Supplementary Appendix

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

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All other authors declare that there are no competing interests to declare.

Data Sharing Statement

The RENOVATE-PCI trial is planning to continue analysis, including post-hoc subgroup analysis. Until then, no individual participant data will be available. Any relevant inquiry should be emailed to Dr. Joo Myung Lee (Email: drone80@hanmail.net), Dr. Young Bin Song (Email: youngbin.song@gmail.com), or Dr. Joo-Yong Hahn (Email: jyhahn@skku.edu).

Supplementary Methods

Inclusion and Exclusion Criteria

Inclusion Criteria

① Subject must be at least 19 years of age
② Coronary artery disease requiring PCI
③ Patients with a complex lesion defined as:
    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.

Exclusion criteria

① Target lesions not amenable to PCI based on operators' review
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.

PCI denotes percutaneous coronary intervention, LM left main coronary artery, LAD left anterior descending artery LCX left circumflex artery, RCA right coronary artery.

Primary and Secondary Endpoints

Primary Endpoint	
Target vessel failure	A composite of cardiac death, target vessel MI, and clinically-driven target vessel revascularization.
Secondary Endpoints	
Target vessel failure without procedure-related MI	
Cardiac death or target-vessel MI	
All-cause death	
Cardiac death	
Target vessel MI with procedure-related MI	
Target vessel MI without procedure-related MI	
Any MI with procedure-related MI	
Any MI without procedure-related MI	
Non-target vessel related MI	
Target lesion revascularization	
Target vessel revascularization	
Any revascularization (clinically-driven)	
Stent thrombosis	
Incidence of contrast-induced nephropathy	
Total amount of contrast use	
Total procedural time	
Total medical cost – not reported in this publication	

MI denotes myocardial infarction

Supplementary Statistical Analysis

Hypothesis: An intravascular imaging-guided PCI strategy for patients with complex coronary artery lesions would reduce target vessel failure (a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization), compared with an angiography-guided PCI strategy.

Null hypothesis: An intravascular imaging-guided PCI strategy for patients with complex coronary artery lesions would not reduce target vessel failure (a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization), compared with an angiography-guided PCI strategy.

Reported Event Rates in Previous Studies of Complex PCI

Study	Sample Size	Timepoint	MACE		
			Intravascular Imaging-guided PCI	Angiography-guided PCI	Relative Risk Reduction, %
ADAPT-DES[1]	8665	1 Year	3.1%	4.7%	34.0%
AVIO trial[2]	284	2 Year	16.9%	23.2%	27.2%
HOME DES IVUS[3]	210	1.6 Years	11.0%	12.0%	8.3%
RESET[4]	543	1 Year	4.5%	7.3%	38.4%
CTO-IVUS[5]	402	1 Year	2.6%	7.1%	63.4%
IVUS-XPL[6]	1400	1 Year	2.9%	5.8%	50.0%

The current trial was designed as a superiority trial to follow enrolled patients until a prespecified follow-up duration of the last patient enrolled. Since the follow-up duration of the previous studies varied, we assumed that the annual incidence of target vessel failure in the angiography-guided PCI group would be 6.0%, based on the results of the CTO-IVUS, RESET, and IVUS-XPL studies. These 3 studies were selected because they were randomized trials conducted in South Korea and the follow-up duration was 1 year. As presented in the above table, the relative risk reduction of target vessel failure of the 3 studies ranged from 38.4% to 63.4%. To be conservative, we assumed that the relative risk reduction at 1 year would be 40% and, in turn, the annual incidence of target vessel failure in the intravascular imaging-guided PCI group would be 3.6%.

Sample Size Calculation

- Primary endpoint: Time to occurrence of target vessel failure (a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization)
- Assumed annual event rate of target vessel failure:
  - Intravascular imaging-guided PCI group (3.6%) vs. Angiography-guided PCI group (6%)
- Alpha = 0.05 (2-sided), β = 10%, Power (1- β) = 90%
- Accrual time: 3 years
- Total follow-up time: one year after last patient enrollment (median 2.5 years)

- 2:1 Randomization
- Primary statistical method: Kaplan-Meier survival analysis with log-rank test
- Assumed dropout: total 5.0%

Based on the above assumptions, a total of 1620 patients (1080 and 540 patients for the intravascular imaging-guided group and the angiography-guided group, respectively) would be needed to evaluate the primary hypothesis with consideration of dropouts.

Consideration of 2:1 Randomization

Although previous randomized controlled trials were potentially limited by enrolling a small number of patients, limited follow-up duration, or enrolling patients with highly selected coronary artery lesion subsets, they consistently showed the potential benefit of intravascular imaging-guided PCI compared with angiography-guided PCI.[2,3,5,7,8] In this regard, the executive committee members tried to maximize the potential benefit of intravascular imaging-guided PCI in the treatment of complex coronary artery lesions. While we did not collect the exact proportion of PCI cases done with intravascular imaging guidance from all the participating centers, the adoption rate of intravascular imaging-guided PCI in Korea is about 27.5% to 28.6% according to the Korean Percutaneous Coronary Intervention (K-PCI) Registry that includes 92 participating centers.[9] Considering the adoption rate of intravascular imaging-guided PCI in Korea, a 2:1 randomization ratio should not introduce bias when interpreting the trial results.

Definition of Clinical Events

Death

Death as defined by the Academic Research Consortium is as follows:[10]

All death was considered to be cardiac death unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death, even in patients with coexisting potentially fatal noncardiac disease (eg, cancer, infection), should be classified as cardiac. The cause of death (cardiac vs. non-cardiac) was adjudicated by an independent clinical events adjudication committee.

Cardiac death: Any death due to a 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, was classified as cardiac death.

Non-cardiac death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Myocardial Infarction

The definition of myocardial infarction used in this trial was based on the Third Universal Definition of Myocardial Infarction for spontaneous myocardial infarction,[11] and the Society for Cardiovascular Angiography and Interventions definition for procedure-related myocardial infarction.[12]

Spontaneous Myocardial Infarction

Myocardial infarction was considered to be present when there was evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia.[11] Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

1) Detection of a rise and/or fall of cardiac troponin with at least one value above the 99th percentile upper reference limit and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment–T wave 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 myocardial infarction 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 upper reference limit.

Procedure-Related Myocardial Infarction

Procedure-related myocardial infarction is defined as follows:[12]

1) In patients with normal baseline CK-MB, myocardial infarction was considered to have occurred when the peak CK-MB measured within 48 hours of the procedure rises to at least 10 times the local laboratory upper reference limit; or to at least 5 times the upper reference limit with new pathologic Q-waves in at least 2 contiguous leads or new persistent 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 at least 70 times the local laboratory upper reference limit; or at least 35 times upper reference limit with new pathologic Q-waves in at least 2 contiguous leads, or new persistent LBBB.

2) In patients with an elevated baseline CK-MB (or cTn) in whom the biomarkers are stable or falling, the definition was 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 an 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.

Revascularization

A coronary revascularization procedure may be either a PCI or a coronary artery bypass grafting (CABG) surgery. Revascularization is defined by the Academic Research Consortium[10] as follows:

The coronary segments that were revascularized were sub-classified as:

Target Lesion: A target lesion was defined as 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 at least 2 mm.

Target Vessel: The target vessel was 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 coronary artery 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 was a lesion in the epicardial vessel or branch or 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.

Non-Target Vessel: The non-target vessel was any vessel that was not attempted to be revascularized at the index procedure but was subsequently revascularized.

Target Lesion Revascularization: Target lesion revascularization was defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All target lesion revascularizations were classified prospectively as clinically indicated or not clinically indicated by the investigator prior to repeat angiography. An independent angiographic core laboratory verified that the severity of the percent diameter stenosis met the requirements for clinical indication and overruled cases where investigator reports were not in agreement. The target lesion was defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

Target Vessel Revascularization: Target vessel revascularization was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel was defined as the entire major coronary vessel proximal and distal to the target lesion, which included upstream and downstream branches and the target lesion itself.

Non-Target Lesion Revascularization: Any revascularization in a lesion other than the target lesion was considered a non-target lesion revascularization.

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

All revascularization events were adjudicated as either clinically driven or non-clinically driven. Revascularization was considered clinically driven if the diameter stenosis of the revascularized coronary segment is at least 50% by quantitative coronary angiography and any of the following criteria for ischemia were met:

- A positive functional study corresponding to the area served by the target lesion; or
- Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- Typical ischemic symptoms referable to the target lesion; or
- Positive invasive physiologic test (fractional flow reserve ≤0.80 or instantaneous wave-free ratio ≤0.89); or
- Presence of stenosis with at least 70% diameter stenosis, even in the absence of other criteria

Stent Thrombosis

Stent thrombosis was defined by the Academic Research Consortium[10] as follows:

1) Timing: a) Acute b) Subacute c) Late, and d) Very late

Acute stent thrombosis*	0-24 hours after stent implantation
Subacute stent thrombosis*:	More than 24 hours to 30 days after stent implantation
Late stent thrombosis†:	More than 30 days to 1-year after stent implantation
Very late stent thrombosis†:	More than 1-year after stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0 to 30 days) is currently used to define stent thrombosis occurring from day 0 to day 30 by the international interventional cardiology community.

†This definition includes "primary" as well as "secondary" late stent thrombosis; "secondary" late stent thrombosis was defined as stent thrombosis that occured after a target segment revascularization.

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

Definite stent thrombosis: Definite stent thrombosis was considered to have occurred by either angiographic or pathologic confirmation.

Angiographic confirmation of stent thrombosis: The presence of an intracoronary thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest; or
- New ischemic ECG changes that suggest acute ischemia; or
- Typical rise and fall in cardiac biomarkers (refer to the definition of spontaneous myocardial infarction); or
- Nonocclusive thrombus: Intracoronary thrombus was defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections at the time of coronary angiography, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
- Occlusive thrombus: Was defined as Thrombolysis in Myocardial Infarction (TIMI) Grade 0 flow (no flow of contrast after the thrombotic stenosis) or TIMI Grade 1 flow (flow past the thrombotic stenosis that doesn't fill the vessel entirely) within the stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if the stent originates from the side branch).

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

[2] Probable stent thrombosis: The clinical definition of probable stent thrombosis was considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days; or
- Irrespective of the time after the index procedure, any myocardial infarction that was related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

[3] Possible stent thrombosis: The clinical definition of possible stent thrombosis was considered to have occurred with any unexplained death from 30 days after intracoronary stenting until the end of trial follow-up.

Contrast-Induced Nephropathy

Contrast-induced nephropathy was defined as an increase in serum creatinine of at least 0.5mg/dL or at least 25% from baseline within 48-72 hours after exposure to a contrast agent.[10]

Protocol for Intravascular Imaging Device Use and Angiography-guided PCI

PCI was performed using standard techniques. The drug-eluting stents used were either biodegradable polymer-coated everolimus eluting stents (Synergy, Boston Scientific Corporation, San Jose, CA, USA) or biocompatible polymer-coated everolimus-eluting stents (Xience, Abbott Vascular, St. Paul, MN, USA). The trial limited stent choice to these drug-eluting stents due to the well-validated efficacy and safety profile of biodegradable polymer-coated everolimus eluting stents and biocompatible polymer-coated everolimus-eluting stents,[13] the fact that these two stents have the highest market share in Korea, and the availability of these drug-eluting stents in all participating centers.

For patients assigned to intravascular imaging-guided PCI, the choice of intravascular imaging device (IVUS or OCT) was at the operators' discretion. While use of intravascular imaging was allowed at any step of the PCI procedure (prior to intervention, during PCI, and after stent implantation or angioplasty when performed as a standalone procedure), intravascular imaging evaluation after PCI was mandated for optimization of the stented segment.

Standard protocols for image acquisition were used with the IVUS (Opticross^{TM}, Boston Scientific Corporation, San Jose, CA, USA) or OCT (Dragonfly^{TM}, Abbott Vascular, St. Paul, MN, USA) devices. Before advancing the intravascular imaging catheter, intracoronary nitroglycerin (100 to 200 μg) was administered. For IVUS, the transducer was pulled back automatically at a speed of 0.5 mm per sec. For OCT, preheated contrast media at 37 °C was flushed through the guiding catheter at a rate of 2 to 4 ml per second for approximately 3 to 6 seconds by using an injector pump to obtain the OCT images. However, the final choice of pullback speed for the IVUS device and the injection rate and the amount of contrast media used during OCT imaging was also left to the operators' discretion. In case of a staged procedure during the same hospitalization, it was strongly recommended that the operator follow the initially allocated imaging or angiography guidance strategy.

Protocols for selecting the reference segments for the lesion, for selecting the appropriate size of the stent, and for stent optimization were prespecified based on previous reports in the literature.[14] In brief, proximal and distal reference sites were determined at cross-sections adjacent to the target lesion (at least 5 mm apart) that have the largest lumen and a plaque burden of less than 50% by IVUS. Using OCT, proximal and distal reference sites were determined at cross-sections adjacent to the target lesion (at least 5 mm apart) that have the most normal appearance and are free of lipid-containing plaque. The criteria used to determine optimal stent expansion were residual angiographic diameter stenosis (defined by percent diameter stenosis; ([mean reference vessel diameter – minimum lumen diameter]/mean reference vessel diameter) x 100) less than 10% and minimum stent area (defined by the lumen area measured by intravascular imaging devices at the site of the narrowest lumen inside of the stented segment) greater than 80% of the average reference lumen area or absolute minimum stent area greater than 5.5 mm^2 by IVUS or 4.5 mm^2 by OCT for a stenosis, except if the lesion was in the left main coronary artery. For a left main stenosis, an absolute minimal stent area

greater than 7 mm^2 for distal left main coronary artery and greater than 8 mm^2 for the proximal left main coronary artery were used as optimization criteria, respectively.[14]

An optimized procedural result in the intravascular imaging-guided PCI group was defined as sufficient stent expansion without major stent malapposition and edge dissection. Specific definitions are provided in the table below.

Major stent malapposition was defined as an acute malapposition with the distance between the vessel wall and the stent of at least 0.4 mm with longitudinal length of more than 1 mm. Major edge dissection was defined as a dissection occurring within 5 mm from the edge of the stent, extending to the medial layer with a dissection angle of at least 60° of the circumference of the vessel or at least 3 mm in length of dissection flap. If one of the above findings were identified by the intravascular imaging devices, additional procedures including adjunctive post-dilatation or additional stent implantation followed by further intravascular imaging were recommended to optimize the final results.

To avoid perforation, the non-compliant balloon diameter was recommended to be no larger than the nearest reference vessel diameter, or up to 0.5 mm larger than the mean reference lumen diameter after PCI, based on findings from the intravascular imaging. The maximal inflation pressure of the non-compliant balloon was left up to the operator; however, it was recommended that the non-compliant balloon was inflated to a pressure above the nominal rated pressure for the balloon. In case a major edge dissection was identified by intravascular imaging, additional stent implantation was recommended; the stent size selected was based on findings from the intravascular imaging study. After additional procedural optimization, the intravascular-imaging study was to be repeated until the acquisition of the optimized results, as described above. However, operators could decide to consider the procedure finished if it was believed that there was the potential risk for a complication associated with additional procedural optimization interventions.

	IVUS	**OCT**
Reference Sites	Largest size vessel lumen; Plaque burden <50%; At least 5 mm away from the target lesion	Most normal looking segment; No lipid-containing plaque; At least 5 mm away from the target lesion
Stent Sizing	Vessel diameter (external elastic membrane) is measured at the proximal and distal reference sites. The averaged value of the proximal and distal reference external elastic membrane diameter is used to determine	Vessel diameter is measured at the distal reference sites (in cases where ≥180° of the external elastic membrane can be identified). Stent diameter is determined using the mean external elastic membrane diameter at the distal reference, rounded down to the nearest 0.25

	IVUS	OCT
	the stent diameter.	mm. For example, if the mean external elastic membrane reference diameter is measured as 3.15 mm, then a 3.0 mm stent diameter will be selected. OR The lumen diameter is measured at the distal reference sites (in cases where ≥180° of the external elastic membrane cannot be identified). Stent diameter is determined using the mean lumen diameter at the distal reference, rounded up to the nearest 0.25 mm. For example, if the mean distal reference lumen diameter is 2.55 mm, then a 2.75 mm stent diameter will be selected.
Stent Length	By measuring the distance from the distal to the proximal reference site.	
Stent Optimization		
● **Stent Expansion**	Visually assess that the residual angiographic diameter stenosis is <10% "AND" ● Non-left main coronary artery lesions: In-stent minimal stent lumen area > 80% of the average reference lumen area "OR" a minimal stent area of >5.5 mm^2 by IVUS and >4.5 mm^2 by OCT. ● Left main coronary artery lesions: Minimal stent luminal area of >7 mm^2 for a distal left main coronary artery stenosis and >8 mm^2 for a proximal left main coronary artery stenosis by IVUS.	
● **Stent Apposition**	No major malapposition (defined as an acute malapposition of ≥0.4 mm with longitudinal extension >1 mm) 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 a location that is 5 mm from the edge of the stent, extends to the medial layer with potential to provoke flow disturbances (defined as ≥60° of the circumference of the vessel at the site of a dissection or ≥3 mm in length of the dissection flap)	
Stent optimization technique	**If any of above findings are identified, additional procedural intervention, including additional post-dilatation of the stent or**	

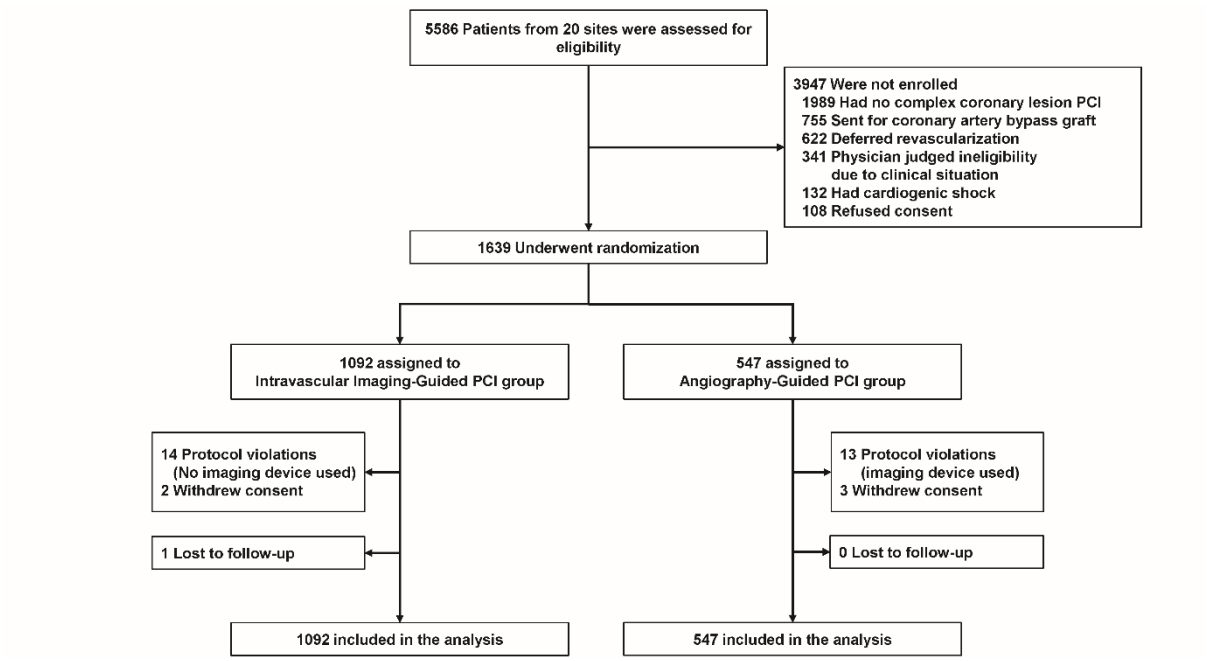
	IVUS	OCT
	additional stent implantation is recommended. For additional post-dilatation of the stent, the diameter of the non-compliant balloon should not be larger than the IVUS or OCT determined mean reference external elastic membrane diameter assessed after stenting of one or both segments (proximal or distal), or if the external elastic membrane cannot be measured, 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 dilation site.	

Among patients assigned to the angiography-guided PCI group, stent optimization was assessed and performed based on angiographic findings. A stent was considered optimized if the angiographic residual diameter stenosis is less than 10% by visual estimation and there was no flow limiting dissection (type C through F dissection). When underexpansion of the stent was suspected based on angiography, adjunctive balloon dilatation using non-compliant balloons was recommended. To avoid perforation, the non-compliant balloon diameter was recommended to be no larger than the nearest reference vessel diameter, or up to 0.5 mm larger than the mean reference lumen diameter after PCI. The maximal inflation pressure of the non-compliant balloon was left to the operator's discretion; however, it was recommended that the non-compliant balloon inflation was pressure was at least above the nominal rated pressure of the balloon. Additional procedural optimization was recommended until the optimized results (as described above) were obtained. Operators could decide to consider the procedure finished if it was believed that there was the potential risk for a complication associated with additional procedural optimization interventions.

After the index PCI procedure, dual antiplatelet therapy was recommended for at least 3 to 6 months in patients with stable ischemic heart disease and 6 to 12 months in those with an acute coronary syndrome, regardless of allocated arms.[15,16] However, the loading, maintenance dose, and duration of dual antiplatelet therapy were left up to the physicians' discretion. Regardless of the patient assignment, guideline directed medical therapy was recommended according to the current American College of Cardiology/ American Heart Association/ Society of Coronary Angiographers and Interventionalists or the European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines.[17,18] All coronary angiograms and intravascular imaging data were analyzed by the independent core laboratories.

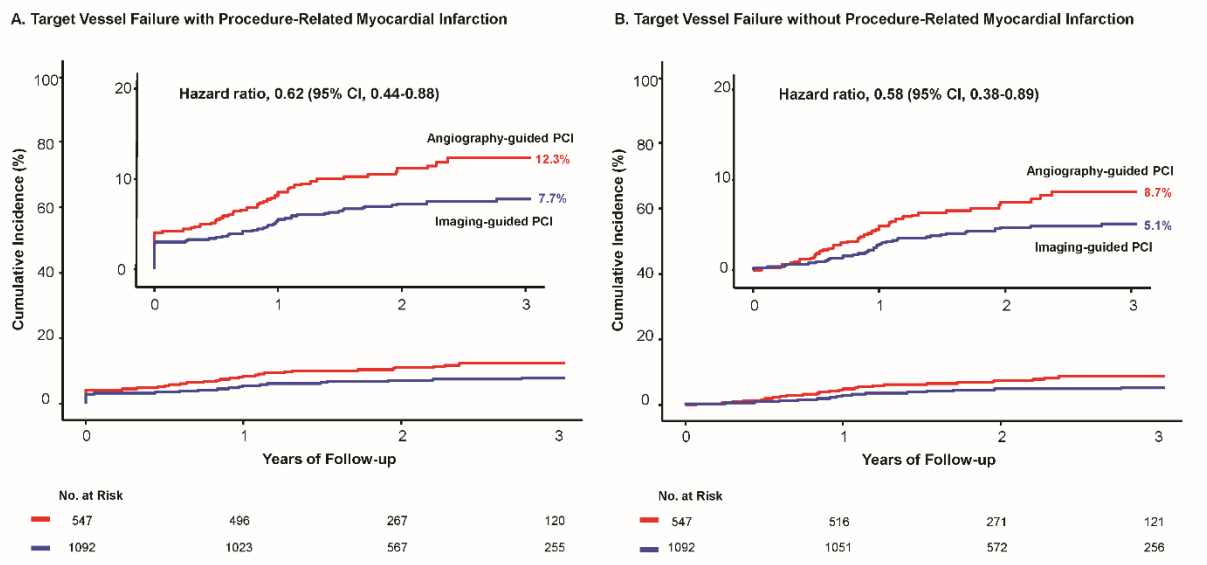
Supplementary Figures

Figure S1. Randomization, Treatment, and Follow-up of Patients



Between May 2018 and May 2021, a total of 1639 patients with complex coronary artery lesions that were going to be treated by PCI underwent randomization in a 2:1 manner to intravascular imaging-guided PCI or angiography-guided PCI. A total of 14 patients in the intravascular imaging-guided PCI group did not have intravascular imaging devices used during the PCI procedure and 13 patients in the angiography-guided group had an intravascular imaging device used during the PCI. Two patients in the intravascular imaging-guided PCI group and 3 patients in the angiography-guided PCI group withdrew their consent. One patient in the intravascular imaging-guided PCI group was lost to follow-up. All patients were analyzed as an intention-to-treat population.
PCI denotes percutaneous coronary intervention.

Figure S2. Kaplan–Meier Curves for the Study Outcomes



The current analyses were unadjusted Kaplan-Meier analyses and Cox proportional hazard regression models from the intention-to-treat population, stratified by the clinical presentation and participating centers.

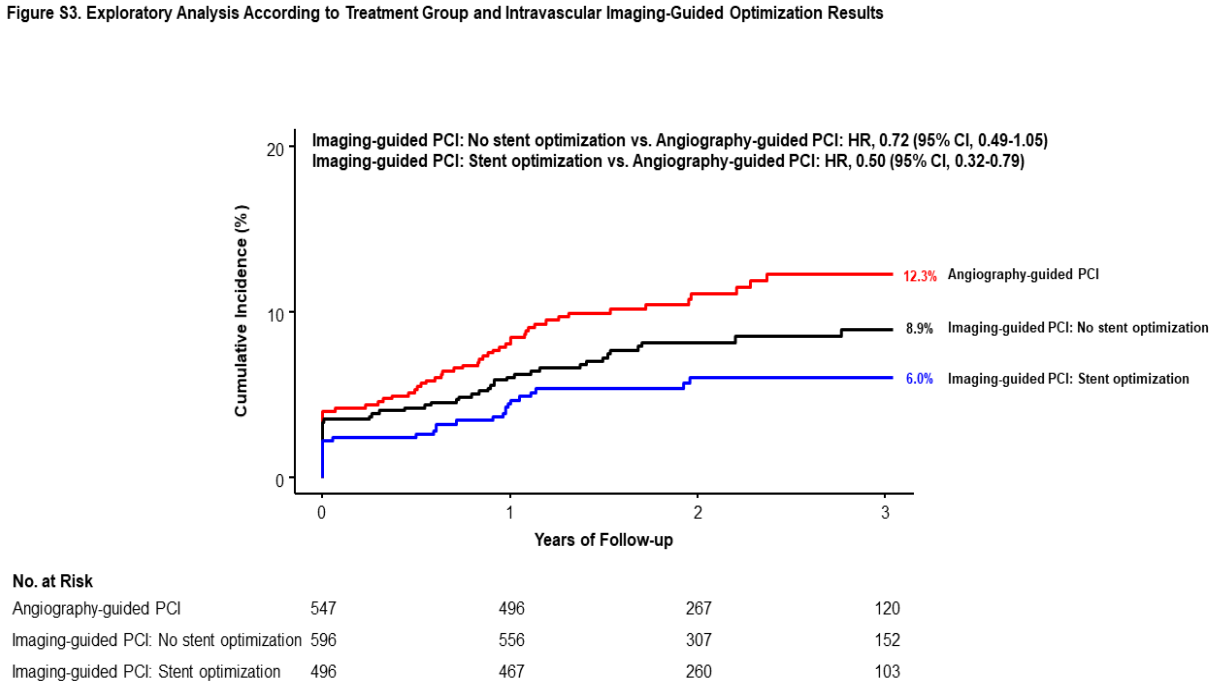
(A) The primary endpoint was target vessel failure, which was a composite of cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization in the intention-to-treat population during the overall study period (i.e., beginning from time of randomization to the day of the first occurrence of a primary endpoint event, the day of the last office or phone visit, or the day of death during follow-up).

(B) Target vessel failure without procedure-related myocardial infarction is compared between the 2 groups.

MI denotes myocardial infarction and PCI percutaneous coronary intervention.

There was no prespecified plan to adjust for multiple testing. Outcomes are reported with 95% confidence intervals, without p values. The 95% confidence intervals are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Figure S3. Exploratory Analysis According to Treatment Group and Intravascular Imaging-Guided Optimization Results



Comparison of the primary endpoint according to randomization group and intravascular imaging-guided optimization is shown. The primary endpoint was a composite of cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization during the overall study period (i.e., beginning from the time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or phone visit, or the day of death during follow-up). This analysis was exploratory.

PCI denotes percutaneous coronary intervention.

There was no prespecified plan to adjust for multiple testing. Outcomes are reported with 95% confidence intervals, without p values. The 95% confidence intervals are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Supplementary Tables

Table S1. Lesion-level Analysis of Quantitative Coronary Angiography and Intravascular Imaging*

Characteristics	Total (N=2438)	Imaging-guided PCI (N=1623)	Angiography-guided PCI (N=815)
Location of target vessel — no. (%)			
Left main artery	237 (9.7)	164 (10.1)	73 (9.0)
Left anterior descending artery	1077 (44.2)	701 (43.2)	376 (46.1)
Circumflex artery	464 (19.0)	313 (19.3)	151 (18.5)
Right coronary artery	660 (27.1)	445 (27.4)	215 (26.4)
Quantitative coronary angiography			
Pre-PCI QCA			
Proximal reference vessel diameter — mm	3.2±0.5	3.2±0.5	3.1±0.5
Distal reference vessel diameter — mm	2.7±0.5	2.7±0.5	2.7±0.4
Minimum lumen diameter — mm	0.44±0.37	0.44±0.37	0.44±0.36
Diameter stenosis — %	85.4±11.6	85.4±11.5	85.2±11.7
Lesion length — mm	27.9±15.6	28.4±15.9	26.8±14.8
Post-PCI QCA†			
Minimum lumen diameter — mm	2.8±0.5	2.8±0.5	2.7±0.5
Diameter stenosis — %	9.8±8.8	9.8±8.9	10.0±8.6
Post-PCI residual stenosis<10% — **no./total no. (%)**	1638/2346 (69.8)	1098/1560 (70.4)	540/786 (68.7)
Intracoronary physiologic assessment — no. (%)	152 (6.2)	110 (6.8)	42 (5.2)
Resting Pd/Pa	0.86±0.09	0.86±0.09	0.87±0.09
Fractional flow reserve	0.70±0.09	0.69±0.09	0.71±0.08
Radial artery access — no. (%)	1879 (77.1%)	1240 (76.4%)	639 (78.4%)
Intravascular imaging devices used — no./total no. (%)‡	1569/2438 (64.4)	1549/1623 (95.4)	20/815 (2.5)
Intravascular ultrasound	1208/1569 (77.0)	1188/1549 (76.7)	20/20 (100.0)
Optical coherence tomography	361/1569 (23.0)	361/1549 (23.3)	0/20 (0.0)
Profile of intravascular imaging use — no./total no. (%)			
Pre-PCI evaluation only	18/1569 (1.1)	16/1549 (1.0)	2/20 (10.0)
Post-PCI evaluation only	371/1569 (23.6)	366/1549 (23.6)	5/20 (25.0)
Both pre- and post-PCI evaluation	1180/1569 (75.2)	1167/1549 (75.3)	13/20 (65.0)
Adjunctive non-compliant balloon used — no. (%)	1351 (55.4)	980 (60.4)	371 (45.5)
Size of adjunctive balloon — mm	3.5±0.6	3.5±0.6	3.5±0.5
Maximum inflation pressure — atm	18.9±4.6	18.7±4.6	19.2±4.6
Rotablation used — no. (%)	59 (2.4%)	42 (2.6)	17 (2.1)
Treatment devices used — no. (%)			
Drug-eluting stent	2286 (93.8)	1527 (94.1)	759 (93.1)

Drug-coated balloon angioplasty	152 (6.2)	96 (5.9)	56 (6.9)
Total no. of devices used per treated lesion	1.3±0.5	1.3±0.5	1.3±0.5
Dimensions of devices — mm			
Mean diameter	3.1±0.5	3.1 ± 0.5	3.0 ± 0.4
Total length	37.6±19.1	38.0±19.5	36.9±18.4
Procedural success — no. (%)	2407 (98.8)	1601 (98.7)	806 (98.9)

***** Data presented as mean ±SD, median (interquartile range), or as number and percentage.

† Quantitative coronary angiography after PCI was not available for 92 lesions in 84 patients.

‡ Fourteen patients assigned to the intravascular imaging-guided PCI group did not have their PCI performed with an intravascular imaging device due to failure to pass the device (9 patients), failed PCI (4 patients), or hemodynamic instability during procedure (1 patient). Thirteen patients in the angiography-guided group had their PCI performed with an intravascular imaging device for treatment of long coronary lesion (2 patients), unprotected left main disease (2 patients), chronic total occlusion (2 patients), severe calcification (3 patients), unclear lesion length (2 patients), an ostial lesion (1 patient), or hemodynamic instability during procedure (1 patient). These patients with protocol violations were analyzed as part of the intention-to-treat population.

PCI denotes percutaneous coronary intervention, and QCA quantitative coronary angiography.

Table S2. Lesion-Level Analysis of Intravascular Imaging and Procedural Optimization in the Intravascular Imaging-guided PCI Group*

Characteristics	IVUS (N#=1188)	OCT (N#=361)
Location of target lesion — no. (%)		
Left main artery	149 (12.5)	15 (4.2)
Left anterior descending artery	487 (41.0)	191 (52.9)
Circumflex artery	228 (19.2)	63 (17.5)
Right coronary artery	324 (27.3)	92 (25.5)
Profile of intravascular imaging use — no./total no. (%)†		
Pre-PCI evaluation only	6/1188 (0.5)	10/361 (2.8)
Post-PCI evaluation only	279/1188 (23.5)	87/361 (24.1)
Both pre- and post-PCI evaluation	903/1188 (76.0)	264/361 (73.1)
Pre-PCI analysis		
Proximal reference		
External elastic membrane area — mm^2	17.6±5.4	13.7±4.5
Mean diameter of external elastic membrane by IVUS — mm	4.7±0.7	NA
Lumen area — mm^2	10.4±3.8	8.4±3.0
Mean lumen diameter — mm	3.6±0.6	3.2±0.6
Plaque burden —%	40.6±11.0	38.5±8.6**
Minimal lumen area — mm^2	2.4±0.9	1.8±1.1
Maximal plaque burden at minimal lumen area — mm^2	80.9±7.0	72.8±10.2**
Distal reference		
External elastic membrane area — mm^2	10.8±4.9	8.6±3.6
Mean diameter of external elastic membrane by IVUS —mm	3.6±0.8	NA
Lumen area — mm^2	6.9±2.8	5.7±2.6
Mean lumen diameter — mm	2.9±0.6	2.6±0.6
Plaque burden — %	33.2±12.8	35.5±9.7**
Lesion length — mm	33.4±18.6	32.7±13.5
Dimensions of stents — mm		
Mean diameter	3.1±0.5	3.1±0.4
Total length	38.9±20.1	37.2±17.8
Post-PCI analysis		
Stent expansion — %	71.6±17.1	75.7±18.7
Minimum stent area — mm^2	5.8±2.1	5.2±1.9
Prespecified optimization criteria‡ — no./total no. (%)		
Plaque burden at stent landing zone < 50%	1090/1188 (91.8%)	NA
Optimal stent expansion§	722/1188 (60.8%)	271/361 (75.1%)
Edge dissection		
Any edge dissection	36/1188 (3.0%)	47/361 (13.0%)
Major edge dissection¶	7/1188 (0.6%)	12/361 (3.3%)
Stent malapposition		

Any stent malapposition	51/1188 (4.3%)	73/361 (20.2%)
Major stent malapposition‖	10/1188 (0.8%)	31/361 (8.6%)
Optimized results (met all the above criteria)	659/1188 (55.5%)	238/361 (65.9%)

* Data presented as mean ±SD, median (interquartile range), or as number (%).

#N represents the number of lesions

† Among the total 1623 lesions in patients assigned to the intravascular imaging-guided PCI group, core laboratory analysis could not be performed for 74 lesions due to insufficient lesion coverage, suboptimal image quality, manual pullback of the IVUS catheter, or lack of raw data from the intravascular imaging procedure.

‡ Protocols for selecting reference segment, selecting appropriated size of stent, and stent optimization were prespecified and are described in the Supplementary Appendix.

§ Optimal stent expansion was defined as a residual angiographic diameter stenosis of <10% and an in-stent minimum stent area of >80% of the average reference lumen area or an absolute in-stent minimum stent area of >5.5 mm^2 by IVUS imaging and >4.5 mm^2 by OCT imaging. For a left main coronary artery stenosis, optimal stent expansion was defined as an in-stent minimum stent area of >7 mm^2 for the distal left main coronary artery and >8 mm^2 for the proximal left main coronary artery was used as optimization criteria.

¶ Major edge dissection was defined as a dissection that occurred 5mm from the edge of the stent, extended to medial layer with potential to create a flow disturbance (defined as ≥60° of the circumference of the vessel at the site of dissection and/or ≥3 mm in length of a dissection flap).

‖ Major malapposition was defined as an acute stent malapposition of ≥0.4 mm with longitudinal extension >1 mm of the stent over its entire length against the vessel wall.

** In cases where there was unclear visualization of the external elastic membrane by OCT at the proximal reference site, the minimal luminal area or the distal reference frames, then plaque burden could not be calculated. Plaque burden by OCT could be calculated in 80 lesions, 20 lesions, and 157 lesions, respectively for the proximal reference segment, minimal luminal area, and distal reference frames.

PCI denotes percutaneous coronary intervention, IVUS, intravascular ultrasound, and OCT, optical coherence tomography.

Table S3. Procedure-Related Complications During the Index Hospitalization

Characteristics	Total (N=1639)	Imaging-guided PCI (N=1092)	Angio-guided PCI (N=547)
Procedure-related complications — no. (%)			
Any complications	55 (3.4)	37 (3.4)	18 (3.3)
Coronary perforation	4 (0.2)	4 (0.4)	0 (0.0)
Emergency re-intervention	5 (0.3)	3 (0.3)	2 (0.4)
Congestive heart failure	4 (0.2)	1 (0.1)	3 (0.5)
Cardiogenic shock	11 (0.7)	10 (0.9)	1 (0.2)
Anaphylactic reaction to contrast agent	3 (0.2)	3 (0.3)	0 (0.0)
Cardiac tamponade	3 (0.2)	3 (0.3)	0 (0.0)
Non-access site bleeding	2 (0.1)	1 (0.1)	1 (0.2)
Access site bleeding	11 (0.7)	7 (0.6)	4 (0.7)
Access site dissection	4 (0.2)	2 (0.2)	2 (0.4)
Arrhythmia	10 (0.6)	8 (0.7)	2 (0.4)

PCI denotes percutaneous coronary intervention.

Table S4. Primary and Secondary Endpoints from Unadjusted Analyses*

Endpoint	Total (N=1639)	Imaging-guided PCI (N=1092)	Angiography-guided PCI (N=547)	Hazard Ratio (95% CI)
Primary endpoint — no. (%)				
Target vessel failure†	136 (9.2)	76 (7.7)	60 (12.3)	0.62 (0.44-0.88)
Secondary endpoints‡ — no. (%)				
Target vessel failure without procedure-related MI	88 (6.3)	48 (5.1)	40 (8.7)	0.58 (0.38-0.89)
Cardiac death or target-vessel related MI	96 (6.4)	53 (5.3)	43 (8.5)	0.61 (0.41-0.92)
All-cause death	70 (5.6)	42 (5.3)	28 (6.4)	0.71 (0.44-1.15)
Cardiac death	33 (2.4)	16 (1.7)	17 (3.8)	0.45 (0.23-0.90)
Myocardial infarction	75 (5.0)	43 (4.4)	32 (6.2)	0.69 (0.44-1.10)
Target-vessel related MI	68 (4.3)	38 (3.7)	30 (5.6)	0.65 (0.40-1.05)
Spontaneous MI§	17 (1.2)	8 (0.9)	9 (1.8)	0.46 (0.17-1.20)
Procedure-related MI¶	52 (3.2)	30 (2.7)	22 (4.0)	0.71 (0.41-1.24)
Non-target vessel related MI	8 (0.8)	5 (0.8)	3 (0.8)	0.92 (0.21-3.95)
Repeat revascularization‖ — no. (%)	87 (6.6)	55 (6.3)	32 (7.1)	0.89 (0.57-1.38)
Target vessel revascularization	57 (4.1)	32 (3.4)	25 (5.5)	0.63 (0.37-1.06)
Target lesion revascularization	44 (3.2)	24 (2.6)	20 (4.4)	0.58 (0.32-1.05)
Definite stent thrombosis** — no. (%)	5 (0.3)	1 (0.1)	4 (0.7)	0.13 (0.02-0.90)
Contrast induced nephropathy†† — no. (%)	40 (2.4)	26 (2.4)	14 (2.6)	0.97 (0.49-1.92)

* Data presented as n (%). The database for the analysis presented here was locked on May 10, 2022. Clinical endpoints were evaluated in the intention-to-treat population during the overall study period (i.e., beginning from time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or phone visit, or the day of death during follow-up). Percentages are 3-year Kaplan–Meier estimates.

† Primary endpoint is target vessel failure, which is a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization.

‡ The individual endpoints listed are the first occurrence of that event.

§ Spontaneous myocardial infarction is defined using the 3rd universal definition of myocardial infarction.

¶ Procedure-related myocardial infarction is defined using the Society for Cardiovascular Angiography and Interventions (SCAI) definition.

‖ Repeat revascularization includes all first clinically indicated elective, urgent, or emergent revascularization procedures that were not planned during index hospitalization or during the overall study period.

** Definite stent thrombosis is defined using Academic Research Consortium criteria.

†† Contrast-induced nephropathy is defined as an increase in serum creatinine of at least 0.5 mg/dL or at least 25% from baseline within 48-72 hours after contrast agent exposure. The event rate is presented as a proportion by group.

MI denotes myocardial infarction, and PCI percutaneous coronary intervention.

Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. All the models were adjusted for the clinical presentation and participating centers (stratification factors).

Table S5. Representativeness of Study Participants

Category	
Disease, problem, or condition under investigation	Patients who have symptomatic coronary artery disease with complex coronary anatomical characteristics and are revascularized by percutaneous coronary intervention (PCI).
Special consideration related to	
Sex	Coronary artery disease affects men more than women and women were less likely to be diagnosed or treated with invasive cardiac procedures than men.[21,22]
Age	The prevalence of coronary artery disease increases with age; older patients were more likely to have cardiovascular risk factors than younger patients; women with coronary artery disease undergoing PCI are typically older than men with coronary artery disease undergoing PCI.
Ethnicity	Some Asian populations tend to have a lower prevalence of coronary artery disease than Western populations (Whites, Blacks, and Hispanics).[23]
Geography	Age, underlying causes, and the prevalence of coronary artery disease varies among countries. The participants enrolled in this trial were from the Republic of Korea, which tends to have a lower prevalence of coronary artery disease than some Western countries.
Other considerations	In the RENOVATE COMPLEX-PCI trial, we did not include patients treated with PCI for non-complex coronary artery lesions; thus, the trial findings cannot be extrapolated to patients with this coronary anatomy.
Overall representativeness of this trial	The participants in the present trial demonstrated the expected ratio of men to women (79.3% men). The age distribution of our cohort reflected the population of patients with coronary artery disease that clinicians might encounter in practice (mean age 65.6 years). The RENOVATE COMPLEX-PCI trial enrolled patients with complex coronary artery lesions who underwent PCI; therefore, the current findings can provide reliable evidence on the prognostic role of intravascular imaging guidance during complex PCI in these patients.

CAD denotes coronary artery disease, and PCI percutaneous coronary intervention.

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