Comparison Between Optical Frequency Domain Imaging and Intravascular Ultrasound for Percutaneous Coronary Intervention Guidance in Biolimus A9-Eluting Stent Implantation
A Randomized MISTIC-1 Non-Inferiority Trial

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BACKGROUND: Given the characteristic differences between intravascular ultrasound (IVUS) and optical frequency domain imaging (OFDI), their approach to therapeutic guidance during percutaneous coronary interventions (PCIs) and arterial healing response after stenting may also vary.

METHODS: MISTIC-1 (The Multimodality Imaging Study in Cardiology cohort 1) is a multicenter, randomized-controlled, noninferiority trial that compared imaging end points between OFDI- and IVUS-guided PCI. Patients with stable coronary artery disease were randomly assigned to either OFDI- or IVUS-guided PCI using a Biolimus A9-eluting stent according to a prespecified protocol for imaging guidance. Stent sizing was based on external elastic lamina in IVUS-guided PCI while lumen up-size in OFDI-guided PCI. Postprocedural OFDI was investigated regardless of randomization, while operators in IVUS-guided PCI arm were blinded to the images. The primary end point was in-segment minimum lumen area assessed using OFDI at 8 months, while the secondary end point was a composite of cardiovascular mortality, target-vessel myocardial infarction, or target-lesion revascularization (device-oriented composite end point). Patients were followed up to 3 years after the index procedure.

RESULTS: A total of 109 patients (mean age 70 years, male 78%) with 126 lesions were enrolled. Postprocedural minimum stent area was 6.31±1.89 and 6.72±2.08 mm² in OFDI and IVUS group, respectively (P=0.26). At the 8-month follow-up, in-segment minimum lumen area was 4.56±1.94 and 4.13±1.86 mm² in OFDI and IVUS group, respectively (P non-inferiority <0.001). Both groups had comparable neointimal healing score (median 0.16 [interquartile range, 0.00–3.14] versus 0.90 [0.00–3.30], respectively; P=0.43). The incidence rate of device-oriented composite end point at 3 years was 7.4% and 7.3% in OFDI and IVUS group, respectively (hazard ratio, 1.05 [95% CI, 0.26–4.18]; P=0.95).

CONCLUSIONS: OFDI-guided PCI was not inferior to IVUS-guided PCI in terms of in-segment minimum lumen area at 8 months. Although a small sample size was acknowledged, OFDI could be an alternative to IVUS when considering intracoronary imaging-guided PCI in selected populations with coronary artery diseases.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary artery disease ■ drug-eluting stent ■ intravascular ultrasound ■ optical coherence tomography ■ percutaneous coronary intervention

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WHAT IS KNOWN
• Recent randomized data showed that intracoronary imaging (ie, intravascular ultrasound)-guided percutaneous coronary intervention (PCI) promoted significantly lower risk of major adverse cardiac events within 1 year compared with conventional angiography-guided PCI.
• Given its higher axial resolution compared with intravascular ultrasound, optical frequency domain imaging provides more comprehensive assessment for stent optimization and procedural complications.
• Few randomized trials have compared the safety and efficacy of optical coherence tomography/ optical frequency domain imaging-guided and intravascular ultrasound-guided PCI, with clinical outcomes beyond 1 year having yet to be reported.

WHAT THE STUDY ADDS
• Optical frequency domain imaging–guided PCI was not inferior to intravascular ultrasound–guided PCI in terms of in-segment minimum lumen area at 8 months (primary end point).
• Neo-intimal healing score at 8 months did not differ between both groups, while half of the lesions treated under optical frequency domain imaging guidance revealed perfect arterial healing after newer generation drug-eluting stent implantation. Both imaging techniques for PCI guidance had comparable device-oriented or patient-oriented composite end point up to 3 years.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| DES          | drug-eluting stent |
| EEL          | external elastic lamina |
| IVUS         | intravascular ultrasound |
| MI           | myocardial infarction |
| MLA          | minimum lumen area |
| OCT          | optical coherence tomography |
| OFDI         | optical frequency domain imaging |
| PCI          | percutaneous coronary intervention |
| QCA          | quantitative coronary angiography |

Intracoronary imaging techniques, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), play an important role in not only characterizing atherosclerotic plaque but also optimizing stent implantation during percutaneous coronary interventions (PCI). IVUS has been recognized as a predominant intracoronary imaging technique in clinical settings and recent studies have suggested that IVUS-guided PCI can better reduce the risk of major adverse cardiac events after stent implantation compared with conventional PCI under angiographic guidance. Optical frequency domain imaging (OFDI) is a light-based intracoronary imaging technique analogous to frequency domain OCT. Given that OFDI has a higher axial resolution (10–20 μm) compared with IVUS (60–150 μm), it allows for a more comprehensive assessment for stent optimization or procedural complications, such as dissection, tissue protrusion, or stent malapposition.

Current European guidelines on myocardial revascularization have updated their OCT/OFDI indications for stent optimization from class IIb to IIa. Nevertheless, procedural steps in imaging guidance have not been well established, while randomized data in the comparison between IVUS- and OCT/OFDI-guided PCI have still been limited. Although studies have shown that OCT/OFDI- and IVUS-guided PCI had comparable angiographic and clinical outcomes within 1 year, longer-term clinical follow-up beyond 1 year has yet to be reported.

Therefore, the present study sought to compare the safety and efficacy of IVUS- and OFDI-guided PCI using a newer generation drug-eluting stent (DES) in terms of imaging end points at 8 months and clinical outcomes up to 3 years.

METHODS
The authors declare that all supporting data are available within the article and its Data Supplement.

Study Design and Patient Population
MISTIC-1 (The Multimodality Imaging Study in Cardiology cohort 1) is a prospective, multicenter, open-label, randomized-controlled, noninferiority trial. Briefly, patients with stable coronary artery disease who underwent elective PCI were prospectively enrolled and randomly assigned to either IVUS or OFDI guidance during PCI using the Biolimus A9-eluting metallic stent (Nobori, Terumo Corp, Tokyo, Japan). The inclusion criteria were age over 20 years and clinically relevant symptoms or myocardial ischemia confirmed by noninvasive or invasive functional testing. Patient exclusion criteria were as follows: (1) renal insufficiency with estimated glomerular filtration rate <45 mL/minute per 1.73 m², (2) left ventricular ejection fraction <30% or a history of congestive heart failure, (3) acute coronary syndrome within 7 days after onset, (4) nonsuitability for DES use or dual antiplatelet therapy 1 year after the index procedure, or (5) life expectancy within 1 year. Lesion exclusion criteria were as follows: (1) lesion length >28 mm estimated by quantitative coronary angiography (QCA), (2) chronic total occlusion, (3) left main stem lesion, (4) bifurcation lesion requiring treatment for side branch, or (5) severely calcified lesion. This study was conducted at 2 cardiovascular centers within Japan (Fujita Health University Hospital and Japanese Red Cross Nagoya Daini Hospital). Randomization was performed in a 1:1 fashion with sealed envelopes for each site. Patients were blinded to the randomization during the entire study period. The study protocol was approved by the institutional review board of each participating center (HM15-580), and written informed consent was obtained from all patients enrolled herein.
PCI Procedure and Imaging Guidance Protocol

During PCI, vascular access and guiding catheter size selection were left to the operator’s discretion. After intracoronary nitrate administration, preprocedural intracoronary imaging was performed using either a 40-MHz IVUS catheter (ViewIT, Terumo Corp, Tokyo, Japan) or an OFDI catheter (FastView, Terumo Corp, Tokyo, Japan) according to the randomization. Images were acquired using an automated pullback speed of 0.5 mm/s for IVUS or 20 mm/s for OFDI. After calibration, OFDI images were obtained under sufficient blood removal through 100% contrast medium injection. Predilation with a 2.0-mm semicompliant balloon was allowed only when catheter passage through the lesion was unsuccessful or blood removal was insufficient potentially resulting in poor image quality for analysis. Stent landing zones (ie, reference sites) were ideally selected within the most normal looking sites that had the largest lumen with a percentage plaque area of ≤50% in the IVUS group, and those without lipidic plaque >2 quadrants or suggestive thin-cap fibroatheroma in the OFDI group.10–12 Stent size in the IVUS group was based on the external elastic lamina, whereas that in the OFDI group was 10% or 0.25-mm larger than mean lumen diameter at reference sites. Post-dilation was left to the operator’s discretion in both groups, although a noncompliant balloon with a nominal diameter 0.25-mm larger than that of the stent was encouraged in the OFDI group. The imaging guidance protocol during the procedure is summarized in Table I in the Data Supplement. Postprocedural OFDI was investigated regardless of randomization, although operators allocated to IVUS-guided PCI arm were blinded to the images.

Study End Points

The primary end point was in-segment minimum lumen area (MLA) assessed using OFDI at the 8-month follow-up on a lesion-level basis. Secondary end point was major adverse cardiac events, namely device-oriented composite end point consisting of cardiovascular mortality, target-vessel myocardial infarction, or clinically driven target-lesion revascularization. Patient-oriented composite end point, defined as a composite of all-cause mortality, all myocardial infarction, or all revascularization, was also assessed. Device-oriented composite end point and patient-oriented composite end point accounted for the first events in each patient, and the definitions of which are summarized in the Appendix in the Data Supplement. Dedicated clinical research coordinators from

Figure 1. Study flow diagram of the MISTIC-1 trial (The Multimodality Imaging Study in Cardiology cohort 1).
*The patient underwent optical frequency domain imaging (OFDI) of 2 lesions at the 8-mo follow-up. IVUS indicates intravascular ultrasound; and PCI, percutaneous coronary intervention.
Average of mean lumen area in aand distal subsegments was approximately half of SD from the previous studies. 13,14 We drew an inference of a noninferiority margin (1.2 mm²) that mm² at 8 months in the control IVUS-guided PCI group, and 2020;13:e009314. DOI: 10.1161/CIRCINTERVENTIONS.120.009314 November 2020 236 Circ Cardiovasc Interv.

Imaging Analyses

Table 1. Patient Demographics

| Patient demographics | OFDI group (N=54) | IVUS group (N=55) |
|----------------------|-------------------|------------------|
| Age, y               | 72 (65–76)        | 71 (65–78)       |
| Male sex, n (%)      | 41 (75.9%)        | 44 (80.0%)       |
| Hypertension, n (%)  | 34 (63.0%)        | 39 (70.9%)       |
| Diabetes, n (%)      | 27 (50.0%)        | 24 (43.6%)       |
| Dyslipidemia, n (%)  | 43 (79.6%)        | 36 (65.5%)       |
| Current smoker, n (%)| 22 (40.7%)        | 12 (21.8%)       |
| Prior MI, n (%)      | 19 (35.2%)        | 16 (29.1%)       |
| Prior PCI, n (%)     | 24 (44.4%)        | 26 (47.3%)       |
| Prior CABG, n (%)    | 0 (0.0%)          | 0 (0.0%)         |

| No. of diseased vessel, n (%) |
|-------------------------------|
| 1 vessel disease              | 34 (63.0%)        | 31 (56.4%)       |
| 2 vessel disease              | 13 (24.1%)        | 18 (32.7%)       |
| 3 vessel disease              | 7 (13.0%)         | 6 (10.9%)        |

| Medications at discharge, n (%) |
|--------------------------------|
| Aspirin                        | 54 (100.0%)       | 55 (100.0%)      |
| Ticlopidine                    | 2 (3.7%)          | 4 (7.3%)         |
| Clopidogrel                    | 42 (77.8%)        | 38 (69.1%)       |
| Prasugrel                      | 10 (18.5%)        | 13 (23.6%)       |
| β blockers                     | 24 (44.4%)        | 23 (41.8%)       |
| ACE inhibitors or ARBs         | 36 (66.7%)        | 34 (61.8%)       |
| Statins                        | 50 (92.6%)        | 49 (89.1%)       |
| Vitamin K antagonist           | 4 (7.4%)          | 6 (10.9%)        |
| Direct oral anticoagulants     | 5 (9.6%)          | 6 (10.9%)        |

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; IVUS, intravascular ultrasound; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OFDI, optical frequency domain imaging; and PCI, percutaneous coronary intervention.

each participating center clinically followed up patients for up to 3 years via electronic medical records or phone call.

Sample Size Calculation

This study was powered to identify noninferiority of the primary end point after comparing OFDI- and IVUS-guided PCI. We assumed an in-segment MLA of 4.5 mm² with a SD of 2.0 mm² at 8 months in the control IVUS-guided PCI group, and we drew an inference of a noninferiority margin (1.2 mm²) that was approximately half of SD from the previous studies.13,14 A total of 96 lesions (48 lesions in each group) was determined to yield 90% statistical power at a 1-sided alpha level of 0.05. Assuming 10% study attrition rate during follow-up OFDI investigations, 106 patients were planned to be enrolled.

Imaging Analyses

QCA and OFDI analysis were performed in an independent imaging core laboratory using dedicated offline software (CAAS version 5.8, Pie Medical Imaging, Maastricht, the Netherlands and Qlvs version 3.0, MEDIS, Leiden, the Netherlands, respectively). Briefly, OFDI geometric measurements were analyzed on a lesion-level basis with a sampling rate of 1.0 mm, whereas qualitative analyses for tissue prolapse, dissection, and thrombus were performed on a frame-by-frame fashion if detected. Major dissection was defined as that with a maximum flap root thickness >300 μm, flap length >1.0 mm, and axial involvement beyond the intimal layer.15,16

The stent expansion index was calculated as follows:

\[
\frac{\text{Minimum stent area}}{\text{Average of mean lumen area in proximal and distal subsegments}} \times 100 \%
\]

We then performed a post hoc analysis of stent optimization, which covered all of the following postprocedural criteria: (1)
Stent expansion index ≥80%; (2) prevalence of malapposed stent strut <20%; and (3) absence of major edge dissection. The neointimal healing score consisting of malapposed and/or uncovered struts was also estimated. The methodology and definitions of other imaging analyses are summarized in the Appendix in the Data Supplement.

**Statistical Analysis**
Continuous variables were expressed as median (interquartile range) and compared using the Mann-Whitney U test, whereas categorical variables were expressed numbers (percentages) and compared using Fisher exact test. Given that several patients with multiple lesions were included in the present study, the primary end point was evaluated using generalized estimating equations, taking the lesions as a within-subject variable. Distribution of neointimal healing score or in-segment MLA in each group was displayed as a box plot paired with a cumulative frequency distribution curve. The time until the first event for each patient was illustrated using Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using SPSS (version 23.0, SPSS, Inc, Chicago, IL), with a P of <0.05 indicating statistical significance.

**RESULTS**
A study flow diagram is presented in Figure 1. Since June 2014 until August 2016, a total of 109 patients

| Table 3. QCA Analysis | OFDI group | IVUS group | P value |
|------------------------|------------|------------|---------|
|                       | (N =62)    | (N =64)    |         |
| **Post-procedure**     |            |            |         |
| Reference vessel diameter, mm |   |   |      |
| Proximal               | 3.00 (2.61 to 3.38) | 2.89 (2.66 to 3.23) | 0.37 |
| In-stent               | 2.73 (2.41 to 3.05) | 2.74 (2.38 to 3.04) | 0.89 |
| Distal                 | 2.64 (2.29 to 2.99) | 2.61 (2.39 to 2.96) | 0.81 |
| Diameter stenosis, %   |            |            |         |
| Proximal               | 10.2 (6.6 to 19.4) | 11.2 (5.7 to 17.8) | 0.64 |
| In-stent               | 4.2 (0.0 to 11.5) | 0.4 (0.0 to 9.1) | 0.31 |
| Distal                 | 14.4 (7.2 to 20.8) | 13.1 (7.4 to 20.3) | 0.76 |
| Minimum lumen diameter, mm |   |   |      |
| Proximal               | 2.50 (2.21 to 2.93) | 2.56 (2.19 to 2.80) | 0.89 |
| In-stent               | 2.65 (2.33 to 2.97) | 2.69 (2.34 to 3.07) | 0.56 |
| Distal                 | 2.19 (1.89 to 2.72) | 2.19 (1.85 to 2.54) | 0.93 |
| In-segment             | 2.15 (1.84 to 2.48) | 2.18 (1.81 to 2.48) | 0.63 |
| Follow-up              | (N =57)    | (N =59)    |         |
| Reference vessel diameter, mm |   |   |      |
| Proximal               | 2.85 (2.48 to 3.08) | 2.78 (2.39 to 3.16) | 0.99 |
| In-stent               | 2.68 (2.35 to 2.97) | 2.74 (2.34 to 3.00) | 0.95 |
| Distal                 | 2.43 (2.21 to 2.90) | 2.56 (2.24 to 2.89) | 0.47 |
| Diameter stenosis, %   |            |            |         |
| Proximal               | 10.5 (7.8 to 19.0) | 12.2 (4.3 to 17.3) | 0.70 |
| In-stent               | 8.5 (1.4 to 15.7) | 4.0 (0.0 to 13.7) | 0.27 |
| Distal                 | 11.4 (5.6 to 16.8) | 10.2 (5.2 to 17.4) | 0.94 |
| Minimum lumen diameter, mm |   |   |      |
| Proximal               | 2.41 (2.04 to 2.78) | 2.49 (2.16 to 2.80) | 0.79 |
| In-stent               | 2.33 (2.08 to 2.89) | 2.54 (2.19 to 2.89) | 0.45 |
| Distal                 | 2.17 (1.86 to 2.59) | 2.25 (1.88 to 2.54) | 0.78 |
| In-segment             | 2.07 (1.84 to 2.55) | 2.11 (1.81 to 2.47) | 0.79 |
| Late lumen loss, mm    |            |            |         |
| Proximal               | 0.15 (–0.16 to 0.37) | 0.05 (–0.16 to 0.29) | 0.38 |
| In-stent               | 0.19 (–0.03 to 0.42) | 0.19 (–0.08 to 0.45) | 0.83 |
| Distal                 | –0.01 (–0.21 to 0.23) | –0.02 (–0.23 to 0.19) | 0.71 |
| In-segment             | 0.02 (–0.29 to 0.23) | 0.03 (–0.17 to 0.32) | 0.38 |
| Binary restenosis, n (%) | 0 (0.0%) | 2 (3.4%) | 0.37 |

IVUS indicates intravascular ultrasound; OFDI, optical frequency domain imaging; and QCA, quantitative coronary angiography.
## Table 4. OFDI Analysis

|                                | OFDI group     | IVUS group     | *P* value |
|--------------------------------|----------------|----------------|-----------|
| **Post-procedure**             |                |                |           |
| No. of analyzed strut per lesion | 199 (140 to 301) | 224 (151 to 273) | 0.70      |
| Length of stented segment, mm  | 18.2 (13.7 to 25.3) | 18.1 (14.1 to 25.1) | 0.79      |
| Mean stent area, mm\(^2\)      | 7.45 (5.73 to 8.54) | 7.78 (6.41 to 9.80) | 0.19      |
| Minimum stent area, mm\(^2\)   | 6.24 (4.62 to 7.70) | 6.50 (5.09 to 8.37) | 0.31      |
| Mean lumen area, mm\(^2\)      |                |                |           |
| Proximal segment (5 mm)        | 7.72 (5.95 to 9.10) | 7.16 (5.54 to 9.23) | 0.47      |
| Stented segment                | 7.59 (5.90 to 8.74) | 7.94 (6.58 to 10.0) | 0.18      |
| Distal segment (5 mm)          | 5.82 (4.41 to 7.91) | 5.54 (4.67 to 7.60) | 0.76      |
| Minimum lumen area, mm\(^2\)   |                |                |           |
| Proximal segment (5 mm)        | 6.53 (4.93 to 8.14) | 5.95 (4.31 to 7.66) | 0.25      |
| Stented segment                | 6.34 (4.78 to 7.61) | 6.62 (5.12 to 8.48) | 0.27      |
| Distal segment (5 mm)          | 4.57 (3.13 to 6.69) | 4.53 (3.72 to 6.02) | 0.80      |
| In-segment                     | 4.57 (3.13 to 5.86) | 4.21 (3.49 to 5.48) | 0.71      |
| Stent expansion index, %        | 92.2 (82.1 to 100.0) | 97.9 (91.6 to 100.0) | 0.03      |
| Malapposed struts, %           | 3.5 (1.2 to 6.8) | 3.4 (1.2 to 6.3) | 0.70      |
| Tissue prolapse, n (%)          | 53 (88.3) | 56 (87.5) | 0.89      |
| Smooth protrusion               | 36 (60.0) | 33 (51.6) | 0.34      |
| Disrupted fibrous tissue protrusion | 35 (58.3) | 41 (64.1) | 0.51      |
| Irregular protrusion            | 14 (23.3) | 26 (40.6) | 0.04      |
| Dissection, n (%)               | 16 (26.7) | 19 (29.7) | 0.71      |
| Proximal segment (5 mm)         | 10 (16.7) | 11 (17.2) | 0.94      |
| Stented segment                 | 46 (76.7) | 55 (85.9) | 0.18      |
| Distal segment (5 mm)           | 8 (13.3) | 12 (18.8) | 0.41      |
| Thrombus, n (%)                 | 6 (10.0) | 13 (20.3) | 0.11      |
| Stent optimization achieved, n (%) | 45 (75.0) | 54 (84.4) | 0.19      |
| **Follow-up**                   |                |                |           |
| No. of analyzed strut per lesion | 210 (133 to 294) | 222 (149 to 258) | 0.81      |
| Length of stented segment, mm   | 17.6 (13.3 to 25.8) | 17.9 (13.9 to 23.5) | 0.98      |
| Mean stent area, mm\(^2\)      | 7.25 (5.58 to 8.66) | 7.60 (6.01 to 9.72) | 0.26      |
| Minimum stent area, mm\(^2\)   | 6.06 (4.35 to 7.70) | 6.28 (4.77 to 8.13) | 0.43      |
| Mean lumen area, mm\(^2\)      |                |                |           |
| Proximal segment (5 mm)         | 7.72 (5.92 to 9.06) | 6.61 (4.94 to 8.50) | 0.16      |
| Stented segment                 | 6.71 (5.30 to 8.24) | 7.32 (5.42 to 9.44) | 0.29      |
| Distal segment (5 mm)           | 5.46 (4.21 to 7.54) | 5.32 (4.23 to 7.46) | 0.93      |
| Minimum lumen area, mm\(^2\)   |                |                |           |
| Proximal segment (5 mm)         | 6.23 (4.75 to 7.99) | 4.81 (3.62 to 7.33) | 0.04      |
| Stented segment                 | 5.39 (4.28 to 7.21) | 5.94 (4.03 to 7.58) | 0.62      |
| Distal segment (5 mm)           | 4.33 (3.23 to 5.92) | 4.25 (3.60 to 5.95) | 0.91      |
| In-segment                      | 4.33 (2.95 to 5.50) | 3.71 (2.89 to 5.21) | 0.18      |
| Δ Minimum lumen area (post—fup), mm\(^2\) | 0.28 (−0.24 to 0.93) | 0.67 (0.03 to 1.27) | 0.11      |
| Stented segment                 | 0.65 (0.31 to 1.17) | 0.82 (0.39 to 1.20) | 0.27      |
| Distal segment (5 mm)           | −0.04 (0.49 to 0.42) | 0.05 (−0.46 to 0.53) | 0.71      |
| In-segment                      | 0.13 (−0.28 to 0.45) | 0.19 (−0.14 to 0.74) | 0.24      |
| Mean neointima area, mm\(^2\)  | 0.37 (0.24 to 0.56) | 0.37 (0.19 to 0.65) | 0.98      |
| Mean neointima volume, mm\(^3\) | 6.30 (3.31 to 13.87) | 6.88 (2.67 to 12.80) | 0.78      |

(Continued)
were enrolled and allocated to either OFDI- (54 patients with 62 lesions) or IVUS-guided PCI (55 patients with 64 lesions). Eight patients in each group had multiple lesions ($P=0.97$). None of the patients had an ostial right coronary artery lesion or required shifting to another imaging guidance.

**Patient, Lesion, and Procedural Characteristics**

Both groups had comparable patient and lesion characteristics, except for the number of current smokers (Tables 1 and 2). Preprocedural QCA indicated no difference in lesion length and reference vessel diameter. Radial access was predominantly used ($\geq 80\%$), while both groups had comparable nominal stent diameter and stent length. Ventricular tachyarrhythmia during image acquisition accounted for imaging-related complications in 2 cases within the OFDI group. Although no differences in procedure time and fluoroscopic time were observed between the 2 groups, the OFDI group had a significantly higher total radiocontrast volume than the IVUS group (146.5±47.0 versus 121.3±38.2 mL; $P=0.007$).

**Imaging Analyses Post-Procedure and at 8-Month Follow-Up**

Data about postprocedural QCA analysis and at 8-month follow-up are presented in Table 3. Both groups had comparable late lumen loss across all segments. Binary restenosis was observed in 2 cases (3.4%) within the IVUS group.

Data about postprocedural OFDI analyses and at 8-month follow-up are presented in Table 4. Both groups showed no difference in postprocedural minimum stent area. The IVUS group had a significantly higher stent expansion index than the OFDI group (97.9% versus 92.2%; $P=0.03$), with 84.4% and 75.0% of the patients achieving stent optimization, respectively ($P=0.19$). Postprocedural tissue prolapse was observed in several stented segments, while IVUS group had a significantly higher incidence of irregular protrusion than the OFDI group (40.6% versus 23.3%; $P=0.04$). Despite the moderate interobserver agreement for the detection of uncovered struts at follow-up ($\kappa$ statistic 0.45 [0.20–0.73]), they were rarely observed in both groups. The IVUS group had a

| Location of MLA site, n (%) | OFDI group | IVUS group | $P$ value |
|-----------------------------|------------|------------|-----------|
| Proximal segment (5 mm)     | 9 (16.7)   | 20 (34.5)  | 0.03      |
| Stented segment             | 9 (14.5)   | 8 (12.5)   | 0.74      |
| Distal segment (6 mm)       | 36 (66.7)  | 30 (51.7)  | 0.11      |
| Malapposed struts, %        | 0.0 (0.0 to 0.0) | 0.0 (0.0 to 0.6) | 0.02      |
| Uncovered struts, %         | 0.0 (0.0 to 1.4) | 0.0 (0.0 to 1.5) | 0.86      |
| Neointimal healing score    | 0.16 (0.00 to 3.14) | 0.90 (0.00 to 3.30) | 0.43      |

IVUS indicates intravascular ultrasound; MLA, minimum lumen area; and OFDI, optical frequency domain imaging.

![Figure 2. Neointimal healing score at the 8-mo follow-up.](image)

**Figure 2.** Neointimal healing score at the 8-mo follow-up. A, Box plot and (B) cumulative frequency distribution curve. IVUS indicates intravascular ultrasound; OFDI, optical frequency domain imaging; and PCI, percutaneous coronary intervention.
significantly higher percentage of malapposed struts at follow-up than the OFDI group. Neointimal healing score was comparable between the 2 groups, while 50.0% (27/54 lesions) and 43.1% (25/58 lesions) of the patients in the OFDI and IVUS groups had perfect healing (ie, neointimal healing score 0.00), respectively (Figure 2).

**In-Segment MLA at Follow-Up (Primary End Point)**

Figure 3 highlights the distributions of in-segment MLA assessed using OFDI at the 8-month follow-up. Accordingly, the OFDI and IVUS groups had an in-segment MLA of 4.56±1.94 and 4.13±1.86 mm², respectively (P=0.24), with a mean difference (⊿MLA$_{IVUS-OFDI}$) of −0.43 mm² and an upper limit of the 1-sided 95% CI of 0.16 (P<0.001 for noninferiority). Our exploratory analyses suggested that the proportion of MLA site was different specifically in the proximal segment between the groups (34.5% for IVUS versus 16.7% for OFDI; P=0.03) and the IVUS group had a smaller MLA than the OFDI group (4.81 versus 6.23 mm²; P=0.04).

**Clinical Outcomes Within and Beyond 1 Year (Secondary End Point)**

Clinical outcomes are summarized in Table 5. Device-oriented composite end point was observed in 7.4% (4/54) and 7.3% (4/55) of the patients in the OFDI and IVUS groups within 1 year, respectively (hazard ratio, 1.05 [95% CI, 0.26–4.18]; P=0.95), with no other incidences of the event having been observed in both groups between 1 and 3 years (Figure 4A). Patient-oriented composite end point was observed in 20.4% (11/54) and 18.2% (10/55) of the patients in the OFDI and IVUS groups within 1 year and in 9.3% (5/54) and 5.5% (3/55) of the patients in the same groups between 1 and 3 years, respectively (Figure 4B). Stent thrombosis was not observed in either group during the entire follow-up period.

**DISCUSSION**

The main findings of the present study can be summarized as follows: (1) OFDI-guided PCI was noninferior to IVUS-guided PCI in terms of in-segment MLA at 8 months; (2) no difference in neointimal healing score was observed at 8 months; and (3) clinical outcomes were comparable up to 3 years.

Given the differences in spatial resolution and penetration depth between light-based (eg, OCT/OFDI) and ultrasound-based (eg, IVUS) imaging techniques, their approach to imaging guidance for sizing or optimization of metallic DES may also vary. Two previous randomized trials, namely ILUMIEN III (Optical Coherence Tomography Compared With Intravascular Ultrasound and With Angiography to Guide Coronary Stent Implantation) and OPINION (Optical Frequency Domain Imaging vs Intravascular Ultrasound in Percutaneous Coronary Intervention), utilized different criteria for imaging guidance.8,9 Specifically, the OPINION trial considered lumen diameter for stent sizing during OFDI-guided PCI, while the ILUMIEN III trial considered external elastic lamina...
during OCT-guided PCI similarly to IVUS-guided PCI. Although both studies encouraged utilizing the most normal looking site for the stent landing zone, the OFDI group had a significantly smaller mean stent diameter than the IVUS group in the OPINION trial (2.92 versus 2.99 mm), whereas no such difference had been present in the ILUMIEN III trial (3.00 versus 3.00 mm). The current study found no significant differences in either mean stent diameter or postprocedural minimum stent area between both groups presumably because of our lumen up-sizing protocol for stent sizing in the OFDI group. One may argue that a low frequency of post-dilatation (≈65%) had been performed in the present study.

In the OPINION trial, however, post-dilatation was performed only in ≈30% of the patients. The IVUS group had a significantly higher stent expansion index than the OFDI group, and this finding is in line with that in the OPINION trial. Our post hoc analysis revealed that only 75% and 84% of the patients in the OFDI and IVUS group fulfilled the criteria of stent optimization, respectively. Our results suggest the need for more aggressive post-dilatation in future studies to achieve a higher index of stent expansion.

The primary end point of this study—in-segment MLA at follow-up—represents a comprehensive assessment of both imaging techniques incorporating acute effects...

| Table 5. Clinical Adverse Events up to 3 Years of Follow-Up |
|-------------------------------------------------------------|
| Nonhierarchical clinical events | OFDI group (N=54) | IVUS group (N=55) | P value |
|--------------------------------|-----------------|-----------------|--------|
| (0–365 d) | | | |
| All-cause mortality | 2 (3.7%) | 2 (3.6%) | 0.99 |
| Cardiac death, n (%) | 1 (1.9%) | 0 (0.0%) | 0.23 |
| Noncardiac death, n (%) | 1 (1.9%) | 2 (3.6%) | 0.57 |
| All myocardial infarction, n (%) | 2 (3.7%) | 1 (1.8%) | 0.54 |
| Q-wave, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Non Q-wave, n (%) | 2 (3.7%) | 1 (1.8%) | 0.54 |
| Target vessel related, n (%) | 2 (3.7%) | 1 (1.8%) | 0.54 |
| Non target vessel related, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| All revascularization, n (%) | 7 (13.0%) | 7 (12.7%) | 0.97 |
| Target lesion revascularization, n (%) | 1 (1.9%) | 3 (5.5%) | 0.31 |
| Target vessel revascularization, n (%) | 5 (9.3%) | 4 (7.3%) | 0.71 |
| Non target vessel revascularization, n (%) | 2 (3.7%) | 3 (5.5%) | 0.66 |
| Stent thrombosis (def./prob.), n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Major bleeding, n (%) | 1 (1.9%) | 2 (3.6%) | 0.57 |
| Device-oriented composite end point, n (%) | 4 (7.4%) | 4 (7.3%) | 0.98 |
| Patient-oriented composite end point, n (%) | 11 (20.4%) | 10 (18.2%) | 0.77 |
| (366–1095 d) | | | |
| All-cause mortality | 3 (5.6%) | 2 (3.6%) | 0.63 |
| Cardiac death, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Noncardiac death, n (%) | 3 (5.6%) | 2 (3.6%) | 0.63 |
| All myocardial infarction, n (%) | 1 (1.9%) | 0 (0.0%) | 0.23 |
| Q-wave, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Non Q-wave, n (%) | 1 (1.9%) | 0 (0.0%) | 0.23 |
| Target vessel related, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Non target vessel related, n (%) | 1 (1.9%) | 0 (0.0%) | 0.23 |
| All revascularization, n (%) | 1 (1.9%) | 1 (1.8%) | 0.99 |
| Target lesion revascularization, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Target vessel revascularization, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Non target vessel revascularization, n (%) | 1 (1.9%) | 1 (1.8%) | 0.99 |
| Stent thrombosis (def./prob.), n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Major bleeding, n (%) | 2 (3.7%) | 2 (3.6%) | 0.99 |
| Device-oriented composite end point, n (%) | 0 (0.0%) | 0 (0.0%) | N/A |
| Patient-oriented composite end point, n (%) | 5 (9.3%) | 3 (5.5%) | 0.44 |

IVUS indicates intravascular ultrasound; N/A, not available; and OFDI, optical frequency domain imaging.
(eg, minimum stent area) and late responses (eg, arterial healing) after stenting. Studies have shown that optimal deployment and landing zones of the prosthesis are major determinants of edge vascular response.\textsuperscript{11,19} Our imaging guidance protocol utilized substantially different criteria about not only stent sizing but also landing zones. Given its higher image resolution, OFDI can theoretically be considered superior to IVUS in identifying acute complications, such as edge dissection or stent malapposition.\textsuperscript{8} No randomized study has yet examined imaging outcomes at follow-up as the primary end point among various imaging guidance modalities. The present study demonstrated that in-segment MLA at 8 months was comparable between the OFDI and IVUS groups, albeit being numerically larger in the OFDI group, thereby meeting noninferiority of the primary end point. Serial imaging analyses showed no difference in late lumen loss (mm) for QCA or ΔMLA (mm\textsuperscript{2}) for OFDI in any segments between the 2 groups. Intracoronary imaging analyses, however, showed that the IVUS group had a significantly higher proportion of MLA sites specifically located in the adjacent 5-mm segment proximal to the stent and significantly smaller MLA compared with the OFDI group. These findings suggest potential differences in edge vascular response between both imaging techniques with respect to procedural guidance, despite no difference in the incidence rate of binary restenosis or clinical outcomes. Although one potential explanation may be technical differences in landing zone selection or stent sizing algorithm, confirming such would be difficult because of small sample size and low incidence rate of restenosis.

Arterial healing after DES implantation has been recognized as a major determinant of stent failure, such as restenosis or stent thrombosis.\textsuperscript{20} The excellent axial resolution of OCT/OFDI facilitates imaging assessment of healing response, such as stent apposition or neointimal coverage.\textsuperscript{21} The present study revealed that OFDI and IVUS guidance had comparable neointimal healing score, while 50% of the lesions treated using a Bio

**Figure 4. Kaplan-Meier curves.**

(A) Device-oriented composite end point (DoCE) and (B) patient-oriented composite end point (PoCE). DoCE is a composite of cardiovascular mortality, target-vessel myocardial infarction, or clinically driven target-lesion revascularization, whereas PoCE is a composite of all-cause mortality, all myocardial infarction, or all revascularization. IVUS indicates intravascular ultrasound; MI, myocardial infarction; OFDI, optical frequency domain imaging; and PCI, percutaneous coronary intervention.
A9-eluting Nobori stent under OFDI guidance demonstrated perfect healing at 8 months, a finding similar to that presented in a previous trial using an Everolimus-eluting XIENCE stent.22

Our data showed no difference between the groups in terms of device-oriented composite end point or patient-oriented composite end point up to 3 years. Although the present study lacked sufficient power to detect differences in clinical outcome measures, our findings were consistent with those present in 2 previous randomized trials that powered to compare the clinical outcomes between OCT/OFDI- and IVUS-guided PCI within 1 year.6,8 Our imaging (angiographic or OFDI) findings may support that both imaging-guided PCI strategies may have comparable outcomes beyond 1 year after PCI.

Several limitations of the current study warrant consideration. First, we did not compare our outcomes with conventional angiography-guided PCI. Second, considering a small sample size and a relatively large noninferiority margin for the primary end point, our results may be considered hypothesis-generating. Because of the lack of sample size specifically for clinical outcome measures, our results beyond 1 year follow-up will need confirmation in larger-scale studies such as ILUMIEN III or OPINION trials.8,9 Third, our protocol required the exclusion of those with acute coronary syndrome or complex lesions, such as left main stem, chronic total occlusion, bifurcation, or severely calcified lesions. The ILUMIEN IV trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03507777) will specifically address a wider spectrum of complex lesions. Fourth, our protocol did not require IVUS investigations to be systematically performed in the OFDI-guided group. Therefore, a comprehensive assessment of IVUS measurements, such as plaque volume or vessel remodeling, was challenging because of the lack of a full analysis dataset. Fifth, the neointimal healing score between both groups may have varied because of moderate interobserver agreement for the detection of uncovered struts. Finally, our study covered only a small number of cardiovascular centers within Japan. Despite utilizing a prespecified protocol for imaging guidance, the generalizability of this protocol and our results need further elucidation.

CONCLUSIONS

OFDI-guided PCI using a Biolimus A9-eluting metallic stent was not inferior to IVUS-guided PCI in terms of mid-term in-segment MLA. OFDI could be an alternative to IVUS when considering intracoronary imaging-guided PCI using newer generation DES in selected populations with coronary artery diseases.

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Disclosures

None.

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