Protocol

Protocol for: Lee JM, Choi KH, Song YB, et al. Intravascular imaging–guided or angiography-guided complex PCI. N Engl J Med 2023;388:1668-79. DOI: 10.1056/NEJMoa2216607

This trial protocol has been provided by the authors to give readers additional information about the work.

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Trial Protocol

Trial protocols has been provided by the authors to give readers additional information about their work.

Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention:

The RENOVATE-COMPLEX-PCI Trial

On behalf of the RENOVATE-COMPLEX-PCI investigators

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Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention (RENOVATE-COMPLEX-PCI)

Version No: 1.3.0

Cardiovascular Research Center,
Heart Vascular Stroke Institute,
Samsung Medical Center,
Sungkyunkwan University School of Medicine
Principle Investigator: Joo-Yong Hahn

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Research Summary	
Study Title	**Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention (RENOVATE-COMPLEX-PCI)**
Principal Investigator	Joo-Yong Hahn, MD, PhD (Samsung Medical Center)
Trial management	Joo Myung Lee, MD, MPH, PhD (Samsung Medical Center)

Purpose / Objectives:

The aim of the study is to compare clinical outcomes between intravascular imaging-guided versus angiography-guided percutaneous coronary intervention (PCI) in patients with coronary complex coronary artery lesions.

Study Design

(1) Trial Design

Prospective multicenter randomized controlled trial to compare clinical outcomes between intravascular imaging-guided versus angiography-guided PCI in complex coronary artery lesions.

(2) Target population

Patients with 19-85 years undergoing PCI for the complex coronary artery lesions will be enrolled. The definitions of complex coronary artery lesions are as follows.

*** Definition of Complex Coronary Artery Lesions**

[1] True bifurcation lesion (Medina 1,1,1/1,0,1/0,1,1) with side branch ≥2.5mm size
[2] Chronic total occlusion (≥3 months) as target lesion
[3] PCI for unprotected left main (LM) disease (LM ostium, body, distal LM bifurcation including non-true bifurcation)
[4] Long coronary lesions (implanted stent ≥38 mm in length)
[5] Multi-vessel PCI (≥2 major epicardial coronary arteries treated at one PCI session)
[6] Multiple stents needed (≥3 more stent per patient)
[7] In-stent restenosis lesion as target lesion
[8] Severely calcified lesion (encircling calcium in angiography)

(3) Entry criteria

1) Inclusion criteria

① Subject age 19-85 years old
② Coronary artery disease requiring PCI
③ Patients with complex coronary artery lesions

2) Exclusion criteria

① Target lesions not amenable for PCI by operators' decision
② Cardiogenic shock (Killip class IV) at presentation
③ Intolerance to Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Heparin, or Everolimus
④ Known true anaphylaxis to contrast medium (not allergic reaction but anaphylactic shock)
⑤ Pregnancy or breast feeding

⑥ Non-cardiac co-morbid conditions are present with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment)

⑦ Unwillingness or inability to comply with the procedures described in this protocol.

(4) Primary Hypothesis

Intravascular imaging-guided PCI for complex coronary artery lesions would reduce risk of target vessel failure (TVF, a composite of cardiac death, target vessel myocardial infarction [MI), and clinically-driven target vessel revascularization [TVR]), compared with angiography-guided PCI.

- ➔ **Primary end point: TVF (a composite of cardiac death, target vessel MI, and clinically-driven TVR)**
- ➔ **Secondary end points: TVF without procedure-related MI, cardiac death or target-vessel MI, all-cause death, cardiac death, any MI, target vessel MI with or without procedure-related MI, non-target vessel related MI, any revascularization, TVR, target lesion revascularization (TLR), Academic Research Consortium (ARC)-defined definite stent thrombosis, total procedural time, total amount of contrast use, incidence of contrast-induced nephropathy.**

(5) Sample size calculation

Based on the previous trials which compared Intravascular imaging-guided PCI versus angiography-guided PCI in complex coronary artery lesions and previous studies that evaluated post-PCI clinical event rates after angiography-guided PCI for complex coronary artery lesions, the following assumptions were made.

- Primary end point: Time to occurrence of TVF
- Expected annual rate of TVF:
  Intravascular imaging-guidance group (3.6%) vs. Angiography-guidance group (6%)
- Accrual time: 3 years
- Total follow-up time: 1~4 years (median 2.5 years, till 1 year after the last patient enrollment)
- 2:1 Randomization

Based on the above assumption, **a total of 1620 patients** (1080 and 540 patients for intravascular imaging guidance group and angiography guidance group, respectively) will provide 90% power at a 2-sided alpha of 5%.

(6) Study Procedure

1) Intravascular imaging-guided PCI group

The choice of intravascular imaging devices such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) during PCI will be left to the operator's discretion. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended. Use of intravascular imaging devices will be allowed at any step of PCI (pre-PCI, during PCI and post-PCI), but intravascular imaging evaluation after stent implantation will be mandatory. In this group, the recommendations for selecting reference segment, selecting appropriated size of stent, and stent optimization are as follows. Commercially available IVUS (OpticrossTM, Boston Scientific Corporation, San Jose, CA, USA) or OCT (DragonflyTM, Abbott Vascular, St. Paul, MN, USA) systems will be used for the intravascular imaging-guided PCI group.

	IVUS	OCT
Reference Site	Largest lumen Plaque burden < 50%	Most normal looking segment No Lipidic plaque
Stent Sizing	By measuring vessel diameter (external elastic membrane) at proximal and distal reference sites	Operator can decide 1 of 2 methods [1] By measuring vessel diameter at proximal and distal reference sites (in case of ≥180° of the external elastic membrane can be identified) [2] By measuring lumen diameter at proximal and distal reference sites (in case of ≥180° of the external elastic membrane cannot be identified)
Stent Length	By measuring distance from distal to proximal reference site	
Stent Optimization	• In-stent minimal lumen area ≥ 90% of the average reference lumen area • No major malapposition (defined as a distance from stent strut to adjacent intima ≥200 um) of the stent over its entire length against the vessel wall • No major edge dissection extended to media layer with potential to provoke flow disturbances (defined as ≥60° of the circumference of the vessel at site of dissection and/or ≥3 mm in length of dissection flap) • No untreated (residual) stenosis (defined as MLA ≥60% of adjacent reference segment lumen area) within 10mm from proximal or distal stent edges ⇨ **If 1 of above findings are notified, additional procedure including additional stent implantation will be recommended.**	

2) Angiography-guided PCI group

The PCI procedure in this group will be performed as standard procedure. After deployment of stent, stent optimization will be done based on angiographic findings. The optimization guided by angiography should meet the criteria of angiographic residual diameter stenosis <10% by visual estimation and the absence of flow limiting dissection (type C through F dissection). When angiographic under-expansion of the stent is suspected, adjunctive balloon dilatation will be strongly recommended. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended.

3) Adjunctive treatment/procedure 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. Any adjunctive pharmacologic treatment will be left to the operator's discretion. For example, a loading dose of aspirin (300 mg) and clopidogrel (600 mg) or aspirin (300 mg) and prasugrel (60 mg) or aspirin (300 mg) and ticagrelor (180 mg), or use of GPIIbIIIa inhibitor, etc**.** In case of PCI is performed, dual antiplatelet therapy is recommended for at least 3-6 months in patients with stable ischemic heart disease and 6-12 months in those with acute coronary syndrome, regardless of allocated arms. However, the loading, maintenance dose, and duration of dual antiplatelet therapy will be based on the physician's preference. In addition, in both groups, the use of invasive physiologic assessment at pre- and post-PCI will be left to operator's discretion, however, post-PCI imaging evaluation and optimization of the stent will be strongly recommended in the Imaging group. If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

(7) Randomization

Patients will be randomized to either the Intravascular imaging guidance group or angiography guidance group at the time of enrollment with 2:1 ratio. Stratified randomization according to acute coronary syndrome, type of imaging devices, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

(8) Study Duration and Dates

IRB Approval dates ~ 31.DEC.2022

(9) Follow-up

After the index procedure, clinical follow-up will occur at 1, 6, 12 months, and annually thereafter.

(10) Pre-specified subgroup analysis

① Comparison of TVF according to type of intravascular imaging devices (IVUS or OCT), compared with angiography-guided group.

② Comparison of immediate post-PCI minimum stent cross-sectional area between IVUS and OCT.

Funding Agency	Abbott Vascular

1. Title of Study

Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention (RENOVATE-COMPLEX-PCI)

2. Clinical Research Center

(1) Samsung Medical Center, Sungkyunkwan University School of Medicine
(2) Keimyung University, Dongsan Medical Center
(3) Hanyang University Hospital
(4) Chung-Ang University Hospital
(5) Chungbuk National University Hospital
(6) Seoul National University Bundang Hospital
(7) Uijeongbu St. Mary's Hospital(8) Gangbuk Samsung Hospital
(9) Pusan National University Yangsan Hospital
(10) Gyeongsang National University Hospital
(11) Samsung Changwon Hospital
(12) Wonkwang University Medical Center
(13) Hallym University Pyeongchon Sacred Heart Hospital
(14) Korea University Anam Hospital
(15) Ilsan Paik Hospital
(16) Hallym University Gangdong Sacred Heart Hospital
(17) Kyung Hee University Gangdong Hospital
(18) Myongjii Hospital
(19) Seoul St. Mary's Hospital
(20) Ewha Woman's University Seoul Hospital
(21) Chungnam National University Hospital
(22) Incheon St. Mary's Hospital

3. Principal Investigator, Staff, Co-researchers

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	Kook-Jin Chun, MD, PhD	Pusan National University Yangsan Hospital, Yangsan, Korea
Administrator of study device	Young-Bae Park	Cardiovascular center, Samsung Medical Center, Sungkyunkwan University School of Medicine

4. Funding Agencies

Abbott Vascular, USA

5. Background and Hypothesis

5.1. Background

After introduction of the 2nd generation drug-eluting stents (DES), the rates of device-related failure or target lesion failure such as restenosis and stent thrombosis has been markedly decreased, compared with the era of bare metal stents or 1st generation DES.[1-5] Nevertheless, patients undergoing percutaneous coronary intervention (PCI) for complex coronary artery lesions, for example, chronic total occlusion (CTO), left main disease, true bifurcation lesion, long lesion, multi-vessel PCI, multiple overlapping stents, or severely calcified lesions have significantly worse clinical outcomes than those with non-complex coronary artery lesions.[6-8]

During the PCI procedure, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are useful tools for providing information on preintervention lesion characteristics, including vulnerable plaques, lesion severity, length, and morphology; on postintervention optimal stent implantation for stent expansion, extension, and apposition; and on possible complications after stent implantation.[9-11] Therefore, intravascular imaging guidance may improve clinical outcomes after complex PCI. However, although previous randomized controlled trial (RCT) and registries showed significantly lower rates of major adverse clinical events following IVUS-guided PCI compared with angiography-guided PCI,[12-17] the RCTs were limited with small sample size and dealt with very selected lesion subsets such as CTO or long lesion. Moreover, it is uncertain whether OCT-guided PCI improves clinical outcomes compared with angiography-guided PCI. Meanwhile, appropriate imaging modality may differ according to patient and lesion characteristics. One of the ways to maximize the advantage of intravascular imaging is choice of intravascular imaging devices by the operator's discretion. Therefore, the current RENOVATE-COMPLEX-PCI (Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention) is designed to investigate whether PCI under guidance of intravascular imaging devices (IVUS or OCT) chosen by operators would improve clinical outcomes compared with

angiography-guided PCI in patients with complex coronary artery lesions. Although use of IVUS seems to be more common in Korea than in Western countries, the rate of IVUS use during PCI is less than 30% in Korea.[18] If the RENOVATE trial demonstrates superiority of intravascular imaging-guided PCI, penetration of intravascular imaging will increase in Korea as well as over the world on the strength of solid evidence.

5.2. Hypothesis

Intravascular imaging-guided PCI for patients with complex coronary artery lesions would reduce target vessel failure (TVF, a composite of cardiac death, target vessel myocardial infarction (MI), and clinically driven target vessel revascularization [TVR]), compared with angiography-guided PCI.

6. Study Objectives

6.1. Study purpose

The primary objective of this study is to compare clinical outcomes between intravascular imaging-guided versus angiography-guided PCI in patients with complex coronary artery lesions.

6.2. Primary end point

TVF, defined as a composite of cardiac death, target vessel MI, and clinically-driven target vessel revascularization.

6.3. Secondary end point

① TVF without procedure-related MI

② Cardiac death or target-vessel MI

③ All-cause death

④ Cardiac death

⑤ Any MI

⑥ Target vessel MI with or without procedure-related MI

⑦ Non-target vessel related MI

⑧ Any revascularization, Target vessel revascularization, target lesion revascularization (TLR)

⑨ Academic Research Consortium (ARC)-defined definite stent thrombosis

⑩ total procedural time

⑪ total amount of contrast use

⑫ incidence of contrast-induced nephropathy, defined as an increase in serum creatinine of ≥0.5mg/dL or ≥25% from baseline within 48-72 hours after contrast agent exposure

6.4. Definition of Clinical Events

Cardiac death	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.
Myocardial Infarction	The definition of myocardial infarction used in this trial is based on the Third Universal Definition of Myocardial Infarction for spontaneous myocardial infarction,[19] and the Society for Cardiovascular Angiography and Interventions (SCAI) definition for procedure-related myocardial infarction.[20] <u>Spontaneous Myocardial Infarction</u> Myocardial infarction was defined when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI: 1) Detection of a rise and/or fall of cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: ■ Symptoms of ischemia. ■ New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). ■ Development of pathological Q waves in the ECG. ■ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. ■ Identification of an intracoronary thrombus by angiography or autopsy. 2) Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. 3) Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. <u>Procedure-related Myocardial Infarction</u> Procedure-related myocardial infarctions were defined as follows: 1) In patients with normal baseline CK-MB, the definition is based on when the peak CK-MB measured within 48 hours of the procedure rises to ≥10 x the local laboratory URL or to ≥5 URL with new pathologic Q-waves in ≥2 contiguous leads or new persistent left bundle branch block (LBBB), or in the absence of CK-MB measurements and a normal baseline cardiac troponin (cTn), a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70 x the local laboratory URL, or ≥35 x URL with new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB. 2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarkers are stable or falling, the definition is based on when CK-MB (or

	cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level. 3) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling, the definition is based on when CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.
Repeat revascularization and Target Lesion/Vessel	A coronary revascularization procedure may be either a PCI or a coronary artery bypass grafting (CABG). Revascularization is defined by the Academic Research Consortium as follows: The coronary segments revascularized were sub-classified as: Target Lesion: a lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The left main 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 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: Any revascularization in a lesion other than the target lesion is considered a non-target lesion revascularization. Non-Target Vessel Revascularization: Any revascularization in a vessel other than the target vessel is considered a non-target vessel revascularization. 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

7. Study Population

Patients who undergoing PCI for the complex coronary artery lesions will be enrolled.

8. Study Period

IRB approval date ~ 2022.12.31
Subject enrollment: IRB approval date ~ 2020.09 (roughly 36 months of enrollment)
End of follow-up period: 2021. 09 (1 years after the end of recruitment)
Analysis and report: ~2022.12.31

9. Eligible criteria, Sample size calculation

9.1. Eligible Criteria

(1) Inclusion Criteria

① Subject age 19-85 years old

② Coronary artery disease requiring PCI

③ Patients with complex lesion

1) True bifurcation lesion (Medina 1,1,1/1,0,1/0,1,1) with side branch ≥2.5mm size

2) Chronic total occlusion (≥3 months) as target lesion
3) Unprotected LM disease PCI (LM ostium, body, distal LM bifurcation including non-true bifurcation)
    4) Long coronary lesions (implanted stent ≥38 mm in length)
    5) Multi-vessel PCI (≥2 vessels treated at one PCI session)
    6) Multiple stents needed (≥3 more stent per patient)
    7) In-stent restenosis lesion as target lesion
    8) Severely calcified lesion (encircling calcium in angiography)

④ Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive evaluation and PCI and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.

(2) Exclusion criteria

① Target lesions not amenable for PCI by operators' decision

② Cardiogenic shock (Killip class IV) at presentation

③ Intolerance to Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Heparin, or Everolimus

④ Known true anaphylaxis to contrast medium (not allergic reaction but anaphylactic shock)

⑤ Pregnancy or breast feeding

⑥ Non-cardiac co-morbid conditions are present with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment)

⑦ Unwillingness or inability to comply with the procedures described in this protocol.

9.2. Sample Size Calculation

Hypothesis: Intravascular imaging-guided PCI for patients with complex coronary artery lesions would reduce TVF (a composite of cardiac death, target vessel MI, and TVR), compared with angiography-guided PCI.

Null hypothesis: The annual rate of TVF (a composite of cardiac death, target vessel MI, and TVR will be not different between imaging-guided and angiography-guided PCI groups for treatment of complex lesion.

Based on the previous trials which compared Intravascular imaging-guided PCI versus angiography-guided PCI in complex coronary artery lesions[12, 21] and previous studies which evaluated post-PCI clinical event rates after angiography-guided PCI for complex coronary artery lesions,[22, 23] the following assumptions were made.

- Primary end point: Time to occurrence of TVF
- Expected annual rate of TVF:
- Intravascular imaging-guidance group (3.6%) vs. Angiography-guidance group (6%)
- Accrual time: 3 years
- Total follow-up time: 1~4 years (median 2.5 years, till 1 year after the last patient enrollment)
- 2:1 Randomization
- Drop-out rates: 5.0%

$$E = \frac{(z_{1-\alpha/k} + z_{1-\beta})^2}{\pi_1(1-\pi_1)\ln^2(\Delta)} = \frac{1}{\lambda}(z_{1-\alpha/k} + z_{1-\beta})^2 \left\{\frac{1+\lambda}{\ln(\Delta)}\right\}^2$$

$$N = \frac{E}{p_E}$$

$$p_E = 1 - \frac{1}{6}\left\{\widetilde{S}(f) + 4\widetilde{S}(0.5R + f) + \widetilde{S}(T)\right\}$$

Based on the above assumption, **a total of 1620 patients** (1080 and 540 patients for intravascular imaging guidance group and angiography guidance group, respectively) will provide 90% power at a 2-sided alpha of 5%.

9.3. Recruitment

All consecutive patients with coronary artery complex lesion will be screened for enrollment in this study. A member of each research team should review the patients' medical history for eligibility. If all eligibility criteria are met and written informed consent is provided, the patient may be enrolled in the study. Prior to collecting study data, the details of the study will be explained to the participant including: (1) that participation is voluntary, and there is no penalty for withdrawal, (2) potential risks and benefits for participation, and (3) contact information for additional concerns.

10. Research Materials and Indication for Revascularization

All the PCI cases in this trial will include either Synergy stent system (Boston Scientific) or Xience stent system family (Abbott Vascular), with an anticipated proportion of 70% and 30% respectively.

10.1. Intravascular imaging-guided PCI group

In the intravascular imaging-guided PCI group, commercially available IVUS (OpticrossTM, Boston Scientific Corporation, San Jose, CA, USA) or OCT (DragonflyTM, Abbott Vascular, St. Paul, MN, USA) systems will be used. The choice of intravascular imaging devices such as IVUS or OCT during PCI will be left to the operator's discretion. All IVUS or OCT images will be obtained after administration of intracoronary nitroglycerin (200 μg). When deciding the use of IVUS by the operator, the transducer will be pulled back automatically at a speed of 0.5 mm/s. When deciding the use of OCT by the operator, preheated contrast media at 37 °C will be flushed through the guiding catheter at a rate of 2–4 ml/s for approximately 3–6 s by using an injector pump to obtain the OCT images. The final choice of pullback speed of IVUS device and injection rate/amount of contrast media during OCT use will be also left to the operator's discretion. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended. Use of intravascular imaging devices will be allowed at any step of PCI (pre-PCI, during PCI and post-PCI), but intravascular imaging evaluation after stent implantation will be mandatory. In this group, the recommendations for selecting reference segment, selecting appropriated size of stent, and stent optimization are as follows.

	IVUS	**OCT**
Reference Site	Largest lumen Plaque burden < 50%	Most normal looking segment No Lipidic plaque

	IVUS	OCT
Stent Sizing	By measuring vessel diameter (external elastic membrane) at proximal and distal reference sites	Operator can decide 1 of 2 methods [1] By measuring vessel diameter at proximal and distal reference sites (in case of ≥180° of the external elastic membrane can be identified) [2] By measuring lumen diameter at proximal and distal reference sites (in case of ≥180° of the external elastic membrane cannot be identified)
Stent Length	By measuring distance from distal to proximal reference site	
Stent Optimization	• In-stent minimal lumen area ≥ 90% of the average reference lumen area • No major malapposition (defined as a distance from stent strut to adjacent intima ≥200 um) of the stent over its entire length against the vessel wall • No major edge dissection extended to media layer with potential to provoke flow disturbances (defined as ≥60° of the circumference of the vessel at site of dissection and/or ≥3 mm in length of dissection flap) • No untreated (residual) stenosis (defined as MLA ≥60% of adjacent reference segment lumen area) within 10mm from proximal or distal stent edges ⇨ **If 1 of above findings are notified, additional procedure including additional stent implantation will be recommended.**	

10.2. Angiography-guided PCI group

The PCI procedure in this group will be performed as standard procedure. After deployment of stent, stent optimization will be done based on angiographic findings. The optimization guided by angiography should meet the criteria of angiographic residual diameter stenosis < 10% by visual estimation and the absence of flow limiting dissection (type C through F dissection). When angiographic under-expansion of the stent is suspected, adjunctive balloon dilatation will be strongly recommended. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended.

10.3. Adjunctive treatment/procedure 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. Any adjunctive pharmacologic treatment will be left to the operator's discretion. For example, a loading dose of aspirin (300 mg) and clopidogrel (600 mg) or aspirin (300 mg) and prasugrel (60 mg) or aspirin (300 mg) and ticagrelor (180 mg), or use of GPIIbIIIa inhibitor, etc**.** In case of PCI is performed, dual antiplatelet therapy is recommended for at

least 3-6 months in patients with stable ischemic heart disease and 6-12 months in those with acute coronary syndrome, regardless of allocated arms.[24, 25] However, the loading, maintenance dose, and duration of dual antiplatelet therapy will be based on the physician's preference. In addition, in both groups, the use of invasive physiologic assessment at pre- and post-PCI will be left to operator's discretion, however, post-PCI imaging evaluation and optimization of the stent will be strongly recommended in the Imaging group. If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

11. Methods

11.1. Study designs

Screening will be performed for patients who suspected coronary artery disease without exclusion criteria. And then, informed consent will be obtained after explanation of study protocol. Following angiography, patients with complex lesion that are eligible for coronary intervention will be randomized 2:1 to receive either intravascular imaging-guided strategy or angiography-guided strategy for treatment of the lesions.

As for the intravascular imaging-guided strategy arm, choice of type of imaging device (IVUS or OCT) will be left to the operator's discretion. Use of intravascular imaging devices will be allowed at any step of PCI (pre-PCI, during PCI and post-PCI), but intravascular imaging evaluation after stent implantation will be mandatory.

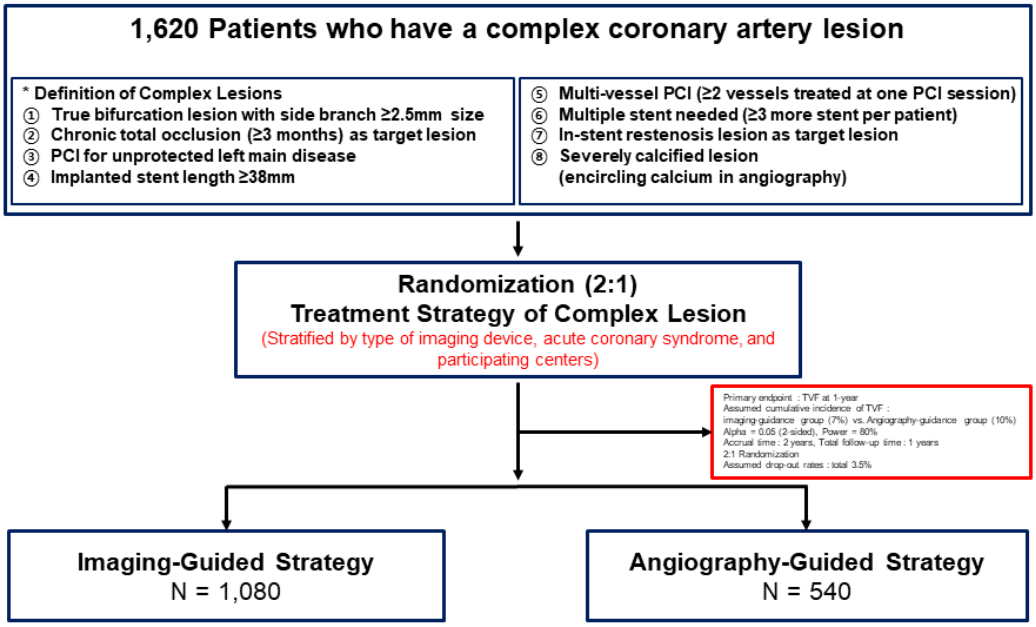
If any violation of the protocols (for example, intravascular imaging was used in angiography-guided strategy arm, or intravascular imaging was not used in imaging-guided strategy arm) according to operator's discretion, the specific reasons will be mandatorily described in electronic case report form.

It is strongly recommended that PCI would be performed at the index procedure after randomization. However, staged procedure during the same hospitalization would be allowed when operator decided to delay the procedure due to concern about the risk of PCI, such as use of large amount of contrast, worsening heart or kidney function, or unstable vital sign. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended.

Regardless of allocated arms, best available medical treatment will be the performed according to the current ACC/AHA/SCAI or ESC/EACTS guidelines.

Any adjunctive pharmacologic treatment and use of invasive physiologic method will be left to the operator's discretion. In case of PCI is performed, dual antiplatelet therapy is recommended for at least 3-6 months in patients with stable ischemic heart disease and 6-12 months in those with acute coronary syndrome, regardless of allocated arms.[24, 25] If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

11.2. Flow chart



11.3. Randomization

Patients will be randomized to either the Intravascular imaging guidance group or angiography guidance group at the time of enrollment with 2:1 ratio. Stratified randomization according to acute coronary syndrome, type of imaging devices, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

12. Schedule of Assessments and Procedures

Visit	Screening & Baseline -30day	Post-Procedure	Follow-Up				
			1-month ±14days	6-month ±30days	12-month ±30days	2, 3, 4 years ±90days	SCV
Medical/Clinical/ History (age, sex, risk factors, clinical Dx, angina status)	×						
Informed Consent	×						
Inclusion/Exclusion Criteria	×						
Brief Physical Examination	×						
Vital status	×	×	×	×	×		
Weight, height	×						
12 lead ECG	×	×					
Angiogram	×						

Randomization[1)]	×						
Quantitative coronary angiography[2)]	×	×					
Intravascular imaging[3)]	×	×					
Invasive physiologic assessment[4)]	x	x					
CBC	×				x		
Electrolytes, LFT	×				x		
Creatinine, BUN	×	×			x		
Fasting plasma TG, LDL, HDL, total cholesterol	×				x		
Fasting glucose level	×				×		
HgbA1C	×				×		
Medications[5)]	×		×	×	×		
CK-MB, Troponin I Or Troponin T[6)]	×	×					
NT-proBNP	×				×		
Clinical event[7)]		×	×	×	×	x	x

***** Screening will be performed for patients who suspected coronary artery disease without exclusion criteria. And then, informed consent will be obtained after explanation of study protocol. Following angiography, patients with complex lesion that are eligible for coronary intervention will be randomized.
***** There will be no mandatory laboratory follow-up.

1) 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 acute coronary syndrome, type of imaging devices, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization. Enrollment is possible even if the DEB or ballooning was used without stenting for revascularization.

2) The raw data of pre- and post-PCI coronary angiography will be collected and undergo quantitative coronary angiographic evaluation in the Core-Laboratory in Samsung Medical Center.

3) Choice of intravascular imaging (IVUS or OCT) will be left to the operator's discretion. The raw data of the intravascular imaging will be analyzed in the Core-Laboratory in Samsung Medical Center. In the intravascular imaging group, intravascular imaging evaluation after stent implantation will be mandatory.

4) Use of invasive physiologic method (for example, fractional flow reserve, instantaneous wave free ratio, coronary flow reserve, or index of microcirculatory resistance) will be left to the operator's discretion. The raw data of the invasive physiologic method will be analyzed in the Core-Laboratory in Samsung Medical Center.

5) Medication data included medication at baseline (before admission) and post-discharge

6) The baseline and post-procedural cardiac enzyme (CK, CK-MB, Troponin I) measurement is mandatory to assess the peri-procedural myocardial infarction, defined according to ARC criteria.

[7] Only end point-related clinical events (all-cause death, cardiac death, cerebrovascular events, MI, stent thrombosis, and repeat revascularization) will be collected.

13. Measurement of study outcome variables

13.1. Visit 1 Screening & Baseline(-30day)

① Informed consent

Before any examination, they will be informed about the study aims, procedures, and possible risks and the Investigator will ensure that the patient or the patient's legally acceptable representative has provided written informed consent. Written consent should include signature and date of legally authorized representatives and investigator.

A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

② Inclusion/exclusion criteria

Review of subject eligibility

③ Medical/clinical/ history

Demographic information (age, sex, risk factors, clinical diagnosis, angina status, cardiac history, and cardio-cerebral event) will be recorded at Screening& Baseline.

Relevant medical history, including history of current disease, other pertinent cardiac history, and information regarding underlying diseases will be recorded at Screening & Baseline

④ Brief physical examination, height, weight, and vital signs

Height, weight, blood pressure, and pulse will be collected

⑤ 12 lead ECG and coronary angiogram

Coronary angiogram will be obtained at baseline visit and post-procedure. ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, or significant arrhythmias, heart failure or other signs or symptoms of clinical instability

⑥ Randomization

Patients will be randomized to either the intravascular imaging-guided strategy or angiography-guided strategy at the time of enrollment with 2:1 ratio. Stratified randomization by acute coronary syndrome, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

⑦ Quantitative coronary angiography/Invasive physiologic assessment data

The raw data of pre- and post-PCI coronary artery angiography will be collected and undergo quantitative coronary angiographic evaluation in the Core-Laboratory in Samsung Medical Center. Coronary physiologic study will be strongly recommended for intermediate lesions, especially when patients have no objective evidence of ischemia. Method for invasive physiologic study (for example, fractional flow reserve, instantaneous wave free ratio, coronary flow reserve, or index of microcirculatory resistance) will be left to the operator's discretion. The raw data of the invasive physiologic method will be analyzed in the Core-Laboratory in Samsung Medical Center.

⑧ Intravascular imaging

Choice of intravascular imaging (IVUS or OCT) will be left to the operator's discretion. The raw data of the intravascular imaging will be analyzed in the Core-Laboratory in Samsung Medical Center.

⑨ 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.

13.2. Visit 2 (Post-Procedure)

① 12 lead ECG and coronary angiogram

Coronary angiogram will be obtained at baseline visit and-post procedure. ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, or significant arrhythmias, heart failure or other signs or symptoms of clinical instability

② Quantitative coronary angiography/Invasive physiologic assessment data

The raw data of pre- and post-PCI coronary artery angiography will be collected and undergo quantitative coronary angiographic evaluation in the Core-Laboratory in Samsung Medical Center. Coronary physiologic study will be strongly recommended for intermediate lesions, especially when patients have no objective evidence of ischemia. Method for invasive physiologic study (for example, fractional flow reserve, instantaneous wave free ratio, coronary flow reserve, or index of microcirculatory resistance) will be left to the operator's discretion. The raw data of the invasive physiologic method will be analyzed in the Core-Laboratory in Samsung Medical Center.

③ Adverse events/serious adverse event

Information regarding occurrence of adverse events (any death, any MI or any revascularization etc.) will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to procedure will be recorded on the case report form (e-CRF).

13.3. Follow-up

Follow-up will occur at 1, 6, and 12 months, and annually thereafter. Investigator or designee may conduct follow-up as office visits.

① Vital signs

Blood pressure and pulse will be collected.

② 12 lead ECG

ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, or significant arrhythmias, heart failure or other signs or symptoms of clinical instability

③ Concomitant medication

④ Adverse events/serious adverse event

Information regarding occurrence of adverse events (any death, any MI or any revascularization etc.) will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to procedure will be recorded on the case report form (e-CRF).

14. Potential risk and adequacy of protection against risks

Complications of PCI for complex lesion include coronary dissection, thrombus formation, side branch occlusion, arterial rupture/perforation, and embolization. However, PCI for these lesions is not considered to have a direct potential risk associated with the procedure, because it is a standard treatment option in clinical practice. In intravascular imaging-guided strategy arm, potential complications related to IVUS or OCT include coronary dissection, thrombus formation, side branch

occlusion, arterial rupture/perforation, and embolization. In case of angiography-guided strategy arm, it is difficult to obtain optimized stent implantation because of the lack of intravascular imaging information. These are potential risks of the present study. Methods of safety-related monitoring in this study will be described number 16.

15. Subject withdrawal

Once enrolled, each Subject should remain in the study until the required follow-up period is completed. However, all Subjects have the right to withdraw at any point during the study without penalty or loss of benefit. The investigator may discontinue any Subject at any time if medically necessary.
The following events will result in terminating the patient's follow-up:

① Patient voluntary withdrawal

② Patient withdrawn by investigator as clinically indicated

If the study treatment(s) or observations are discontinued in any Subject, the reason will be recorded, and the data coordinating center must be notified promptly.

16. Violence of study protocol

Although the treatment strategy of coronary complex lesion in subjects with ischemic heart disease will be decided by randomization process to either intravascular imaging-guided strategy or angiography-guided strategy, whether used the intravascular imaging or not will be decided by operators according to the clinical situation. However, the followings will be recorded as protocol violation and the reason will be recorded and the data coordinating center must be notified promptly.

① Intravascular imaging was used in angiography-guided strategy arm

② Intravascular imaging was not used in imaging-guided strategy arm

17. Event adjudication and reporting, Data safety and monitoring plan

17.1. Data safety and monitoring plan

Type of Report	Prepared by Staffs for:	Time limit of notification
Serious adverse event	IRB	According to IRB regulation of Site
	DCC/EC/Principle investigator DSMB	Within 48 hours
Annual progress report	EC/Principle investigator	Submitted per 1 year
Deviations from investigational plan	IRB	According to IRB regulation of Site
	EC/Principle investigator	Notify within 7 days.
Final summary report	EC/Principle investigator	Within 1 month

*DCC: Data Coordinating Center, EC: Executive Committee (Co-researchers)

17.2. Executive Committee

	Name	Center	Position
Chairman	Joo-Yong Hahn	Samsung Medical Center, Sungkyunkwan	Professor

		University School of Medicine	
Committee members	Young Bin Song	Samsung Medical Center, Sungkyunkwan University School of Medicine	Associate Professor
	Jeong Hoon Yang	Samsung Medical Center, Sungkyunkwan University School of Medicine	Associate Professor
	Joo Myung Lee	Samsung Medical Center, Sungkyunkwan University School of Medicine	Assistant Professor

17.3. Serious Adverse Events

The definition of serious adverse events is in the following paragraph. **It must be reported to the principle investigator within 48 hours after recognition of the event and to the IRB according to IRB regulation of site.**

① Results in persistent or significant disability or incapacity (significant, persistent or permanent change or disruption in subject's body function/structure, physical activity or quality of life

② Requires in-patient hospitalization or prolongs hospitalization

③ Results in a congenital anomaly/birth defect or,

④ Life-threatening events or death

Clinical events include not only TVF, all death, stent thrombosis, but also other end point events. Clinical events and safety data will be reported to principle investigator regularly and examined by staffs for subject's safety throughout the study.

The coordinating center needs to report progress to Executive committee and principle investigator annually. This study will not be stopped early based on efficacy results.

17.4. Event adjudication Committee

All primary and secondary events will be independently adjudicated by Event Adjudication Committee.

	Name	Center	Position
Chairman	Kim Yong-Seok	Dongkuk University College of Medicine, Ilsan Hospital	Professor
Committee members	Dong Ryeol Ryu	Kangwon University Hospital	Professor
	Kyutae Park	Myongji Hospital	Professor

17.5. Data Safety and Monitoring Board

All serious adverse events will be reviewed by independent DSMB.

	Name	Center	Position
Chairman	Kiyuk Chang	Seoul St. Mary's Hospital, The Catholic University of Korea	Professor
Committee members	SeonWoo Kim	Samsung Medical Center, Biostatistics and Clinical Epidemiology Center	Ph. D
	Sung Woo Cho	Inje University Seoul Paik Hospital	Professor

17.6. Data safety monitoring plan

The principle investigator will make the monitoring manager to visit and examine coordinating centers regularly. A designated trial monitor will review data not only for completeness, but also for accordance of the hospital data and eCRF data. Compliance with the protocol and adverse events will be also examined. 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 coordinating centers will permit access to such records.

The monitoring manager: Suyoun Shin, RN (Medical Research Coordinating Center, Samsung Medical Center A-CRO Team)

18. Statistical Consideration and Analysis

18.1. Analysis Population

All subjects are to be randomized in a 2:1 fashion to either intravascular imaging-guided strategy or angiography-guided strategy groups. All primary and secondary end points will be analyzed both on an intention-to-treat basis (all subjects analyzed as part of their assigned treatment group). 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.

Per-protocol population will be defined as population who did not violate the study protocol. The definition of protocol violation is as follows;

① **Intravascular imaging will be used in angiography-guided strategy arm**

② **Intravascular imaging will be not used in imaging-guided strategy arm**

Analysis with Per-protocol population will be performed for sensitivity analysis. The baseline coronary angiographic characteristics will be analyzed on per-lesion.

18.2. Primary End point Analysis

The primary end point (the rates of TVF) will be primarily analyzed on an intention-to-treat basis (all subjects analyzed as part of their assigned treatment group), and then, per-protocol basis. The primary end point will be compared between imaging-guided PCI and angiography-guided PCI with the use of a two-sided log-rank test. The treatment effect as measured by the hazard ratio (the relative risk) and its associated 95 percent confidence interval will be estimated with the use of the Cox proportional-hazards model. All primary and secondary end points will be analyzed on per-patient basis.

18.3. Secondary End point Analysis

The individual components of TVF will be analyzed on an intention-to-treat basis and per-protocol basis. Other secondary end points including all-cause and cardiac death, target vessel MI, any MI, target lesion revascularization, target vessel revascularization, any revascularization, definite stent thrombosis will be analyzed using Kaplan-Meier survival with log rank test and Cox proportional hazard model. Incidence of contrast-induced nephropathy will be analyzed using χ^2-test. Total procedural time and total amount of used contrast will be compared between the two groups with independent sample t-test.

Primary End point	Statistical methods	Time point of analysis

TVF (target-vessel failure, a composite of cardiac death, target-vessel MI, and target-vessel revascularization	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 years after last patient enrollment
Secondary End point	**Statistical methods**	**Time point of analysis**
TVF without procedure-related MI	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Cardiac death or target vessel MI	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
All-cause and cardiac death	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Target-vessel myocardial infarction	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Any myocardial infarction	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Target-lesion revascularization (clinically driven revascularization)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Target-vessel revascularization (clinically driven revascularization)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Any revascularization (clinically driven revascularization)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Stent thrombosis (definite)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Incidence of contrast-induced nephropathy	χ^2-test	Hospital discharge
Total amount of contrast use	Independent sample t-test	Hospital discharge
Total procedural time	Independent sample t-test	Hospital discharge

18.4. 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. Patients who will be lost to follow-up will be censored at the time of the last known contact.

18.5. Multivariable Analyses

Multivariable predictors of all primary and secondary end points will be determined using multivariate regression models, using either binary or Cox's proportional hazard method. Forward or backward

stepwise selection algorithms will be used to select predictors as needed. Baseline demographic and clinical variables that are predictive at the 0.1 level will be included in the models. The purpose of this is twofold: to do a covariate adjusted analysis of treatment for all primary and secondary end points and to identify the risk factors which are associated with the study end points. The included covariates in univariate analysis will be as with Table 1.

Table 1.

Demographics	***Cardiac Risk Factors***	***Medication at discharge***
Age, years	Current smoker	Aspirin
Gender	Previous PCI	Clopidogrel
Diabetes mellitus	Previous CABG	Prasugrel
Hypertension	Previous MI	Ticagrelor
Dyslipidemia	Previous CHF	Statin
Peripheral artery disease	Previous CVA	ACE inhibitor or ARB
Chronic kidney disease	Family history of CAD	Beta-blocker
	LV ejection fraction	Calcium-channer blocker
	LV dysfunction (LVEF<50%)	

18.6. Pre-specified subgroup analysis

① Comparison of TVF according to type of intravascular imaging devices (IVUS or OCT), compared with angiography-guided group.

② Comparison of immediate post-PCI minimum stent cross-sectional area between IVUS and OCT.

19. Care for the safety of the subjects

19.1. 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.

19.2. Elements of Informed Consent

This trial will involve patients with complex coronary artery lesion, who underwent PCI. We anticipate enrolling 1620 patients with a mean age in the 60s. Pregnant women and patients under the age of 18 will be excluded from the trial for ethical and safety concerns.

Prior to collecting study data, the details of the study will be explained to the participant including: (1) that participation is voluntary, and there is no penalty for withdrawal, (2) potential risks and benefits for participation, and (3) contact information for additional concerns. Patients are informed of the purpose of the study, the treatment alternative, the random manner of assignment to treatment, the need to be

available for telephone follow-up and return clinic visits at regular intervals for questionnaires and/or medical tests, and of their options to accept or refuse entry into the study without affecting their clinical care.

All patients or legally authorized patient representatives must sign the current IRB approved informed consent form prior to any study-related activities and the index procedure. Failure to obtain signed informed consent will render the patient ineligible for the study. The signed informed consent will be kept in the patient's medical records and a copy given to the patient or legally authorized patient representative. All sources of research materials will be in the form of medical records, coronary angiograms, electrocardiograms and routine blood work. This material will be obtained both for routine medical care as well as for research purposes.

19.3. 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 electronic case report form (eCRF). Patient data will be protected by the use of locked cabinets at the Clinical Centers and use of passwords, data encryption and secure, limited access storage of electronic data. The explicit issue of privacy and confidentiality is outlined in the Informed Consent Form.

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Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention (RENOVATE-COMPLEX-PCI)

Version No: 2.2.0

Cardiovascular Research Center,
Heart Vascular Stroke Institute,
Samsung Medical Center,
Sungkyunkwan University School of Medicine
Principle Investigator: Joo-Yong Hahn

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Research Summary	
Study Title	**Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention (RENOVATE-COMPLEX-PCI)**
Principal Investigator	Joo-Yong Hahn, MD, PhD (Samsung Medical Center)
Trial management	Joo Myung Lee, MD, MPH, PhD (Samsung Medical Center)

Purpose / Objectives:

The aim of the study is to compare clinical outcomes between intravascular imaging-guided versus angiography-guided percutaneous coronary intervention (PCI) in patients with coronary complex coronary artery lesions.

Study Design

(1) Trial Design

Prospective multicenter randomized controlled trial to compare clinical outcomes between intravascular imaging-guided versus angiography-guided PCI in complex coronary artery lesions.

(2) Target population

Patients over 19 years undergoing PCI for the complex coronary artery lesions will be enrolled. The definitions of complex coronary artery lesions are as follows.

*** Definition of Complex Coronary Artery Lesions**

[1] True bifurcation lesion (Medina 1,1,1/1,0,1/0,1,1) with side branch ≥2.5mm size
[2] Chronic total occlusion (≥3 months) as target lesion
[3] PCI for unprotected left main (LM) disease (LM ostium, body, distal LM bifurcation including non-true bifurcation)
[4] Long coronary lesions (implanted stent ≥38 mm in length)
[5] Multi-vessel PCI (≥2 major epicardial coronary arteries treated at one PCI session)
[6] Multiple stents needed (≥3 more stent per patient)
[7] In-stent restenosis lesion as target lesion
[8] Severely calcified lesion (encircling calcium in angiography)
[9] Left anterior descending (LAD), left circumflex artery (LCX), and right coronary artery (RCA) ostial lesion

(3) Entry criteria

1) Inclusion criteria

① Subject age ≥19 years old
② Coronary artery disease requiring PCI
③ Patients with complex coronary artery lesions

2) Exclusion criteria

① Target lesions not amenable for PCI by operators' decision
② Cardiogenic shock (Killip class IV) at presentation
③ Intolerance to Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Heparin, or Everolimus
④ Known true anaphylaxis to contrast medium (not allergic reaction but anaphylactic shock)
⑤ Pregnancy or breast feeding

⑥ Non-cardiac co-morbid conditions are present with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment)

⑦ Unwillingness or inability to comply with the procedures described in this protocol.

(4) Primary Hypothesis

Intravascular imaging-guided PCI for complex coronary artery lesions would reduce risk of target vessel failure (TVF, a composite of cardiac death, target vessel myocardial infarction [MI), and clinically-driven target vessel revascularization [TVR]), compared with angiography-guided PCI.

➔ **Primary end point: TVF (a composite of cardiac death, target vessel MI, and clinically-driven TVR)**

➔ **Secondary end points: TVF without procedure-related MI, cardiac death or target-vessel MI, all-cause death, cardiac death, any MI, target vessel MI with or without procedure-related MI, non-target vessel related MI, any revascularization, TVR, target lesion revascularization (TLR), Academic Research Consortium (ARC)-defined definite stent thrombosis, total procedural time, total amount of contrast use, incidence of contrast-induced nephropathy, total medical cost.**

(5) Sample size calculation

Based on the previous trials which compared Intravascular imaging-guided PCI versus angiography-guided PCI in complex coronary artery lesions and previous studies that evaluated post-PCI clinical event rates after angiography-guided PCI for complex coronary artery lesions, the following assumptions were made.

- Primary end point: Time to occurrence of TVF
- Expected annual rate of TVF:
  Intravascular imaging-guidance group (3.6%) vs. Angiography-guidance group (6%)
- Accrual time: 3 years
- Total follow-up time: 1~4 years (median 2.5 years, till 1 year after the last patient enrollment)
- 2:1 Randomization

Based on the above assumption, **a total of 1620 patients** (1080 and 540 patients for intravascular imaging guidance group and angiography guidance group, respectively) will provide 90% power at a 2-sided alpha of 5%.

(6) Study Procedure

1) Intravascular imaging-guided PCI group

The choice of intravascular imaging devices such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) during PCI will be left to the operator's discretion. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended. Use of intravascular imaging devices will be allowed at any step of PCI (pre-PCI, during PCI and post-PCI), but intravascular imaging evaluation after stent implantation will be mandatory. In this group, the recommendations for selecting reference segment, selecting appropriated size of stent, and stent optimization are as follows. Commercially available IVUS (OpticrossTM, Boston Scientific Corporation, San Jose, CA, USA) or OCT (DragonflyTM, Abbott Vascular, St. Paul, MN, USA) systems will be used for the intravascular imaging-guided PCI group.

	IVUS	OCT
Reference Site	Largest lumen Plaque burden < 50%	Most normal looking segment No Lipidic plaque
Stent Sizing	By measuring vessel diameter (external elastic membrane) at proximal and distal reference sites. The averaged value of the proximal and distal reference external elastic membrane diameter will be used as stent diameter	Operator can decide 1 of 2 methods [1] By measuring vessel diameter at the distal reference sites (in case of ≥180° of the external elastic membrane can be identified). In this case, stent diameter will be determined using mean external elastic membrane diameter at the distal reference, rounded down to the nearest 0.25 mm (Ex> mean external elastic membrane reference diameter 3.15 mm, 3.0 mm stent diameter will be chosen). [2] By measuring lumen diameter at the distal reference sites (in case of ≥180° of the external elastic membrane cannot be identified). In this case, stent diameter will be determined using mean lumen diameter at the distal reference, rounded up to the nearest 0.25 mm (Ex> mean distal reference lumen diameter 2.55 mm, 2.75 mm stent diameter will be chosen).
Stent Length	By measuring distance from distal to proximal reference site	
Stent Optimization		
● **Stent Expansion**	Visually assess residual angiographic diameter stenosis <10% "AND" ① In non-LM lesions: In-stent minimal lumen area (MSA) > 80% of the average reference lumen area "OR" MSA>5.5 mm^2 (IVUS) and >4.5 mm^2 (OCT) ② In LM stenosis : MSA>7 mm^2 for distal LM and >8 mm^2 for proximal LM (IVUS)	
● **Stent Apposition**	No major malapposition (defined as an acute malapposition of ≥0.4mm with longitudinal extension >1mm) of the stent over its entire length against the vessel wall	
● **Edge Dissection**	No major edge dissection in the proximal or distal reference segments, defined as 5 mm from the edge of the stent, extended to media layer with potential to provoke flow disturbances (defined as ≥60° of the circumference of the vessel at site of dissection and/or ≥3 mm in length of dissection flap)	
Optimization technique of the stent	**If 1 of above findings are notified, additional procedure including adjunctive post-dilatation or additional stent implantation for residual reference segment disease will be mandatorily recommended.** In adjunctive post-dilatation procedure, the diameter of the non-compliant post dilatation balloon chosen should not be larger than the post-PCI IVUS/OCT determined mean reference external elastic membrane diameter of one or both segments (proximal or distal), or no more than 0.5 mm larger than the mean reference segment lumen diameter of one or both segments (proximal or distal) nearest to the dilatation site (if the EEL cannot be measured).	

2) Angiography-guided PCI group

The PCI procedure in this group will be performed as standard procedure. After deployment of stent, stent optimization will be done based on angiographic findings. The optimization guided by angiography should meet the criteria of angiographic residual diameter stenosis <10% by visual estimation and the absence of flow limiting dissection (type C through F dissection). When angiographic under-expansion of the stent is suspected, adjunctive balloon dilatation will be strongly recommended. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended.

3) Adjunctive treatment/procedure 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. Any adjunctive pharmacologic treatment will be left to the operator's discretion. For example, a loading dose of aspirin (300 mg) and clopidogrel (600 mg) or aspirin (300 mg) and prasugrel (60 mg) or aspirin (300 mg) and ticagrelor (180 mg), or use of GPIIbIIIa inhibitor, etc**.** In case of PCI is performed, dual antiplatelet therapy is recommended for at least 3-6 months in patients with stable ischemic heart disease and 6-12 months in those with acute coronary syndrome, regardless of allocated arms. However, the loading, maintenance dose, and duration of dual antiplatelet therapy will be based on the physician's preference. In addition, in both groups, the use of invasive physiologic assessment at pre- and post-PCI will be left to operator's discretion, however, post-PCI imaging evaluation and optimization of the stent will be strongly recommended in the Imaging group. If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

(7) Randomization

Patients will be randomized to either the Intravascular imaging guidance group or angiography guidance group at the time of enrollment with 2:1 ratio. Stratified randomization according to acute coronary syndrome, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

(8) Study Duration and Dates

IRB Approval dates ~ 31.DEC.2022

(9) Follow-up

After the index procedure, clinical follow-up will occur at 1, 6, 12 months, and annually thereafter.

(10) Pre-specified subgroup analysis

① Comparison of TVF according to type of intravascular imaging devices (IVUS or OCT), compared with angiography-guided group.

② Comparison of immediate post-PCI minimum stent cross-sectional area between IVUS and OCT.

③ Analysis of the primary end point will be performed in pre-specified subgroups according to age (dichotomized at the of ≥65 years), sex, diabetes mellitus, chronic kidney disease, clinical presentation (stable ischemic heart disease and acute coronary syndrome), complex lesion type, number of complexity (≥ 3 or < 3), and LV dysfunction (EF <50% and ≥50%).

Funding Agency	Boston Scientific and Abbott Vascular

1. Title of Study

Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention (RENOVATE-COMPLEX-PCI)

2. Clinical Research Center

(1) Samsung Medical Center, Sungkyunkwan University School of Medicine
(2) Keimyung University, Dongsan Medical Center
(3) Hanyang University Hospital
(4) Chung-Ang University Hospital
(5) Chungbuk National University Hospital
(6) Seoul National University Bundang Hospital
(7) Uijeongbu St. Mary's Hospital(8) Gangbuk Samsung Hospital
(9) Pusan National University Yangsan Hospital
(10) Gyeongsang National University Hospital
(11) Samsung Changwon Hospital
(12) Wonkwang University Medical Center
(13) Hallym University Pyeongchon Sacred Heart Hospital
(14) Korea University Anam Hospital
(15) Ilsan Paik Hospital
(16) Hallym University Gangdong Sacred Heart Hospital
(17) Kyung Hee University Gangdong Hospital
(18) Myongjii Hospital
(19) Seoul St. Mary's Hospital
(20) Ewha Woman's University Seoul Hospital
(21) Chungnam National University Hospital
(22) Incheon St. Mary's Hospital

3. Principal Investigator, Staff, Co-researchers

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	Young-Hyo Lim, MD, PHD	Hanyang University Seoul Hospital, College of Medicine, Hanyang University, Seoul, Korea
	Yun-Hyeong Cho, MD, PHD	Hanyang University Myongji Hospital,

		Goyang, Korea
	Jin-Man Cho, MD, PhD	Kyung Hee University Hospital at Gangdong, Seoul, Korea
	Woo Jin Jang, MD, PhD	Ewha Womans University College of Medicine, Seoul, Korea
	Kook-Jin Chun, MD, PhD	Pusan National University Yangsan Hospital, Yangsan, Korea
Administrator of study device	Young-Bae Park	Cardiovascular center, Samsung Medical Center, Sungkyunkwan University School of Medicine

4. Funding Agencies

Boston Scientific, USA
Abbott Vascular, USA

5. Background and Hypothesis

5.1. Background

After introduction of the 2nd generation drug-eluting stents (DES), the rates of device-related failure or target lesion failure such as restenosis and stent thrombosis has been markedly decreased, compared with the era of bare metal stents or 1st generation DES.[1-5] Nevertheless, patients undergoing percutaneous coronary intervention (PCI) for complex coronary artery lesions, for example, chronic total occlusion (CTO), left main disease, true bifurcation lesion, long lesion, multi-vessel PCI, multiple overlapping stents, or severely calcified lesions have significantly worse clinical outcomes than those with non-complex coronary artery lesions.[6-8]

During the PCI procedure, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are useful tools for providing information on preintervention lesion characteristics, including vulnerable plaques, lesion severity, length, and morphology; on postintervention optimal stent implantation for stent expansion, extension, and apposition; and on possible complications after stent implantation.[9-11] Therefore, intravascular imaging guidance may improve clinical outcomes after complex PCI. However, although previous randomized controlled trial (RCT) and registries showed significantly lower rates of major adverse clinical events following IVUS-guided PCI compared with angiography-guided PCI,[12-17] the RCTs were limited with small sample size and dealt with very selected lesion subsets such as CTO or long lesion. Moreover, it is uncertain whether OCT-guided PCI improves clinical outcomes compared with angiography-guided PCI. Meanwhile, appropriate imaging modality may differ according to patient and lesion characteristics. One of the ways to maximize the advantage of intravascular imaging is choice of intravascular imaging devices by the operator's discretion. Therefore, the current RENOVATE-COMPLEX-PCI (Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention) is designed to investigate whether PCI under guidance of intravascular imaging devices (IVUS or OCT) chosen by operators would improve clinical outcomes compared with angiography-guided PCI in patients with complex coronary artery lesions. Although use of IVUS seems to be more common in

Korea than in Western countries, the rate of IVUS use during PCI is less than 30% in Korea.[18] If the RENOVATE trial demonstrates superiority of intravascular imaging-guided PCI, penetration of intravascular imaging will increase in Korea as well as over the world on the strength of solid evidence.

5.2. Hypothesis

Intravascular imaging-guided PCI for patients with complex coronary artery lesions would reduce target vessel failure (TVF, a composite of cardiac death, target vessel myocardial infarction (MI), and clinically driven target vessel revascularization [TVR]), compared with angiography-guided PCI.

6. Study Objectives

6.1. Study purpose

The primary objective of this study is to compare clinical outcomes between intravascular imaging-guided versus angiography-guided PCI in patients with complex coronary artery lesions.

6.2. Primary end point

TVF, defined as a composite of cardiac death, target vessel MI, and clinically-driven target vessel revascularization.

6.3. Secondary end point

① TVF without procedure-related MI
② Cardiac death or target-vessel MI
③ All-cause death
④ Cardiac death
⑤ Any MI
⑥ Target vessel MI with or without procedure-related MI
⑦ Non-target vessel related MI
⑧ Any revascularization, Target vessel revascularization, target lesion revascularization (TLR)
⑨ Academic Research Consortium (ARC)-defined definite stent thrombosis
⑩ total procedural time
⑪ total amount of contrast use
⑫ incidence of contrast-induced nephropathy, defined as an increase in serum creatinine of ≥0.5mg/dL or ≥25% from baseline within 48-72 hours after contrast agent exposure
⑬ Total medical cost

6.4. Definition of Clinical Events

Cardiac death	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.
Myocardial Infarction	The definition of myocardial infarction used in this trial is based on the Third

	Universal Definition of Myocardial Infarction for spontaneous myocardial infarction,[19] and the Society for Cardiovascular Angiography and Interventions (SCAI) definition for procedure-related myocardial infarction.[20] Spontaneous Myocardial Infarction Myocardial infarction was defined when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI: 1) Detection of a rise and/or fall of cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: ■ Symptoms of ischemia. ■ New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). ■ Development of pathological Q waves in the ECG. ■ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. ■ Identification of an intracoronary thrombus by angiography or autopsy. 2) Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. 3) Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. Procedure-related Myocardial Infarction Procedure-related myocardial infarctions were defined as follows: 1) In patients with normal baseline CK-MB, the definition is based on when the peak CK-MB measured within 48 hours of the procedure rises to ≥10 x the local laboratory URL or to ≥5 URL with new pathologic Q-waves in ≥2 contiguous leads or new persistent left bundle branch block (LBBB), or in the absence of CK-MB measurements and a normal baseline cardiac troponin (cTn), a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70 x the local laboratory URL, or ≥35 x URL with new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB. 2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarkers are stable or falling, the definition is based on when CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level. 3) In patients with elevated baseline CK-MB (or cTn) in whom the

	biomarker levels have not been shown to be stable or falling, the definition is based on when CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.
Repeat revascularization and Target Lesion/Vessel	A coronary revascularization procedure may be either a PCI or a coronary artery bypass grafting (CABG). Revascularization is defined by the Academic Research Consortium as follows: The coronary segments revascularized were sub-classified as: Target Lesion: a lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The left main 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 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: Any revascularization in a lesion other than the target lesion is considered a non-target lesion revascularization.

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

7. Study Population

Patients who undergoing PCI for the complex coronary artery lesions will be enrolled.

8. Study Period

IRB approval date ~ 2022.12.31
Subject enrollment: IRB approval date ~ 2020.09 (roughly 36 months of enrollment)
End of follow-up period: 2021. 09 (1 years after the end of recruitment)
Analysis and report: ~2022.12.31

9. Eligible criteria, Sample size calculation

9.1. Eligible Criteria

(1) Inclusion Criteria

① Subject age ≥19 years old

② Coronary artery disease requiring PCI

③ Patients with complex lesion

1) True bifurcation lesion (Medina 1,1,1/1,0,1/0,1,1) with side branch ≥2.5mm size
2) Chronic total occlusion (≥3 months) as target lesion
3) Unprotected LM disease PCI (LM ostium, body, distal LM bifurcation including non-true bifurcation)
4) Long coronary lesions (implanted stent ≥38 mm in length)
5) Multi-vessel PCI (≥2 vessels treated at one PCI session)
6) Multiple stents needed (≥3 more stent per patient)
7) In-stent restenosis lesion as target lesion

8) Severely calcified lesion (encircling calcium in angiography)
9) Ostial coronary lesion (LAD, LCX, RCA)

④ Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive evaluation and PCI and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.

(2) Exclusion criteria

① Target lesions not amenable for PCI by operators' decision

② Cardiogenic shock (Killip class IV) at presentation

③ Intolerance to Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Heparin, or Everolimus

④ Known true anaphylaxis to contrast medium (not allergic reaction but anaphylactic shock)

⑤ Pregnancy or breast feeding

⑥ Non-cardiac co-morbid conditions are present with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment)

⑦ Unwillingness or inability to comply with the procedures described in this protocol.

9.2. Sample Size Calculation

Hypothesis: Intravascular imaging-guided PCI for patients with complex coronary artery lesions would reduce TVF (a composite of cardiac death, target vessel MI, and TVR), compared with angiography-guided PCI.

Null hypothesis: The annual rate of TVF (a composite of cardiac death, target vessel MI, and TVR will be not different between imaging-guided and angiography-guided PCI groups for treatment of complex lesion.

Based on the previous trials which compared Intravascular imaging-guided PCI versus angiography-guided PCI in complex coronary artery lesions[12, 21] and previous studies which evaluated post-PCI clinical event rates after angiography-guided PCI for complex coronary artery lesions,[22, 23] the following assumptions were made.

- Primary end point: Time to occurrence of TVF
- Expected annual rate of TVF:
  Intravascular imaging-guidance group (3.6%) vs. Angiography-guidance group (6%)
- Accrual time: 3 years
- Total follow-up time: 1~4 years (median 2.5 years, till 1 year after the last patient enrollment)
- 2:1 Randomization
- Drop-out rates: 5.0%

$$E = \frac{(z_{1-\alpha/k} + z_{1-\beta})^2}{\pi_1(1-\pi_1)\ln^2(\Delta)} = \frac{1}{\lambda}(z_{1-\alpha/k} + z_{1-\beta})^2 \left\{\frac{1+\lambda}{\ln(\Delta)}\right\}^2$$

$$N = \frac{E}{p_E}$$

$$p_{\mathrm{E}} = 1 - \frac{1}{6}\left\{\widetilde{S}(f) + 4\widetilde{S}(0.5R + f) + \widetilde{S}(T)\right\}$$

Based on the above assumption, **a total of 1620 patients** (1080 and 540 patients for intravascular imaging guidance group and angiography guidance group, respectively) will provide 90% power at a 2-sided alpha of 5%.

9.3. Recruitment

All consecutive patients with coronary artery complex lesion will be screened for enrollment in this study. A member of each research team should review the patients' medical history for eligibility. If all eligibility criteria are met and written informed consent is provided, the patient may be enrolled in the study. Prior to collecting study data, the details of the study will be explained to the participant including: (1) that participation is voluntary, and there is no penalty for withdrawal, (2) potential risks and benefits for participation, and (3) contact information for additional concerns.

10. Research Materials and Indication for Revascularization

All the PCI cases in this trial will include either Synergy stent system (Boston Scientific) or Xience stent system family (Abbott Vascular), with an anticipated proportion of 70% and 30% respectively.

10.1. Intravascular imaging-guided PCI group

In the intravascular imaging-guided PCI group, commercially available IVUS (OpticrossTM, Boston Scientific Corporation, San Jose, CA, USA) or OCT (DragonflyTM, Abbott Vascular, St. Paul, MN, USA) systems will be used. The choice of intravascular imaging devices such as IVUS or OCT during PCI will be left to the operator's discretion. All IVUS or OCT images will be obtained after administration of intracoronary nitroglycerin (200 μg). When deciding the use of IVUS by the operator, the transducer will be pulled back automatically at a speed of 0.5 mm/s. When deciding the use of OCT by the operator, preheated contrast media at 37 °C will be flushed through the guiding catheter at a rate of 2–4 ml/s for approximately 3–6 s by using an injector pump to obtain the OCT images. The final choice of pullback speed of IVUS device and injection rate/amount of contrast media during OCT use will be also left to the operator's discretion. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended. Use of intravascular imaging devices will be allowed at any step of PCI (pre-PCI, during PCI and post-PCI), but intravascular imaging evaluation after stent implantation will be mandatory. In this group, the recommendations for selecting reference segment, selecting appropriated size of stent, and stent optimization are as follows.

	IVUS	**OCT**
Reference Site	Largest lumen Plaque burden < 50%	Most normal looking segment No Lipidic plaque
Stent Sizing	By measuring vessel diameter (external elastic membrane) at proximal and distal reference sites. The averaged value of the proximal and distal reference external elastic membrane diameter will be used as stent diameter	Operator can decide 1 of 2 methods [1] By measuring vessel diameter at the distal reference sites (in case of ≥180° of the external elastic membrane can be identified). In this case, stent diameter will be determined using mean external elastic membrane diameter at the distal reference, rounded down to the nearest 0.25 mm (Ex> mean external elastic membrane reference diameter 3.15 mm, 3.0

	IVUS	OCT
		mm stent diameter will be chosen). [2] By measuring lumen diameter at the distal reference sites (in case of ≥180° of the external elastic membrane cannot be identified). In this case, stent diameter will be determined using mean lumen diameter at the distal reference, rounded up to the nearest 0.25 mm (Ex> mean distal reference lumen diameter 2.55 mm, 2.75 mm stent diameter will be chosen).
Stent Length	By measuring distance from distal to proximal reference site	
Stent Optimization		
● **Stent Expansion**	Visually assess residual angiographic diameter stenosis <10% "AND" ● In non-LM lesions: In-stent minimal lumen area (MSA) > 80% of the average reference lumen area "OR" MSA >5.5 mm^2 (IVUS) and >4.5 mm^2 (OCT) ● In LM stenosis: MSA >7 mm^2 for distal LM and >8 mm^2 for proximal LM (IVUS)	
● **Stent Apposition**	No major malapposition (defined as an acute malapposition of ≥0.4mm with longitudinal extension >1mm) of the stent over its entire length against the vessel wall	
● **Edge Dissection**	No major edge dissection in the proximal or distal reference segments, defined as 5mm from the edge of the stent, extended to media layer with potential to provoke flow disturbances (defined as ≥60° of the circumference of the vessel at site of dissection and/or ≥3 mm in length of dissection flap)	
Optimization technique of the stent	**If 1 of above findings are notified, additional procedure including adjunctive post-dilatation or additional stent implantation for residual reference segment disease will be mandatorily recommended.** In adjunctive post-dilatation procedure, the diameter of the non-compliant post dilatation balloon chosen should not be larger than the post-PCI IVUS/OCT determined mean reference external elastic membrane diameter of one or both segments (proximal or distal), or no more than 0.5 mm larger than the mean reference segment lumen diameter of one or both segments (proximal or distal) nearest to the dilatation site (if the EEL cannot be measured).	

10.2. Angiography-guided PCI group

The PCI procedure in this group will be performed as standard procedure. After deployment of stent, stent optimization will be done based on angiographic findings. The optimization guided by angiography should meet the criteria of angiographic residual diameter stenosis < 10% by visual estimation and the absence of flow limiting dissection (type C through F dissection). When angiographic under-expansion of the stent is suspected, adjunctive balloon dilatation will be strongly recommended. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended.

10.3. Adjunctive treatment/procedure 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. Any adjunctive pharmacologic treatment will be left to the operator's discretion. For example, a loading dose of aspirin (300 mg) and clopidogrel (600 mg)

or aspirin (300 mg) and prasugrel (60 mg) or aspirin (300 mg) and ticagrelor (180 mg), or use of GPIIbIIIa inhibitor, etc**.** In case of PCI is performed, dual antiplatelet therapy is recommended for at least 3-6 months in patients with stable ischemic heart disease and 6-12 months in those with acute coronary syndrome, regardless of allocated arms.[24, 25] However, the loading, maintenance dose, and duration of dual antiplatelet therapy will be based on the physician's preference. In addition, in both groups, the use of invasive physiologic assessment at pre- will be left to operator's discretion, however, post-PCI imaging evaluation and optimization of the stent will be strongly recommended in the Imaging group. If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

11. Methods

11.1. Study designs

Screening will be performed for patients who suspected coronary artery disease without exclusion criteria. And then, informed consent will be obtained after explanation of study protocol. Following angiography, patients with complex lesion that are eligible for coronary intervention will be randomized 2:1 to receive either intravascular imaging-guided strategy or angiography-guided strategy for treatment of the lesions.

As for the intravascular imaging-guided strategy arm, choice of type of imaging device (IVUS or OCT) will be left to the operator's discretion. Use of intravascular imaging devices will be allowed at any step of PCI (pre-PCI, during PCI and post-PCI), but intravascular imaging evaluation after stent implantation will be mandatory.

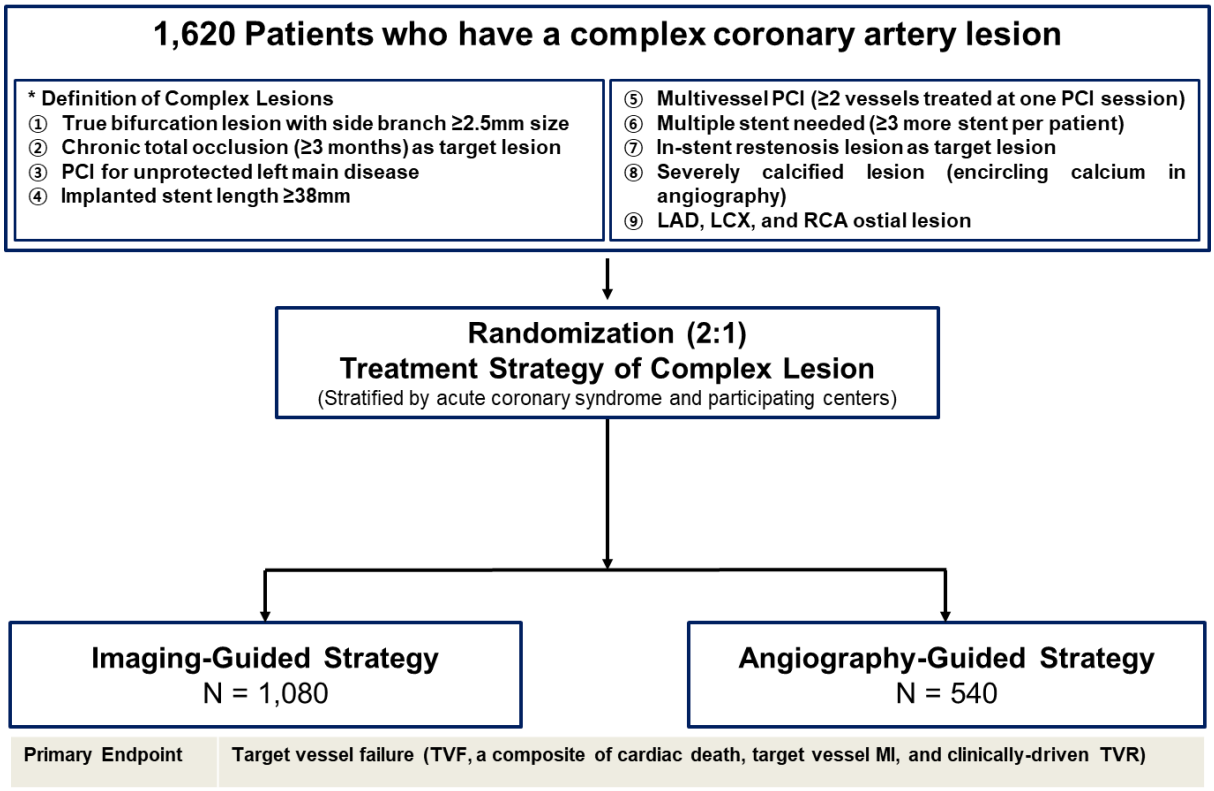
If any violation of the protocols (for example, intravascular imaging was used in angiography-guided strategy arm, or intravascular imaging was not used in imaging-guided strategy arm) according to operator's discretion, the specific reasons will be mandatorily described in electronic case report form.

It is strongly recommended that PCI would be performed at the index procedure after randomization. However, staged procedure during the same hospitalization would be allowed when operator decided to delay the procedure due to concern about the risk of PCI, such as use of large amount of contrast, worsening heart or kidney function, or unstable vital sign. In case of staged procedure during the same hospitalization, following the initially allocated strategy would be strongly recommended.

Regardless of allocated arms, best available medical treatment will be the performed according to the current ACC/AHA/SCAI or ESC/EACTS guidelines.

Any adjunctive pharmacologic treatment and use of invasive physiologic method will be left to the operator's discretion. In case of PCI is performed, dual antiplatelet therapy is recommended for at least 3-6 months in patients with stable ischemic heart disease and 6-12 months in those with acute coronary syndrome, regardless of allocated arms.[24, 25] However, the loading, maintenance dose, and duration of dual antiplatelet therapy will be based on the physician's preference. If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

11.2. Flow chart



11.3. Randomization

Patients will be randomized to either the Intravascular imaging guidance group or angiography guidance group at the time of enrollment with 2:1 ratio. Stratified randomization according to acute coronary syndrome, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

12. Schedule of Assessments and Procedures

Visit	Screening & Baseline -30day	Post-Procedure	Follow-Up				
			1-month ±14days	6-month ±30days	12-month ±30days	2, 3, 4 years ±90days	SCV
Medical/Clinical/ History (age, sex, risk factors, clinical Dx, angina status)	×						
Informed Consent	×						
Inclusion/Exclusion Criteria	×						
Brief Physical Examination	×						
Vital status	×	×	×	×	×		
Weight, height	×						
12 lead ECG	×	×					

Angiogram	×						
Randomization[1)]	×						
Quantitative coronary angiography[2)]	×	×					
Intravascular imaging[3)]	×	×					
Invasive physiologic assessment[4)]	x	x					
CBC	×				x		
Electrolytes, LFT	×				x		
Creatinine, BUN	×	×			x		
Fasting plasma TG, LDL, HDL, total cholesterol	×				x		
Fasting glucose level	×				×		
HgbA1C	×				×		
Medications[5)]	×		×	×	×		
CK-MB, Troponin I Or Troponin T[6)]	×	×					
NT-proBNP	×				×		
Clinical event[7)]		×	×	×	×	x	x

***** Screening will be performed for patients who suspected coronary artery disease without exclusion criteria. And then, informed consent will be obtained after explanation of study protocol. Following angiography, patients with complex lesion that are eligible for coronary intervention will be randomized.

* There will be no mandatory laboratory follow-up.

1) 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 acute coronary syndrome, and participating center will be performed. Enrollment is possible even if the DEB or ballooning was used without stenting for revascularization.

2) The raw data of pre- and post-PCI coronary angiography will be collected and undergo quantitative coronary angiographic evaluation in the Core-Laboratory in Samsung Medical Center.

3) Choice of intravascular imaging (IVUS or OCT) will be left to the operator's discretion. The raw data of the intravascular imaging will be analyzed in the Core-Laboratory in Samsung Medical Center. In the intravascular imaging group, intravascular imaging evaluation after stent implantation will be mandatory.

4) Use of invasive physiologic method (for example, fractional flow reserve, instantaneous wave free ratio, coronary flow reserve, or index of microcirculatory resistance) will be left to the operator's discretion. The raw data of the invasive physiologic method will be analyzed in the Core-Laboratory in Samsung Medical Center.

5) Medication data included medication at baseline (before admission) and post-discharge

6) The baseline and post-procedural cardiac enzyme (CK, CK-MB, Troponin I) measurement is mandatory to assess the peri-procedural myocardial infarction, defined according to ARC criteria.

7) Only end point-related clinical events (all-cause death, cardiac death, cerebrovascular events, MI, stent thrombosis, and repeat revascularization) will be collected.

13. Measurement of study outcome variables

13.1. Visit 1 Screening & Baseline(-30day)

① Informed consent

Before any examination, they will be informed about the study aims, procedures, and possible risks and the Investigator will ensure that the patient or the patient's legally acceptable representative has provided written informed consent. Written consent should include signature and date of legally authorized representatives and investigator.

A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

② Inclusion/exclusion criteria

Review of subject eligibility

③ Medical/clinical/ history

Demographic information (age, sex, risk factors, clinical diagnosis, angina status, cardiac history, and cardio-cerebral event) will be recorded at Screening& Baseline.

Relevant medical history, including history of current disease, other pertinent cardiac history, and information regarding underlying diseases will be recorded at Screening & Baseline

④ Brief physical examination, height, weight, and vital signs

Height, weight, blood pressure, and pulse will be collected

⑤ 12 lead ECG and coronary angiogram

Coronary angiogram will be obtained at baseline visit and post-procedure. ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, or significant arrhythmias, heart failure or other signs or symptoms of clinical instability

⑥ Randomization

Patients will be randomized to either the intravascular imaging-guided strategy or angiography-guided strategy at the time of enrollment with 2:1 ratio. Stratified randomization by acute coronary syndrome, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

⑦ Quantitative coronary angiography/Invasive physiologic assessment data

The raw data of pre- and post-PCI coronary artery angiography will be collected and undergo quantitative coronary angiographic evaluation in the Core-Laboratory in Samsung Medical Center. Coronary physiologic study will be strongly recommended for intermediate lesions, especially when patients have no objective evidence of ischemia. Method for invasive physiologic study (for example, fractional flow reserve, instantaneous wave free ratio, coronary flow reserve, or index of microcirculatory resistance) will be left to the operator's discretion. The raw data of the invasive physiologic method will be analyzed in the Core-Laboratory in Samsung Medical Center.

⑧ Intravascular imaging

Choice of intravascular imaging (IVUS or OCT) will be left to the operator's discretion. The raw data of the intravascular imaging will be analyzed in the Core-Laboratory in Samsung Medical Center.

⑨ 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.

13.2. Visit 2 (Post-Procedure)

① 12 lead ECG and coronary angiogram

Coronary angiogram will be obtained at baseline visit and-post procedure. ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, or significant arrhythmias, heart failure or other signs or symptoms of clinical instability

② Quantitative coronary angiography/Invasive physiologic assessment data

The raw data of pre- and post-PCI coronary artery angiography will be collected and undergo quantitative coronary angiographic evaluation in the Core-Laboratory in Samsung Medical Center. Coronary physiologic study will be strongly recommended for intermediate lesions, especially when patients have no objective evidence of ischemia. Method for invasive physiologic study (for example, fractional flow reserve, instantaneous wave free ratio, coronary flow reserve, or index of microcirculatory resistance) will be left to the operator's discretion. The raw data of the invasive physiologic method will be analyzed in the Core-Laboratory in Samsung Medical Center.

③ Adverse events/serious adverse event

Information regarding occurrence of adverse events (any death, any MI or any revascularization etc.) will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to procedure will be recorded on the case report form (e-CRF).

13.3. Follow-up

Follow-up will occur at 1, 6, and 12 months, and annually thereafter. Investigator or designee may conduct follow-up as office visits.

① Vital signs

Blood pressure and pulse will be collected.

② 12 lead ECG

ECG at follow up visits will only be obtained when clinically indicated such as recurrent chest pain, ischemia, or significant arrhythmias, heart failure or other signs or symptoms of clinical instability

③ Concomitant medication

④ Adverse events/serious adverse event

Information regarding occurrence of adverse events (any death, any MI or any revascularization etc.) will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to procedure will be recorded on the case report form (e-CRF).

14. Potential risk and adequacy of protection against risks

Complications of PCI for complex lesion include coronary dissection, thrombus formation, side branch occlusion, arterial rupture/perforation, and embolization. However, PCI for these lesions is not considered to have a direct potential risk associated with the procedure, because it is a standard treatment option in clinical practice. In intravascular imaging-guided strategy arm, potential complications related to IVUS or OCT include coronary dissection, thrombus formation, side branch occlusion, arterial rupture/perforation, and embolization. In case of angiography-guided strategy arm, it is difficult to obtain optimized stent implantation because of the lack of intravascular imaging information. These are potential risks of the present study. Methods of safety-related monitoring in this study will be described number 16.

15. Subject withdrawal

Once enrolled, each Subject should remain in the study until the required follow-up period is completed. However, all Subjects have the right to withdraw at any point during the study without penalty or loss of benefit. The investigator may discontinue any Subject at any time if medically necessary.
The following events will result in terminating the patient's follow-up:

① Patient voluntary withdrawal

② Patient withdrawn by investigator as clinically indicated

If the study treatment(s) or observations are discontinued in any Subject, the reason will be recorded, and the data coordinating center must be notified promptly.

16. Violence of study protocol

Although the treatment strategy of coronary complex lesion in subjects with ischemic heart disease will be decided by randomization process to either intravascular imaging-guided strategy or angiography-guided strategy, whether used the intravascular imaging or not will be decided by operators according to the clinical situation. However, the followings will be recorded as protocol violation and the reason will be recorded and the data coordinating center must be notified promptly.

① Intravascular imaging was used in angiography-guided strategy arm

② Intravascular imaging was not used in imaging-guided strategy arm

17. Event adjudication and reporting, Data safety and monitoring plan

17.1. Data safety and monitoring plan

Type of Report	Prepared by Staffs for:	Time limit of notification
Serious adverse event	IRB	According to IRB regulation of Site
	DCC/EC/Principle investigator DSMB	Within 48 hours
Annual progress report	EC/Principle investigator	Submitted per 1 year
Deviations from investigational plan	IRB	According to IRB regulation of Site
	EC/Principle investigator	Notify within 7 days.
Final summary report	EC/Principle investigator	Within 1 month

*DCC: Data Coordinating Center, EC: Executive Committee (Co-researchers)

17.2. Executive Committee

	Name	Center	Position
Chairman	Joo-Yong Hahn	Samsung Medical Center, Sungkyunkwan University School of Medicine	Professor
Committee members	Young Bin Song	Samsung Medical Center, Sungkyunkwan University School of Medicine	Associate Professor
	Jeong Hoon Yang	Samsung Medical Center, Sungkyunkwan University School of Medicine	Associate Professor
	Joo Myung Lee	Samsung Medical Center, Sungkyunkwan	Assistant

		University School of Medicine	Professor

17.3. Serious Adverse Events

The definition of serious adverse events is in the following paragraph. **It must be reported to the principle investigator within 48 hours after recognition of the event and to the IRB according to IRB regulation of site.**

① Results in persistent or significant disability or incapacity (significant, persistent or permanent change or disruption in subject's body function/structure, physical activity or quality of life

② Requires in-patient hospitalization or prolongs hospitalization

③ Results in a congenital anomaly/birth defect or,

④ Life-threatening events or death

Clinical events include not only TVF, all death, stent thrombosis, but also other end point events. Clinical events and safety data will be reported to principle investigator regularly and examined by staffs for subject's safety throughout the study.

The coordinating center needs to report progress to Executive committee and principle investigator annually. This study will not be stopped early based on efficacy results.

17.4. Event adjudication Committee

All primary and secondary events will be independently adjudicated by Event Adjudication Committee.

	Name	Center	Position
Chairman	Hyun-Jong Lee	Sejong General Hospital, Bucheon, Korea	Professor
Committee members	Dong Ryeol Ryu	Kangwon University Hospital, Chuncheon, Korea	Professor
	Kyutae Park	Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, Korea	Professor

17.5. Data Safety and Monitoring Board

All serious adverse events will be reviewed by independent DSMB.

	Name	Center	Position
Chairman	Kiyuk Chang	Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea	Professor
Committee members	SeonWoo Kim	Samsung Medical Center, Biostatistics and Clinical Epidemiology Center, Seoul, Korea	Ph. D
	Dong-Yeon Kim	Seoul Medical Center, Seoul, Korea	Professor

17.6. Data safety monitoring plan

The principle investigator will make the monitoring manager to visit and examine coordinating centers regularly. A designated trial monitor will review data not only for completeness, but also for accordance of the hospital data and eCRF data. Compliance with the protocol and adverse events will be also examined. 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 coordinating centers will permit access to such records.

The monitoring manager: Suyoun Shin, RN (Medical Research Coordinating Center, Samsung Medical Center A-CRO Team)

18. Statistical Consideration and Analysis

18.1. Analysis Population

All subjects are to be randomized in a 2:1 fashion to either intravascular imaging-guided strategy or angiography-guided strategy groups. All primary and secondary end points will be analyzed both on an intention-to-treat basis (all subjects analyzed as part of their assigned treatment group). 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.

Per-protocol population will be defined as population who did not violate the study protocol. The definition of protocol violation is as follows;

① **Intravascular imaging will be used in angiography-guided strategy arm**

② **Intravascular imaging will be not used in imaging-guided strategy arm**

Analysis with Per-protocol population will be performed for sensitivity analysis. The baseline coronary angiographic characteristics will be analyzed on per-lesion.

18.2. Primary End point Analysis

The primary end point (the rates of TVF) will be primarily analyzed on an intention-to-treat basis (all subjects analyzed as part of their assigned treatment group), and then, per-protocol basis. The primary end point will be compared between imaging-guided PCI and angiography-guided PCI with the use of a two-sided log-rank test. The treatment effect as measured by the hazard ratio (the relative risk) and its associated 95 percent confidence interval will be estimated with the use of the Cox proportional-hazards model. All primary and secondary end points will be analyzed on per-patient basis.

18.3. Secondary End point Analysis

The individual components of TVF will be analyzed on an intention-to-treat basis and per-protocol basis. Other secondary end points including all-cause and cardiac death, target vessel MI, any MI, target lesion revascularization, target vessel revascularization, any revascularization, definite stent thrombosis will be analyzed using Kaplan-Meier survival with log rank test and Cox proportional hazard model. Incidence of contrast-induced nephropathy will be analyzed using χ^2-test. Total procedural time, total amount of used contrast, and total medical cost will be compared between the two groups with independent sample t-test.

Primary End point	**Statistical methods**	**Time point of analysis**
TVF (target-vessel failure, a composite of cardiac death, target-vessel MI, and target-vessel revascularization	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 years after last patient enrollment
Secondary End point	**Statistical methods**	**Time point of analysis**
TVF without procedure-related MI	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment

Cardiac death or target vessel MI	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
All-cause and cardiac death	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Target-vessel myocardial infarction	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Any myocardial infarction	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Target-lesion revascularization (clinically driven revascularization)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Target-vessel revascularization (clinically driven revascularization)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Any revascularization (clinically driven revascularization)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Stent thrombosis (definite)	Kaplan-Meier survival estimates and log-rank tests Cox proportional hazard model	1 year after last patient enrollment
Incidence of contrast-induced nephropathy	χ^2-test	Hospital discharge
Total amount of contrast use	Independent sample t-test	Hospital discharge
Total procedural time	Independent sample t-test	Hospital discharge
Total medical cost	Independent sample t-test	Total follow-up time

18.4. 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. Patients who will be lost to follow-up will be censored at the time of the last known contact.

18.5. Multivariable Analyses

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

Table 1.

Demographics	***Cardiac Risk Factors***	***Medication at discharge***

Age, years	Current smoker	Aspirin
Gender	Previous PCI	Clopidogrel
Diabetes mellitus	Previous CABG	Prasugrel
Hypertension	Previous MI	Ticagrelor
Dyslipidemia	Previous CHF	Statin
Peripheral artery disease	Previous CVA	ACE inhibitor or ARB
Chronic kidney disease	Family history of CAD	Beta-blocker
	LV ejection fraction	Calcium-channer blocker
	LV dysfunction (LVEF<50%)	

18.6. Pre-specified subgroup analysis

① Comparison of TVF according to type of intravascular imaging devices (IVUS or OCT), compared with angiography-guided group.

② Comparison of immediate post-PCI minimum stent cross-sectional area between IVUS and OCT.

③ Analysis of the primary end point will be performed in pre-specified subgroups according to age (dichotomized at the of ≥65 years), sex, diabetes mellitus, chronic kidney disease, clinical presentation (stable ischemic heart disease and acute coronary syndrome), complex lesion type, number of complexity (≥ 3 or < 3), and LV dysfunction (EF <50% and ≥50%).

19. Care for the safety of the subjects

19.1. 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.

19.2. Elements of Informed Consent

This trial will involve patients with complex coronary artery lesion, who underwent PCI. We anticipate enrolling 1620 patients with a mean age in the 60s. Pregnant women and patients under the age of 18 will be excluded from the trial for ethical and safety concerns.

Prior to collecting study data, the details of the study will be explained to the participant including: (1) that participation is voluntary, and there is no penalty for withdrawal, (2) potential risks and benefits for participation, and (3) contact information for additional concerns. Patients are informed of the purpose of the study, the treatment alternative, the random manner of assignment to treatment, the need to be available for telephone follow-up and return clinic visits at regular intervals for questionnaires and/or medical tests, and of their options to accept or refuse entry into the study without affecting their clinical care.

All patients or legally authorized patient representatives must sign the current IRB approved informed consent form prior to any study-related activities and the index procedure. Failure to obtain signed informed consent will render the patient ineligible for the study. The signed informed consent will be

kept in the patient's medical records and a copy given to the patient or legally authorized patient representative. All sources of research materials will be in the form of medical records, coronary angiograms, electrocardiograms and routine blood work. This material will be obtained both for routine medical care as well as for research purposes.

19.3. 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 electronic case report form (eCRF). Patient data will be protected by the use of locked cabinets at the Clinical Centers and use of passwords, data encryption and secure, limited access storage of electronic data. The explicit issue of privacy and confidentiality is outlined in the Informed Consent Form.

20. References

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Summary of changes (amendments) in protocol

Version	Release Date	Summary of Changes	Reason for Changes
1.3	Dec. 04th, 2017	Initial Release	
1.4	Dec. 06th, 2017	Addition of funding agency: Abbott Vascular and Boston Scientific	Additional funding from Boston Scientific
1.5	Feb. 02th, 2018	Change of stratified randomization protocol. : Original protocol Stratified randomization according to acute coronary syndrome, type of imaging devices, and participating center will be performed. : Changed protocol Stratified randomization according to acute coronary syndrome, and participating center will be performed.	Selection of imaging devices (IVUS or OCT) depends on lesion characteristics, patient feasibility, and operator's discretion.
1.6	Jul. 20th, 2018	Delete the upper limit of patient's age. : Original protocol Subject age 19-85 years old : Changed protocol Subject must be at least 19 years of age	Executive committee decided that patient's age will not have significant impact to interpret the study hypothesis and results.
		Change of stent sizing and optimization protocols **IVUS** **Reference Site** Largest lumen Plaque burden < 50% **Stent Sizing** By measuring vessel diameter (external elastic membrane) at proximal and distal reference sites. The averaged value of the proximal and distal reference external elastic membrane diameter will be used as stent diameter.	Applying ESC Expert Consensus for the use of Intravascular Imaging devices

		Stent Length By measuring distance from distal to proximal reference site **Stent Expansion** Visually assess residual angiographic diameter stenosis <10% "AND" ● In non-LM lesions: In-stent minimal lumen area (MSA) > 80% of the average reference lumen area "OR" MSA>5.5 mm^2 (IVUS) and >4.5 mm^2 (OCT) ● In LM stenosis: MSA>7 mm^2 for distal LM and >8 mm^2 for proximal LM (IVUS) **Stent Apposition** No major malapposition (defined as an acute malapposition of ≥0.4mm with longitudinal extension >1mm) of the stent over its entire length against the vessel wall **Edge Dissection** No major edge dissection in the proximal or distal reference segments, defined as 5mm from the edge of the stent, extended to media layer with potential to provoke flow disturbances (defined as ≥60° of the circumference of the vessel at site of dissection and/or ≥3 mm in length of dissection flap) **Optimization technique of the stent** If 1 of above findings are notified, additional procedure including adjunctive post-dilatation or additional stent implantation for residual reference segment disease will be mandatorily recommended. In adjunctive post-dilatation procedure, the diameter of the non-compliant post dilatation balloon chosen should not be larger than the post-PCI IVUS/OCT determined mean reference external elastic membrane diameter of one or both segments (proximal or distal), or no more than 0.5 mm larger than the mean reference segment lumen diameter of one or both segments (proximal or distal) nearest to the dilatation site (if the EEL cannot be measured).	
		Change of stent sizing and optimization protocols **OCT** **Reference Site** Most normal looking segment No Lipidic plaque **Stent Sizing**	Applying ESC Expert Consensus for the use of Intravascular Imaging devices

		Operator can decide 1 of 2 methods [1] By measuring vessel diameter at the distal reference sites (in case of ≥180° of the external elastic membrane can be identified). In this case, stent diameter will be determined using mean external elastic membrane diameter at the distal reference, rounded down to the nearest 0.25 mm (Ex> mean external elastic membrane reference diameter 3.15 mm, 3.0 mm stent diameter will be chosen). [2] By measuring lumen diameter at the distal reference sites (in case of ≥180° of the external elastic membrane cannot be identified). In this case, stent diameter will be determined using mean lumen diameter at the distal reference, rounded up to the nearest 0.25 mm (Ex> mean distal reference lumen diameter 2.55 mm, 2.75 mm stent diameter will be chosen). **Stent Length** By measuring distance from distal to proximal reference site **Stent Expansion** Visually assess residual angiographic diameter stenosis <10% "AND" ● In non-LM lesions: In-stent minimal lumen area (MSA) > 80% of the average reference lumen area "OR" MSA>5.5 mm^2 (IVUS) and >4.5 mm^2 (OCT) ● In LM stenosis: MSA>7 mm^2 for distal LM and >8 mm^2 for proximal LM (IVUS) **Stent Apposition** No major malapposition (defined as a distance from stent strut to adjacent intima ≥200 um) of the stent over its entire length against the vessel wall **Edge Dissection** No major edge dissection in the proximal or distal reference segments, defined as 5mm from the edge of the stent, extended to media layer with potential to provoke flow disturbances (defined as ≥60° of the circumference of the vessel at site of dissection and/or ≥3 mm in length of dissection flap) **Optimization technique of the stent** If 1 of above findings are notified, additional procedure including adjunctive post-dilatation or additional stent implantation for residual reference segment disease will be mandatorily recommended. In adjunctive post-dilatation procedure, the diameter of the non-compliant post dilatation balloon chosen should not be larger than the post-PCI IVUS/OCT	

		determined mean reference external elastic membrane diameter of one or both segments (proximal or distal), or no more than 0.5 mm larger than the mean reference segment lumen diameter of one or both segments (proximal or distal) nearest to the dilatation site (if the EEL cannot be measured).	
1.7	Oct. 20th, 2018	Addition of coronary ostial lesion as criteria of complex lesion Left anterior descending (LAD), left circumflex artery (LCX), and right coronary artery (RCA) ostial lesion	Executive committee judged the ostial lesion would be also subject of complex lesion
2.0	Feb. 07th, 2019	Addition of secondary end point: Total medical cost	For planned cost-effectiveness analysis
2.1	Oct. 22th, 2019	Addition of planned subgroup analysis: Analysis of the primary end point will be performed in pre-specified subgroups according to age (dichotomized at the of ≥65 years), sex, diabetes mellitus, chronic kidney disease, clinical presentation (stable ischemic heart disease and acute coronary syndrome), complex lesion type, number of complexity (≥ 3 or < 3), and LV dysfunction (EF <50% and ≥50%).	For planned subgroup analysis
2.2	Dec. 03th, 2020	Addition of new Data Safety and Monitoring Boards (DSMB) member	To maintain specialty of DSMB

Statistical Analysis Plan

Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention:

The RENOVATE-COMPLEX-PCI Trial

On behalf of the RENOVATE-COMPLEX-PCI investigators

Table of Contents

Original Statistical Analysis Plan

1. Statistical Overview

This trial is a prospective, open label, two-arm, randomized multi-center trial to test the superiority of intravascular imaging-guided PCI compared with angiography-guided PCI regarding the risk of primary end point (target vessel failure defined as a composite of cardiac death, target vessel-related myocardial infarction, or clinically-driven target vessel revascularization) in treatment of patients with complex coronary artery lesions.

2. Sample Size

Hypothesis: Intravascular imaging-guided PCI for patients with complex coronary artery lesions would reduce target vessel failure (a composite of cardiac death, target vessel-related myocardial infarction, and clinically-driven target vessel revascularization), compared with angiography-guided PCI in treatment of patients with complex coronary artery lesions.

Based on the previous trials which compared Intravascular imaging-guided PCI versus angiography-guided PCI in complex coronary artery lesions[1,2] and previous studies which evaluated post-PCI clinical event rates after angiography-guided PCI for complex coronary artery lesions,[3,4] the following assumptions were made.

- Primary end point: Time to occurrence of TVF
- Expected annual rate of TVF:
- Intravascular imaging-guidance group (3.6%) vs. Angiography-guidance group (6%)
- Accrual time: 3 years

- Total follow-up time: 1~4 years (median 2.5 years, till 1 year after the last patient enrollment)
- 2:1 Randomization
- Drop-out rates: 5.0%

Based on the above assumption, **a total of 1620 patients** (1080 and 540 patients for intravascular imaging guidance group and angiography guidance group, respectively) will provide 90% power at a 2-sided alpha of 5%.

3. Randomization

Patients will be randomized to either the intravascular imaging-guided PCI group or angiography-guided PCI group at the time of enrollment with 2:1 ratio. Stratified randomization according to acute coronary syndrome, type of imaging devices, and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

4. Analysis

Continuous variables will be presented as mean ± SD and compared with the Student t test. Categorical variables will be presented as counts and percentages and compared with the $\chi 2$ or Fisher exact test as appropriate. Cumulative event rates will be estimated with the Kaplan–Meier method and compared using log-rank tests. Hazard ratios with 95% confidence interval (CI) will be estimated by the Cox proportional-hazards method.

Analysis Populations

All primary and secondary endpoints will be analyzed both on an intention-to-treat ba sis (all patients analyzed as part of their assigned treatment group) and on a per prot ocol basis (patients analyzed as part of their assigned treatment group only if they act ually received their assigned treatment. For an intention-to-treat analysis, all patients w ho 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 w as administered, or whether crossover occurred. For the per protocol analysis, only en rolled patients who actually received the assigned treatment will be included in the an alysis sample. Per-protocol population will be defined as population who did not viola te the study protocol. The definition of protocol violation is as follows;

① Intravascular imaging will be used in angiography-guided strategy arm

② Intravascular imaging will be not used in imaging-guided strategy arm

Analysis with Per-protocol population will be performed for sensitivity analysis. The baseline coronary angiographic characteristics will be analyzed on per-lesion.

Primary Endpoint Analysis

The primary endpoint will be analyzed on an intention-to-treat and per protocol basis. The null hypothesis will be evaluated on the intention-to-treat population. The primary end point will be compared between imaging-guided PCI and angiography-guided PCI with the use of a two-sided log-rank test. The treatment effect as measured by the hazard ratio (the relative risk) and its associated 95 percent confidence interval will be estimated with the use of the Cox

proportional-hazards model. Primary end point will be analyzed on per-patient basis.

Secondary End point Analysis

Secondary end points will include individual components of the primary end point, target vessel failure without procedure-related myocardial infarction, a composite of cardiac death or target vessel-related myocardial infarction, definite stent thrombosis, total procedural time, total amount of contrast agent used during the index hospitalization, and incidence of contrast-induced nephropathy. Individual components of the primary end point, target vessel failure without procedure-related myocardial infarction, a composite of cardiac death or target vessel-related myocardial infarction, definite stent thrombosis will be analyzed using Kaplan-Meier survival with log rank test and Cox proportional hazard model. Incidence of contrast-induced nephropathy will be analyzed using χ^2-test. Total procedural time and total amount of used contrast will be compared between the two groups with independent sample t-test.

Subgroup Analyses

Prespecified subgroup analysis of the primary and secondary endpoints will be performed:

① Comparison of primary and secondary endpoints according to type of intravascular imaging devices (IVUS or OCT), compared with angiography-guided group.

② Comparison of immediate post-PCI minimum stent cross-sectional area between IVUS and OCT.

Treatment of missing values

The primary analysis of the study end points will not be covariate adjusted. No imputation

methods will be used to infer missing values of baseline variables. For the study end points, we will censor patients lost to follow-up and regard them as not having the primary end point when estimating Kaplan–Meier event rates.

Final Statistical Analysis Plan

1. Statistical Overview

This trial is a prospective, open label, two-arm, randomized multi-center trial to test the superiority of intravascular imaging-guided PCI compared with angiography-guided PCI regarding the risk of primary end point (target vessel failure defined as a composite of cardiac death, target vessel-related myocardial infarction, or clinically-driven target vessel revascularization) in treatment of patients with complex coronary artery lesions.

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- Total follow-up time: 1~4 years (median 2.5 years, till 1 year after the last patient enrollment)
- 2:1 Randomization
- Drop-out rates: 5.0%

Based on the above assumption, **a total of 1620 patients** (1080 and 540 patients for intravascular imaging guidance group and angiography guidance group, respectively) will provide 90% power at a 2-sided alpha of 5%.

3. Randomization

Patients will be randomized to either the intravascular imaging-guided PCI group or angiography-guided PCI group at the time of enrollment with 2:1 ratio. Stratified randomization according to acute coronary syndrome and participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

4. Analysis

Continuous variables will be presented as mean ± SD and compared with the Student t test. Categorical variables will be presented as counts and percentages and compared with the $\chi 2$ or Fisher exact test as appropriate. Cumulative event rates will be estimated with the Kaplan–Meier method and compared using log-rank tests. Hazard ratios with 95% confidence interval (CI) will be estimated by the Cox proportional-hazards method.

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Secondary End point Analysis

Secondary end points will include individual components of the primary end point, target vessel failure without procedure-related myocardial infarction, a composite of cardiac death or target vessel-related myocardial infarction, definite stent thrombosis, total procedural time, total amount of contrast agent used during the index hospitalization, and incidence of contrast-induced nephropathy. Individual components of the primary end point, target vessel failure without procedure-related myocardial infarction, a composite of cardiac death or target vessel-related myocardial infarction, definite stent thrombosis will be analyzed using Kaplan-Meier survival with log rank test and Cox proportional hazard model. Incidence of contrast-induced nephropathy will be analyzed using χ^2-test. Total procedural time, total amount of used contrast, and total medical charge will be compared between the two groups with independent sample t-test.

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② Comparison of immediate post-PCI minimum stent cross-sectional area between IVUS and OCT.

③ Analysis of the primary end point will be performed in pre-specified subgroups according to age (dichotomized at the of ≥65 years), sex, diabetes mellitus, chronic

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Treatment of missing values

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

Summary of Changes (Amendments) in Statistical Analysis Plan

Version	Release Date	Summary of Changes	Reason for Changes
1.3	Dec. 04th, 2017	Initial Release	
1.5	Feb. 02th, 2018	Change of stratified randomization protocol. : Original protocol Stratified randomization according to acute coronary syndrome, type of imaging devices, and participating center will be performed. : Changed protocol Stratified randomization according to acute coronary syndrome, and participating center will be performed.	Selection of imaging devices (IVUS or OCT) depends on lesion characteristics, patient feasibility, and operator's discretion.
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		dysfunction (EF <50% and ≥50%).	

References

1. Kim BK, Shin DH, Hong MK, et al. Clinical Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Zotarolimus-Eluting Versus Biolimus-Eluting Stent Implantation: Randomized Study. Circ Cardiovasc Interv 2015;8:e002592.
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