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ORIGINAL ARTICLE

Clinical Benefit of Intravascular Imaging Compared With Conventional Angiography in Left Main Coronary Artery Intervention

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BACKGROUND: The RENOVATE-COMPLEX-PCI (Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention) demonstrated that intravascular imaging–guided percutaneous coronary intervention (PCI) improved clinical outcome compared with angiography-guided PCI for patients with complex coronary artery lesions. This study aims to assess whether the prognostic benefit of intravascular imaging–guided procedural optimization persists in patients undergoing PCI for left main coronary artery disease.

METHODS: Of 1639 patients enrolled in the RENOVATE-COMPLEX-PCI, 192 patients with left main coronary artery disease were selected for the current prespecified substudy. Selected patients were randomly assigned to either the intravascular imaging–guided PCI group (n=138) or the angiography-guided PCI group (n=54). The primary end point was target vessel failure defined as a composite of cardiac death, target vessel–related myocardial infarction, or clinically driven target vessel revascularization.

RESULTS: At a median follow-up of 2.1 years (interquartile range 1.1 to 3.0 years), intravascular imaging–guided PCI was associated with lower incidence of primary end point compared with angiography-guided PCI (6.8% versus 25.1%; hazard ratio, 0.31 [95% CI, 0.13–0.76]; *P*=0.010). This significant reduction in primary end point was mainly driven by a lower risk of cardiac death or spontaneous target vessel–related myocardial infarction (1.6% versus 12.7%; hazard ratio, 0.16 [95% CI, 0.03–0.82]; *P*=0.028). Intravascular imaging–guided PCI was independently associated with a lower risk of primary end point, even after adjusting for various clinical factors (hazard ratio, 0.29 [95% CI, 0.12–0.72]; *P*=0.007).

CONCLUSIONS: Intravascular imaging–guided PCI showed clinical benefit over angiography-guided PCI for left main coronary artery disease in reducing the risk of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization.

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Key Words: angiography ■ coronary artery ■ patients ■ percutaneous coronary intervention ■ prognosis

See Editorial by Mukherjee

WHAT IS KNOWN

- Previous studies have shown that the use of intravascular imaging can lead to improved outcomes in percutaneous coronary intervention (PCI) for patients with unprotected left main coronary artery disease.
- However, there have been limited randomized controlled trials and previous studies shared limitations such as small sample size, short follow-up duration, exclusive use of intravascular ultrasound only, or exclusion of acute coronary syndrome.

WHAT THE STUDY ADDS

- The current prespecified substudy of the RENOVATE-COMPLEX-PCI trial (Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention) evaluated prognostic benefit of intravascular imaging—both intravascular ultrasound and optical coherence tomography—on unprotected left main coronary artery disease presenting either as stable ischemic heart disease or acute coronary syndrome.
- Intravascular imaging–guided PCI for left main coronary artery disease showed significantly lower risk of a composite of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization than the angiography-guided PCI group.
- These results imply that benefits of intravascular imaging are sustained in left main coronary artery PCI. Further study is warranted to confirm the current results.

Nonstandard Abbreviations and Acronyms

HR	hazard ratio
IVUS	intravascular ultrasound
LMCA	left main coronary artery
OCT	optical coherence tomography
PCI	percutaneous coronary intervention

Unprotected left main coronary artery (LMCA) disease, observed in 5% to 7% of patients undergoing coronary angiography, is a condition known for its higher mortality and morbidity.[1] Traditionally, coronary artery bypass grafting has been a treatment of choice for LMCA disease; however, not all patients are suitable candidates for bypass surgery because of underlying comorbidities, advanced age, or patient refusal to thoracotomy. In the current era, percutaneous coronary intervention (PCI) has been a feasible alternative to coronary bypass surgery for treatment of LMCA disease.[2,3] Although PCI for LMCA disease is still associated with a higher incidence of major adverse cardiac events compared with surgery, several studies have shown comparable mortality between the 2 treatments.[4] This might be partially due to development and widespread use of intravascular imaging, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), which have proven to improve clinical outcomes in various scenarios of PCI.[5]

Several observational studies and meta-analyses have consistently reported that the use of these intravascular imaging techniques is associated with improved clinical outcomes after PCI for LMCA disease.[6,7] However, it is important to note that only 2 randomized controlled trials have evaluated the efficacy of intravascular imaging in LMCA disease.[8,9] Although both trial results observed a lower incidence of major adverse cardiac events after LMCA PCI in the IVUS-guided group than in the angiography-guided group, these trials have not been considered definitive due to limitations such as small sample size, exclusive use of IVUS without considering other imaging modalities, or exclusion of patients with acute coronary syndrome.[8,9]

Recently published RENOVATE-COMPLEX-PCI (Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention) has shown that intravascular imaging–guided PCI for complex coronary artery lesions was superior to angiography-guided PCI in reducing the risk of a composite of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization.[10] Thus, we performed a prespecified substudy investigating whether

the benefit of intravascular imaging would be maintained for patients with LMCA disease who were included in the RENOVATE-COMPLEX-PCI.

METHODS

Anonymized patient level data will be made available after discussion with the Executive Committee members of the trial for reasonable requests. Consent was not obtained for data sharing but the presented data are anonymized and risk of identification is minimal.

Trial Design and Patient Selection

The RENOVATE-COMPLEX-PCI was an investigator-initiated, randomized, open-label, multicenter, superiority trial conducted in 20 sites in Korea. The design and primary results have been described previously.[10] In brief, patients 19 years of age or older undergoing PCI for complex coronary artery lesions were enrolled. Complex coronary artery lesions were defined as having true bifurcation lesion with side branch ≥2.5 mm size, chronic total occlusion, unprotected left main disease, long coronary lesions, multivessel PCI, multiple stents needed, in-stent restenosis, severely calcified lesions, or coronary ostial lesions. Key exclusion criteria were coronary lesions not amenable for PCI by operator discretion, cardiogenic shock at presentation, and known hypersensitivity or contraindication to aspirin, clopidogrel, prasugrel, ticagrelor, heparin, everolimus, or contrast media. The trial protocol was approved by the institutional review board at each participating site and published previously.[10] All participating centers, trial personnel, and detailed inclusion and exclusion criteria of this trial are listed in the Supplemental Appendix.

For the current prespecified substudy, patients with unprotected LMCA lesions were exclusively selected among the 1639 patients enrolled in the trial. As a result, the current study evaluated 192 patients undergoing intravascular imaging–guided (n=138) and angiography-guided PCI (n=54; Figure 1).

Randomization and Treatment

After diagnostic coronary angiography, eligible patients were randomly assigned in a 2:1 ratio to receive intravascular imaging–guided PCI or angiography-guided PCI in permuted blocks, with block sizes of 6 and stratified by clinical presentation (stable ischemic heart disease or acute coronary syndrome) and participating centers using a web-based randomization program (S-Soft, Seoul, Korea).

PCI was performed using standard techniques. The drug-eluting stents used were either biodegradable polymer-coated everolimus-eluting stents (Synergy stent system, Boston Scientific Corporation, San Jose, CA) or biocompatible polymer-coated everolimus-eluting stents (Xience stent system family, Abbott Vascular, St. Paul, MN). In patients assigned to intravascular imaging–guided PCI, the choice of intravascular imaging device (between IVUS and OCT) was left to the operator's discretion. Although use of intravascular imaging devices was allowed at any step of PCI (pre-PCI, during PCI, and post-PCI), intravascular imaging evaluation after PCI was mandated for optimization of the stented segment. Standard protocols for image acquisition were applied during trial enrollment using commercially available IVUS (Opticross, Boston Scientific Corporation, San Jose, CA) or OCT (Dragonfly, Abbott Vascular, St. Paul, MN) systems. Detailed protocols for image acquisition, optimization of stented segment, and medical treatment after PCI are described in the Supplemental Appendix.

In brief, criteria of stent expansion were residual angiographic diameter stenosis <10% and minimum stent area >80% of the average reference lumen area or absolute minimal stent area >7 mm^2 for distal left main and >8 mm^2 for proximal left main stenosis.[11] Major stent malapposition was defined as an acute malapposition with the distance between vessel wall and stent of ≥0.4 mm with longitudinal length of >1 mm. Major edge dissection was defined as dissection occurring within 5 mm from the edge of the stent, extending to media layer with dissection angle of ≥60° of the circumference of the vessel and ≥3 mm in length of dissection flap. If one of the above findings were noted in the intravascular imaging devices, additional procedures including adjunctive post-dilatation or additional stent implantation were mandatorily recommended to optimize the final PCI results. In patients assigned to angiography-guided PCI, stent optimization was done based on angiographic findings—optimization for the stented segment needed to meet the criteria of angiographic residual diameter stenosis <10% by visual estimation and absence of flow-limiting dissection (type C through F dissection).

After the index 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 for those with acute coronary syndrome, regardless of allocated groups. However, the loading, maintenance dose, and duration of dual antiplatelet therapy were left to physician's discretion. Regardless of treatment arm allocation, guideline-directed medical treatment was performed according to the current clinical guidelines.[2,3] All angiograms and intravascular imaging data were analyzed in the independent core laboratories (Supplemental Appendix).

End Points and Definitions

The primary end point was target vessel failure, defined as a composite of cardiac death, target vessel–related myocardial infarction, or clinically driven target vessel revascularization. Secondary end points included individual components of the primary end point, target vessel failure without procedure-related myocardial infarction, a composite of cardiac death or target vessel–related myocardial infarction, definite stent thrombosis, total procedural time, total amount of contrast agent used during the index hospitalization, and incidence of contrast-induced nephropathy. The definition of myocardial infarction used in this trial was based on the third universal definition for spontaneous myocardial infarction,[12] and the Society for Cardiovascular Angiography and Interventions definition for procedure-related myocardial infarction.[13] Detailed definitions of each clinical event are described in the Supplemental Appendix.

Clinical follow-up was conducted during outpatient clinic visits scheduled at 1, 6, and 12 months, and yearly thereafter. Patients unable to attend outpatient clinical visits were contacted by telephone. Cross-validation of survival status was performed using the Korean National Health Insurance database.

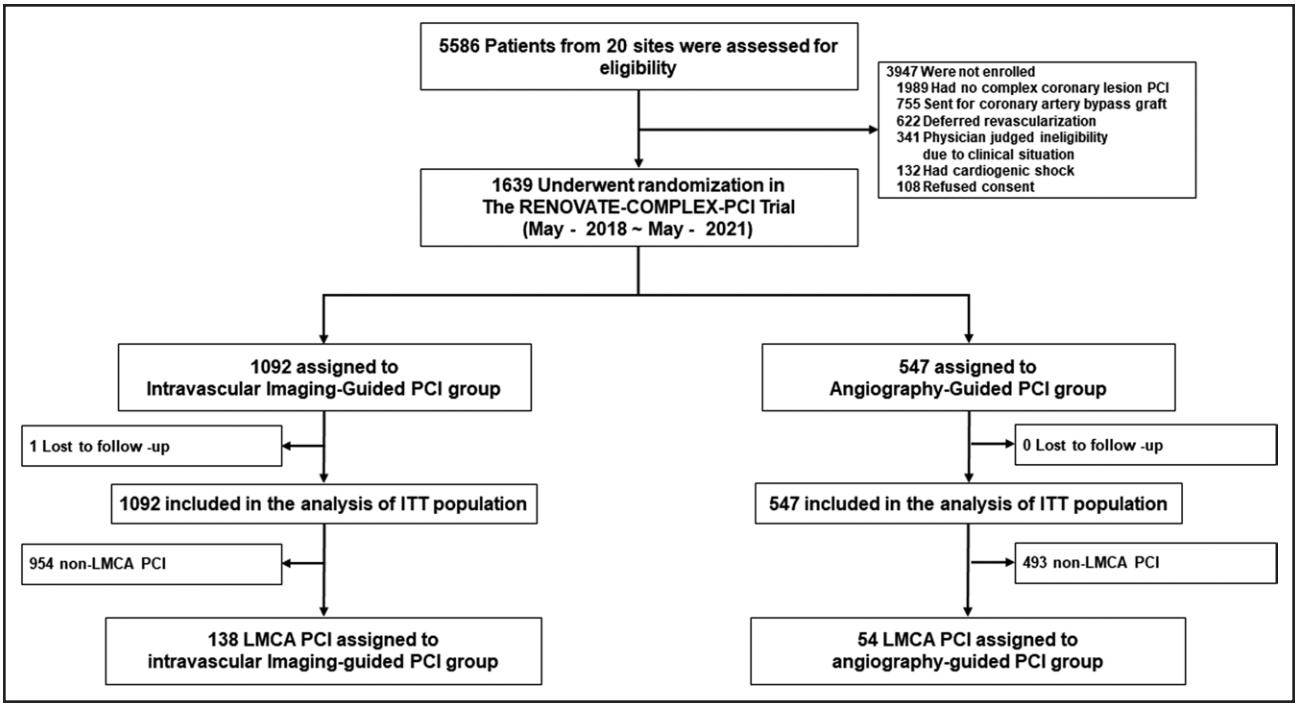

Figure 1. Study flow.
Among 1639 patients originally enrolled in the RENOVATE-COMPLEX-PCI (Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention), 192 patients were selected, with 138 patients undergoing intravascular imaging–guided percutaneous coronary intervention (PCI) and 54 patients undergoing angiography-guided PCI. ITT indicates intention to treat; and LMCA, left main coronary artery.

Statistical Analysis

The full statistical analysis plan including sample size calculation in the RENOVATE-COMPLEX-PCI has been published previously.[10] All analyses were performed on an intention-to-treat basis. Categorical variables are reported as the number and relative frequency (%) and were compared using the χ^2 test and Fisher exact test. Continuous variables are reported as the mean±SD and were compared using Student *t* test or Mann-Whitney *U* test. Kaplan-Meier analyses were performed for time-to-event outcomes with treatment effects estimated by Cox proportional hazard regression models, and results were presented as hazard ratios (HR) with 95% CIs. The proportional hazards assumption was evaluated with a 2-sided score test of the scaled Schoenfeld residuals over time at the 0.05 level. No imputation methods were used to infer missing values of baseline variables.

To provide up-to-date evidence regarding the efficacy and safety of intravascular imaging–guided PCI in LMCA disease, previous observational studies or randomized clinical trials were searched and summarized using study-level meta-analysis. PubMed, EMBASE, Cochrane Central Register of Controlled Trials, the US National Institutes of Health registry of clinical trials, and relevant websites were searched for pertinent published or unpublished studies using a search strategy included "intravascular imaging," "intravascular ultrasound," "optical coherence tomography," "left main coronary artery stenosis," or "percutaneous coronary intervention." The electronic search strategy was complemented by manual examination of references cited by included articles, recent reviews, editorials, and meta-analyses. No restrictions were imposed on language, study period, or sample size. All nonrandomized observational studies or randomized controlled trials up to March 2023, comparing all-cause death or cardiac death between intravascular imaging–guided PCI and angiography-guided PCI were evaluated for inclusion. Mixed-effects models were used to compare 2 groups and relative risk with 95% CI were presented as summary statistics. The pooled relative risk and 95% CI were calculated using the restricted maximum likelihood method for mixed effects. Statistical heterogeneity was quantified using the I^2 statistics.

All probability values were 2-sided, and $P<0.05$ were considered statistically significant. Statistical analyses were performed using STATA/SE 12.0 (Stata Corp LP, College Station, TX) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

Among 1639 patients originally enrolled in the RENOVATE-COMPLEX-PCI, 192 patients were selected, with 138 patients undergoing intravascular imaging–guided PCI and 54 patients undergoing angiography-guided PCI. In the intravascular imaging–guided PCI group, IVUS was used in 92.8% (128 patients) and OCT was used in 7.2% (10 patients). Three patients assigned to the intravascular imaging–guided PCI groups underwent PCI without guidance of intravascular imaging. However, 2 patients in the angiography-guided PCI group

underwent PCI guided by IVUS. Although the protocol mandated post-PCI imaging in the intravascular imaging group, 4 cases used the intravascular imaging only at pre-PCI phase due to various reasons. Baseline characteristics between the 2 groups were similar (Table 1). Overall, most patients were male (162 patients, 84.4%) and 66.5±10.0 years old. Acute coronary syndrome was present in 105 patients (54.7%) and stable ischemic heart disease in 87 patients (45.3%). When compared with the patients who underwent non-LMCA PCI, those with LMCA PCI showed no significant differences in baseline characteristics (Table S1).

Procedural Characteristics

Angiographic characteristics and lesion complexity between the 2 groups were well balanced (Table 2). About half of the patients had distal left main true bifurcation lesion and 42.2% of patients underwent multivessel PCI. Transradial approach was more commonly used than transfemoral approach. Intravascular imaging–guided PCI had significantly longer procedure time than angiography-guided PCI, but the number of devices used, and final mean diameters were similar between the 2 groups. Although the use of adjunctive balloon dilatation was similar between the 2 groups, the intravascular imaging–guided PCI group used significantly larger size of noncompliant balloon with similar maximum inflation pressure with the angiography-guided PCI group. Quantitative coronary angiography findings are also comparable between the 2 groups. Among patients in the intravascular imaging–guided PCI group, prespecified stent optimization was achieved in 83 patients (60.1%). Compared with those who underwent non-LMCA PCI, those of LMCA PCI group had more complex coronary lesions, and transradial approach was less frequently

Table 1. Baseline Demographic Characteristics*

Characteristics	Total (N=192)	Imaging-guided PCI (N=138)	Angio-guided PCI (N=54)	*P* value
Age, y	66.5±10.0	66.7±10.1	65.9±10.0	0.595
Male, n (%)	162 (84.4%)	116 (84.1%)	46 (85.2%)	0.999
Initial presentation, n (%)				
Stable ischemic heart disease	87 (45.3%)	57 (41.3%)	30 (55.6%)	0.348
Acute coronary syndrome	105 (54.7%)	81 (58.7%)	24 (44.4%)	0.348
Unstable angina	75 (39.1%)	59 (42.8%)	16 (29.6%)	0.348
Acute myocardial infarction	30 (15.6%)	22 (15.9%)	8 (14.8%)	0.348
Medical history, n (%)				
Hypertension	123 (64.1%)	90 (65.2%)	33 (61.1%)	0.714
Diabetes	69 (35.9%)	50 (36.2%)	19 (35.2%)	0.999
Dyslipidemia	91 (47.4%)	68 (49.3%)	23 (42.6%)	0.501
Current smoking	31 (16.1%)	21 (15.2%)	10 (18.5%)	0.733
Family history of coronary artery disease	9 (4.7%)	5 (3.6%)	4 (7.4%)	0.462
Chronic renal insufficiency	38 (19.8%)	25 (18.1%)	13 (24.1%)	0.465
Previous PCI	35 (18.2%)	26 (18.8%)	9 (16.7%)	0.886
Previous myocardial infarction	11 (5.7%)	6 (4.3%)	5 (9.3%)	0.331
Previous stroke	16 (8.3%)	10 (7.2%)	6 (11.1%)	0.561
Peripheral vascular disease	7 (3.6%)	4 (2.9%)	3 (5.6%)	0.649
LV ejection fraction, %	58.7±11.6	58.4±11.9	59.3±11.0	0.240
Discharge medication, n (%)				
Aspirin	189 (98.4%)	136 (98.6%)	53 (98.1%)	0.999
P2Y12 inhibitor				
Clopidogrel	144 (75.0%)	98 (71.0%)	46 (85.2%)	0.064
Ticagrelor	29 (15.1%)	22 (15.9%)	7 (13.0%)	0.769
Prasugrel	17 (8.9%)	16 (11.6%)	1 (5.9%)	0.064
Oral anticoagulant	10 (5.2%)	7 (5.1%)	3 (5.6%)	0.892
Statin	185 (96.4%)	133 (96.4%)	52 (96.3%)	0.979
Beta-blocker	87 (45.3%)	65 (47.1%)	22 (40.7%)	0.526
ACE inhibitor or ARB	110 (57.3%)	75 (54.3%)	35 (64.8%)	0.248

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LV, left ventricle; and PCI, percutaneous coronary intervention.
*Data presented as mean±SD or as n (%).

Table 2. Baseline Angiographic and Procedural Characteristics*

Characteristics	Total (N=192)	Imaging-guided PCI (N=138)	Angio-guided PCI (N=54)	*P* value
Angiographic characteristics				
Lesion location in left main coronary artery				
Ostium	19 (9.9%)	14 (10.1%)	5 (9.3%)	0.372
Body	78 (40.6%)	59 (42.8%)	19 (35.1%)	0.372
Distal with true bifurcation (medina 1,1,1/1,0,1/1,1,0)	95 (49.5%)	65 (47.1%)	30 (55.6%)	0.372
Medina classification†				
Medina 1,1,1	54 (56.8%)	36 (55.4%)	18 (60.0%)	0.604
Medina 1,0,1	6 (6.3%)	5 (7.7%)	1 (3.3%)	0.604
Medina 1,1,0	35 (36.8%)	24 (36.9%)	11 (36.7%)	0.604
No. of complex lesions ≥ 3, n (%)	122 (63.5%)	86 (62.3%)	36 (66.7%)	0.692
Arteries with stenosis, n (%)				
1 vessel disease	48 (25.0%)	37 (26.8%)	11 (20.4%)	0.579
2 vessel disease	76 (39.5%)	52 (37.7%)	24 (44.4%)	0.579
3 vessel disease	68 (35.4%)	49 (35.5%)	19 (35.2%)	0.579
Severely calcified lesion (encircling calcium on angiography)	28 (14.6%)	18 (13.0%)	10 (18.5%)	0.460
Quantitative coronary angiography				
Pre-PCI				
Proximal reference vessel diameter, mm	3.5±0.5	3.5±0.6	3.4±0.5	0.648
Distal reference vessel diameter, mm	2.9±0.5	2.9±0.5	3.0±0.5	0.290
Minimum lumen diameter, mm	0.5±0.4	0.5±0.4	0.5±0.4	0.300
Diameter stenosis, %	83.6±11.6	82.9±11.6	85.2±11.4	0.220
Lesion length, mm	24.2±15.2	25.0±15.2	22.1±15.1	0.227
Post-PCI				
Minimum lumen diameter, mm	3.0±0.5	3.0±0.6	3.0±0.5	0.227
Diameter stenosis, %	9.9±7.9	10.1±8.3	9.6±6.6	0.756
Post-PCI residual stenosis<10%	129 (68.3%)	94 (69.1%)	35 (66.0%)	0.814
Procedural characteristics				
Radial access, n (%)	128 (66.7%)	95 (68.8%)	33 (61.1%)	0.395
Intravascular imaging devices used, n (%)				
Intravascular ultrasound	128 (66.7%)	126 (91.3%)	2 (3.7%)	<0.001
Optical coherence tomography	9 (4.7%)	9 (6.5%)	0 (0.0%)	<0.001
Not done	55 (28.6%)	3 (2.2%)	52 (96.3%)	<0.001
Profile of intravascular imaging use, n (%)				
Pre-PCI evaluation only	4 (2.1%)	4 (2.9%)	0 (0.0%)	<0.001
Post-PCI evaluation only	74 (38.5%)	74 (53.6%)	0 (0.0%)	<0.001
Both pre-PCI and post-PCI evaluation	59 (30.7%)	57 (41.3%)	2 (3.7%)	<0.001
Dimensions of stents, mm				
Mean diameter	3.3±0.4	3.3±0.4	3.3±0.4	0.381
Total length	36.6±21.3	37.8±22.5	33.6±17.8	0.229
Multivessel PCI (≥2 major coronary arteries treated)	81 (42.2%)	57 (41.3%)	24 (44.4%)	0.815
Multiple stents implanted (≥3 stents per patient)	40 (20.8%)	29 (21.0%)	11 (20.4%)	0.999
Stenting strategy				
Simple crossover	147 (76.6%)	107 (77.5%)	40 (74.1%)	0.630
Crossover with final kissing balloon	20 (10.4%)	15 (10.9%)	5 (9.3%)	0.630
Upfront 2-stent implantation‡	25 (13.0%)	16 (11.6%)	9 (16.7%)	0.630
Culotte	6 (24.0%)	4 (25.0%)	2 (22.2%)	
Crush	11 (44.0%)	8 (50.0%)	3 (33.3%)	
T-and-protrusion	8 (32.0%)	4 (25.0%)	4 (44.4%)	

(*Continued*)

Table 2. Continued

Characteristics	Total (N=192)	Imaging-guided PCI (N=138)	Angio-guided PCI (N=54)	*P* value
Adjunctive noncompliant balloon used, n (%)	136 (70.8%)	99 (71.7%)	37 (68.5%)	0.791
Maximum size of adjunctive noncompliant balloon, mm	4.0±0.7	4.0±0.7	3.8±0.6	0.046
Maximum inflation pressure, atm	19.0±4.1	19.4±4.0	18.2±4.1	0.103
Total no. of devices used per patient	2.1±1.3	2.1±1.4	2.1±1.1	0.657
Volume of contrast media used, ml	197.2±99.0	196.5±97.6	198.9±103.4	0.883
Procedural time, min	71.0 (50.0–95.0)	77.0 (51.0–100.0)	60.0 (46.5–75.0)	0.003
Procedural success, n (%)	190 (99.0%)	136 (98.6%)	54 (100.0%)	0.921

PCI indicates percutaneous coronary intervention.
*Data presented as mean±SD, median (Q1–Q3), or as n (%).
†The number is calculated as a proportion to the number of distal lesions with true bifurcations.
‡The number is calculated as a proportion to the number of cases with upfront 2-stent techniques.

used. Larger lumen diameter both in pre- and post-PCI was observed by quantitative coronary angiography, with shorter lesion length. Finally, larger stents and adjunctive balloons were used in the LMCA PCI group. Procedural time, proportion of multivessel PCI, and procedural success were not significantly different (Table S2).

End Points

At a median follow-up of 2.1 years (interquartile range, 1.1–3.0 years), patients with LMCA PCI showed higher all-cause death than those with non-LM PCI; however, other primary and secondary end points were comparable between the 2 groups (Table S3). Among patients with LMCA PCI, the primary end point occurred in 9 of 138 patients in the intravascular imaging–guided group and 11 of 54 patients in the angiography-guided group (Kaplan-Meier event rates at 3 years, 6.8% versus 25.1%; hazard ratio, 0.31 [95% CI, 0.13–0.76]; *P*=0.010; Table 3; Figure 2). The risk of target vessel failure excluding procedure-related myocardial infarction was also significantly lower in the intravascular imaging–guided group than in the angiography-guided PCI group (4.0% versus 21.5%; hazard ratio, 0.21 [95% CI, 0.07–0.64]; *P*=0.006; Figure 2).

Individual components of the primary and secondary end points are presented in Table 3. The significantly lower risk of clinical events in the intravascular imaging–guided group was mainly driven by lower incidence of cardiac death or spontaneous target vessel–related myocardial infarction (1.6% versus 12.7%; hazard ratio, 0.16 [95% CI, 0.03–0.82]; *P*=0.028). Incidence of other secondary outcomes was comparable between the 2 groups. In multivariable analysis, intravascular imaging–guided PCI was the only protective independent predictor for occurrence of the primary end point (Table 4).

Meta-Analysis of the Previous Studies

A total of 18 studies were included in the meta-analysis; 15 were observational studies,[14–28] and 3 were randomized clinical trials,[8–10] including our own study. A total of 21 701 patients were included, of which 10 904 patients underwent intravascular imaging–guided PCI and 10 797 patients underwent angiography-guided PCI.

Pooled analyses of all-cause death or cardiac death are presented in Figure 3. Regardless of study design, meta-analyses of both observational studies and randomized controlled trials showed significantly reduced risk of all-cause death and cardiac death in the intravascular imaging–guided PCI group than in the angiography-guided PCI group (Figure 3). The summary relative risk of all-cause death was 0.53 (95% CI, 0.49–0.59; *P*<0.001) and relative risk of cardiac death was 0.37 (95% CI, 0.26–0.53; *P*<0.001), both indicating significantly lower risk of all-cause death and cardiac death in the intravascular imaging–guided PCI group than in the angiography-guided PCI group. No evidence of heterogeneity was noted regarding both all-cause death and cardiac death.

DISCUSSION

This prespecified substudy of RENOVATE-COMPLEX-PCI aimed to evaluate the impact of intravascular imaging–guided PCI for revascularization of unprotected LMCA disease. The findings of our study provide compelling evidence for the benefits of intravascular imaging–guided PCI in the treatment of LMCA disease. A composite outcome of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization was observed significantly less in the imaging–guided PCI group than in the angiography-guided PCI group. Furthermore, a meta-analysis of currently available studies comparing intravascular imaging–guided PCI to angiography-guided PCI in LMCA disease also shows that intravascular imaging–guided PCI is associated with significantly lower rates of both all-cause and cardiac death compared with angiography-guided PCI.

Evaluation of LMCA disease by angiography alone is known to have limitations, much more so than the disease involving the other coronary arteries.[29] By the

Table 3. Primary and Secondary End Points*

End Point	Total (N=192)	Imaging-guided PCI (N=138)	Angio-guided PCI (N=54)	Hazard ratio (95% CI)	*P* value
Primary end point					
Target vessel failure†	20 (12.3%)	9 (6.8%)	11 (25.1%)	0.31 (0.13–0.76)	0.010
Secondary end points‡					
Target vessel failure without procedure-related MI	14 (9.3%)	5 (4.0%)	9 (21.5%)	0.21 (0.07–0.64)	0.006
Cardiac death or target vessel–related MI	14 (8.6%)	7 (5.2%)	7 (16.4%)	0.39 (0.14–1.12)	0.080
Cardiac death or spontaneous target vessel–related MI	7 (5.0%)	2 (1.6%)	5 (12.7%)	0.16 (0.03–0.82)	0.028
All-cause death	16 (12.7%)	9 (9.7%)	7 (20.1%)	0.51 (0.19–1.38)	0.186
Cardiac death	6 (4.4%)	1 (0.7%)	5 (12.7%)	0.08 (0.01–0.69)	0.022
Myocardial infarction	9 (4.8%)	6 (4.5%)	3 (5.6%)	0.90 (0.23–3.47)	0.875
Target vessel–related MI	9 (4.8%)	6 (4.5%)	3 (5.6%)	0.78 (0.19–3.10)	0.720
Spontaneous MI§	2 (1.2%)	1 (0.9%)	1 (1.9%)	0.38 (0.02–6.06)	0.493
Procedure-related MI‖	7 (3.6%)	5 (3.6%)	2 (3.7%)	0.98 (0.19–5.04)	0.979
Nontarget vessel–related MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A	
Repeat revascularization¶	12 (7.4%)	7 (6.0%)	5 (11.1%)	0.60 (0.20–1.85)	0.378
Target vessel revascularization	9 (5.6%)	4 (3.4%)	5 (11.1%)	0.30 (0.08–1.12)	0.074
Target lesion revascularization	6 (3.7%)	2 (1.6%)	4 (8.9%)	0.19 (0.04–1.04)	0.056
Definite stent thrombosis#	1 (0.5%)	0 (0.0%)	1 (1.9%)	N/A	
Contrast-induced nephropathy**	2 (1.0%)	2 (1.4%)	0 (0.0%)	N/A	

MI indicates myocardial infarction; N/A, not applicable; PCI, percutaneous coronary intervention; and SCAI, Society for Cardiovascular Angiography and Interventions.

*Data presented as n (%). The database for the analysis presented here was locked on May 10, 2022. Clinical end points were evaluated in the intention-to-treat population during the overall study period (ie, 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. Hazard ratios and 95% CIs were calculated from univariate analysis.

†Primary end point is target vessel failure, a composite of cardiac death, target vessel MI, target vessel revascularization.

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

§Spontaneous myocardial infarction is defined as third universal definition of myocardial infarction.

‖Procedure-related myocardial infarction is defined as the SCAI definition.

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

#Definite stent thrombosis is defined as Academic Research Consortium criteria.

**Contrast-induced nephropathy is defined as an increase in serum creatinine of ≥0.5 mg/dL or ≥25% from baseline within 48 to 72 h after contrast agent exposure. Event rate is presented as proportion among group.

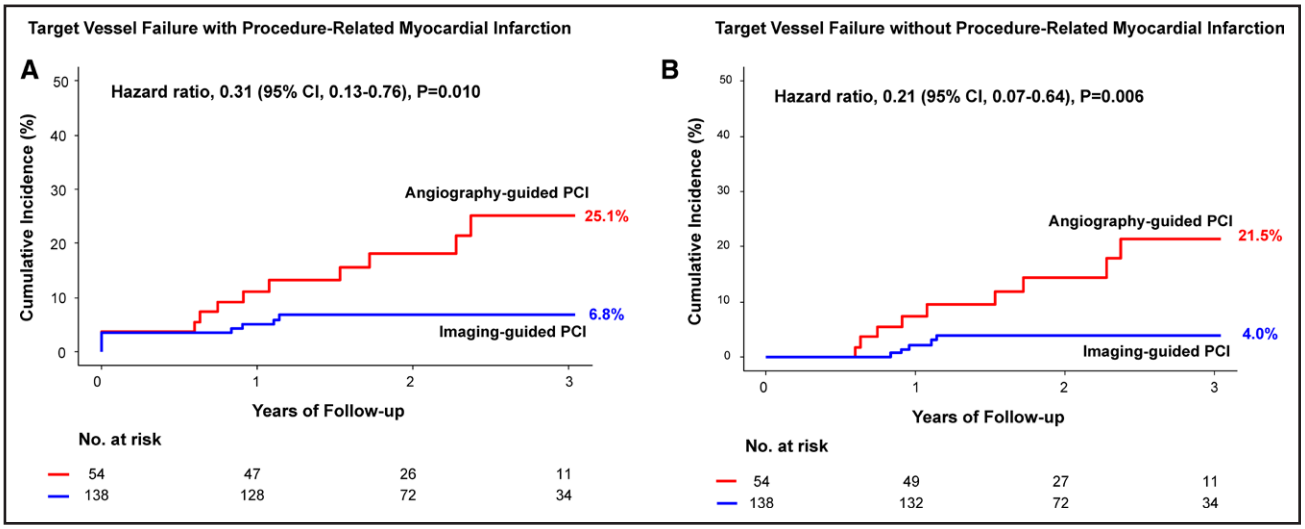

Figure 2. Comparison of target vessel failure between intravascular imaging–guided vs angiography-guided percutaneous coronary intervention (PCI) in left main coronary artery PCI.

A, The risk of target vessel failure was significantly lower in the intravascular imaging–guided PCI group than in the angiography-guided PCI group. **B**, The significant difference persisted even after excluding procedure-related myocardial infarction.

Table 4. Independent Predictors for Target Vessel Failure after Left Main PCI

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Intravascular imaging–guided PCI	0.31 (0.13–0.76)	0.010	0.29 (0.12–0.72)	0.007
Age ≥65 y	1.05 (0.44–2.54)	0.912	1.14 (0.45–2.89)	0.782
Male	1.31 (0.44–3.90)	0.634	1.84 (0.34–3.45)	0.902
Acute coronary syndrome	1.71 (0.68–4.28)	0.256	1.84 (0.72–4.73)	0.206
Hypertension	0.68 (0.28–1.65)	0.398	0.73 (0.28–1.87)	0.511
Diabetes	0.42 (0.14–1.27)	0.125	0.43 (0.14–1.36)	0.153
Hyperlipidemia	1.39 (0.57–3.34)	0.468	1.76 (0.68–4.58)	0.243
Chronic kidney disease	1.27 (0.47–3.50)	0.644	1.57 (0.47–5.29)	0.468
Left ventricular ejection fraction < 50%	0.92 (0.27–3.14)	0.894	1.36 (0.33–5.56)	0.672

Discriminant ability of the multivariable model was 0.689 (95% CI 0.635–0.743). HR indicates hazard ratio; and PCI, percutaneous coronary intervention.

1990s, some studies had already highlighted the discordant findings between angiography and IVUS in the context of LMCA disease.[30,31] Furthermore, several observational studies[14–17,19] and meta-analyses[6,7] have consistently shown the clinical benefit of IVUS-guided PCI compared with angiography-guided PCI for unprotected LMCA disease.

However, there are relatively few randomized controlled trials specifically addressing this issue. Tan et al[8] conducted a 2-year follow-up study involving 123 elderly patients (aged ≥70 years) with stable ischemic disease, showing that IVUS-guided PCI for LMCA disease was associated with lower incidence of a composite of death, nonfatal myocardial infarction, and repeat revascularization compared with angiography-guided PCI. Similarly, Liu et al. conducted a 1-year follow-up study with 336 patients with stable ischemic heart disease, showing that IVUS-guided PCI for LMCA disease was associated with lower incidence of a composite of cardiac death, myocardial infarction, and target vessel revascularization.[9] These 2 trials support the beneficial impact of intravascular imaging–guided PCI for unprotected LMCA disease but are limited by a small study population, exclusion of acute coronary syndrome, and use of IVUS only. Indeed, the use of OCT for the evaluation of LMCA disease is hampered by the need for blood clearance before imaging, and the clinical guidelines only recommend IVUS to evaluate significance of LMCA lesion.[2,3] In contrast, our study differs in that the full spectrum of ischemic heart disease was included and OCT use was allowed at operator discretion for revascularization of LMCA lesion.

The reduction of target vessel failure in the intravascular imaging–guided PCI group was mainly driven by significantly lower risk of cardiac death or spontaneous target vessel–related myocardial infarction. The incidence of target vessel revascularization was similar

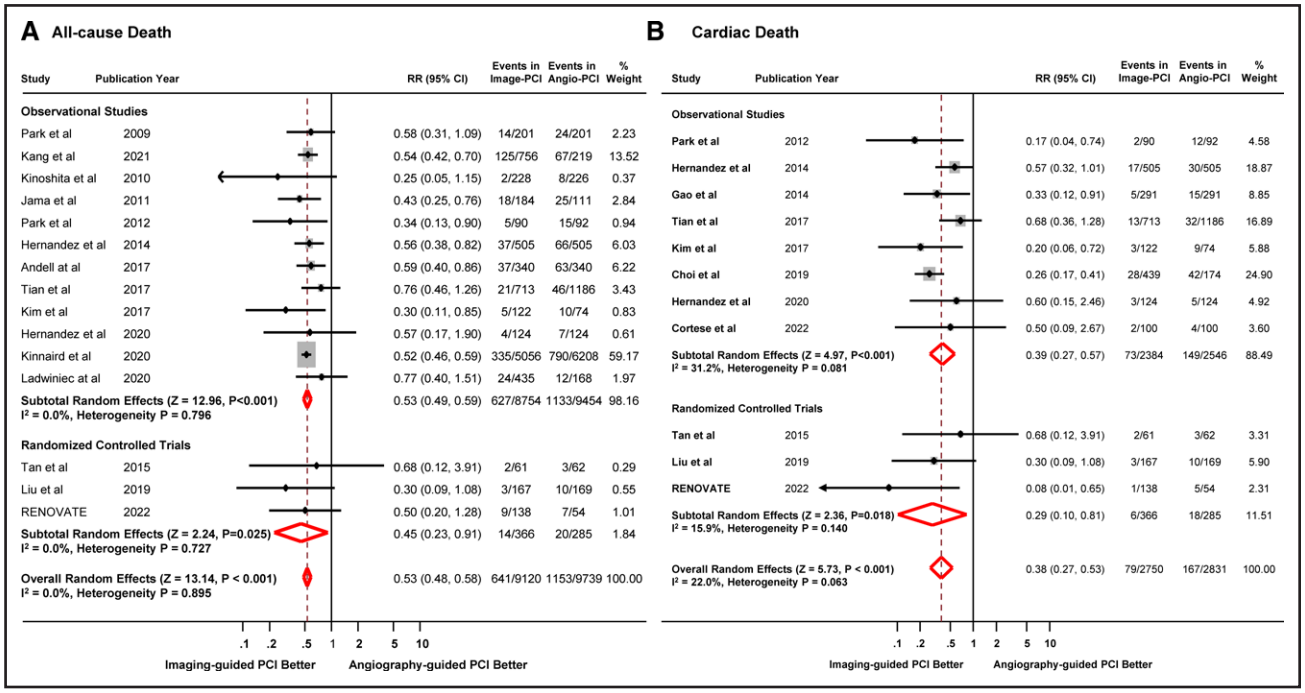

Figure 3. Treatment effect of intravascular imaging–guided percutaneous coronary intervention (PCI) compared with angiography-guided PCI for left main coronary artery PCI.
Meta-analysis of 18 studies using intravascular imaging for left main coronary artery PCI shows significantly lower risk of (**A**) all-cause death and (**B**) cardiac death compared with angiography-guided PCI alone. RENOVATE indicates Randomized Controlled Trial of Intravascular Imaging Guidance Versus Angiography-Guidance on Clinical Outcomes After Complex Percutaneous Coronary Intervention; and RR, relative risk.

between the 2 groups. It should be noted that previous studies on LMCA disease, which demonstrated better clinical outcomes with intravascular imaging–guided PCI compared with angiography-guided PCI, also showed that the significant difference in the primary composite outcome was mainly attributed to mortality, while the incidence of target vessel revascularization, myocardial infarction, or stent thrombosis was comparable between the 2 groups.[9,15,16,19,23] One possible explanation for this finding is that because restenosis or thrombosis of stents in LMCA could lead to sudden death, the clinical event could be under-detected and only be counted as mortality. Alternatively, this could be due to the small number of patients selected in the present substudy. It is important to highlight that while all-cause death was similar between the 2 groups in our study, a meta-analysis incorporating 18 studies, including the current study, demonstrated a significantly lower incidence of all-cause death in the imaging–guided PCI group compared with the angiography-guided PCI group. This implies that the benefits of intravascular imaging may become more evident with a larger sample size. Furthermore, ongoing trials dedicated to LMCA disease, such as the OPTIMAL (Optimization of Left Main PCI With Intravascular Ultrasound; https://www.clinicaltrials.gov; Unique identifier: NCT04111770) and OCTOBER (Optical Coherence Tomography Optimized Bifurcation Event Reduction; https://www.clinicaltrials.gov; Unique identifier: NCT03171311) trials, are expected to provide further insights and clarify the benefits of intravascular imaging–guided PCI for LMCA disease.

In the RENOVATE-COMPLEX-PCI, larger mean stent diameter and more use of adjuvant noncompliant balloon dilatation in the imaging–guided PCI group compared with the angiography-guided PCI group were noted, which could explain the improved clinical outcomes in the former group.[10] Although procedural characteristics during and after PCI, including mean stent size, total length, quantitative coronary angiography findings, and the use of adjuvant dilatation, were similar between the imaging–guided PCI and the angiography-guided PCI groups in this substudy, the use of larger size of adjunctive noncompliant balloon in the intravascular imaging–guided PCI group was noted. These findings are in line with ADAPT-DES study (Dual Antiplatelet Therapy With Drug Eluting Stents) which showed larger maximum device diameter in the IVUS-guided group,[32] or the recently published IVUS-XPL sub-analysis, which presented that IVUS-guided post-adjunctive dilatation used larger balloon with higher inflation pressure than angiography-guided post-adjunctive dilatation.[33] This could be explained by more confident selection of larger-sized adjunctive balloon with the aid of the intravascular imaging, as angiographic examination by visual assessment might lead to underestimation of vessel size, in couple with the precaution to avoid complications such as stent edge dissection or perforation, and shows that the use of the intravascular imaging might have led to more effective stent dilatation.

Although direct influence on the procedure itself is not shown from the analysis result, it should be considered that the use of intravascular imaging assists in making decisions regarding stent implantation technique, selection of optimal stent size and landing zones, complete stent apposition, and correction of stent underexpansion. These factors may contribute to improving clinical outcomes, although they cannot be directly translated to a numerical difference in quantitative coronary angiography.[34] Although the RENOVATE-COMPLEX-PCI and previous trials comparing the use of intravascular imaging to angiography alone in PCI reported significant difference in post-PCI quantitative coronary angiographic findings,[35,36] the difference was very small, indicating other angiographic and procedural factors also play a role in improving clinical outcomes.

The current substudy, along with the main trial, adopted the most contemporary optimization criteria using either IVUS or OCT,[11] which was prespecified at the beginning of the trial. More than half of the imaging–guided PCI group (60.1%, 83/138 patients) achieved optimization according to this criteria, and though post-PCI quantitative coronary angiography findings were similar between the 2 groups, it is known that angiographically measured diameter does not correlate with IVUS-measured diameter.[37] Furthermore, our analysis also shows that among various clinical factors, use of intravascular imaging was the only predictor of lower incidence of target vessel failure, emphasizing the use of intravascular imaging for LMCA PCI.

Limitations

There are some limitations to be considered in our substudy. First, the current prespecified substudy was not powered enough to evaluate the potential difference in secondary end points. The small size of the study population also precludes further analysis such as comparison of outcome according to lesion location, stent strategy, stent optimization status, etc. In addition, randomization was not stratified according to the presence of unprotected LMCA disease. Second, masking the operator was not possible, but we minimized the risk for any potential bias by using an end point analysis with precisely defined criteria, angiographic, and imaging analyses at the core laboratories, including blinded clinical event adjudication. Third, although the trial allowed use of both IVUS and OCT, majority of the intravascular imaging–guided PCI group used IVUS, most likely due to the limitation in evaluating LMCA ostial disease using OCT. Fourth, only 41.3% of patients in the intravascular imaging–guided PCI group used imaging devices both pre-PCI and post-PCI phase, and the information on imaging could not be utilized for

decision-making of stent size and length, landing site, treating strategies in more than half of intravascular imaging–guided PCI group. Furthermore, since patients in the angiography-guided PCI group did not undergo intravascular imaging, differences could only be explained by findings of quantitative coronary angiography and not of intravascular imaging. Further randomized controlled trials are needed to confirm the current findings. Fifth, it should be noted that the RENOVATE-COMPLEX-PCI was not dedicated trial for LMCA intervention. Therefore, information regarding the upfront 2-stenting and related stenting techniques were not systematically collected from the beginning of the trial. This should be further clarified in currently ongoing dedicated trial for LMCA interventions such as OPTIMAL and OCTOBER trials.

Conclusions

In patients with LMCA lesions, intravascular imaging–guided PCI was superior to angiography-guided PCI in reducing the risk of a composite of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization.

ARTICLE INFORMATION

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