and exclusion criteria. After the patient is enrolled in the present study, the patient will be randomized to study groups. The treatment strategy for PCI 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.

#### **4.1. Index PCI**

The initial index PCI procedure must be carried out in all cases within 7 days. Staged procedures carried out within four weeks will not be considered as repeat procedures. The goals of the procedure are to achieve optimal angiographic efficacy of PCI with implantation of DES using IVUS or angiography guidance in selected target lesion sites while minimizing the risk of procedure-related complications. A study-certified interventional operator should perform all PCI procedures. The procedure should be performed in a cardiac catheterization laboratory that is capable of providing high quality digital images. A full range of commercially available guiding catheters, balloon catheters, and guidewires should be readily available. PCI may be performed by the brachial, radial, or femoral approach. Each procedure is preceded by a coronary angiogram of the vessels to be treated (diagnostic angiogram). At least 2 projections of each vessel should be obtained in orthogonal views.

In the angiography-guided group, stent size and length are chosen by visual estimation, and adjunct high-pressure dilation is performed if an optimal result, defined as angiographic residual diameter stenosis <30% by visual estimation and the absence of angiographically detected dissection, is not achieved. In the IVUS-guided group, stent size and length are selected by on-line IVUS measurements, and adjunct high-pressure dilation will be performed according to the discretion of operators based on the IVUS findings. Use of IVUS will be allowed at any step of PCI (pre-PCI, during PCI and post-PCI); IVUS examination pre-IVUS and during PCI is not mandatory and post-PCI IVUS examination is mandatory. Post-PCI IVUS criteria for stent optimization is minimal stent cross-sectional area > lumen cross-sectional area at distal reference segments.

For each patient, a hierarchy of lesion priority is established such that PCI with DES implantation is attempted first in lesions that are most likely to be responsible for the patient's ischemia. In targeted lesions treated with stent, the final angiographic objective is a <30% residual stenosis. In all treated vessels, necessary means should be taken to achieve TIMI grade-3 distal flow. The index long lesion to be included in the primary per patient analysis will be determined randomly by a computer program prior to QCA analysis. The other long lesions will also be assessed and will be included in the per lesion analysis. However, other lesions requiring PCI with stenting will be analyzed separately.

Direct stenting will be allowed and will be left up to the discretion of the operator. If the allocated stent cannot be delivered to the target lesion site, another commercially approved DES or BMS or balloon PTCA may be used to complete optimal PCI. Other approved PCI techniques, including directional atherectomy and rotational atherectomy may be utilized prior to stent implantation at the interventional operator's discretion. Use of glycoprotein IIb/IIIa inhibitor or intra-aortic balloon pump is left to the operator's discretion. Anticoagulation therapy during the procedure is left to the operator or institution's preference.

During the index procedure, bailout stenting of treatment-unintended segments will be allowed if the subject experiences the following: a) major dissection (type C or greater), b)

occlusive complication as evidenced by a decrease in target vessel flow, c) chest pain or ischemic ECG changes that do not respond to repeat balloon inflations, medical therapy or lytic agents, and d) unplanned additional stent is required to cover the target lesion. A bailout procedure itself will not be considered a MACE, unless the subject sustained cardiac death, emergent CABG procedure, or MI.

#### **4.2. Stent Selection**

The vessel size will be determined either by quantitative angiography or by IVUS for appropriate stent size selection.

##### **4.2.2. DES for Long Lesions**

Xience Prime™ stent (diameter 2.5 – 4.0 mm, length 28, 33 or 38 mm; Abbott Vascular, Santa Clara, CA) will be primarily used to treat all long lesions suitable for DES placement. If more stents are needed to cover a long lesion, additional Xience Prime™ stents of appropriate length will be deployed in an overlapping manner.

##### **4.2.3. DES for Other Lesions**

Other shorter lesions requiring PCI will be mainly treated with Xience Prime™ stent. If an additional stent needs to be used for bailout purposes, Xience Prime™ should be considered as the first implanted stent. If a patient needs to be treated with PCI for other lesions later during the course of the trial, either Xience Prime™ will be used for the treatment of the lesions.

#### **4.3. Adjunctive Pharmacological Therapy**

##### **4.3.1. 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.

**Thienopyridines (clopidogrel):** It will be recommended that patients receive oral 300-600 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 600 mg 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 months or 12 months. Triple antiplatelet therapy will not be allowed in this study.

##### **4.3.2. In the Cardiac Catheterization Laboratory:**

Unfractionated heparin, dosage per label instructions and local standard of care (target ACT 250 sec) 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 procedural administration of heparin or abciximab is allowed according to the operator's decision.

### 4.3.3. Post-procedure and after Discharge

Post procedure and after discharge, aspirin 100mg daily must be maintained indefinitely and Clopidogrel will be given according to the randomly assigned duration of dual antiplatelet therapy (6 or 12 months) Triple antiplatelet therapy including cilostazol is not allowed in this study. Also, other antiplatelet or antithrombotic agents like as triflusal or ticlopidine are not allowed.

### 5. Post Index Procedure Management: Follow-up

After PCI, the schedule of measurements is summarized in the following tables.

**Table 1. Schedule measurements**

Measurement Component	Base	Post-procedure (at discharge)	POST-Randomization (months)				
			1M ±7days	3M ±1M	6M ±1M	12M ±1M	Additive follow-up
Informed consent	X						
Inclusion/Exclusion criteria	X						
Clinical/Medical history	X						
Vital Status & Physical exam	X	X	X	X	X	X	X
Weight & Height	X						
ECG(12 lead)	X	X	X			X	X
Enzymes (CK, CK-MB, Troponin I or T) <sup>1</sup>	X	X					
CBC, LFT	X						
BUN/Cr, electrolyte	X	X	X			X	
Total cholesterol, triglyceride, HDL, LDL	X		X			X	
hsCRP	X		X			X	
Fasting glucose level	X		X			X	
Fasting insulin level	X						
HbA1C	X		X			X	
Pregnancy test (if applicable)	X						
Current Medication	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X

<sup>1</sup>Cardiac enzymes should be measured at 6-8 hours and 24 hours after PCI.

## **5.1. Clinical Follow-up**

Clinical follow-up will occur at the following time points; 1 month, 3 months, 6 months, 9 months, and 1 year. Clinical follow-up measurements, as previously shown in Table 1, will be preceded based on the study schedule.

### **5.1.1. Maintenance of Dual Antiplatelet Therapy during Follow-up**

Dual antiplatelet therapy (clopidogrel 75mg/day + aspirin 100 – 200mg/day) should be continued for the designated period of either 6 months or 12 months according to the randomization.

### **5.1.2. In Cases of Discontinuing Dual Antiplatelet Therapy**

Unplanned discontinuation of dual antiplatelet therapy during the course of the trial should be avoided if possible. However, if discontinuation of dual antiplatelet therapy is not avoidable due to invasive procedures or serious bleeding events, the duration of the discontinuation should be kept as minimally as possible.

The duration and the cause of discontinuation of dual antiplatelet therapy should be precisely described.

- 1) Name of discontinued antiplatelet agents
- 2) Date of discontinuation of antiplatelet therapy
- 3) Date of resuming antiplatelet therapy
- 4) Duration of discontinuation period
- 5) Cause of discontinuation
  - Invasive procedure (name of procedure, diagnosis)
  - Bleeding (source of bleeding, severity of bleeding according to TIMI criteria)
  - Side effects of antiplatelet agent
  - Others: \_\_\_\_\_

After discontinuation of antiplatelet, it should be precisely monitored whether clinical events such as death, MI, stent thrombosis or others might occur simultaneously.

Follow-up 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, revascularization, 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.

## **5.2. Coronary angiogram**

The copies of coronary angiogram should be submitted to the Angiographic Core Lab for the quantitative coronary analysis.

- The baseline coronary angiogram after randomization

## **6. Ethical Considerations and Confidentiality**

## **6.1 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.

## **6.2 Participant Safety**

### **6.2.1 Elements of Informed Consent**

This trial will involve patients with coronary artery disease who have been deemed eligible for coronary revascularization. We anticipate enrolling 1400 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. The interview for obtaining the informed consent will occur in a separate calm room.

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

Appendix B presents the prototype Informed Consent Forms to be modified for each IRB submission in Korean.

### **6.2.2 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 or ticlopidine 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 15 years.

#### Pharmacological risks

Patients treated with stents will be given aspirin and clopidogrel or ticlopidine to try to minimize the likelihood of thrombus formation at the stent site. Use of dual antiplatelet therapy is recommended by 2007 AHA/ACC PCI guidelines.<sup>23</sup> 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. In the event of leucopenia or thrombocytopenia, Clopidogrel will be discontinued. 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.

#### **6.2.3 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.

### **6.3 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 CRFs. 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.

## **7. Study Organization**

### **7.1. Executive Committee**

The Executive Committee will be composed of the study Chairperson and selected members among the investigators. This committee is responsible for overseeing the administrative progress of the study and will approve the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. This committee will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications by members of the Steering Committee. The executive committee also holds the right to modify or stop the study prematurely based on recommendations from the data safety monitoring board.

### **7.2. Steering Committee**

The Steering Committee will be composed of the principal investigators from the centers participating in this trial. The committee is responsible for the day-to-day administrative management of the trial and will meet on a regular base to monitor subject enrollment, clinical site progress, and protocol compliance. It will be the responsibility of the steering committee to provide assistance and education to individual sites and researchers to help with trial management, record keeping, and reporting requirements. The steering committee will prepare reports to be reviewed by the Executive Committee.

### **7.3. Data Safety Monitoring Board (DSMB)**

The DSMB will be composed of general and interventional cardiologists, and a biostatistician. Names of the actual members will not be announced, but may be provided to the regulatory agency upon request. The DSMB will function in accordance with applicable regulatory guidelines. The board members are independent and will not be participating in the trial. The DSMB committee will review the safety data from this study and make recommendations based on safety analyses of unanticipated device effects (UADEs), serious adverse events (SAEs), protocol deviation, device failures, and 30-day follow-up reports. The frequency of the DSMB meetings will be determined prior to study commencement. Additionally, the DSMB may call a meeting at any time if there is reason to suspect that safety is an issue. The DSMB is responsible for making recommendations regarding any safety or compliance issues throughout the course of the study and may recommend

to the Executive Committee to modify or stop the study. However, all final decisions regarding study modifications rest with the Executive Committee.

All cumulative safety data will be reported to the DSMB and reviewed on an ongoing basis throughout enrollment and follow-up periods to ensure patient safety. Every effort will be made to allow the DSMB to conduct an unbiased review of patient safety information. All DSMB reports will be made available to the appropriate agencies upon request but will otherwise remain strictly confidential.

Prior to the DSMB's first review of the data, the DSMB charter will be drafted. The DSMB will develop a consensus understanding of all trial endpoints and definitions used in the event adjudication process. All DSMB reports will remain strictly confidential, but will be made available to the regulatory body upon request.

#### **7.4. 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 data 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.

#### **7.5. Data Coordination and Site Management**

Data coordination and site management services will be performed at the Severance Cardiovascular Center.

### **8. 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.

#### **8.1. 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.

#### **8.2. 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.

### **8.3 Authorship: Primary Outcome Paper**

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

### **8.4 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.

## **9. Quality Assurance, 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.

### **9.1. 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. Myeong-Ki Hong. 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, 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.

**9.2 Data collection: Case Report Forms (CRF)**

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.

**9.3 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 CRFs. 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 CRF for data entry; 3) medical record abstraction; 4) specimen/media collection and handling; 5) data handling; 6) interview techniques and 7) quality control expectations.

#### **9.4 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.

### **10. Core Labs**

#### **10.1. Angiographic Core Lab Measurements**

The central angiographic core laboratory 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 PCI 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. (5) To perform qualitative and quantitative analysis of all baseline and follow-up films. (6) To confirm the endothelialization of each stent. 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 PCI 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. All data will be collected on individual case report forms identified by clinical site, patient identification and procedure date. Appendix contains more details on the Angiographic Core Laboratory.

### **11. Adverse events/Serious adverse events/Unexpected adverse device effects definitions**

#### **11.1. 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.

### **11. 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).

### **11. 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

## **12. Event Adjudication and Reporting**

### **12.1. Investigator Responsibilities:**

#### **12.1.1. 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.

#### **12.1.2. 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.

### **12.2 Designee’s responsibilities**

#### **12.2.1. 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.

### **12.2.2. 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.

### **12.2.3 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.

## **13. Regulatory Responsibilities**

### **13.1. 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 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

### **13.2 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.

### **13.3. 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.

### **13.4. 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.

## **14. Protocol deviations and amendments**

### **14.1 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.

### **14.2 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.

**15. 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.

**15.1. 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.
- All records should be kept in a safe place which can be locked up.
- Patient’s identification should be coded and not be easily recognizable.
- The access to the computers which contain information on patients’ medical records is restricted to only those with authorization.

**15.2. 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
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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.

### 16. 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.

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Principal Investigator (print)

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Principal Investigator (signature)

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Date

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Institution Name/Location

## Appendix A; Definition of Study Endpoints

### 1. MACE (major adverse cardiac events)

Defined as composite of cardiac death, target lesion related MI and ischemia driven TLR

### 2. 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. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent. Also, clinically indicated revascularization is considered clinically indicated if angiography at follow up shows a percent diameter stenosis  $\geq 50\%$  (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  $\geq 70\%$  even in the absence of the above-mentioned ischemic signs or symptoms.

### 3. Cardiac death

Defined as death due to myocardial infarction, cardiac perforation or tamponade, arrhythmia, stroke within 30 days of the procedure or related to the procedure, death due to a complication of the procedure, and any death in which a cardiac cause cannot be excluded, as adjudicated by blinded clinical events committee.

### 4. Target lesion related MI

Myocardial Infarction Classification and Criteria for Diagnosis is defined by the Academic Research Consortium and Third Universal Definition of MI, and clinically relevant MI after PCI is defined by an Expert Consensus Document from the Society for Cardiovascular Angiography and Interventions (SCAI)<sup>24</sup> as follows:

Classification	Biomarker Criteria	Additional Criteria
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

**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. All late events that are not associated with a revascularization procedure should be classified as spontaneous.

**Clinically relevant MI after coronary revascularization:**

**(1) In patients with normal baseline CK-MB**

The peak CK-MB measured within 48 hours of the procedure rises to  $\geq 10$  times the local laboratory ULN, or to  $\geq 5$  times ULN with new pathologic Q-waves in  $\geq 2$  contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to  $\geq 70$  times the local laboratory ULN, or  $\geq 35$  times ULN with new pathologic Q-waves in  $\geq 2$  contiguous leads or new persistent LBBB.

**(2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling**

The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

**(3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling**

The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

**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.

**5. Target vessel revascularization**

Target vessel revascularization is defined as revascularization of target vessel [any clinically driven (as defined for TLR) repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel], recurrent Q-wave or non-Q-wave myocardial infarction, or cardiac death that could not be clearly attributed to a vessel other than the target vessel.

**6. Stent Thrombosis**

The definition of stent thrombosis to be used in this study will follow ARC (Academic Research Consortium) proposed standard definitions.

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

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

- . **Acute onset of ischemic symptoms at rest**

- . **New ischemic ECG changes that suggest acute ischemia**

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

- . **Nonocclusive thrombus:** Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

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

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

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

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

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

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

## **7. Cerebrovascular accident (CVA)**

Sudden onset of vertigo, numbness, aphasia, dysarthria or central neurologic deficit secondary to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persist 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)

## **8. 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.

## **9. 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  $\geq 50\%$  diameter stenosis or any dissection of grade C or higher.

## 10. Bleeding/Hemorrhagic Complications

An episode of bleeding is defined by the TIMI criteria as:

1. Major: Overt clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) associated with a drop in hemoglobin of greater than 5 g/dl (0.5 g/l) or in hematocrit of greater than 15% (absolute) *\*Note: A patient who experiences an intracranial hemorrhage should be considered to have a major hemorrhage.*
2. Minor: Overt clinical bleeding associated with a fall in hemoglobin of 3 to less than or equal to 5 g/dl (0.5 g/l) or in hematocrit of 9% to less than or equal to 15% (absolute)
3. None: No bleeding event that meets the major or minor definition *\*Note: In calculating the fall in hemoglobin or hematocrit, a transfusion of whole blood or packed red blood cells is counted as 1 g/dl (0.1 g/l) hemoglobin or 3% absolute in hematocrit. This would be in addition to the actual fall in hemoglobin or hematocrit.*

\*To account for transfusion, Hgb and Hct measurements will be adjusted for any packed red blood cells or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be assumed to result in an increase of 1 g/dL in Hgb or of 3% in Hct. Thus, to calculate the true change in Hgb or Hct if there has been an intervening transfusion between two blood measurements, the following calculations should be performed:

$$\text{Hgb} = [\text{baseline Hgb} \cdot \text{post transfusion Hgb}] + [\text{number of transfused units}]$$

$$\text{Hct} = [\text{baseline Hct} \cdot \text{post transfusion Hct}] + [\text{number of transfused units} \times 3]$$

The following will be classified as “Instrumented” Major Bleeding that is considered to be associated with the catheterization laboratory visit:

1. Major Percutaneous Entry Site: Bleeding occurred at the percutaneous entry site during or after the catheterization laboratory visit until discharge. The bleeding should require a transfusion and/or prolong the health care facility stay, and/or cause a drop in Hgb > 5 g/dL. Bleeding at the percutaneous entry site can be external or a hematoma >10 cm for femoral access or > 2 cm for radial access; or > 5 cm for brachial access.
2. Major Retroperitoneal, Gastrointestinal, and Genital/Urinary: Bleeding occurred during or after the catheterization laboratory visit until discharge. The bleeding either requires surgical intervention (eg, to relieve nerve compression), and/or requires a transfusion and/or prolong the health care facility stay, and/or cause a drop in hemoglobin > 5.0 g/dL.
3. Major Other/Unknown: Bleeding occurred at other or unknown locations during or after the catheterization laboratory visit until discharge. The bleeding should require a transfusion and/or prolong the health care facility stay, and/or cause a drop in Hgb > 5 g/dL.

## 11. ACC/AHA Classification Scheme of Coronary Lesions

<u>Type A Lesions</u> (High Success, >85%; Low Risk)	<u>Type B Lesions*</u> (Moderate Success, 60-85%; Moderate risk)	<u>Type C Lesions</u> (Low Success, <60%; High Risk)
. Discrete (< 10 mm length)	. Tubular (10-20 mm length)	. Diffuse (> 2 cm length)
. Little or no calcification	. Moderate-to-heavy calcification	. Total occlusions > 3 mo old
. Concentric	. Eccentric	. Excessive tortuosity of
. Less than totally occlusive	. Total occlusions < 3 mo old	

<ul style="list-style-type: none"> <li>. Readily accessible</li> <li>. Not ostial in location</li> <li>. Nonangulated segment, &lt; 45°</li> <li>. No major branch involvement</li> <li>. Smooth contour</li> <li>. Absence of thrombus</li> </ul>	<ul style="list-style-type: none"> <li>. Moderate tortuosity of proximal segment</li> <li>. Ostial in location</li> <li>. Moderately angulated segment, &gt; 45°, &lt; 90°</li> <li>. Bifurcation lesions requiring double guide wires</li> <li>. Irregular contour</li> <li>. Some thrombus present</li> <li>* Type B1 lesions: One adverse characteristic</li> <li>* Type B2 lesions: ≥ two adverse characteristics</li> </ul>	<ul style="list-style-type: none"> <li>proximal segment</li> <li>. Inability to protect major side branches</li> <li>. Extremely angulated segments &gt; 90°</li> <li>. Degenerated vein grafts with friable lesions</li> </ul>
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### 12. 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

### 13. 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.

### 14. Clinical Lesion Success

20% 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

### 15. Clinical Procedure Success

Achievement of a final in-stent diameter stenosis of 20% or less by online QCA or visual assessment over the entire stent length, with TIMI–3 flow and no more than an NHLBI type A peri-stent dissection 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

## **Appendix B. Informed Consent**

Attached document in Korean

## **Appendix C. 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 be 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 injection; 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).
- 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 left 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.

#### Appendix D. List of Committees and Participating Centers

	Centers	Investigators
Executive Committee		Yangsoo Jang, MD Myeong-Ki Hong, MD Jung Han Yoon, MD Dong Woon Cheon, MD Byung Ok Kim, MD Hyuck Moon Kwon, MD
Clinical Event Committee		Eui-Young Choi, MD Chi Young Shim, MD Se-Jung Yoon, MD Jang Young Kim, MD
Steering Committee		Joo Young Yang, MD Yangsoo Jang, MD Hyuck Moon Kwon, MD Jung-Han Yoon, MD Dong Woon Cheon, MD Myeong-Ki Hong, MD Seung Whan Lee, MD Byung Ok Kim, MD Bum Kee Hong, MD
Data Safety Monitoring Board		Chul-Min Ahn, MD Hyuck Jai Chang, MD Seong Hoon Choi, MD Deok Kyu Cho, MD
Angiographic Core Lab	Yonsei University Medical Center Cardiovascular Hospital Angiographic Core Laboratory	
IVUS Core Lab	Yonsei University Medical Center Cardiovascular Hospital IVUS Core Laboratory	
Data Coordinating Center	Preventive Medicine, Yonsei University Medical School, Seoul, Korea	Changsoo Kim, MD
Participating Centers	<ol style="list-style-type: none"> <li>1. Yonsei University Severance Hospital, Seoul</li> <li>2. Yonsei University Gangnam Severance Hospital, Seoul</li> <li>3. Ulsan University Hospital, Ulsan</li> <li>4. Wonju Christian Hospital, Wonju</li> <li>5. Gachon Gil University Hospital, Incheon</li> </ol>	

	<ol style="list-style-type: none"> <li>6. Dankook University Hospital, Cheonan</li> <li>7. NHIC Ilsan Hospital, Goyang</li> <li>8. Kwandong University Myongji Hospital, Goyang</li> <li>9. Seoul Eulji Hospital, Seoul</li> <li>10. Wonkwang University Hospital, Iksan</li> <li>11. Sejong General Hospital, Bucheon</li> <li>12. Inje University Ilsan Paik Hosital, Goyang</li> <li>13. Keimyung University Dongsan Hospital, Daegu</li> <li>14. Eulji University Hospital, Daejeon</li> <li>15. Hallym University Kangnam Sacred Heart Hospital</li> <li>16. Kangwon National University Hospital, Chuncheon</li> <li>17. Chunnam National University Hospital, Kwangju</li> <li>18. Hallym University Chunchun Scared Hospital, Chunchun</li> <li>19. Jeonnju Presbyterian Medical Center, Jeonju, Korea</li> <li>20. CHA Univeristy Medical Center, Seongnam, Korea</li> </ol>	
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