LAte-lumen ChanGEs AfteR Drug-Coated Balloon Angioplasty Versus Drug-Eluting Stents in De novo Coronary Lesions (LARGER-DCB)

Version No: 2.0

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Research Summary

Study Title	**Late-lumen Changes After Drug-Coated Balloon Angioplasty Versus Drug-Eluting Stents in De novo Coronary Lesions (LARGER-DCB)**
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Countries Involved	**Republic of Korea**

Purpose / Objectives:

The aim of the study is to compare the late-lumen loss of drug-coated balloon angioplasty with drug-eluting stent implantation in large de novo coronary lesions.

Backgrounds

Drug-eluting stent (DES) is the standard of care for patients with coronary artery disease who are eligible for percutaneous coronary intervention (PCI).[1] During long-term follow-up, remained metallic stent strut continuously related with stent-related cardiovascular events.[2] As an alternative option to DES, drug-coated balloon (DCB) which has benefit of having shorter DAPT maintenance duration due to the absence of metallic scaffolds and polymers, has been introduced. Based on meta-analysis based on many randomized clinical trials (RCT),[3,4] its use has been established in in-stent restenosis of bare-metal stents and DES.[5]

Furthermore, recent RCTs demonstrated efficacy and safety of DCB in de novo coronary lesions in small vessels with reference vessel size <3.0mm.[6,7] For the patients with de novo, non-complex coronary artery lesions, REC-CAGEFREE I tested the non-inferiority of DCB angioplasty with DES implantation, irrespective of vessel diameter.[8] Overall, 2272 patients were randomly assigned to the DCB or the DES group. At 2 years, adverse events occurred in 6.4% of DCB group and 3.4% of DES group and failed to prove the non-inferiority of DCB angioplasty (P for non-inferiority=0.65). Regarding the heterogenous results, it is questionable that DCB angioplasty for large de novo lesions is safe and effective compared with DES implantation.

On this background, the current study aims to compare late-lumen loss (LLL) between DCB and DES to treat de novo coronary artery stenosis by intravascular ultrasound (IVUS).

Protocol Summary

1. Trial Design

A prospective, multi-center, off-label, randomized controlled, non-inferiority trial. The current trial will evaluate non-inferiority of DCB angioplasty, compared with DES implantation to treat de novo coronary artery stenosis, in terms of late-lumen loss by IVUS.

2. Target Population

Patients with de novo coronary artery stenosis undergoing PCI.

3. Enrollment Criteria

(1) Inclusion criteria

1) Subject must be at least 19 years of age
2) Subject who is able to understand risks, benefits and treatment alternatives and sign informed consent voluntarily
3) Patients with at least one lesion with greater than 50% diameter stenosis or fractional flow reserve ≤0.80 requiring revascularization in de novo coronary artery of reference vessel size ≥3.0 mm

(2) Exclusion criteria

1) Patients unable to provide consent

2) Patients with known intolerance to aspirin, $P2Y_{12}$ inhibitors, or components of drug-eluting stents
3) Patients with angiographic findings of
    1) Left main coronary artery disease
    2) In-stent restenosis is the cause of target lesion
    3) Target lesion in bypass graft
    4) True bifurcation lesion that requires upfront 2-stenting
4) Patients who have non-cardiac co-morbid conditions with life expectancy <1 year
5) Patients who may result in protocol non-compliance (site investigator's medical judgment)
6) Patients with cardiogenic shock or cardiac arrest
7) Patients with severe left ventricular systolic dysfunction (ejection fraction <30%)
8) Patients with severe valvular heart disease requiring open heart surgery
9) Pregnant or lactating women

4. Study End Points

(1) Primary efficacy end point

Mean difference of late-lumen loss between DCB and DES in IVUS

(2) Secondary efficacy end points

1) Mean difference of minimal lumen diameter (MLD) in quantitative coronary angiography (QCA)
2) Mean difference of %diameter stenosis in QCA
3) Mean difference of MLD in IVUS

(3) Secondary clinical end points

1) Cardiovascular death
2) All-cause death
3) Target-vessel myocardial infarction (MI)
4) Non-fatal MI
5) Clinically indicated target-lesion revascularization (TLR)
6) Clinically indicated target-vessel revascularization (TVR)
7) Any revascularization
8) Vessel or stent thrombosis (definite or probable by Academic Research Consortium [ARC] definition)
9) Cardiovascular death or target-vessel MI
10) All-cause death or non-fatal MI
11) Target vessel failure (TVF, a composite of cardiovascular death, target-vessel MI, and clinically indicated TVR)
12) Target lesion failure (TLF, a composite of cardiovascular death, target-vessel MI, and clinically indicated TLR)
13) Cardiovascular death, target-vessel MI, or vessel or stent thrombosis
14) All-cause death, non-fatal MI, or TVR
15) BARC type 2, 3, or 5 bleeding
16) Cerebrovascular accident (CVA)
    - Ischemic stroke
    - Hemorrhagic stroke
    - Transient ischemic attack (TIA)

5. Sample Size Calculation

Primary hypothesis: DCB angioplasty would be noninferior to DES late-lumen loss (LLL) in large de novo coronary stenosis.

Secondary Hypothesis (Superiority): If non-inferiority is established, test for superiority of DCB over DES in LLL.

For the primary analysis, the treatment contrast is defined as:

Δ = mean LLL in the DCB group − mean LLL in the DES group

Because a lower LLL indicates a more favorable vascular response, a more negative value of Δ indicates greater benefit of DCB over DES.

Based on the previous trial that compared late-lumen loss after DCB or DES assessed by QCA or IVUS,[9-14] the expected LLL of DCB is -0.41 mm^2 and DES is 0.18 mm^2, with a pooled standard deviation of 1.28 on IVUS.

The non-inferiority margin was set at +0.472 mm^2, which corresponds to approximately 80% of the expected between-group difference derived from previous literature and was determined after clinical and statistical discussion. Under this framework, DCB would be considered non-inferior if the upper bound of the treatment difference does not exceed this margin.

The non-inferiority hypotheses are defined as follows:

- H0: $\Delta \geq +0.472$ mm^2
- H1: $\Delta < +0.472$ mm^2

- LLL of DCB group: -0.41 mm^2
- LLL of DES group: +0.18 mm^2
- Standard deviation of both groups: 1.28 (DCB group 1.29 and DES group 1.27)
- Non-inferiority margin: +0.472 mm^2
- Type I Error (Alpha):
  - Non-inferiority test: 1-sided alpha of 0.025
  - Superiority Test (if non-inferiority is met): 2-sided alpha of 0.05
- Power: 80%
- Drop-out rate 10%

Based on the above assumption, **a total of 256 patients** (128 patients for DCB group and 128 patients for DES group) will be needed to show non-inferiority of DCB compared to DES with 80% of statistical power at a 1-sided alpha of 2.5%. If non-inferiority is confirmed, the sequential testing of superiority of DCB will be tested at a significance level of 2-sided alpha of 5.0%. The planned sample size will provide statistical power of 99% to test the potential superiority of DCB than DES in terms of LLL.

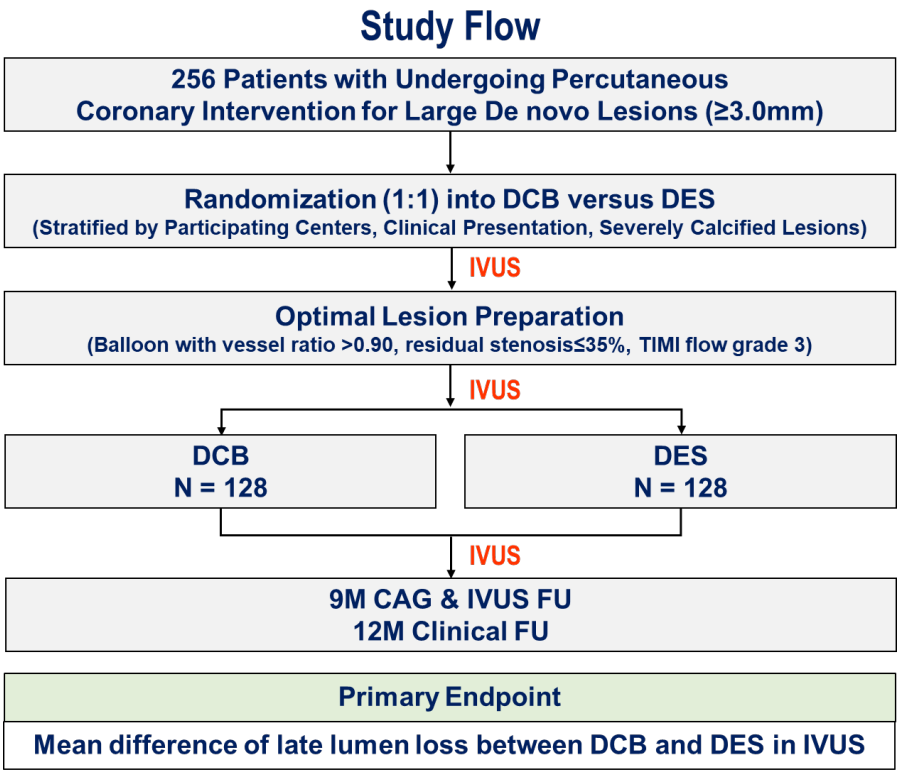
6. Randomization

Patients will be randomized to either the DCB group or the DES group with 1:1 ratio during the index procedure after diagnostic angiography. Stratified randomization according to participating center, clinical presentation (acute coronary syndrome [ACS] or chronic coronary syndrome [CCS]), and severely calcified lesions (encircling calcium in angiography) will be performed. All processes will be done by a web-based randomization program with a permutated block size of 4, run by an independent organization.

(1) Experimental (Standard therapy): DCB group
(2) Control group (Standard therapy): DES group

7. Study Procedure

(1) Flow chart



(2) Optimal lesion preparation and treatment according to allocated group

IVUS (OPTICROSS, Boston Scientific, USA) will be essential to select proper size of predilatation balloon (semi- or non-compliant balloon), DCB, or DES. Optimal lesion preparation is defined as satisfying all of the followings: 1) a fully inflated balloon of the correct size for the vessel (balloon with vessel ratio >0.90); 2) ≤35% residual stenosis; 3) TIMI (Thrombolysis In Myocardial Infarction) flow grade 3; and 4) the absence of a flow-limiting coronary artery dissection.[15] After successful lesion preparation, patients will receive either DCB or DES according to randomly allocated groups.

(3) Drug-coated balloon angioplasty

In DCB group, commercially available DCB (Agent, Boston Scientific, USA) will be used. DCB angioplasty will be recommended as follows to fully optimized procedural results. First, DCB size should be 1:1 ratio with reference vessel size. Second, delivery time of DCB should be within 30 seconds. Third, total inflation time of DCB will be recommended from 30 to 60 seconds.[15,16]

(4) Drug-eluting stent

In DES group, latest second-generation DES will be used in accordance with standard practice guideline.[5,17]

(5) Bail-out stenting in DCB group

In case of 1) flow disturbance after lesion preparation (TIMI glow grade <3), 2) significant re-coil or residual stenosis after lesion preparation (residual stenosis ≥50%), 3) major dissection with significant ischemic changes (dissection type D, E, or F), bail-out implantation of DES will be permitted.[15] Patients treated by bail-out stenting will be analyzed as originally assigned DCB group in the intention-to-treat analysis and will be analyzed as DES group in the per-protocol analysis of the as-treated population. However, primary hypothesis will be tested according to the intention-to-treat analysis.

(6) Intravascular Imaging devices

IVUS will be mandatory during pre-interventional lesion assessment and planning and post-interventional optimization. In DCB arm, optimal size of pre-dilatation balloon and DCB will be decided based on the information from intravascular imaging devices. In DES arm, optimal size of pre-dilatation balloon, stent size, and post-stent implantation optimization will be decided based on the information from IVUS.[18]

(7) Adjunctive medical treatment for both arms

Regardless of allocated arms, best available medical treatment will be the performed according to the current ACC/AHA/SCAI or ESC/EACTS guidelines.[5,17] Patients will be recommended to receive 1-3 months dual antiplatelet therapy of aspirin plus a P2Y12 inhibitor. Thereafter, patients will receive single antiplatelet therapy (a P2Y12 inhibitor alone will be preferred).[19,20] In patients who need oral anticoagulant therapy, aspirin can be discontinued at hospital discharge. In ACS patients, a potent P2Y12 inhibitor (Ticagrelor or Prasugrel) or conventional P2Y12 inhibitor (Clopidogrel) can be used at the discretion of the operator according to appropriate assessment of bleeding risk which is recommended by the current guidelines. Any adjunctive pharmacologic treatment will be left to the operator's discretion.

8. Prespecified Subgroup Analysis

(1) Primary and Secondary efficacy end point will be assessed in pre-specified subgroups below.

1) Age (age ≥65 vs. <65)
2) Sex
3) Diabetes mellitus vs. non-diabetes mellitus
4) Acute coronary syndrome vs. chronic coronary syndrome
5) Optimal vs. Suboptimal lesion-preparation in DCB procedure
6) Complex vs. non-complex lesion

(2) Secondary clinical end point will be assessed in pre-specified subgroups below.

1) Age (age ≥65 vs. <65)
2) Sex
3) Diabetes mellitus vs. non-diabetes mellitus
4) Acute coronary syndrome vs. chronic coronary syndrome
5) Ischemic territory (proximal lesion in major epicardial coronary artery vs. others)
6) Complex vs. non-complex lesion
7) 1-month vs. 3-month dual antiplatelet therapy

9. Study Duration and Dates

IRB approval date ~ 2028.12.31
Subject enrollment: IRB approval date ~ 2026.12 (accrual period: 1.5 years)
End of follow-up period: 2027.12 (1 year after last patient enrollment)
Analysis and report: ~2028.12.31

10. Follow-up

After the randomization, angiographic and IVUS follow-up will be done at 9 months. Clinical follow-up will be done at 6 and 12 months, and annually thereafter until 1 year from last patient enrollment.

Funding Agency	Boston Scientific (USA)

1. Title of Study

Late-lumen Changes After Drug-Coated Balloon Angioplasty Versus Drug-Eluting Stents in De novo Coronary Lesions (LARGER-DCB)

2. Clinical Research Center

① Chonnam National University Hospital, Chonnam National University Medical School, South Korea
② Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
③ Jeonbuk National University Hospital, Jeonju, South Korea
④ Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea\
⑤ Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, South Korea
⑥ Ewha Womans University Mokdong Hospital, Seoul, South Korea
⑦ Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea
⑧ Keimyung University Dongsan Hospital, Daegu, South Korea

3. Principal Investigator, Staff, Co-researchers

	Name	Center	Position
Trial Principle investigator	Young Joon Hong	Chonnam National University Hospital, Chonnam National University Medical School	Professor
Trial Management	Seung Hun Lee	Chonnam National University Hospital, Chonnam National University Medical School	Associate Professor
	Joo Myung Lee	Samsung Medical Center, Sungkyunkwan University School of Medicine	Associate Professor
Co-researchers	Seung Hun Lee	Chonnam National University Hospital, Chonnam National University Medical School	Associate Professor
	Joon Ho Ahn	Chonnam National University Hospital, Chonnam National University Medical School	Associate Professor
	Joo Myung Lee	Samsung Medical Center, Seoul, South Korea	Associate Professor
	Yi Sik Kim	Jeonbuk National University Hospital	Professor
	Eun Seok Shin	Ulsan University Hospital, University of Ulsan College of Medicine	Professor
	Jung Ho Heo	Kosin University Gospel Hospital, Kosin University College of Medicine	Professor
	Sodam Jung	Ewha Womans University Mokdong Hospital	Assistant Professor
	Dong Oh Kang	Korea University Guro Hospital, Korea University College of Medicine	Assistant Professor
	Hyuck-Jun Yoon	Keimyung University Dongsan Hospital	Professor

	Yonghwan Lim	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor
	Seok Oh	Chonnam National University Hospital, Chonnam National University Medical School	Assistant Professor

4. Funding Agencies

Boston Scientific (USA)

5. Background and Hypothesis

5.1. Background

Drug-eluting stent (DES) is the standard of care for patients with coronary artery disease who are eligible for percutaneous coronary intervention (PCI).[1] During long-term follow-up, remained metallic stent strut continuously related with stent-related cardiovascular events.[2] As an alternative option to DES, drug-coated balloon (DCB) which has benefit of having shorter DAPT maintenance duration due to the absence of metallic scaffolds and polymers, has been introduced. Based on meta-analysis based on many randomized clinical trials (RCT),[3,4] its use has been established in in-stent restenosis of bare-metal stents and DES.[5]

Furthermore, recent RCTs demonstrated efficacy and safety of DCB in de novo coronary lesions in small vessels with reference vessel size <3.0mm.[6,7] For the patients with de novo, non-complex coronary artery lesions, REC-CAGEFREE I tested the non-inferiority of DCB angioplasty with DES implantation, irrespective of vessel diameter.[8] Overall, 2272 patients were randomly assigned to the DCB or the DES group. At 2 years, adverse events occurred in 6.4% of DCB group and 3.4% of DES group and failed to prove the non-inferiority of DCB angioplasty (P for non-inferiority=0.65). Regarding the heterogenous results, it is questionable that DCB angioplasty for large de novo lesions is safe and effective compared with DES implantation.

On this background, the current study aims to compare late-lumen loss (LLL) between DCB and DES to treat de novo coronary artery stenosis by intravascular ultrasound (IVUS).

5.2. Hypothesis

DCB angioplasty would be noninferior to DES late-lumen loss in large de novo coronary stenosis.

6. Study Plans

6.1 Study Design

A prospective, multi-center, off-label, randomized controlled, non-inferiority trial.

6.2. Study Timeline

IRB approval date ~ 2028.12.31
Subject enrollment: IRB approval date ~ 2026.12 (accrual period: 1.5 years)
End of follow-up period: 2027. 12 (1 year after last patient enrollment)
Total follow-up duration: 1~2.5 years (Median 1.5 years)
Analysis and report: ~2028.12.31

6.3. Study Population

A total of 256 patients (128 per each group) will be enrolled at multiple centers in South Korea. Patients with large de novo coronary stenosis (≥3.0 mm) undergoing PCI will be eligible. All eligible patients will be on either DCB or DES group as randomized.

6.4. Eligibility Criteria

6.4.1. Inclusion Criteria

(1) Subject must be at least 19 years of age
(2) Subject who is able to understand risks, benefits and treatment alternatives and sign informed consent voluntarily
(3) Patients with at least one lesion with greater than 50% diameter stenosis or fractional flow reserve ≤0.80 requiring revascularization in de-novo coronary artery of reference vessel size ≥3.0 mm

6.4.2. Exclusion Criteria

(1) Patients unable to provide consent
(2) Patients with known intolerance to aspirin, P2Y12 inhibitors, or components of drug-eluting stents
(3) Patients with angiographic findings of
    1) Left main coronary artery disease
    2) In-stent restenosis is the cause of target lesion
    3) Target lesion in bypass graft
    4) True bifurcation lesion that requires upfront 2-stenting
(4) Patients who have non-cardiac co-morbid conditions with life expectancy <1 year
(5) Patients who may result in protocol non-compliance (site investigator's medical judgment)
(6) Patients with cardiogenic shock or cardiac arrest
(7) Patients with severe left ventricular systolic dysfunction (ejection fraction <30%)
(8) Patients with severe valvular heart disease requiring open heart surgery
(9) Pregnant or lactating women

6.5. Sample Size Calculation

Primary hypothesis: DCB angioplasty would be noninferior to DES late-lumen loss (LLL) in large de novo coronary stenosis.
Secondary Hypothesis (Superiority): If non-inferiority is established, test for superiority of DCB over DES in LLL.

For the primary analysis, the treatment contrast is defined as:

Δ = mean LLL in the DCB group − mean LLL in the DES group

Because a lower LLL indicates a more favorable vascular response, a more negative value of Δ indicates greater benefit of DCB over DES.

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The non-inferiority margin was set at +0.472 mm^2, which corresponds to approximately 80% of the expected between-group difference derived from previous literature and was determined after clinical and statistical discussion. Under this framework, DCB would be considered non-inferior if the upper bound of the treatment difference does not exceed this margin.

The non-inferiority hypotheses are defined as follows:

- H0: $\Delta \geq +0.472$ mm^2
- H1: $\Delta < +0.472$ mm^2

- LLL of DCB group: -0.41 mm^2
- LLL of DES group: +0.18 mm^2
- Standard deviation of both groups: 1.28 (DCB group 1.29 and DES group 1.27)
- Non-inferiority margin: +0.472 mm^2
- Type I Error (Alpha):
  - Non-inferiority test: 1-sided alpha of 0.025
  - Superiority Test (if non-inferiority is met): 2-sided alpha of 0.05
- Power: 80%
- Drop-out rate 10%

Based on the above assumption, **a total of 256 patients** (128 patients for DCB group and 128 patients for DES group) will be needed to show non-inferiority of DCB compared to DES with 80% of statistical power at a 1-sided alpha of 2.5%. If non-inferiority is confirmed, the sequential testing of superiority of DCB will be tested at a significance level of 2-sided alpha of 5.0%. The planned sample size will provide statistical power of 99% to test the potential superiority of DCB than DES in terms of LLL.

6.6. Patient Follow-up

After the randomization, angiographic and IVUS follow-up will be done at 9 months. Clinical follow-up will be done at 6 and 12 months, and annually thereafter until 1 year from last patient enrollment.

6.7. Early Study Termination

No statistical rule for early trial termination is defined. An independent Data Safety Monitoring Board (DSMB) will review the safety data including death, myocardial infarction (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 13.1 Steering Committee and DSMB). The Steering Committee will make the final decision for early study termination based on DSMB recommendations.

6.8. Measures to Avoid/Minimize Bias

To minimize bias in assessing clinical events, an independent Clinical Event Adjudication Committee (CEAC) (refer to section 13.2 Clinical Event Adjudication Committee) and DSMB (refer to section 13.1 Steering Committee and DSMB) will be established. 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.

7. End points

7.1. Primary Efficacy End Point

Mean difference of late-lumen loss between DCB and DES in IVUS

7.2. Secondary Efficacy End points

① Mean difference of minimal lumen diameter (MLD) in quantitative coronary angiography (QCA)

② Mean difference of %diameter stenosis in QCA

③ Mean difference of MLD in IVUS

7.3. Secondary Clinical End Points

① Cardiovascular death
② All-cause death
③ Target-vessel myocardial infarction (MI)
④ Non-fatal MI
⑤ Clinically indicated target-lesion revascularization (TLR)
⑥ Clinically indicated target-vessel revascularization (TVR)
⑦ Any revascularization
⑧ Vessel or stent thrombosis (definite or probable by Academic Research Consortium [ARC] definition)
⑨ Cardiovascular death or target-vessel MI
⑩ All-cause death or non-fatal MI
⑪ Target vessel failure (TVF, a composite of cardiovascular death, target-vessel MI, and clinically indicated TVR)
⑫ Target lesion failure (TLF, a composite of cardiovascular death, target-vessel MI, and clinically indicated TLR)
⑬ Cardiovascular death, target-vessel MI, or vessel or stent thrombosis
⑭ All-cause death, non-fatal MI, or TVR
⑮ BARC type 2, 3, or 5 bleeding
⑯ Cerebrovascular accident (CVA)
  - Ischemic stroke
  - Hemorrhagic stroke
  - Transient ischemic attack (TIA)

7.4. Definitions of End Points

Cardiovascular death	Cardiovascular death includes sudden cardiac death, death due to acute MI, heart failure or cardiogenic shock, other cardiovascular causes, or any unknown death without undisputed non-cardiac cause.
MI	The definition of myocardial infarction used in this trial is adapted from the Fourth Universal Definition of Myocardial Infarction.[21] • Clinical criteria for MI: The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia. • Criteria for Myocardial Injury: Detection of an elevated cardiac troponin (cTn) value above the 99th percentile upper reference limit (URL) is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.
Type 1 MI (Spontaneous MI)	Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and with at least 1 of the following: • Symptoms of acute myocardial ischemia; • New ischemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional

	wall motion abnormality in a pattern consistent with an ischemic etiology; • Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.
Type 2 MI (MI secondary to an ischemic imbalance)	Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, requiring at least 1 of the following: • Symptoms of acute myocardial ischemia; • New ischemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
Type 3 MI (MI resulting in death)	Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.
Type 4 and 5 MI	Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (>99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% of the baseline value when it is above the 99th percentile URL but it is stable or falling.
Type 4a MI (PCI-Related MI ≤48 Hours After the Index Procedure)	Coronary intervention–related MI is arbitrarily defined by an elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values. In patients with elevated preprocedure cTn in whom the cTn level are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value must still be at least 5 times the 99th percentile URL. In addition, 1 of the following elements is required: • New ischemic ECG changes; • Development of new pathological Q waves*; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; • Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.
Type 4b MI (MI related to stent/scaffold thrombosis)	A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI.
Type 4c MI (Restenosis Associated with PCI)	This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.
Type 5 MI (CABG-Related MI ≤48 Hours After the Index Procedure)	CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated preprocedure cTn in whom cTn levels are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value still must be >10 times the 99th percentile URL. In addition, 1 of the following elements is required: • Development of new pathological Q waves; • Angiographic documented new graft occlusion or new native coronary

	artery occlusion; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.
TLR, TVR, and Repeat revascularization	The coronary segments revascularized will be sub-classified as: • Target Lesion: A lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The LM target lesion extends from the left main stem ostium to the end of the 5 mm proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel has a vessel diameter of ≥2 mm. • Target Vessel: The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main and any vessel originating from the left main coronary artery or its major branches is, by definition, considered a target vessel for the purposes of this trial. • Target Vessel Non-Target Lesion: The target vessel non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography (QCA). • Non-Target Vessel: Any vessels which was not attempted to be revascularized at index procedure All revascularization events will be adjudicated as either clinically-driven or non-clinically-driven. Revascularization will be considered clinically-driven if the diameter stenosis of the revascularized coronary segment is ≥50% by QCA and any of the following criteria for ischemia are met: ① A positive functional study corresponding to the area served by the target lesion; or ② Ischemic ECG changes at rest in a distribution consistent with the target vessel; or ③ Typical ischemic symptoms referable to the target lesion; or ④ positive invasive physiologic test (fractional flow reserve ≤0.80 or instantaneous wave-free ratio ≤0.89); or ⑤ presence of stenosis with ≥70% diameter stenosis, even in the absence of other criteria
BARC (Bleeding Academic Research Consortium) bleeding	**Type 2:** Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, hospitalization, or treatment by a health care professional **Type 3:** • a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding • b. Overt bleeding plus hemoglobin drop of 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents • c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision

<table>
<tr><td></td><td colspan="2">Type 5:
• a. Probable fatal bleeding
• b. Definite fatal bleeding (overt or autopsy or imaging confirmation)</td></tr>
<tr><td>Stent thrombosis</td><td colspan="2">Academic Research Consortium (ARC) definition of stent thrombosis is classified and defined as follows.
• Definite/Confirmed stent thrombosis refers angiographic or pathologic confirmation of partial or total thrombotic occlusion within the per-stent region with either i) acute ischemic symptoms, ii) ischemic EKG changes, iii) elevated cardiac biomarkers.
• Probable stent thrombosis is defined as any unexplained death within 30 days of stent implantation or any myocardial infarction, which 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.
• Possible stent thrombosis is defined as any unexplained death beyond 30 days of stent implantation.</td></tr>
<tr><td rowspan="4">Cerebrovascular accident (CVA)</td><td colspan="2">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 persists for > 72 hours.</td></tr>
<tr><td>Hemorrhagic</td><td>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.</td></tr>
<tr><td>Nonhemorrhagic</td><td>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.</td></tr>
<tr><td>Transient Ischemic Neurological Attack (TIA)</td><td>A sudden onset of reversible focal neurological deficits due to vascular lesions of the brain that lasts ≤ 24 hours.</td></tr>
</table>

8. Randomization

8.1. Randomization

Patients will be screened for eligibility and, if qualified, a written informed consent will be obtained from all patients. After obtaining informed consent, patients will be randomly assigned to a treatment group via the internet by the independent online randomization system. Randomization will be done immediately after the initial coronary angiogram, but before PCI. Stratified randomization according to participating center, clinical presentation (acute coronary syndrome [ACS] or chronic coronary syndrome [CCS]), and severely calcified lesions (encircling calcium in angiography) will be performed.

All processes will be done by a web-based randomization program with a permutated block size of 4, run by an independent organization.

Patients will be randomized to either DCB group or DES group with 1:1 ratio.

(1) Experimental group (Standard therapy): DCB
(2) Control group (Standard therapy): DES

8.2. Stratification

To ensure balance among the strata, randomization will be stratified by participating center, clinical presentation (acute coronary syndrome [ACS] or chronic coronary syndrome [CCS]), and severely calcified lesions (encircling calcium in angiography). All processes will be done by a web-based randomization program with a permutated block size of 4, run by an independent organization.

9. Patient Enrollment and Withdrawal

9.1. Patient Enrollment

A total of 256 patients derived from a population of Korean patients with large de novo coronary stenosis undergoing PCI will be enrolled in the study. 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.

9.2. Patient Screening

Consecutive patients presenting at participating centers will be evaluated for entry into the study. All consecutive patients should be invited to participate in the study.
Screening will be performed for patients without exclusion criteria. If patients meet enrollment criteria, informed consent will be obtained after explanation of study protocol.
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. Patients will be entered into the eCRF only after informed consent has been obtained.

9.3. Patient Discontinuation (Withdrawal Criteria)

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

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

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

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.
Even patients with lost to follow-up according to the above criteria, cross-validation of vital status will be performed using the National Health Insurance Data and Korean Statistics od Death Record.

9.4. 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 (ex, telephone, emails, and postcards). The following contact procedure is recommended at each time point:

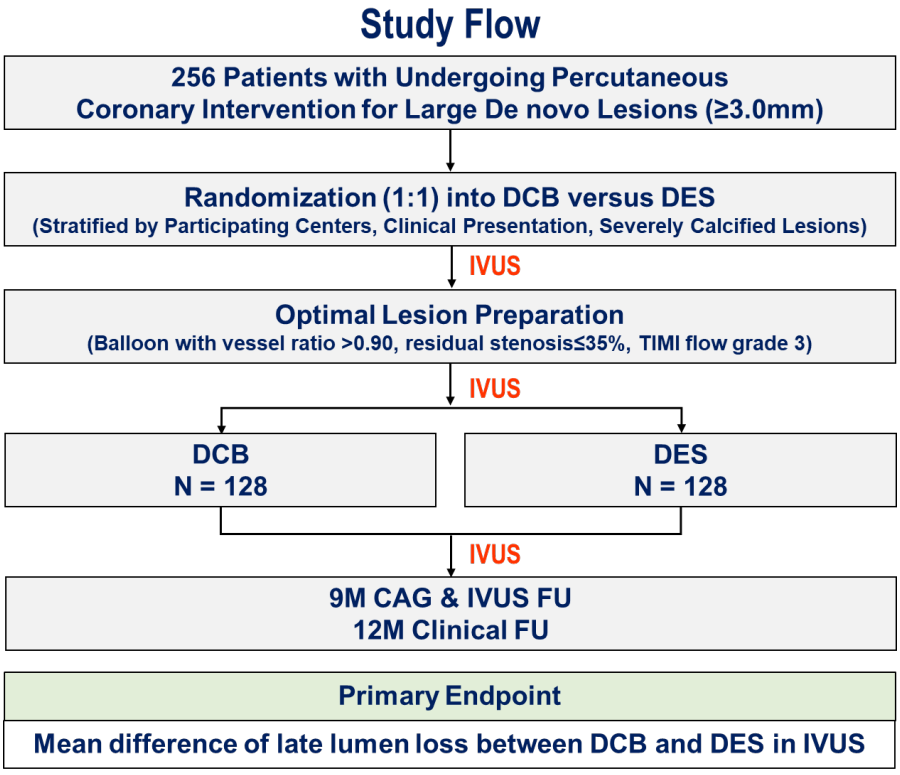
- A minimum of 2 telephone calls on different days over the specified follow-up windows should be recorded in the source documentation including date, time, and site personnel initials for staff attempting to contact the patient.
- If these attempts are unsuccessful, a certified letter should be sent to the patient.
- cross-checking of National Health Insurance Data will be performed for all patients to confirm vital status of enrolled patients.

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.

10. Study Protocols

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 11.1 Schedule of Events. It is recommended that each enrolling investigator review the most recently updated IFU and assess the contraindications, warnings, and precaution sections for treating potential patients.

10.1. Flow Chart



10.2. Study Procedure

(1) **Optimal lesion preparation and treatment according to allocated group**
IVUS (OPTICROSS, Boston Scientific, USA) will be recommended to select proper size of

predilatation balloon (semi- or non-compliant balloon), DCB, or DES. Optimal lesion preparation is defined as satisfying all of the followings: 1) a fully inflated balloon of the correct size for the vessel (balloon with vessel ratio >0.90); 2) ≤35% residual stenosis; 3) TIMI (Thrombolysis In Myocardial Infarction) flow grade 3; and 4) the absence of a flow-limiting coronary artery dissection.[15] After successful lesion preparation, patients will receive either DCB or DES according to randomly allocated groups.

(2) **Drug-coated balloon angioplasty**
In DCB group, commercially available DCB (Agent, Boston Scientific, USA) will be used. DCB angioplasty will be recommended as follows to fully optimized procedural results. First, DCB size should be 1:1 ratio with reference vessel size. Second, delivery time of DCB should be within 30 seconds. Third, total inflation time of DCB will be recommended from 30 to 60 seconds.[15,16]

(3) **Drug-eluting stent**
In DES group, latest second-generation DES will be used in accordance with standard practice guideline.[5,17]

(4) **Bail-out stenting in DCB group**
In case of 1) flow disturbance after lesion preparation (TIMI glow grade <3), 2) significant recoil or residual stenosis after lesion preparation (residual stenosis ≥50%), 3) major dissection with significant ischemic changes (dissection type D, E, or F), bail-out implantation of DES will be permitted.[15] Patients treated by bail-out stenting will be analyzed as originally assigned DCB group in the intention-to-treat analysis and will be analyzed as DES group in the per-protocol analysis of the as-treated population. However, primary hypothesis will be tested according to the intention-to-treat analysis.

(5) **Intravascular Imaging devices**
IVUS will be mandatory during pre-interventional lesion assessment and planning and post-interventional optimization. In DCB arm, optimal size of pre-dilatation balloon and DCB will be decided based on the information from intravascular imaging devices. In DES arm, optimal size of pre-dilatation balloon, stent size, and post-stent implantation optimization will be decided based on the information from IVUS.[18]

(6) **Adjunctive medical treatment**
Regardless of allocated arms, best available medical treatment will be the performed according to the current ACC/AHA/SCAI or ESC/EACTS guidelines.[5,17] Patients will be recommended to receive 1-3 months dual antiplatelet therapy of aspirin plus a P2Y12 inhibitor. Thereafter, patients will receive single antiplatelet therapy (a P2Y12 inhibitor alone will be preferred).[19,20] In patients who need oral anticoagulant therapy, aspirin can be discontinued at hospital discharge. In ACS patients, a potent P2Y12 inhibitor (Ticagrelor or Prasugrel) or conventional P2Y12 inhibitor (Clopidogrel) can be used at the discretion of the operator according to appropriate assessment of bleeding risk which is recommended by the current guidelines. Any adjunctive pharmacologic treatment will be left to the operator's discretion.

10.3. Schedule of Measurements

Visit	Screening & Baseline	Post-Procedure	Follow-Up				
			6-month ±30days	9-month ±30days	12-month ±30days	24-month ±30days	SCV
Medical/Clinical/History (age, sex, risk factors, clinical Dx, angina status)	×						
Inclusion/Exclusion Criteria	×						

Visit	Screening & Baseline	Post-Procedure	Follow-Up				
			6-month ±30days	9-month ±30days	12-month ±30days	24-month ±30days	SCV
Brief Physical Examination	×						
Vital status	×		×	×	×	×	×
Weight, height	×						
12 lead ECG	×						
Informed Consent	×						
Randomization[1)]	×						
Coronary angiogram	×			×			
IVUS	×			×			
CBC, Electrolytes, LFT, Creatinine, BUN	×			×			
CK-MB, Troponin I or T, NT-proBNP	×			×			
Fasting plasma TG, LDL, HDL, total cholesterol	×			×			
Fasting glucose level, $HbA1_C$	×			×			
Echocardiography[2)]	×						
Medications[3)]	×	×	×	×	×	×	×
Clinical event[4)]			×	×	×	×	×

1) Randomization will be done immediately after the initial coronary angiogram, but before PCI. The subject identification code will be assigned consecutively from XX (institution number)-0001 by the interactive web response system of e-CRF. Stratified randomization according to participating center, clinical presentation (acute coronary syndrome [ACS] or chronic coronary syndrome [CCS]), and severely calcified lesions (encircling calcium in angiography) will be performed. All processes will be done by a web-based randomization program with a permutated block size of 4, run by an independent organization
2) Echocardiography should be taken before or after the procedure. If not performed, it will be recorded with the closest result before the randomization.
3) Medication data included medication at baseline (before admission) and post-discharge.
4) Only endpoint-related clinical events (all-cause death, cardiovascular death, MI, repeat revascularization, stent thrombosis, bleeding) will be collected. Follow-up visits will allow telephone contact if clinic visits are unavailable.

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

11. Measurement of Study Outcome Variables

11.1. Visit 1 Screening & Baseline, Post-procedure

(1) Medical/Clinical/ History
Demographic information (age, sex, risk factors, angina status, cardiac history, and cardio-cerebral event) will be recorded at Screening& Baseline.
Relevant medical history, including history of current disease, other pertinent cardiac history, and information regarding underlying diseases will be recorded at Screening & Baseline.

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

(3) 12 lead ECG
ECG will be obtained at Screening & baseline visits.

(4) Inclusion/Exclusion Criteria
Review of subject eligibility

(5) Informed consent
Patients will be informed about the study aims, procedures, and possible risks and the investigator will ensure that the patient or the patient's legally acceptable representative has provided written informed consent. Written consent should include signature and date of legally authorized representatives and investigator.
A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

(6) Randomization
Patients will undergo randomization processes depending on the number of studies enrolled. Randomization will be done immediately after the initial coronary angiogram, but before PCI.
Patients will be randomized to either DCB or DES group with 1:1 ratio. All processes will be done by a web-based randomization program with a permutated block size of 4, run by an independent organization.

(7) Blood tests
Blood tests including CBC (complete blood count), chemistry, and cardiac-related blood tests will be collected at Screening & Baseline.

(8) Coronary angiography
Angiogram will be obtained at the time of index procedure.

(9) IVUS
IVUS will be obtained during at the time of index procedure.

(10) Echocardiography
Exam should be taken before or after PCI.

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

11.2. Follow-up

After the randomization, angiographic and IVUS follow-up will be done at 9 months. Clinical follow-up will be done at 6 and 12 months, and annually thereafter until 1 year from last patient enrollment.

Follow-ups should be office visits, but telephone contact will be allowed. Data collected during all follow-up visits will include vital signs, blood tests, concomitant medications, angina class and major adverse ischemic events including death, MI, repeat revascularization, stent thrombosis, stroke, bleeding, and Adverse Events/ Serious Adverse Events. Original source documents must be submitted for any clinical events (MI, repeat revascularization, stent thrombosis, stroke, bleeding 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 (CK-MB, troponins) must be obtained and recorded.

12. Ethical Considerations and Confidentiality

12.1. 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.

12.2. Participant Safety

12.2.1. Elements of Informed Consent

We anticipate enrolling a total of 256 patients with a mean age in the 60-70s. Pregnant women and patients under the age of 19 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 is given to the patient or legally authorized patient representative.
All sources of research materials will be in the form of medical records, coronary angiograms, electrocardiograms and routine blood work. This material will be obtained both for routine medical care as well as for research purposes.

12.2.2. Potential Risks

Risks of PCI
Complications that may be associated with PCI 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. However, performing interventional procedures on these lesions is a standard treatment currently used in clinical practice, and **participation in this study does not have an additional direct risk associated with the procedure.**

Pharmacological Risks
Patients treated with PCI will be given aspirin, clopidogrel, ticagrelor and prasugrel to minimize the likelihood of thrombus formation at the stent site. Nonetheless, aspirin 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. Ticagrelor may cause bleeding, dyspnea, nausea, dizziness, gout, and transient increased of serum creatinine. Reported side effects of prasugrel includes bleeding, hypertension, headache, hyperlipidemia, nausea, back pain. However, these drugs are standard medications currently used in clinical practice after coronary interventions, and **taking these**

medications cannot be viewed as an additional risk from participation of the study.

12.2.3. 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 48 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 group. 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 Steering committee upon the recommendations of the DSMB. This study will not be stopped early based on efficacy results.

12.3. 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 Center 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.

13. Study Organization

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

The Steering committee comprised of the chairperson and the primary investigators of the main participating center, approved the study design, protocol, and amendments issued to the DSMB and the participating center. 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 Steering committee. In addition, the DSMB will help to conduct the trial appropriately by reviewing and reporting the cumulative investigational data for accuracy and completeness, ensuring protocol compliance. The DSMB will develop a consensus understanding of all trial endpoints and definitions used in the event adjudication process.

13.2. Clinical Event Adjudication Committee (CEAC)

CEAC is comprised of interventional and non-interventional cardiologists who are not participants in the study. The CEAC is charged with the development of specific criteria used for the categorization of clinical events and clinical 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.

13.3. Data Coordination and Site Management

Data coordination and site management services will be performed at the Heart Vascular Stroke Institute, Samsung Medical Center.

14. Statistical Analysis

14.1. Analysis Population

Subjects are to be randomized in a 1:1 fashion to either DCB or DES groups. All primary and secondary endpoints will be analyzed both on an intention-to-treat basis (all subjects analyzed as part of their assigned treatment group), on a per-protocol basis (patients analyzed as part of their assigned treatment group only if they actually received their assigned treatment group and without major protocol violation), and as-treated basis (patients are categorized according to the actual treatment during the procedure). For intention-to-treat analysis, all subjects 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, or they withdraw the informed consent.
Per-protocol population will be defined as population who did not violate the study protocol. The definition of protocol violation is as follows;

(1) Using neither DCB nor DES for PCI
(2) Using different devices contrary to the assigned devices

Analysis with per-protocol population or as-treated population will be performed as exploratory and sensitivity analysis for that of intention-to-treat population. The baseline coronary angiographic characteristics will be analyzed on per-lesion.

14.2. Sample Size Calculation

Primary hypothesis: DCB angioplasty would be noninferior to DES late-lumen loss (LLL) in large de novo coronary stenosis.
Secondary Hypothesis (Superiority): If non-inferiority is established, test for superiority of DCB over DES in LLL.

For the primary analysis, the treatment contrast is defined as:

Δ = mean LLL in the DCB group − mean LLL in the DES group

Because a lower LLL indicates a more favorable vascular response, a more negative value of Δ indicates greater benefit of DCB over DES.

Based on the previous trial that compared late-lumen loss after DCB or DES assessed by QCA or IVUS,[9-14] the expected LLL of DCB is -0.41 mm^2 and DES is 0.18 mm^2, with a pooled standard deviation of 1.28 on IVUS.

The non-inferiority margin was set at +0.472 mm^2, which corresponds to approximately 80% of the expected between-group difference derived from previous literature and was determined after clinical and statistical discussion. Under this framework, DCB would be considered non-inferior if the upper bound of the treatment difference does not exceed this margin.

The non-inferiority hypotheses are defined as follows:

- H0: $\Delta \geq +0.472$ mm^2
- H1: $\Delta < +0.472$ mm^2

- LLL of DCB group: -0.41 mm^2
- LLL of DES group: +0.18 mm^2
- Standard deviation of both groups: 1.28 (DCB group 1.29 and DES group 1.27)
- Non-inferiority margin: +0.472 mm^2
- Type I Error (Alpha):
  - Non-inferiority test: 1-sided alpha of 0.025
  - Superiority Test (if non-inferiority is met): 2-sided alpha of 0.05
- Power: 80%
- Drop-out rate 10%

Based on the above assumption, **a total of 256 patients** (128 patients for DCB group and 128 patients for DES group) will be needed to show non-inferiority of DCB compared to DES with 80% of statistical power at a 1-sided alpha of 2.5%. If non-inferiority is confirmed, the sequential testing of superiority of DCB will be tested at a significance level of 2-sided alpha of 5.0%. The planned sample size will provide statistical power of 99% to test the potential superiority of DCB than DES in terms of LLL.

14.3. Primary Efficacy End Point Analysis

Primary efficacy end point will be analyzed on an intention-to-treat basis, and then, per-protocol basis. Primary efficacy end point will be analyzed on per-patient basis. Analyses will be performed 9 months after last patient enrollment. A 1-sided t-test or analysis of covariance (ANCOVA) to compare mean late-lumen loss between DCB and DES in IVUS, adjusting for any significant baseline covariates that might impact the outcome. If non-inferiority is met, conduct a 2-sided t-test for superiority, with appropriate confidence intervals and p-values.

Primary End point	Statistical methods	Time point of analysis
Mean difference in LLL between the DCB and DES groups	Non-inferiority test: 1-sided t-test or ANCOVA Sequential superiority test: 2-sided t-test	9 months after last patient enrollment

14.4. Secondary Efficacy End Points Analyses

Secondary efficacy end points will be analyzed on an intention-to-treat basis, and then, per-protocol basis. Secondary efficacy end points will be analyzed on per-patient basis. Analyses will be performed 9 months after last patient enrollment. A 1-sided t-test or ANCOVA to compare differences of parameters between DCB and DES in QCA or IVUS, adjusting for any significant baseline covariates that might impact the outcome. If non-inferiority is met, conduct a 2-sided t-test for superiority, with appropriate confidence intervals and p-values.

Major Secondary End point	Statistical methods	Time point of analysis
Mean difference of minimal lumen diameter (MLD) in QCA	Non-inferiority test: 1-sided t-test or ANCOVA Sequential superiority test: 2-sided t-test	9 months after last patient enrollment
Mean difference of %diameter stenosis in QCA	Non-inferiority test: 1-sided t-test or ANCOVA Sequential superiority test: 2-sided t-test	9 months after last patient enrollment
Mean difference of MLD in IVUS	Non-inferiority test: 1-sided t-test or ANCOVA Sequential superiority test: 2-sided t-test	9 months after last patient enrollment

14.5. Secondary Clinical End points Analyses

Secondary clinical end points will be analyzed on an intention-to-treat basis and per-protocol basis. Secondary clinical end points will be analyzed on per-patient basis. Analyses will be performed 1 year after last patient enrollment. Cox proportional hazard regression and Kaplan-Meier analysis will be used to determine the cumulative incidences of the secondary clinical end points. For the secondary outcomes, HRs and 95% CIs will be generated using Cox proportional hazards models. All statistical analysis will be stratified according to participating centers, clinical presentations, and severe calcified lesion (randomization stratification factors).

Secondary End point	Statistical methods	Time point of analysis
Cardiovascular death	Cox's proportional hazard method	1 year after last patient enrollment
All-cause death	Cox's proportional hazard method	1 year after last patient enrollment
Target vessel-MI	Cox's proportional hazard method	1 year after last patient enrollment
Non-fatal MI	Cox's proportional hazard method	1 year after last patient enrollment
Clinically indicated TLR	Cox's proportional hazard method	1 year after last patient enrollment
Clinically indicated TVR	Cox's proportional hazard method	1 year after last patient enrollment
Any revascularization	Cox's proportional hazard method	1 year after last patient enrollment
Vessel or stent thrombosis (definite or probable)	Cox's proportional hazard method	1 year after last patient enrollment
Cardiovascular death or target vessel-related MI	Cox's proportional hazard method	1 year after last patient enrollment
All-cause death or non-fatal MI	Cox's proportional hazard method	1 year after last patient enrollment
TVF	Cox's proportional hazard method	1 year after last patient enrollment
TLF	Cox's proportional hazard method	1 year after last patient enrollment
Cardiovascular death, target-vessel MI, or vessel or stent thrombosis	Cox's proportional hazard method	1 year after last patient enrollment
All-cause death, non-fatal MI, or TVR	Cox's proportional hazard method	1 year after last patient enrollment
BARC type 2, 3, or 5 bleeding	Cox's proportional hazard method	1 year after last patient enrollment
CVA	Cox's proportional hazard method	1 year after last patient enrollment

14.6. 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 endpoints, patients lost to follow-up and subsequently lost to assessment of study endpoints will be considered to be censored in the estimation of all analyses.

14.7. Multivariable Analyses

Multivariable predictors of primary and secondary efficacy end points will be univariate analysis, which tests each variable for association with LLL. Variables with p-values < 0.10 will be considered for

multivariable analysis.
Multivariable predictors of secondary clinical end points will be determined using Cox's proportional hazard models. Forward or backward stepwise selection algorithms will be used to select predictors as needed. Baseline demographic and clinical variables that are predictive at the 0.1 level of p value will be included in the models. The purpose of this is twofold: to do a covariate-adjusted analysis of treatment for all primary and secondary endpoints and to identify the risk factors which are associated with the study endpoints.
The included covariates in univariate analysis will be as with **Table 1**.

Table 1.

Demographics	***Cardiac Risk Factors***	***Procedural Factors***	***Medications***
Age, years	Current smoker	Lesion location	Aspirin
Gender	Previous MI	Total lesion length	Clopidogrel
Height, Weight	Previous PCI	Reference vessel size	Prasugrel
Diabetes mellitus	Previous CABG	Balloon or stent diameter	Ticagrelor
Hypertension	Previous CHF		Statin
Dyslipidemia	Family history of CAD		Ezetimibe
Peripheral artery disease	Previous CVA		ACE inhibitor or ARB
Chronic kidney disease	LV ejection fraction		Beta-blocker
Clinical presentation	LV dysfunction (LVEF<50%)		Warfarin or NOAC
			Calcium-channel blocker

14.8. Pre-specified subgroup analysis

(1) Primary and Secondary efficacy end points will be assessed in pre-specified subgroups below.
1) Age (age ≥65 vs. <65)
2) Sex
3) Diabetes mellitus vs. non-diabetes mellitus
4) Acute coronary syndrome vs. chronic coronary syndrome
5) Optimal vs. Suboptimal lesion-preparation in DCB procedure
6) Complex vs. non-complex lesion

(2) Secondary clinical end point will be assessed in pre-specified subgroups below.
1) Age (age ≥65 vs. <65)
2) Sex
3) Diabetes mellitus vs. non-diabetes mellitus
4) Acute coronary syndrome vs. chronic coronary syndrome
5) Ischemic territory (proximal lesion in major epicardial coronary artery vs. others)
6) Complex vs. non-complex lesion
7) 1-month vs. 3-month dual antiplatelet therapy

15. 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 Steering committee.

15.1 Data Analysis and Release of Results

No results will be released publicly before the 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 Steering Committee after the approval of the DSMB.

15.2 Review Process

The Steering 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 Steering Committee. No study results will be released to the scientific or lay community without the approval of the Steering Committee.

15.3 Authorship: Primary Outcome Paper

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

15.4. Other Study Papers, Abstracts and Presentations

Manuscripts on Ancillary Studies or Subset Analyses should be approved by the Steering 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 primary investigator or an investigator designated by the primary investigator. Each presentation of results on behalf of the investigators should have the approval of the Steering Committee.

16. 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;
- 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.

16.1. Protocol Adherence

There are three key components, each of which is pre-specified. The DATABASE will be programmed to monitor: eligibility criteria, correct treatment administration, and completion in a timely manner of all required data collection (no missed visits, missed studies or specimens). Eligibility criteria are also checked for all or a random sample of patients at every clinic site visit by auditing the patient’s record/worksheet.
It is the Investigator's responsibility to ensure that there are no deviations from the protocol except in cases of medical emergencies when the deviation is necessary to protect the life or physical well-being of the patient. The DCC will monitor these aspects of protocol adherence continually. In addition, clinic site personnel will have clearly specified timeframes for entry of all data and for resolution of any edit queries. All of these aspects of protocol can be monitored at the DCC via real-time reporting, in aggregate and by clinic site.
Any of the protocol violations listed below will be reviewed immediately by the DCC and communicated to the principal investigator. All remedial actions will be jointly decided and, in general, implemented by the DCC. Any clinical site being considered for temporary or permanent termination of patient recruitment may be visited administratively by the monitoring group. The major protocol violations for this study consist of, but are not limited to, the following:

Protocol Violations:

- Eligibility not confirmed, or subject found to be ineligible;
- Informed consent not obtained (or not obtained in a timely manner);
- Randomized therapy not implemented per protocol (crossover to other treatment, 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 primary investigator 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 primary investigator will also be given notice that further violations by investigators at that site may result in site suspension (after an administrative site visit). If a site is suspended early in the trial, all patient recruitment and follow-up (except for vital status and safety) may be terminated. A site suspended later in the trial may still be required to complete follow-up on those subjects already randomized, assuming that the site's adherence to the follow-up protocol is satisfactory or can be remediated. 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.

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

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

16.3. 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.

16.4. 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.

17. Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

Definitions

17.1 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 administered a pharmaceutical product 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 use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

AE may be treatment emergent (i.e., occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

17.2 Serious Adverse Event (SAE)

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

- 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 dyspraxias 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).

18. Event Adjudication and Reporting

18.1 Investigator Responsibilities

18.1.1. Adverse Events

AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of a SAE
The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against investigational product (yes or no)
- Action taken with regard to investigational product / comparator / combination agent
- Outcome

The following variables will be collected for SAEs as applicable:

- Center number (if applicable)
- Patient identification
- Age
- Sex
- Investigational product(s) dose, start & stop date
- Event term as reported by the investigator
- SAE onset & stop date
- Investigator's assessment of seriousness, according to ICH definitions
- Date of death (if applicable)
- Causality assessment in relation to investigational product
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to additional study drug (if applicable)
- SAE outcome

AEs will be notified to Steering Committee according to the clinical relevance with the study. SAEs will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period.
During the course of the study, all SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.
The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

18.1.2 Serious Adverse Events (SAE)

All events meeting the SAE criteria must be reported to the DCC within 48 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 CRF for each serious adverse event, whether related or not to study product 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 AEs should be followed until resolution or stabilization
The site IRB 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 CRF as such, and will be recorded specifically as an AE/SAE.
Planned hospital admissions and/or planned surgical operations for an illness or disease which existed before the patient was randomized in a clinical study are not to be considered AEs. However, baseline conditions which deteriorate during a clinical study may be considered AEs.
It should be noted here that all clinical endpoints, including MI/CVA, 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 DCC in order to allow an independent assessment of these events by the CEAC members.
All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through study period. The investigator and/or Sponsor are responsible for informing the IRB/Ethics Committee and the Regulatory Authority of the SAE as per local requirements.
SAEs will be notified to IRB, if judged necessary by Steering Committee.

18.2 Endpoint and SAE 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.
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.

19. Regulatory Responsibilities

19.1. Investigator Responsibilities

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

- Sign and adhere to the Investigator Agreement
- Participate in Investigator meetings and training sessions as scheduled by Sponsor
- Maintain up-to-date angiographic and intravascular ultrasound equipment (if applicable)
- Be willing to provide original cine films/CD ROMs/intravascular ultrasound videotape for analysis
- Have access to cardiac surgery
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply angiographic material suitable for quantitative analysis
- Obtain written Informed Consent from each study participant before any study specific procedures are performed in accordance with GCP
- Complete all electronic case report forms for completed patients visits and/or applicable events (i.e., SAE, 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,

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

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

19.3. Informed Consent

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

19.4. 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.

20. Protocol Deviations and Amendments

20.1. 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 Steering 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 Ethics Committee will be informed of all protocol changes by the investigator in accordance with the IRB or Ethics Committee established procedure. No deviations from the protocol of any type will be made without complying with all the IRB or Ethics Committee 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.

20.2. Protocol Amendments

In case any revisions to the protocol are required, protocol amendments will be provided to investigators by the Steering 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.

21. 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.

21.1 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 each subject's case history, including study-required Case Report Forms, evidence of informed consent, all relevant observations of adverse 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.

21.2. 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	Per local regulations
	DCC/SC/Principal investigator/DSMB	Within 48 hours
Patient withdrawal	DCC	Notify within 7 days
Annual progress report	SC/Principal investigator	Submitted per 1 year
Deviations from investigational plan	IRB	Per local standard.
	SC/Principal investigator	Notify within 7 days.
Informed consent not obtained	DCC/IRB	Notify within 7 days.
Final summary report	SC/Principal investigator	Within 1 month.

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

22. Investigational Agreement

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

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).

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).

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.

Bleeding/Hemorrhagic Complications
An episode of bleeding is defined by the BARC criteria as:

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	Coronary artery bypass graft surgery-related bleeding within 48 hours
Type 5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

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 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

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.

Myocardial Infarction (MI)
The definition of myocardial infarction used in this trial is adapted from the Fourth Universal Definition of Myocardial Infarction.

1. Clinical criteria for MI
The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia.

2. Criteria for Myocardial Injury
Detection of an elevated cardiac troponin (cTn) value above the 99th percentile upper reference limit (URL) is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.

3. Criteria for Type 1 MI
Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and with at least 1 of the following:
• Symptoms of acute myocardial ischemia;
• New ischemic ECG changes;
• Development of pathological Q waves;
• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
• Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

4. Criteria for Type 2 MI
Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, requiring at least 1 of the following:

• Symptoms of acute myocardial ischemia;
• New ischemic ECG changes;
• Development of pathological Q waves;
• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

5. Criteria for Type 3 MI
Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

6. Criteria for Cardiac Procedural Myocardial Injury
Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (>99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% of the baseline value when it is above the 99th percentile URL but it is stable or falling.

6-1. Criteria for PCI-Related MI ≤48 Hours After the Index Procedure (Type 4a MI)
Coronary intervention–related MI is arbitrarily defined by an elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values. In patients with elevated preprocedure cTn in whom the cTn level are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value must still be at least 5 times the 99th percentile URL. In addition, 1 of the following elements is required:
• New ischemic ECG changes;
• Development of new pathological Q waves*;
• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
• Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.

6-2. Criteria for MI Related to Stent/Scaffold Thrombosis (Type 4b MI)
A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI.

6-3. Restenosis Associated with PCI (Type 4c MI)
This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.

6-4. Criteria for CABG-Related MI ≤48 Hours After the Index Procedure (Type 5 MI)
CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated preprocedure cTn in whom cTn levels are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value still must be >10 times the 99th percentile URL. In addition, 1 of the following elements is required:
• Development of new pathological Q waves;
• Angiographic documented new graft occlusion or new native coronary artery occlusion;
• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

7. Criteria for Prior or Silent/Unrecognized MI
Any 1 of the following criteria meets the diagnosis for prior or silent/unrecognized MI:
• Pathological Q waves as described in below Table, with or without symptoms, in the absence of nonischemic causes;
• Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology;
• Pathological findings of a prior MI.

Table. Electrocardiographic Changes Associated with Prior Myocardial Infarction (In the Absence of Left Ventricular Hypertrophy and Left Bundle Branch Block)

Any Q wave in leads V2 –V3 >0.02 s or QS complex in leads V2 –V3.
Q wave ≥0.03 s and ≥1 mm deep or QS complex in leads I, II, aVL, aVF or V4 – V6 in any 2 leads of a contiguous lead grouping (I, aVL; V1 – V6; II, III, aVF)
R wave >0.04 s in V1 – V2 and R/S >1 with a concordant positive T wave in absence of conduction defect.

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

Repeat coronary revascularization
See revascularization

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

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

Revascularization
Revascularization is defined by the Academic Research Consortium as follows:

Target lesion revascularization: TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs should be classified prospectively as clinically indicated* or not clinically indicated by the investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.
Target vessel Revascularization: TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.
Non-Target Lesion Revascularization (non-TLR): Any revascularization in a lesion other than the target lesion is considered a non-target lesion revascularization.
Non-Target Vessel Revascularization (non-TVR): Any revascularization in a vessel other than the target vessel is considered a non-target vessel revascularization.

*Clinically indicated revascularization: A revascularization is considered clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥ 50% (core laboratory quantitative coronary angiography assessment) and if one of the following occurs:
(1) A positive history of recurrent angina pectoris, presumably related to the target vessel;
(2) Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel;
(3) Abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve);
(4) A TLR or TVR with a diameter stenosis ≥ 70% even in the absence of the above-mentioned ischemic signs or symptoms.

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

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

Timing

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

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0-30 days) is currently used in the community.
† Including “primary” as well as “secondary” late stent thrombosis; “secondary” late stent thrombosis is a stent thrombosis after a target segment revascularization.

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

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

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

. Acute onset of ischemic symptoms at rest
. New ischemic ECG changes that suggest acute ischemia
. Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
. Nonocclusive thrombus: Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
. Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

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

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

. Any unexplained death within the first 30 days [‡ For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.]
. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

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

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

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

23. References

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