ORIGINAL ARTICLE

Intravascular Imaging–Guided or Angiography-Guided Complex PCI

J.M. Lee, K.H. Choi, Y.B. Song, J.-Y. Lee, S.-J. Lee, S.Y. Lee, S.M. Kim, K.H. Yun, J.Y. Cho, C.J. Kim, H.-S. Ahn, C.-W. Nam, H.-J. Yoon, Y.H. Park, W.S. Lee, J.-O. Jeong, P.S. Song, J.-H. Doh, S.-H. Jo, C.-H. Yoon, M.G. Kang, J.-S. Koh, K.Y. Lee, Y.-H. Lim, Y.-H. Cho, J.-M. Cho, W.J. Jang, K.-J. Chun, D. Hong, T.K. Park, J.H. Yang, S.-H. Choi, H.-C. Gwon, and J.-Y. Hahn, for the RENOVATE-COMPLEX-PCI Investigators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hahn can be contacted at jyhahn@skku.edu or at the Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, South Korea.

*A list of the RENOVATE-COMPLEX-PCI Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. J.M. Lee and K.H. Choi and Drs. Y.B. Song and Hahn contributed equally to this article.

This article was published on March 5, 2023, at NEJM.org.

N Engl J Med 2023;388:1668-79.
DOI: 10.1056/NEJMoa2216607

CME at NEJM.org

ABSTRACT

BACKGROUND

Data regarding clinical outcomes after intravascular imaging–guided percutaneous coronary intervention (PCI) for complex coronary-artery lesions, as compared with outcomes after angiography-guided PCI, are limited.

METHODS

In this prospective, multicenter, open-label trial in South Korea, we randomly assigned patients with complex coronary-artery lesions in a 2:1 ratio to undergo either intravascular imaging–guided PCI or angiography-guided PCI. In the intravascular imaging group, the choice between intravascular ultrasonography and optical coherence tomography was at the operators' discretion. The primary end point was a composite of death from cardiac causes, target-vessel–related myocardial infarction, or clinically driven target-vessel revascularization. Safety was also assessed.

RESULTS

A total of 1639 patients underwent randomization, with 1092 assigned to undergo intravascular imaging–guided PCI and 547 assigned to undergo angiography-guided PCI. At a median follow-up of 2.1 years (interquartile range, 1.4 to 3.0), a primary end-point event had occurred in 76 patients (cumulative incidence, 7.7%) in the intravascular imaging group and in 60 patients (cumulative incidence, 12.3%) in the angiography group (hazard ratio, 0.64; 95% confidence interval, 0.45 to 0.89; P=0.008). Death from cardiac causes occurred in 16 patients (cumulative incidence, 1.7%) in the intravascular imaging group and in 17 patients (cumulative incidence, 3.8%) in the angiography group; target-vessel–related myocardial infarction occurred in 38 (cumulative incidence, 3.7%) and 30 (cumulative incidence, 5.6%), respectively; and clinically driven target-vessel revascularization in 32 (cumulative incidence, 3.4%) and 25 (cumulative incidence, 5.5%), respectively. There were no apparent between-group differences in the incidence of procedure-related safety events.

CONCLUSIONS

Among patients with complex coronary-artery lesions, intravascular imaging–guided PCI led to a lower risk of a composite of death from cardiac causes, target-vessel–related myocardial infarction, or clinically driven target-vessel revascularization than angiography-guided PCI. (Supported by Abbott Vascular and Boston Scientific; RENOVATE-COMPLEX-PCI ClinicalTrials.gov number, NCT03381872).

Percutaneous coronary intervention (PCI) with the use of second-generation drug-eluting stents has markedly reduced the rates of stent-related or target-vessel–related adverse clinical events, as compared with first-generation drug-eluting stents or bare metal stents.[1] However, patients with complex coronary-artery lesions who undergo PCI have worse clinical outcomes than patients who undergo PCI for coronary-artery lesions that are not complex.[2,3] During PCI procedures, imaging with intravascular ultrasonography and optical coherence tomography (OCT) provides useful information about lesion characteristics and is used to select the appropriate stent size, to determine the stent landing zone in the coronary artery, and to determine if the stent is not well expanded or if there is a stent edge dissection, which can increase the risks of stent thrombosis, myocardial infarction, and repeat revascularization.[4] Therefore, procedural guidance with intravascular imaging may improve clinical outcomes after PCI for complex coronary-artery lesions.

Previous randomized, controlled trials have shown lower rates of major adverse clinical events after intravascular ultrasonography–guided PCI than after angiography-guided PCI[5-9] but have not been considered to be definitive owing to limited sample size or the inclusion of highly selected coronary-lesion subsets. Guidelines from the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions and from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery recommend that intravascular ultrasonography or OCT be considered in selected patients in order to optimize stent implantation.[10,11] Therefore, we conducted the Randomized Controlled Trial of Intravascular Imaging Guidance versus Angiography-Guidance on Clinical Outcomes after Complex Percutaneous Coronary Intervention (RENOVATE-COMPLEX-PCI) to investigate whether intravascular imaging–guided PCI with the use of intravascular ultrasonography or OCT would improve clinical outcomes as compared with angiography-guided PCI in patients with complex coronary-artery lesions.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, prospective, multicenter, randomized, open-label trial at 20 sites in South Korea. All the participating centers and trial personnel are listed in the Supplementary Appendix, which is available with the full text of this article at NEJM.org. The trial protocol (available at NEJM.org) was approved by the institutional review board at each participating site. All the patients provided written informed consent before randomization. A data and safety monitoring board oversaw the trial, and an independent clinical-event adjudication committee whose members were unaware of the trial-group assignments assessed all clinical events (see the Supplementary Appendix).

The executive committee and the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The funders (Abbott Vascular and Boston Scientific) had no role in the trial design; in the collection, analysis, or interpretation of the data; or in the writing of the manuscript. The first and last authors had unrestricted access to the data, were involved in the analysis and interpretation of the data, wrote the first and subsequent drafts of the manuscript, and made the decision to submit the manuscript for publication.

Patients

Patients 19 years of age or older who were undergoing PCI for complex coronary-artery lesions were candidates for enrollment. Complex coronary-artery lesions were defined as true bifurcation lesions according to the Medina classification system[12] with a side-branch diameter of at least 2.5 mm; a chronic total occlusion; unprotected left main coronary artery disease; long coronary-artery lesions that would involve an expected stent length of at least 38 mm; multivessel PCI involving at least two major epicardial coronary arteries being treated at the same time; a lesion that would necessitate the use of multiple stents (at least three planned stents); a lesion involving in-stent restenosis; a severely calcified lesion; or ostial lesions of a major epicardial coronary artery. Patients were excluded if they had coronary lesions that were not appropriate

A Quick Take is available at NEJM.org

candidates for PCI as determined by the operator, cardiogenic shock (Killip class IV) at presentation, or a known hypersensitivity or a contraindication to aspirin, clopidogrel, prasugrel, ticagrelor, heparin, everolimus, or contrast medium or if they were pregnant or breast-feeding. An expanded definition of complex coronary-artery lesions and details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

RANDOMIZATION

Eligible patients were randomly assigned in a 2:1 ratio to undergo either intravascular imaging–guided PCI or angiography-guided PCI after diagnostic coronary angiography. Randomization was performed by means of a Web-based randomization program (Apache 2, PHP 5.3, and MySOL5; S-Soft) in permuted blocks, with block sizes of six, and was stratified according to clinical presentation (stable ischemic heart disease or acute coronary syndrome) and participating center.

INTERVENTIONS

PCI was performed with the use of standard techniques for coronary-artery-lesion preparation and stent implantation that were selected at the discretion of the operator. The drug-eluting stents that were implanted in patients were either biodegradable or biocompatible polymer-coated everolimus-eluting stents. Detailed protocols for intravascular image acquisition, optimization of the implanted coronary-artery stent, and dual antiplatelet therapy after PCI are provided in the Supplementary Appendix.

For patients who had been assigned to the intravascular imaging group, the choice of intravascular ultrasonography or OCT was made at the operators' discretion. Intravascular imaging could be used at any time during the PCI procedure but was mandated after stent implantation to determine whether the stented segment was optimized.

Stent optimization was defined as sufficient stent expansion without major stent malapposition to the vessel wall or edge dissection. The criteria for sufficient stent expansion included a residual stenosis diameter of less than 10% of the reference-vessel diameter for the target lesion as assessed on angiography and a minimum stent area of more than 80% of the mean reference lumen area or an absolute minimum stent area of more than 5.5 mm^2 on the basis of intravascular ultrasonography or more than 4.5 mm^2 on the basis of OCT for stenoses not in the left main coronary artery. For stenoses in the left main coronary artery, an absolute minimum stent area of more than 7 mm^2 for the distal left main coronary artery and more than 8 mm^2 for the proximal left main coronary artery were used as optimization criteria.[4]

Major stent malapposition was defined as an acute malapposition with the distance between the coronary-artery vessel wall and the stent of at least 0.4 mm, with a length of the malapposition of more than 1 mm. Major edge dissection was defined as a dissection occurring within 5 mm from the edge of the stent and extending to the medial layer of the vessel with a dissection angle of at least 60 degrees of the circumference of the vessel or with a length of the dissection flap of at least 3 mm. If stent optimization did not occur, additional dilation of the stent or additional stent implantation was recommended, and repeat evaluation on intravascular imaging was mandated.

In patients who had been assigned to the angiography group, stent optimization was determined on the basis of angiographic findings. The stented segment was considered to be optimized if the residual stenosis diameter on angiography was less than 10% of the reference-vessel diameter on the basis of visual estimation and there was no flow-limiting coronary-artery dissection. All the angiograms and intravascular imaging data were analyzed by the independent core laboratories after the completion of the PCI procedure (see the Supplementary Appendix).

TRIAL END POINTS

The primary end point was target-vessel failure, which was defined as a composite of death from cardiac causes, target-vessel–related myocardial infarction, or clinically driven target-vessel revascularization. The primary end point was assessed in the intention-to-treat population (i.e., all the patients who had undergone randomization) during the overall trial period (i.e., 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 telephone visit, or the day of

death during follow-up). Secondary end points included the individual components of the primary end point, target-vessel failure without procedure-related myocardial infarction, a composite of target-vessel–related myocardial infarction or death from cardiac causes, and definite stent thrombosis. Definitions of all the secondary end points and detailed definitions of clinical events are provided in the Supplementary Appendix.

Serious adverse events that were related to PCI or intravascular imaging included coronary perforation, emergency reintervention, congestive heart failure, cardiogenic shock, anaphylactic reaction to the contrast agent, cardiac tamponade, bleeding related to the access site or other bleeding, arterial dissection at the vascular access site, or arrhythmia. These adverse events were monitored by the data and safety monitoring board. Clinical follow-up was conducted during outpatient clinic visits scheduled at 1 month, 6 months, and 12 months and yearly thereafter. Patients who were unable to attend outpatient clinical visits were contacted by telephone. Cross-validation of survival status was performed with the use of the Korean National Health Insurance database.

STATISTICAL ANALYSIS

We estimated that a sample size of 1620 would provide the trial with at least 90% power, at a two-sided significance level of 5%, to reject the null hypothesis. The null hypothesis was that there would be no between-group difference for the primary composite end point as assessed by the log-rank test given an anticipated enrollment period of 3 years, follow-up of 1 year after the enrollment of the last patient, and withdrawal by 5% of the patients. The annual incidence of the primary end point was expected to be 3.6% in the intravascular imaging group and 6.0% in the angiography group. These estimates were based on the results of previous studies, as described in the Supplementary Appendix.[3,5,9] No interim analysis was planned.

All the analyses were performed on an intention-to-treat basis. The primary end-point analysis included an estimation of the cumulative-incidence function of target-vessel failure and a comparison of the randomized groups with the use of the method of Fine and Gray to adjust for the potential competing risk of death from noncardiac causes.[13] As a sensitivity analysis, Kaplan–Meier analyses were performed for time-to-event end points with treatment effects estimated by means of Cox proportional-hazards regression models, and results are presented as hazard ratios with 95% confidence intervals. The proportional-hazards assumption was evaluated with a two-sided score test of the scaled Schoenfeld residuals over time at the 0.05 level. Subgroup analysis of the primary end point was performed according to the type of intravascular imaging device and clinical factors. No imputation methods were used to infer missing values of baseline variables. All the models were adjusted for the patient's clinical presentation and for participating centers.

Because the statistical analysis plan did not include a provision for correction for multiplicity when tests for secondary end points were conducted, results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects for secondary end points. Statistical analyses were performed with the use of R software, version 4.1.2 (R Foundation for Statistical Computing), and SPSS Statistics for Windows software, version 20.0 (IBM). The statistical analysis plan is available with the protocol.

RESULTS

PATIENTS

From May 2018 through May 2021, a total of 1639 patients with complex coronary-artery lesions underwent randomization; 1092 patients were assigned to undergo intravascular imaging–guided PCI, and 547 to undergo angiography-guided PCI (Fig. S1 in the Supplementary Appendix). Intravascular imaging devices were not used in 14 patients in the intravascular imaging group owing to failure to pass the device across the lesion, failed PCI, or hemodynamic instability during the procedure. In 13 patients in the angiography group, intravascular imaging devices were used during the procedure. Patients with protocol violations were included in the analysis as part of the intention-to-treat population. The clinical characteristics of the patients

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Total (N=1639)	Intravacular Imaging–Guided PCI Group (N=1092)	Angiography-Guided PCI Group (N=547)
Age — yr	65.6±10.2	65.3±10.3	66.0±10.0
Male sex — no. (%)	1300 (79.3)	869 (79.6)	431 (78.8)
Initial presentation — no. (%)			
Stable ischemic heart disease	807 (49.2)	532 (48.7)	275 (50.3)
Acute coronary syndrome	832 (50.8)	560 (51.3)	272 (49.7)
Unstable angina	534 (32.6)	361 (33.1)	173 (31.6)
Acute myocardial infarction	298 (18.2)	199 (18.2)	99 (18.1)
Non-STEMI	258 (15.7)	171 (15.7)	87 (15.9)
STEMI	40 (2.4)	28 (2.6)	12 (2.2)
Medical history — no. (%)			
Hypertension	1005 (61.3)	682 (62.5)	323 (59.0)
Diabetes mellitus	617 (37.6)	394 (36.1)	223 (40.8)
Insulin-treated diabetes mellitus	51 (3.1)	28 (2.6)	23 (4.2)
Dyslipidemia	840 (51.3)	560 (51.3)	280 (51.2)
Current smoking	307 (18.7)	212 (19.4)	95 (17.4)
Chronic renal insufficiency	296 (18.1)	203 (18.6)	93 (17.0)
Previous PCI	395 (24.1)	268 (24.5)	127 (23.2)
Previous myocardial infarction	117 (7.1)	75 (6.9)	42 (7.7)
Previous stroke	112 (6.8)	70 (6.4)	42 (7.7)
Peripheral arterial disease	44 (2.7)	27 (2.5)	17 (3.1)
Left ventricular ejection fraction — %	58.7±11.6	58.4±11.9	59.3±11.0
Medication at discharge — no. (%)			
Aspirin	1606 (98.0)	1069 (97.9)	537 (98.2)
$P2Y_{12}$ inhibitor	1603 (97.8)	1067 (97.7)	536 (98.0)
Clopidogrel	1216 (74.2)	799 (73.2)	417 (76.2)
Ticagrelor	209 (12.8)	148 (13.6)	61 (11.2)
Prasugrel	178 (10.9)	120 (11.0)	58 (10.6)
Oral anticoagulant	75 (4.6)	46 (4.2)	29 (5.3)
Statin	1567 (95.6)	1041 (95.3)	526 (96.2)
Beta-blocker	710 (43.3)	466 (42.7)	244 (44.6)
ACE inhibitor or ARB	945 (57.7)	622 (57.0)	323 (59.0)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

at baseline appeared to be similar in the two groups (Table 1). Overall, 807 patients (49.2%) presented with stable ischemic heart disease, and 832 patients (50.8%) presented with an acute coronary syndrome.

PROCEDURAL CHARACTERISTICS

The characteristics of the coronary-artery target lesion and the PCI procedures appeared to be well balanced between the two groups, including the types of complex coronary-artery lesions

Table 2. Target-Lesion and Procedural Characteristics.*

Characteristic	Total (N=1639)	Intravacular Imaging–Guided PCI Group (N=1092)	Angiography-Guided PCI Group (N=547)
Target-lesion characteristics			
Complex coronary lesions — no. (%)†			
True bifurcation lesion	359 (21.9)	233 (21.3)	126 (23.0)
Chronic total occlusion	319 (19.5)	220 (20.1)	99 (18.1)
Unprotected left main coronary artery disease	192 (11.7)	138 (12.6)	54 (9.9)
Diffuse long coronary-artery lesion	898 (54.8)	617 (56.5)	281 (51.4)
Multivessel PCI involving ≥2 major coronary arteries	622 (37.9)	409 (37.5)	213 (38.9)
Lesion necessitating use of ≥3 stents	305 (18.6)	208 (19.0)	97 (17.7)
Lesion with in-stent restenosis	236 (14.4)	158 (14.5)	78 (14.3)
Severely calcified lesion	231 (14.1)	157 (14.4)	74 (13.5)
Ostial lesions of major coronary artery	251 (15.3)	182 (16.7)	69 (12.6)
≥3 Complex coronary lesions — no. (%)	505 (30.8)	352 (32.2)	153 (28.0)
No. of vessels with disease — no. (%)			
1	526 (32.1)	342 (31.3)	184 (33.6)
2	621 (37.9)	420 (38.5)	201 (36.7)
3	492 (30.0)	330 (30.2)	162 (29.6)
Procedural characteristics			
Total no. of target lesions treated	1.5±0.7	1.5±0.7	1.5±0.7
Intravascular imaging device used — no./total no. (%)‡	1091/1639 (66.6)	1078/1092 (98.7)	13/547 (2.4)
Intravascular ultrasonography	813/1091 (74.5)	800/1078 (74.2)	13/13 (100)
Optical coherence tomography	278/1091 (25.5)	278/1078 (25.8)	0/13
Volume of contrast media used — ml	207.3±116.5	214.2±118.5	193.7±111.3
Median procedural time (IQR) — min	65 (47–89)	70 (51–95)	53.5 (40–75)
Procedural success — no. (%)	1613 (98.4)	1073 (98.3)	540 (98.7)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Diffuse long coronary-artery lesions were defined as the use of an implanted stent of at least 38 mm in length. Multivessel PCI involved at least two major coronary arteries undergoing PCI during one session. Severely calcified lesions were those with encircling calcium seen on angiography.
‡ A total of 14 patients in the intravascular imaging group did not have intravascular imaging used during their PCI procedure owing to failure to pass the device (in 9 patients), failed PCI (in 4), or hemodynamic instability during the procedure (in 1). A total of 13 patients in the angiography-guided group had intravascular imaging used during the procedure at the operator's discretion for the treatment of long coronary lesion (in 2 patients), unprotected left main disease (in 2), chronic total occlusion (in 2), severe calcification (in 3), unclear lesion length (in 2), ostial lesion (in 1), or hemodynamic instability during the procedure (in 1).

treated with PCI and the severity of coronary artery disease as assessed on angiography (Table 2). Among the 1092 patients in the intravascular imaging group, 800 (73.3%) underwent imaging with the use of intravascular ultrasonography and 278 (25.5%) underwent imaging with the use of OCT. The majority of the PCI procedures were performed by means of radial-artery access, and coronary-artery lesions were treated with drug-eluting stents with procedural success in 1613 of 1639 patients (98.4%). The baseline severity of the coronary-artery lesions, assessed on the basis of the minimum lumen diameter and the percent diameter stenosis, did not appear to differ between the two groups.

Use of intravascular imaging resulted in more

frequent use of adjunctive balloon dilation of the stent with noncompliant balloons (i.e., ultra-high-strength balloons that accommodate high pressure without changing diameter). After PCI, the mean (±SD) minimum lumen diameter was 2.8±0.5 mm in the intravascular imaging group and 2.7±0.5 mm in the angiography group (Table S1).

In the intravascular imaging group, intravascular ultrasonography or OCT was performed before PCI only in 16 of 1549 lesions (1.0%), after PCI only in 366 lesions (23.6%), and both before and after PCI in 1167 lesions (75.3%). Among the lesions that were evaluated by means of intravascular ultrasonography, 659 of 1188 lesions (55.5%) met all stent-optimization criteria, and among the lesions that were evaluated by means of OCT, 238 of 361 lesions (65.9%) met all stent-optimization criteria (Table S2). In the intravascular imaging group, stent optimization occurred in 496 of 1092 patients (45.4%), with stent optimization in 339 of 800 patients (42.4%) who had undergone intravascular ultrasonography and in 157 of 278 patients (56.5%) who had undergone OCT. In the angiography group, stent optimization occurred in 322 of 547 patients (58.9%). The incidence of procedure-related complications during the index hospitalization appeared to be similar in the two groups (Table S3).

PRIMARY AND SECONDARY END POINTS

At a median follow-up of 2.1 years (interquartile range, 1.4 to 3.0), a primary end-point event had occurred in 76 of 1092 patients in the intravascular imaging group and in 60 of 547 patients in the angiography group (cumulative incidence at 3 years, 7.7% vs. 12.3%; hazard ratio, 0.64; 95% confidence interval [CI], 0.45 to 0.89; P=0.008) (Table 3 and Fig. 1A). The risk of target-vessel failure without procedure-related myocardial infarction appeared to be lower in the intravascular imaging group than in the angiography group (cumulative incidence, 5.1% vs. 8.7%; hazard ratio, 0.59; 95% CI, 0.39 to 0.90) (Fig. 1B).

Individual components of the primary and secondary end points are shown in Table 3. The cumulative incidence of target-vessel–related myocardial infarction or death from cardiac causes was 5.3% in the intravascular imaging group and 8.5% in the angiography group (hazard ratio, 0.63; 95% CI, 0.42 to 0.93). The cumulative incidence of definite stent thrombosis was 0.3% in the overall trial population and was 0.1% in the intravascular imaging-guided group and 0.7% in the angiography group (hazard ratio, 0.25; 95% CI, 0.02 to 2.75). Figure 2 shows the results of the prespecified subgroup analysis. The results of the unadjusted analysis were consistent with those of the primary analysis (Table S4 and Fig. S2). In an exploratory analysis, the cumulative incidence of the primary end point was 6.0% among the patients in the intravascular imaging group who had stent optimization, 8.9% among those in the intravascular imaging group who did not have stent optimization, and 12.3% among the patients in the angiography group (Fig. S3).

DISCUSSION

The RENOVATE-COMPLEX-PCI trial showed that, at a median follow-up of 2.1 years, intravascular imaging–guided PCI for complex coronary-artery lesions was associated with a lower incidence of a composite of death from cardiac causes, target-vessel–related myocardial infarction, or clinically driven target-vessel revascularization than angiography-guided PCI. There were no apparent between-group differences in the incidence of procedure-related safety events.

Previous randomized clinical trials have consistently shown a lower risk of clinical events after intravascular ultrasonography–guided PCI than after angiography-guided PCI.[5-9] However, these trials enrolled too few patients for the evaluation of hard clinical end points, focused on a narrow group of lesion subsets, or were limited to short-term follow-up. Although a few observational studies[17-19] and meta-analyses[20,21] have included large numbers of patients, the criteria that were used to define stent optimization were heterogeneous and the inclusion of patients who had been treated with first-generation drug-eluting stents made it unclear that the results would be applicable to contemporary clinical practice. Two randomized, controlled trials have shown similar clinical outcomes with intravascular ultrasonography–guided PCI and with OCT-guided PCI[22,23]; however, data on long-term clinical outcomes after OCT-guided PCI are limited. The main purpose of our trial was to evaluate whether intravascular imaging–guided PCI would lead to a lower long-term risk of target-vessel failure for complex coronary lesions than angiography-guided PCI.

Table 3. Primary and Secondary End Points According to Competing-Risk Analyses.*

End Point	Total (N=1639)	Intravascular Imaging–Guided PCI Group (N=1092)	Angiography-Guided PCI Group (N=547)	Hazard Ratio (95% CI)
	number (cumulative incidence, %)			
Primary end point: target-vessel failure†	136 (9.2)	76 (7.7)	60 (12.3)	0.64 (0.45–0.89)‡
Secondary end points§				
Target-vessel failure without procedure-related myocardial infarction	88 (6.3)	48 (5.1)	40 (8.7)	0.59 (0.39–0.90)
Target-vessel–related myocardial infarction or death from cardiac causes	96 (6.4)	53 (5.3)	43 (8.5)	0.63 (0.42–0.93)
Death from any cause¶	70 (5.6)	42 (5.3)	28 (6.4)	0.71 (0.44–1.15)
Death from cardiac causes	33 (2.4)	16 (1.7)	17 (3.8)	0.47 (0.24–0.93)
Myocardial infarction‖	75 (5.0)	43 (4.4)	32 (6.2)	0.78 (0.48–1.25)
Target-vessel–related myocardial infarction	68 (4.3)	38 (3.7)	30 (5.6)	0.74 (0.45–1.22)
Spontaneous myocardial infarction	17 (1.2)	8 (0.9)	9 (1.8)	0.66 (0.23–1.90)
Procedure-related myocardial infarction	52 (3.2)	30 (2.7)	22 (4.0)	0.77 (0.43–1.35)
Non–target-vessel–related myocardial infarction	8 (0.8)	5 (0.8)	3 (0.8)	1.24 (0.24–6.40)
Repeat revascularization**	87 (6.6)	55 (6.3)	32 (7.1)	0.95 (0.60–1.48)
Target-vessel revascularization	57 (4.1)	32 (3.4)	25 (5.5)	0.69 (0.40–1.18)
Target-lesion revascularization	44 (3.2)	24 (2.6)	20 (4.4)	0.66 (0.36–1.22)
Definite stent thrombosis††	5 (0.3)	1 (0.1)	4 (0.7)	0.25 (0.02–2.75)
Contrast-induced nephropathy‡‡	40 (2.4)	26 (2.4)	14 (2.6)	0.99 (0.51–1.92)

* For clinical outcomes, including death from cardiac causes, death from noncardiac causes was treated as a competing event. For other outcomes, death from any cause was treated as a competing event. Therefore, the hazard ratios are subhazard ratios from a competing-risk analysis. The database for the analysis was locked on May 10, 2022. Clinical end points were evaluated in the intention-to-treat population during the overall trial period (i.e., from time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or telephone visit, or the day of death during follow-up). Percentages are cumulative incidences at 3 years and therefore may not calculate as expected. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary end points, results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects for secondary end points. All the models were adjusted for clinical presentation and participating center (stratification factors).

† The primary end point of target-vessel failure was a composite of death from cardiac causes, target-vessel myocardial infarction, or clinically driven target-vessel revascularization.

‡ P=0.008.

§ The analysis of the individual secondary end points is in regard to the first occurrence of the event.

¶ The hazard ratio and 95% confidence interval for death from any cause was calculated from a Cox proportional-hazards regression analysis, with stratification according to clinical presentation and participating center (stratification factors).

‖ One patient in the angiography-guided group had both a target-vessel–related myocardial infarction that was procedure-related and a non–target-vessel–related myocardial infarction. Spontaneous myocardial infarction was defined according to the third universal definition of myocardial infarction.[14] Procedure-related myocardial infarction was defined according to the Society for Cardiovascular Angiography and Interventions.[15]

** Repeat revascularization included all first clinically indicated elective, urgent, or emergency revascularization procedures that were not planned during the index hospitalization during the overall trial period.

†† Definite stent thrombosis was defined according to the criteria of the Academic Research Consortium.[16]

‡‡ Contrast-induced nephropathy was defined as an increase in the serum creatinine level of at least 0.5 mg per deciliter or as an increase in the level of at least 25% from baseline within 48 to 72 hours after exposure to the contrast agent. For contrast-induced nephropathy, results are presented as calculated percentages.

Several features of this trial differ from those of previous randomized trials comparing intravascular imaging–guided PCI with angiography-guided PCI. The current trial included several types of complex coronary-artery lesions. The benefit of intravascular imaging–guided PCI as compared with angiography-guided PCI was observed consistently across various complex coro-

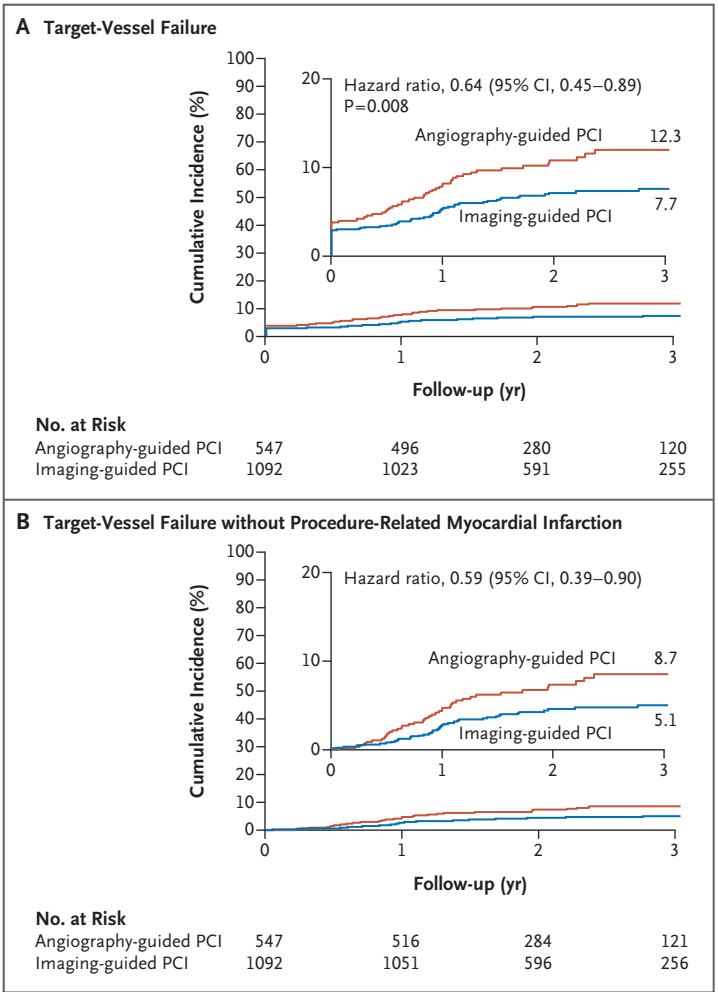

Figure 1. Cumulative Incidences of Trial End Points.

The primary end point was target-vessel failure, which was defined as a composite of death from cardiac causes, target-vessel–related myocardial infarction, or clinically driven target-vessel revascularization in the intention-to-treat population during the overall trial period (i.e., 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 telephone visit, or the day of death during follow-up) (Panel A). The primary end-point analysis included an estimation of the cumulative risk of target-vessel failure and a comparison of the randomized groups with the method of Fine and Gray to adjust for the potential competing risk of death from noncardiac causes. Therefore, the hazard ratios are subhazard ratios from a competing-risk analysis. The secondary end point of target-vessel failure without procedure-related myocardial infarction was compared between the two trial groups (Panel B). In both panels, percentages are cumulative incidences at 3 years and therefore may not calculate as expected. Insets in both panels show the same data on enlarged y axes. PCI denotes percutaneous coronary intervention.

nary-artery lesions. Although the ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial evaluated intravascular ultrasonography–guided PCI in an all-comers population with minimal exclusion criteria,[8] the current trial exclusively enrolled patients with complex coronary-artery lesions. Our trial adopted the most contemporary criteria for stent optimization with the use of intravascular ultrasonography or OCT guidance,[4] which was prespecified at the beginning of the trial, and the choice between intravascular ultrasonography or OCT was left to the operator's discretion. Although in previous trials the benefit of intravascular imaging–guided PCI was mostly due to a lower risk of repeat revascularization in the stented segment rather than to death from cardiac causes or myocardial infarction,[5-7,24] the use of intravascular imaging–guided PCI in our trial appeared to be associated with a 37% lower incidence of target-vessel–related myocardial infarction or death from cardiac causes than angiography-guided PCI. This difference may be attributable to the larger sample size and longer duration of follow-up in our trial than in previous trials and to the fact that this trial exclusively enrolled patients with complex coronary-artery lesions. Our trial supports the use of intravascular imaging–guided PCI for complex coronary-artery lesions.

Our trial has limitations. First, the trial was unblinded, and it was not possible for the operator to be unaware of the patient's assigned trial group. However, we minimized the risk of bias by using an end-point analysis with precisely defined criteria, by having angiographic and imaging analyses performed at the core laboratories, and by having clinical events adjudicated by a committee whose members were unaware of the trial-group assignments. Second, intravascular imaging–defined stent optimization occurred in only 45.4% of the patients. One possible explanation may be that we focused our trial only on complex coronary-artery lesions. Third, given that the patients in the angiography group did not undergo intravascular imaging, we could assess stent optimization in this group only by means of quantitative coronary angiography. In addition, the proportion of target lesions that were evaluated by intravascular imaging before intervention was small because the trial protocol mandated intravascular imaging only after stent deployment. Fourth, more than half the trial population was enrolled at a single center, and the trial included only East Asian patients, which might limit the generalizability of the trial re-

Subgroup	Intravascular Imaging–Guided PCI	Angiography-Guided PCI	Hazard Ratio (95% CI)
	no. of events/total no. of patients (cumulative incidence, %)		
Overall	76/1092 (7.7)	60/547 (12.3)	0.64 (0.45–0.89)
Type of imaging devices			
Intravascular ultrasonography	59/800 (8.0)	60/547 (12.3)	0.66 (0.46–0.95)
Optical coherence tomography	15/278 (5.8)	60/547 (12.3)	0.47 (0.27–0.83)
Type of complex coronary lesions			
True bifurcation	23/233 (10.3)	13/126 (11.8)	0.97 (0.49–1.93)
Chronic total occlusion	9/220 (5.0)	13/99 (14)	0.30 (0.13–0.71)
Unprotected left main coronary artery disease	9/138 (6.8)	11/54 (25)	0.31 (0.13–0.76)
Diffuse long coronary-artery lesion	36/617 (6.5)	31/281 (11.9)	0.52 (0.32–0.83)
Multivessel PCI involving ≥2 major coronary arteries	36/409 (9.5)	22/213 (11.7)	0.84 (0.50–1.44)
Lesion necessitating use of ≥3 stents	16/208 (8.1)	6/97 (6)	1.24 (0.49–3.18)
Lesion with in-stent restenosis	22/158 (15.6)	12/78 (17)	0.90 (0.45–1.82)
Severely calcified lesion	11/157 (7.3)	11/74 (17)	0.46 (0.20–1.06)
Ostial lesions of major coronary artery	8/182 (4.4)	9/69 (16)	0.33 (0.13–0.85)
Initial presentation			
Stable ischemic heart disease	25/532 (5.0)	27/275 (10.4)	0.46 (0.27–0.80)
Acute coronary syndrome	51/560 (10.4)	33/272 (14.6)	0.74 (0.48–1.15)
Age			
<65 yr	36/517 (7.8)	23/238 (10.6)	0.72 (0.42–1.21)
≥65 yr	40/575 (7.4)	37/309 (13.6)	0.57 (0.36–0.88)
Sex			
Male	66/869 (8.3)	46/431 (11.7)	0.70 (0.48–1.02)
Female	10/223 (5.2)	14/116 (14.5)	0.35 (0.16–0.80)
Diabetes mellitus			
Yes	45/394 (12.9)	26/223 (12.3)	0.97 (0.60–1.57)
No	31/698 (4.7)	34/324 (12.2)	0.41 (0.25–0.67)
Chronic kidney disease			
Yes	22/203 (13.3)	19/93 (23)	0.51 (0.27–0.93)
No	54/889 (6.4)	41/454 (9.9)	0.66 (0.44–0.99)
Left ventricular ejection fraction			
<50%	22/210 (12.0)	12/84 (15)	0.72 (0.35–1.45)
≥50%	54/882 (6.7)	48/463 (11.8)	0.58 (0.39–0.85)

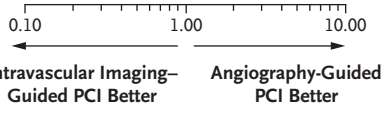

Figure 2. Prespecified Subgroup Analysis of the Primary End Point.

The hazard ratio for the primary end point (composite of death from cardiac causes, target-vessel–related myocardial infarction, or clinically driven target-vessel revascularization) was calculated in the subgroups defined according to the choice of intravascular imaging device (intravascular ultrasonography or optical coherence tomography [OCT]), type of complex coronary lesion, initial presentation (stable ischemic heart disease or acute coronary syndrome), age (<65 years or ≥65 years), sex, presence or absence of diabetes mellitus, presence or absence of chronic kidney disease, and left ventricular ejection fraction (<50% or ≥50%). In the subgroup analysis according to the type of imaging device, the reference group of patients in the angiography group who had a primary end-point event was used. Percentages are cumulative incidences at 3 years and therefore may not calculate as expected. The hazard ratio for the primary end point in the overall population was derived from a competing-risk analysis. Other analyses in the prespecified subgroup analysis were derived from a Cox proportional-hazards regression model. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary end points, results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects for secondary end points.

sults (Table S5). Finally, since intravascular imaging adds cost to the PCI procedure, as compared with the use of angiography alone, cost-effectiveness analyses are necessary to inform clinical decision making.

In this trial involving patients with complex

coronary-artery lesions, intravascular imaging–guided PCI was associated with a lower cumulative incidence of a composite of death from cardiac causes, target-vessel–related myocardial infarction, or clinically driven target-vessel revascularization than angiography-guided PCI.

Supported by grants from Abbott Vascular and Boston Scientific.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Joo Myung Lee, M.D., Ph.D., M.P.H., Ki Hong Choi, M.D., Ph.D., Young Bin Song, M.D., Ph.D., Jong-Young Lee, M.D., Ph.D., Seung-Jae Lee, M.D., Ph.D., Sang Yeub Lee, M.D., Ph.D., Sang Min Kim, M.D., Ph.D., Kyeong Ho Yun, M.D., Ph.D., Jae Young Cho, M.D., Ph.D., Chan Joon Kim, M.D., Ph.D., Hyo-Suk Ahn, M.D., Ph.D., Chang-Wook Nam, M.D., Ph.D., Hyuck-Jun Yoon, M.D., Ph.D., Yong Hwan Park, M.D., Ph.D., Wang Soo Lee, M.D., Ph.D., Jin-Ok Jeong, M.D., Ph.D., Pil Sang Song, M.D., Ph.D., Joon-Hyung Doh, M.D., Ph.D., Sang-Ho Jo, M.D., Ph.D., Chang-Hwan Yoon, M.D., Ph.D., Min Gyu Kang, M.D., Ph.D., Jin-Sin Koh, M.D., Ph.D., Kwan Yong Lee, M.D., Ph.D., Young-Hyo Lim, M.D., Ph.D., Yun-Hyeong Cho, M.D., Ph.D., Jin-Man Cho, M.D., Ph.D., Woo Jin Jang, M.D., Ph.D., Kook-Jin Chun, M.D., Ph.D., David Hong, M.D., Taek Kyu Park, M.D., Ph.D., Jeong Hoon Yang, M.D., Ph.D., Seung-Hyuk Choi, M.D., Ph.D., Hyeon-Cheol Gwon, M.D., Ph.D., and Joo-Yong Hahn, M.D., Ph.D.

The authors' affiliations are as follows: Samsung Medical Center (J.M.L., K.H.C., Y.B.S., D.H., T.K.P., J.H.Y., S.-H.C., H.-C.G., J.-Y.H.) and Kangbuk Samsung Hospital (J.-Y.L., S.-J.L.), Sungkyunkwan University School of Medicine, the Catholic University of Korea, Uijeongbu St. Mary's Hospital (C.J.K., H.-S.A.), Chung-Ang University College of Medicine, Chung-Ang University Hospital (W.S.L.), the Catholic University of Korea, Incheon St. Mary's Hospital (K.Y.L.), Hanyang University Seoul Hospital, College of Medicine, Hanyang University (Y.-H.L.), Kyung Hee University Hospital at Gangdong (J.-M.C.), and Ewha Womans University College of Medicine (W.J.J.), Seoul, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju (S.Y.L., S.M.K.), Chung-Ang University College of Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong (S.Y.L.), Wonkwang University Hospital, Iksan (K.H.Y., J.Y.C.), Keimyung University Dongsan Hospital, Daegu (C.-W.N., H.-J.Y.), Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon (Y.H.P.), Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon (J.-O.J., P.S.S.), Inje University Ilsan-Paik hospital, Goyang (J.-H.D.), the Cardiovascular Center, Hallym University Sacred Heart Hospital, Anyang (S.-H.J.), Seoul National University Bundang Hospital, Seongnam-si (C.-H.Y.), Gyeongsang National University School of Medicine, Gyeongsang National University Hospital, Jinju (M.G.K., J.-S.K.), Hanyang University Myongji Hospital, Goyang (Y.-H.C.), and Pusan National University Yangsan Hospital, Yangsan (K.-J.C.) — all in South Korea.

REFERENCES

1. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873-91.
2. Baber U, Kini AS, Sharma SK. Stenting of complex lesions: an overview. Nat Rev Cardiol 2010;7:485-96.
3. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. J Am Coll Cardiol 2016;68:1851-64.
4. Räber L, Mintz GS, Koskinas KC, et al. Clinical use of intracoronary imaging. 1. Guidance and optimization of coronary interventions: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. Eur Heart J 2018;39:3281-300.
5. Hong S-J, Kim B-K, Shin D-H, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. JAMA 2015;314:2155-63.
6. Chieffo A, Latib A, Caussin C, et al. A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial. Am Heart J 2013;165:65-72.
7. Jakabcin J, Spacek R, Bystron M, et al. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance: randomized control trial: HOME DES IVUS. Catheter Cardiovasc Interv 2010;75:578-83.
8. Gao X-F, Ge Z, Kong X-Q, et al. 3-Year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. JACC Cardiovasc Interv 2021;14:247-57.
9. Kim B-K, Shin D-H, Hong M-K, 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(7):e002592.
10. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145(3):e18-e114.
11. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
12. Medina A, Suárez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. Rev Esp Cardiol 2006;59:183. (In Spanish.)
13. He P, Eriksson F, Scheike TH, Zhang M-J. A proportional hazards regression model for the sub-distribution with covariates adjusted censoring weight for competing risks data. Scand Stat Theory Appl 2016;43:103-22.
14. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
15. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013;62:1563-70.
16. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. Circulation 2018;137:2635-50.
17. Witzenbichler B, Maehara A, Weisz G, et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. Circulation 2014;129:463-70.
18. Kinnaird T, Johnson T, Anderson R, et al. Intravascular imaging and 12-month mortality after unprotected left main stem PCI: an analysis from the British Cardiovascular Intervention Society Database. JACC Cardiovasc Interv 2020;13:346-57.
19. Choi KH, Song YB, Lee JM, et al. Impact of intravascular ultrasound-guided percutaneous coronary intervention on

long-term clinical outcomes in patients undergoing complex procedures. JACC Cardiovasc Interv 2019;12:607-20.
20. Buccheri S, Franchina G, Romano S, et al. Clinical outcomes following intravascular imaging-guided versus coronary angiography-guided percutaneous coronary intervention with stent implantation: a systematic review and Bayesian Network meta-analysis of 31 studies and 17,882 patients. JACC Cardiovasc Interv 2017;10:2488-98.
21. Darmoch F, Alraies MC, Al-Khadra Y, Moussa Pacha H, Pinto DS, Osborn EA. Intravascular ultrasound imaging-guided versus coronary angiography-guided percutaneous coronary intervention: a systematic review and meta-Analysis. J Am Heart Assoc 2020;9(5):e013678.
22. Ali ZA, Maehara A, Généreux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. Lancet 2016;388:2618-28.
23. Kubo T, Shinke T, Okamura T, et al. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): one-year angiographic and clinical results. Eur Heart J 2017;38:3139-47.
24. Kim J-S, Kang T-S, Mintz GS, et al. Randomized comparison of clinical outcomes between intravascular ultrasound and angiography-guided drug-eluting stent implantation for long coronary artery stenoses. JACC Cardiovasc Interv 2013;6:369-76.