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ORIGINAL RESEARCH

# Optical frequency domain imaging-guided versus intravascular ultrasound-guided percutaneous coronary intervention for acute coronary syndromes: the OPINION ACS randomised trial

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ABSTRACT

**BACKGROUND:** The clinical benefits of optical frequency domain imaging (OFDI)-guided percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) remain unclear.

**AIMS:** We sought to compare intravascular ultrasound (IVUS)- and OFDI-guided PCI in patients with ACS.

**METHODS:** OPINION ACS is a multicentre, prospective, randomised, non-inferiority trial that compared OFDI-guided PCI with IVUS-guided PCI using current-generation drug-eluting stents in ACS patients (n=158). The primary endpoint was in-stent minimum lumen area (MLA), assessed using 8-month follow-up OFDI.

**RESULTS:** Patients presented with ST-segment elevation myocardial infarction (55%), non-ST-segment elevation myocardial infarction (29%), or unstable angina pectoris (16%). PCI procedural success was achieved in all patients, with comparably low periprocedural complications rates in both groups. Immediately after PCI, the minimum stent area (p=0.096) tended to be smaller for OFDI versus IVUS guidance. Proximal stent edge dissection (p=0.012) and irregular protrusion (p=0.03) were significantly less frequent in OFDI-guided procedures than in IVUS-guided procedures. Post-PCI coronary flow, assessed using corrected Thrombolysis in Myocardial Infarction frame counts, was significantly better in the OFDI-guided group than in the IVUS-guided group (p<0.001). The least squares mean (95% confidence interval [CI]) in-stent MLA at 8 months was 4.91 (95% CI: 4.53-5.30) mm$^2$ and 4.76 (95% CI: 4.35-5.17) mm$^2$ in the OFDI- and IVUS-guided groups, respectively, demonstrating the non-inferiority of OFDI guidance ($p_{non\text{-}inferiority}$<0.001). The average neointima area tended to be smaller in the OFDI-guided group. The frequency of major adverse cardiac events was similar.

**CONCLUSIONS:** Among ACS patients, OFDI-guided PCI and IVUS-guided PCI were equally safe and feasible, with comparable in-stent MLA at 8 months. OFDI guidance may be a potential option in ACS patients. This study was registered in the Japan Registry of Clinical Trials (jrct.niph.go.jp: jRCTs052190093).

**KEYWORDS:** intravascular ultrasound; optical coherence tomography; optical frequency domain imaging; percutaneous coronary intervention





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Recent clinical trials have demonstrated that intravascular ultrasound (IVUS) guidance significantly improves the clinical outcome of percutaneous coronary intervention (PCI)[1,2]. Optical frequency domain imaging (OFDI; Lunawave [Terumo Corporation]) is an intravascular imaging device, based on optical coherence tomography (OCT) technology, which enables rapid image acquisition of a long coronary segment (up to 150 mm, 40 mm/s) within a few seconds. Since OFDI has >10 times higher resolution than IVUS, it offers more detailed information on the microstructure during PCI. Several clinical trials demonstrated that OCT-guided PCI is non-inferior to IVUS-guided PCI with regard to clinical outcomes in patients with coronary artery disease[3,4]. However, most patients in these trials had chronic coronary syndrome (CCS), and patients with ST-segment elevation myocardial infarction (STEMI) were excluded. Since the culprit plaque of an acute coronary syndrome (ACS) can be more vulnerable and thrombus-rich, the impact of IVUS and OFDI guidance could differ in this setting from that when treating lesions in patients with CCS. Therefore, we conducted the OPINION ACS trial to compare the results of PCI-treated lesions immediately after PCI and at the 8-month follow-up and the clinical outcomes of patients at the 12-month follow-up between OFDI- and IVUS-guided PCI for ACS.

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## Impact on daily practice

Among patients with acute coronary syndrome (ACS), optical frequency domain imaging (OFDI)- and intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) were equally safe and feasible, with comparable in-stent minimum lumen areas at 8 months. IVUS-guided PCI may facilitate larger stent sizing than OFDI-guided PCI, whereas OFDI-guided PCI may reduce the risk of stent edge dissection and a final Thrombolysis in Myocardial Infarction flow of <3 following PCI. Our results indicate that given the post-PCI findings, OFDI guidance might be an option for PCI in ACS patients.

## Methods

### STUDY DESIGN AND POPULATION

The design of the OPINION ACS trial has been previously described[5] (**Supplementary Appendix 1**, **Supplementary Appendix 2**). OPINION ACS is a prospective, multicentre, randomised, active-controlled, open-label, parallel-group, non-inferiority trial comparing OFDI-guided PCI with IVUS-guided PCI using current-generation drug-eluting stents (DES). The primary endpoint was in-stent minimum lumen area (MLA) at 8 months **(Supplementary Figure 1)**. Patients admitted to 10 hospitals in Japan between 14 February 2020 and 28 January 2022 were included. An independent data and safety monitoring committee monitored the safety of the trial. The Translational Research Informatics Center (Kobe, Japan) conducted data management, statistical analysis, and site management. OPINION ACS employed the following eligibility criteria: (1) patients aged 20-85 years; (2) ACS patients scheduled for PCI using a current-generation DES to treat a *de novo* native coronary artery lesion; (3) patients with written informed consent; and (4) patients whose target vessel diameter was 2.25-3.50 mm. ACS includes acute STEMI, non-STEMI (NSTEMI), and unstable angina pectoris. Patients with cardiogenic shock, chronic kidney disease, haemodialysis, or peritoneal dialysis, and female patients who were pregnant or planning to become pregnant were excluded. Eligible patients were then randomly assigned in a 1:1 ratio to receive either OFDI- or IVUS-guided PCI using a web-based randomisation software (conducted at the Translational Research Informatics Center, Kobe, Japan). In this study, we used the minimisation method, which is a dynamic randomisation method that can balance groups with respect to both the numbers in each treatment arm and the characteristics of each group. Randomisation was stratified according to (1) STEMI, (2) history of diabetes, and (3) study site. Participants and investigators were not masked to the allocation.

OPINION ACS was performed according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline as well as according to all applicable Japanese laws, rules, and regulations. The trial protocol was approved by the Institutional Review Board of Kobe University Hospital. All participants provided written informed consent. This study was registered with the Japan Registry of Clinical Trials (jrct.niph.go.jp: jRCTs052190093).

### PROCEDURES

Detailed procedures and antithrombotic therapy have been described previously[5] and are provided in **Supplementary Appendix 3**. In the OFDI-guided PCI group, the proximal and distal reference sites were set at cross-sections adjacent to the target lesion that had the most normal appearance and was free of lipidic plaque. The stent diameter was determined by measuring the lumen diameter at the proximal and distal reference sites, and the stent length was determined by measuring the distance from the distal to the proximal reference site. The stent diameter was determined to be 0.25-0.50 mm greater than the mean lumen diameter at the distal reference site.

## Abbreviations

| | |
|---|---|
| **DES** | drug-eluting stent |
| **IVUS** | intravascular ultrasound |
| **MLA** | minimum lumen area |
| **MSA** | minimum stent area |
| **NSTEMI** | non-ST-segment elevation myocardial infarction |
| **OCT** | optical coherence tomography |
| **OFDI** | optical frequency domain imaging |
| **OPINION** | OPtical frequency domain imaging vs. INtravascular ultrasound in percutaneous coronary interventiON |
| **PCI** | percutaneous coronary intervention |
| **STEMI** | ST-segment elevation myocardial infarction |
| **TIMI** | Thrombolysis in Myocardial Infarction |

In the IVUS-guided PCI group, proximal and distal reference sites were set at cross-sections adjacent to the target lesion that had the largest lumen and a plaque burden of <50%. The stent diameter was determined by measuring the vessel diameter (approximated by the external elastic membrane diameter) at the proximal and distal reference sites, and the stent length was determined by measuring the distance from the distal to the proximal reference site. The stent diameter was determined to be equal to or greater than the mean vessel diameter at the distal reference site and smaller than the mean vessel diameter at the proximal reference site.

Use of thrombus aspiration was left to the operator's discretion. Following stent implantation, acute results were evaluated by iterative intravascular imaging. In cases of incomplete stent expansion (minimum stent area [MSA]/average of proximal and distal reference luminal areas <0.8) or incomplete stent apposition, post-dilation using a balloon with a diameter 0-0.25 mm greater than the mean lumen diameter at the proximal reference site was recommended, if deemed safe and feasible, followed by further intravascular imaging.

In addition to post-PCI imaging using the allocated imaging modality, the OFDI-guided PCI group underwent post-PCI IVUS, whereas the IVUS-guided PCI group underwent post-PCI OFDI. The operators were not blinded to the findings of non-allocated imaging, but no additional procedures were allowed after the final non-allocated imaging. To assess the contrast media volume needed for PCI, we compared the total contrast volume in the OFDI-guided PCI group with that in the IVUS-guided PCI group, excluding the volume needed for the final OFDI image acquisition in the IVUS-guided PCI group. Both groups underwent follow-up angiography with OFDI 8 months after PCI **(Supplementary Figure 1)**.

### STUDY OUTCOMES

The primary endpoint of the OPINION ACS study was the MLA in the stented segment, as determined by the 8-month follow-up OFDI. The secondary endpoints are described in the **Supplementary Appendix 3**.

### QUANTITATIVE ANGIOGRAPHY, OPTICAL FREQUENCY DOMAIN IMAGING, AND INTRAVASCULAR ULTRASOUND ANALYSIS

Off-line angiogram, OFDI, and IVUS analyses were performed using dedicated software (QAngio XA [Medis Medical Imaging]; Lunawave [Terumo Corporation]; echoPlaque [INDEC Medical Systems]) in an independent core laboratory (Micron Inc., Osaka, Japan), blinded to the clinical presentation, lesion and procedural characteristics, and randomisation. Stent edge dissection, haematoma, plaque protrusion, and thin-cap fibroatheroma were qualitatively evaluated[6-9]. In-stent tissue protrusion was divided into 3 categories: smooth, disrupted fibrous tissue, and irregular **(Supplementary Figure 2)**[8]. All angiographic, OFDI, and IVUS parameters were prespecified by the core laboratory. Details of the OFDI and IVUS analyses are provided in **Supplementary Appendix 4**.

### CLINICAL OUTCOME

Clinical follow-up in the OPINION ACS trial was scheduled at discharge and at 8 and 12 months after PCI to evaluate the incidence of cardiac death, myocardial infarction attributed to the target vessel, ischaemia-driven target lesion revascularisation (TLR), target vessel revascularisation (TVR), target vessel failure (a composite of cardiac death, target vessel-related myocardial infarction, and ischaemia-driven TVR), and major adverse cardiac events (a composite outcome of cardiac death, myocardial infarction, and ischaemia-driven TLR) during the follow-up period (**Supplementary Appendix 4**). The incidence of distal embolisation during the PCI was also evaluated. The clinical events were adjudicated by each institution. Detailed statistical analyses are described in **Supplementary Appendix 3**.

## Results

### PATIENT FLOW

A total of 158 patients were enrolled and randomised to undergo either OFDI-guided (n=79) or IVUS-guided PCI (n=79). Nineteen patients were excluded from the analysis due to registration errors related to the process of obtaining informed consent. Details are described in **Figure 1**.

### COMPARISON OF BASELINE AND PROCEDURAL CHARACTERISTICS IN THE OFDI-GUIDED AND IVUS-GUIDED PERCUTANEOUS CORONARY INTERVENTION GROUPS

Patient clinical characteristics were well balanced between the OFDI-guided and IVUS-guided PCI groups **(Table 1, Supplementary Table 1)**. Most patients had STEMI (55%), followed by NSTEMI (29%) or unstable angina pectoris (16%). Angiographic lesion characteristics pre-PCI showed no significant differences between the groups, except for different distributions of target vessels **(Table 1, Supplementary Table 1-Supplementary Table 3)**.

**Table 2** and **Supplementary Table 4** summarise the procedural characteristics. The OFDI-guided PCI group showed a trend towards a smaller stent diameter and shorter total stent length than the IVUS-guided PCI group. The prevalence of distal protection device use was significantly lower in the OFDI-guided PCI group than in the IVUS-guided PCI group. The maximum balloon diameter was significantly smaller in the OFDI-guided PCI group than in the IVUS-guided PCI group. Based solely on the OFDI/IVUS evaluation, additional PCI procedures for lesion preparation before stenting and PCI optimisation after stenting were performed in 41 (63.1%) out of 68 patients in the OFDI-guided PCI group and in 40 (66.7%) out of 66 patients in the IVUS-guided PCI group (p=0.710).

The total fluoroscopic time was significantly shorter in the OFDI-guided PCI group than in the IVUS-guided PCI group. The amount of contrast medium used for PCI was significantly greater in the OFDI-guided PCI group than in the IVUS-guided PCI group. PCI procedural success was achieved in all cases **(Table 2)**. There were no OFDI/IVUS procedure-related complications in either group. Antithrombotic medications at discharge were not significantly different between the 2 groups **(Supplementary Table 5)**.

### OFDI AND IVUS FINDINGS POST-PERCUTANEOUS CORONARY INTERVENTION

The MSA and mean stent area measured by OFDI tended to be smaller, while the frequency of malapposed struts tended

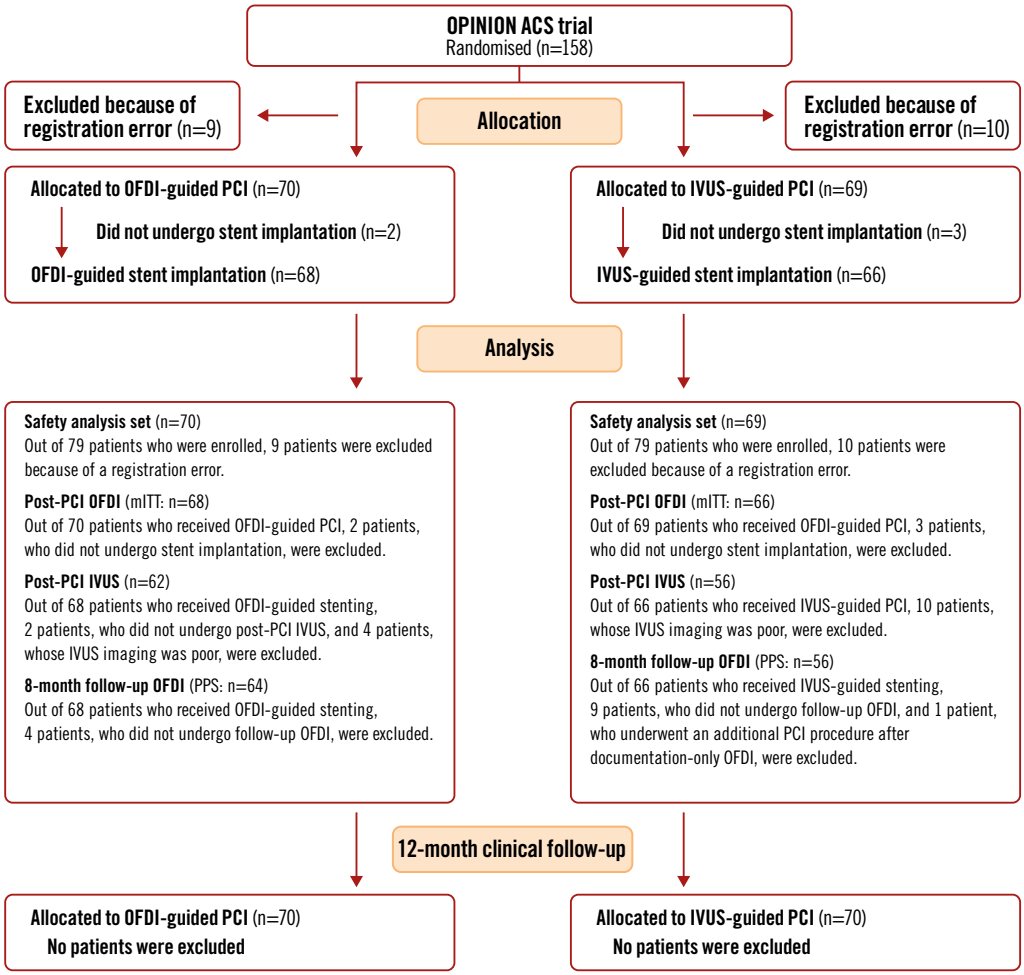



**Figure 1.** *Trial profile of the OPINION ACS study. ACS: acute coronary syndrome; IVUS: intravascular ultrasound; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; mITT: modified intention-to-treat; PPS: per protocol set*

to be higher in the OFDI-guided PCI group than in the IVUS-guided PCI group; however, the malapposed area and volume were comparable between the 2 groups **(Table 3)**.

Overall, the total tissue protrusion volume was significantly smaller in the OFDI-guided PCI group than in the IVUS-guided PCI group **(Table 3)**. Specifically, the prevalence and volume of irregular protrusions were significantly smaller in the OFDI-guided PCI group than in the IVUS-guided PCI group.

Post-PCI IVUS showed that, in adjacent reference segments, the percentage plaque volume and the frequency of lesions with residual stent edge plaque burden >50% were comparable between the groups **(Supplementary Table 6)**. Post-PCI OFDI showed that the frequency of proximal stent edge dissection was significantly lower in the OFDI-guided PCI group than in the IVUS-guided PCI group. The occurrence of haematoma was rare and comparable in both groups **(Table 3, Supplementary Table 6)**.

## THROMBOLYSIS IN MYOCARDIAL INFARCTION FLOW ANALYSIS

Post-PCI angiographic analysis revealed that the prevalence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 was significantly higher in the OFDI-guided PCI group than in the IVUS-guided PCI group **(Supplementary Table 2, Figure 2)**. Coronary flow after PCI, as assessed by corrected TIMI frame counts, was significantly better in the OFDI-guided PCI group than in the IVUS-guided PCI group **(Figure 2)**. There was a significant positive relationship between the corrected TIMI frame count and the volume of irregular protrusion on post-PCI OFDI.

## COMPARISON OF 8-MONTH OPTICAL FREQUENCY DOMAIN IMAGING FINDINGS

The primary endpoint, the least square means (95% confidence interval [CI]) of MLA by OFDI at 8 months, was 4.91 (95% CI: 4.53-5.30) mm$^2$ in the OFDI-guided PCI group and 4.76 (95% CI: 4.35-5.17) mm$^2$ in the IVUS-guided PCI group **(Supplementary Table 7)**. MLA with OFDI guidance was non-inferior to IVUS guidance (1-sided 95% lower CI: –0.31 mm$^2$; p<0.001) **(Central illustration)**. This result was similar to that observed in the modified intention-to-treat population **(Supplementary Table 8)**.

The mean neointimal volume and area were significantly smaller in the OFDI-guided PCI group than in the IVUS-guided PCI group **(Table 4)**. The changes in MLA and mean lumen area from post-PCI to 8-month follow-up OFDI were

**Table 1. Baseline characteristics (modified intention-to-treat).**

| | OPINION ACS (modified intention-to-treat: n=134) | | |
|---|---|---|---|
| | OFDI-guided (n=68) | IVUS-guided (n=66) | *p*-value |
| Age, years | 65.6±11.6 | 66.3±9.5 | 0.975 |
| Male | 52 (76.5) | 58 (87.9) | 0.114 |
| **Coronary risk factors** | | | |
| Hypertension | 47 (69.1) | 37 (56.1) | 0.153 |
| Dyslipidaemia | 44 (64.7) | 40 (60.6) | 0.721 |
| Diabetes mellitus | 25 (36.8) | 23 (34.8) | 0.858 |
| Current smoker | 9 (13.2) | 5 (7.6) | 0.385 |
| Family history of CAD | 6 (8.8) | 8 (12.1) | 0.582 |
| Obesity | 19 (27.9) | 17 (25.8) | 0.846 |
| Prior myocardial infarction | 1 (1.5) | 5 (7.6) | 0.112 |
| Prior PCI | 4 (5.9) | 9 (13.6) | 0.153 |
| Prior CABG | 0 (0) | 1 (1.5) | 0.492 |
| Clinical presentation | | | 1.000 |
| STEMI | 38 (55.9) | 35 (53.0) | 0.971 |
| NSTEMI | 19 (27.9) | 20 (30.3) | |
| Unstable angina pectoris | 11 (16.2) | 11 (16.7) | |
| **Lesion characteristics** | | | |
| Target coronary artery | | | 0.010 |
| LAD | 40 (58.8) | 25 (37.9) | |
| LCx | 11 (16.2) | 8 (12.1) | |
| RCA | 17 (25.0) | 33 (50.0) | |
| Location | | | 0.968 |
| Proximal | 23 (33.8) | 24 (36.4) | |
| Mid | 37 (54.4) | 34 (51.5) | |
| Distal | 8 (11.8) | 8 (12.1) | |
| ACC/AHA lesion type | | | 0.062 |
| A, B1 | 42 (61.8) | 51(77.3) | |
| B2, C | 26 (38.2) | 15 (22.7) | |
| Total occlusion | 28 (41.2) | 25 (37.9) | 0.726 |
| Ulceration | 3 (4.4) | 3 (4.5) | 1.000 |
| Moderate or heavy calcification | 4 (5.9) | 3 (4.5) | 1.000 |
| Thrombus | 25 (36.8) | 29 (43.9) | 0.481 |

Data are mean±standard deviation or n (%). ACC/AHA: American College of Cardiology/American Heart Association; CABG: coronary artery bypass graft; CAD: coronary artery disease; IVUS: intravascular ultrasound; LAD: left anterior descending artery; LCx: left circumflex artery; NSTEMI: non-ST-segment elevation myocardial infarction; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-segment elevation myocardial infarction

significantly smaller in the OFDI-guided PCI group than in the IVUS-guided PCI group (MLA change: –0.92 [95% CI: –1.35 to –0.19] mm$^2$ vs –1.19 [95% CI: –1.84 to –0.80] mm$^2$; p=0.006; average lumen area change: –0.79 [95% CI: –1.25 to 0.37] mm$^2$ vs –1.14 [95% CI: –1.63 to –0.58] mm$^2$; p=0.020). No statistical differences in the mean lumen volume or area at 8-month follow-up were noted between the groups.

The frequency of malapposed struts on 8-month follow-up OFDI was similar between the 2 groups. The frequency of uncovered struts was low in both groups but significantly lower in the IVUS-guided PCI group than in the OFDI-guided PCI group. Most of the dissections detected post-PCI had healed; the stent edge dissection remained in 1 reference segment in each group **(Table 4)**.

## CLINICAL OUTCOMES

The rates of cardiac death, myocardial infarction, target vessel-related myocardial infarction, ischaemia-driven TVR, ischaemia-driven TLR, major adverse cardiac events, stent thrombosis, and stroke were similar between the groups

**Table 2. Procedural characteristics and periprocedural complications (modified intention-to-treat).**

| | OPINION ACS (modified intention-to-treat: n=134) | | |
|---|---|---|---|
| | OFDI-guided (n=68) | IVUS-guided (n=66) | *p*-value |
| **Stent and procedures** | | | |
| Stent diameter, mm | 3.0 (2.8-3.5) | 3.0 (3.0-3.5) | 0.053 |
| Total stent length, mm | 28.0 (21.0-33.0) | 28.0 (24.0-35.0) | 0.087 |
| Number of stents per patient | 1.0 (1.0-1.0) | 1.0 (1.0-1.0) | 0.461 |
| Stent type | | | 0.485 |
| Ultimaster sirolimus-eluting stent[1] | 63 (92.7) | 57 (86.4) | |
| Everolimus-eluting stent | 4 (5.9) | 5 (7.6) | |
| Resolute Onyx[2] | 0 (0) | 1 (1.5) | |
| Orsiro[3] | 1 (1.5) | 3 (4.6) | |
| Others | 0 (0) | 0 (0) | |
| Thrombus aspiration | 25 (36.2) | 23 (34.9) | 1.000 |
| Rotablation | 0 (0) | 2 (3.0) | 0.237 |
| Distal protection | 3 (4.4) | 11 (16.7) | 0.023 |
| Post-dilation | 48 (69.6) | 40 (60.6) | 0.285 |
| Maximum balloon diameter, mm | 3.3 (3.0-3.5) | 3.5 (3.0-4.0) | 0.030 |
| Maximum inflation pressure, atm | 14.0 (12.0-16.0) | 14.0 (12.0-18.0) | 0.528 |
| **Further intervention after imaging** | | | |
| Predilation with upsized balloon | 17 (25.0) | 19 (28.8) | 0.698 |
| Predilation at high pressure | 8 (11.8) | 5 (7.6) | 0.561 |
| Predilation with cutting balloon | 7 (10.3) | 4 (6.1) | 0.531 |
| Rotablation | 0 (0) | 0 (0) | NA |
| Post-dilation | 23 (33.8) | 21 (31.8) | 0.855 |
| Additional stenting | 1 (1.5) | 3 (7.6) | 0.361 |
| Total fluoroscopic time, min | 26.0 (19.5-37.0) | 33.0 (23.0-46.0) | 0.046 |
| Amount of contrast needed for PCI, ml | 144.0 (116.0-180.0) | 118.0 (94.0-140.0) | <0.001 |
| PCI procedural success | 68 (100) | 66 (100) | NA |
| **Periprocedural complications** | | | |
| Life-threatening arrhythmia | 3 (4.3) | 3 (4.5) | 1.000 |
| Coronary dissection | 1 (1.4) | 2 (3.0) | 0.613 |
| Coronary spasm | 1 (1.4) | 1 (1.5) | 1.000 |
| Distal embolisation | 3 (4.3) | 7 (10.6) | 0.200 |
| Side branch occlusion | 4 (5.8) | 3 (4.5) | 1.000 |
| Air emboli | 0 (0) | 0 (0) | NA |
| Acute coronary occlusion | 0 (0) | 0 (0) | NA |
| Periprocedural complications due to imaging modalities | 0 (0) | 0 (0) | NA |

Data are median (interquartile range) or n (%). [1]by Terumo; [2]by Medtronic; [3]by Biotronik. IVUS: intravascular ultrasound; NA: not applicable; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention

**(Supplementary Table 9)**. Details of the cases with ischaemia-driven TVR are shown in **Supplementary Figure 3**. The incidence of contrast-induced nephropathy did not differ between the groups **(Supplementary Table 9)**.

## Discussion

This study is the first prospective randomised trial to compare the impact of IVUS and OFDI guidance in patients undergoing PCI for ACS, with an evaluation of midterm arterial responses using 8-month OFDI and 12-month clinical outcomes. The main findings of this study are as follows. 1) Both OFDI-guided and IVUS-guided PCI achieved high procedural success rates with low and comparable periprocedural complication rates. 2) Post-PCI, the OFDI-guided PCI group showed a trend of a smaller MSA with significantly fewer proximal stent-edge

**Table 3. OFDI results post-PCI (modified intention-to-treat).**

| | OPINION ACS (modified intention-to-treat: n=134) | | |
|---|---|---|---|
| | OFDI-guided (n=68) | IVUS-guided (n=66) | *p*-value |
| **In-stent segment** | | | |
| **3D analysis** | | | |
| Stent volume, mm$^3$ | 190.49 [144.07-232.75] | 217.13 [164.99-288.57] | 0.018 |
| Stent volume index, mm$^3$/mm | 6.77 [5.69-8.88] | 7.69 [6.35-8.97] | 0.071 |
| Lumen volume, mm$^3$ | 187.32 [141.21-224.41] | 217.57 [167.52-284.77] | 0.024 |
| Lumen volume index, mm$^3$/mm | 6.78 [5.70-8.80] | 7.74 [6.29-8.98] | 0.077 |
| **Cross-section-based analysis** | | | |
| Length, mm | 27.62±10.79 | 30.51±12.28 | 0.124 |
| Mean stent area*, mm$^2$ | 7.26 (6.72-7.80) | 7.93 (7.38-8.48) | 0.090 |
| Minimum stent area, mm$^2$ | 5.56 [4.51-7.66] | 6.33 [4.98-7.75] | 0.096 |
| Mean lumen area*, mm$^2$ | 7.21 (6.70-7.72) | 7.80 (7.28-8.31) | 0.112 |
| Minimum lumen area, mm$^2$ | 5.18 [4.32-7.03] | 5.69 [4.85-7.37] | 0.086 |
| Stent expansion index* | 0.90 (0.78-1.00) | 0.88 (0.76-1.06) | 0.772 |
| Cases with optimal stent expansion | 45 (66.2) | 37 (56.1) | 0.335 |
| **Stent malapposition** | | | |
| Malapposed strut*, % | 3.66 (2.58-5.17) | 2.31 (1.60-3.33) | 0.072 |
| Stent malapposition volume, mm$^3$ | 1.86 [0.79-4.82] | 1.88 [0.58-4.10] | 0.690 |
| Mean stent malapposition area*, mm$^2$ | 0.13 (0.10-0.16) | 0.14 (0.10-0.17) | 0.754 |
| **Tissue protrusion** | | | |
| **Quantitative tissue protrusion analysis** | | | |
| Tissue protrusion volume, mm$^3$ | 6.47 [4.17-12.24] | 8.37 [5.57-16.45] | 0.037 |
| Mean tissue protrusion area*, mm$^2$ | 0.33 (0.22-0.43) | 0.41 (0.30-0.51) | 0.276 |
| **Classification of tissue protrusion** | | | |
| Smooth protrusion | 35 (51.5) | 28 (42.4) | 0.305 |
| Disrupted protrusion | 27 (39.7) | 13 (19.7) | 0.014 |
| Irregular protrusion | 58 (85.3) | 64 (97.0) | 0.030 |
| **Quantitative irregular protrusion analysis** | | | |
| Number of irregular protrusions | 1.50 [1.00-2.00] | 2.00 [2.00-3.00] | <0.001 |
| Irregular protrusion volume, mm$^3$ | 2.43 [0.87-4.78] | 4.22 [1.91-10.40] | 0.004 |
| Mean irregular protrusion area*, mm$^2$ | 0.41 (0.33-0.50) | 0.45 (0.38-0.53) | 0.470 |
| Max irregular protrusion length, mm | 6.14 [4.05-11.39] | 12.09 [7.09-17.22] | <0.001 |
| Max irregular protrusion area, mm$^2$ | 0.72 [0.38-1.18] | 0.79 [0.48-1.53] | 0.099 |
| Max irregular protrusion thickness, mm | 0.40 [0.27-0.51] | 0.45 [0.33-0.68] | 0.062 |
| **Stent edge dissection and haematoma** | | | |
| Overall stent edge dissection | 8 (11.8) | 15 (22.7) | 0.111 |
| Proximal edge dissection | 3 (4.7) | 12 (20) | 0.012 |
| Distal edge dissection | 5 (7.4) | 8 (12.5) | 0.388 |
| Haematoma | 2 (2.9) | 2 (3.0) | 1.000 |
| **Proximal reference segment** | | | |
| Length, mm | 5.06 [5.06-5.06] | 5.06 [4.94-5.06] | 0.497 |
| Lumen volume, mm$^3$ | 38.58 [25.25-51.18] | 39.23 [28.94-47.09] | 0.823 |
| Mean lumen area*, mm$^2$ | 7.21 (6.70-7.72) | 7.80 (7.28-8.31) | 0.112 |
| Minimum lumen area, mm$^2$ | 6.71 [4.84-9.53] | 7.17 [5.24-9.38] | 0.450 |
| **Distal reference segment** | | | |
| Length, mm | 5.06 [5.06-5.06] | 5.06 [5.06-5.06] | 0.945 |
| Lumen volume, mm$^3$ | 25.91 [19.42-37.81] | 29.71 [20.58-41.55] | 0.137 |
| Mean lumen area*, mm$^2$ | 5.19 (3.73-7.51) | 5.73 (3.85-7.88) | 0.282 |
| Minimum lumen area, mm$^2$ | 4.39 [2.82-6.49] | 4.75 [3.44-6.85] | 0.420 |

Data are n (%) or median [interquartile range] for crude analysis and mean (95% confidence interval) for multilevel analysis. *assessed by multilevel analysis. Stent volume index indicates stent volume/length. Cases with optimal stent expansion indicate those with a stent expansion index >0.8.
3D: three-dimensional; IVUS: intravascular ultrasound; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention

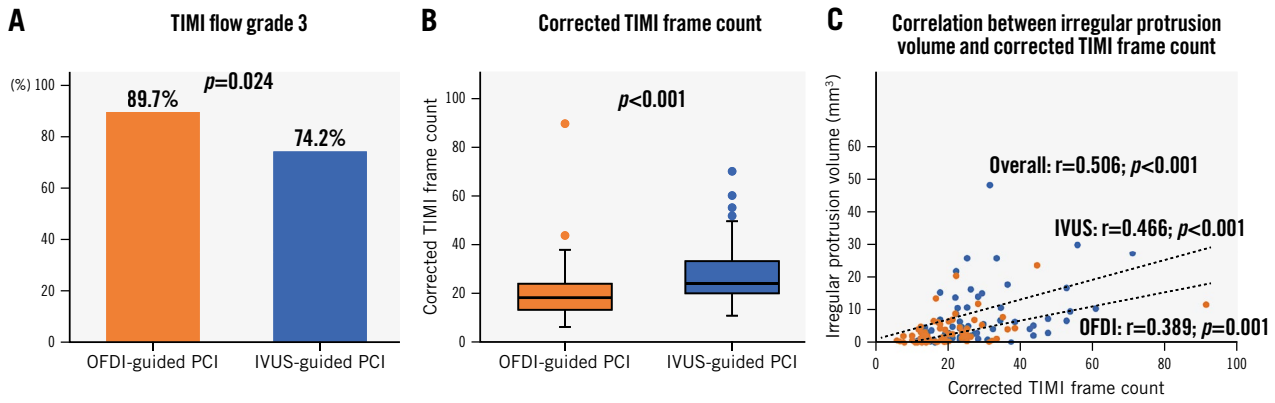
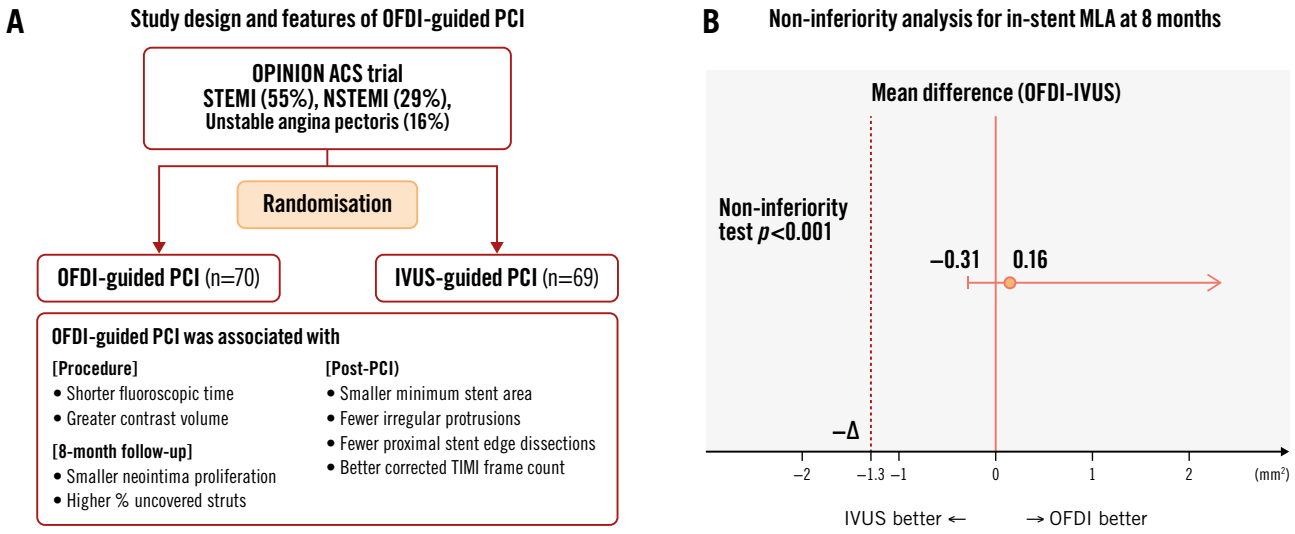



**Figure 2.** *TIMI flow analysis. A) TIMI flow grade 3. B) Corrected TIMI frame count. C) Correlation between irregular protrusion volume and corrected TIMI frame count. IVUS: intravascular ultrasound; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction*

EuroIntervention — Central **Illustration**

**OFDI versus IVUS in percutaneous coronary intervention for acute coronary syndrome.**

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*A) OPINION ACS: study design and features of OFDI-guided PCI. B) Primary endpoint result. ACS: acute coronary syndrome; IVUS: intravascular ultrasound; MLA: minimum lumen area; NSTEMI: non-ST-segment elevation myocardial infarction; OFDI: optical frequency domain imaging; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction*

dissections and irregular protrusions than the IVUS-guided PCI group. The OFDI-guided PCI group achieved a significantly higher prevalence of TIMI flow grade 3 with a better corrected TIMI frame count post-PCI. 3) The primary endpoint of MLA, assessed by 8-month follow-up OFDI, demonstrated the non-inferiority of OFDI guidance due to less neointimal hyperplasia in the OFDI-guided PCI group.

Ensuring safety is crucial in invasive imaging-guided PCI, particularly for ACS patients. A recent multicentre, randomised trial comparing IVUS-guided PCI to angiography-guided PCI in ACS patients demonstrated that IVUS-guided PCI significantly reduced the incidence of target vessel failure at 1 year post-PCI when compared with angiography-guided PCI, with comparable safety endpoint results between the 2 groups[10]. Unlike IVUS, OFDI requires

**Table 4. OFDI results at 8-month follow-up (per protocol set).**

| | OPINION ACS (per protocol set: n=120) | | |
|---|---|---|---|
| | OFDI-guided (n=64) | IVUS-guided (n=56) | *p*-value |
| **In-stent segment** | | | |
| **3D analysis** | | | |
| Stent volume, $mm^3$ | 192.81 [140.74-236.00] | 211.97 [158.58-276.17] | 0.087 |
| Stent volume index, $mm^3/mm$ | 6.83 [5.74-9.07] | 7.81 [5.95-8.96] | 0.405 |
| Lumen volume, $mm^3$ | 168.65 [108.76-209.26] | 177.05 [132.51-233.91] | 0.204 |
| Lumen volume index, $mm^3/mm$ | 5.99 [4.89-8.07] | 6.41 [5.02-7.50] | 0.628 |
| Neointima volume, $mm^3$ | 24.73 [14.31-35.12] | 33.21 [20.45-47.12] | 0.016 |
| **Cross-section-based analysis** | | | |
| Length, mm | 25.25 [19.49-32.15] | 28.35 [23.67-35.19] | 0.063 |
| Mean stent area*, $mm^2$ | 7.33 (6.79-7.88) | 7.86 (7.31-8.41) | 0.182 |
| Minimum stent area, $mm^2$ | 5.67 [4.65-8.15] | 5.97 [5.07-7.45] | 0.529 |
| Mean lumen area*, $mm^2$ | 6.39 (5.88-6.90) | 6.65 (6.13-7.18) | 0.479 |
| Minimum lumen area, $mm^2$ | 4.40 [3.34-6.44] | 4.72 [3.79-5.70] | 0.891 |
| Mean stent eccentricity index* | 0.93 (0.92-0.94) | 0.92 (0.92-0.93) | 0.050 |
| Mean neointima area*, $mm^2$ | 1.03 (0.92-1.13) | 1.24 (1.13-1.35) | 0.007 |
| Mean neointima thickness*, µm | 125 (95-154) | 138 (113-182) | 0.069 |
| **Stent malapposition** | | | |
| Stent with malapposition | 16 (25.0) | 9 (16.1) | 0.265 |
| Malapposed strut*, % | 0.16 (0.09-0.27) | 0.10 (0.05-0.17) | 0.184 |
| Stent malapposition volume, $mm^3$ | 0.45 [0.09-1.54] | 0.36 [0.10-1.48] | 0.650 |
| Mean stent malapposition area*, $mm^2$ | 0.06 (0.03-0.09) | 0.04 (0.01-0.07) | 0.425 |
| Uncovered struts*, % | 1.54 (1.05-2.26) | 0.83 (0.54-1.27) | 0.031 |
| **Proximal reference segment** | | | |
| Length, mm | 5.06 [5.06-5.06] | 5.06 [5.06-5.06] | 0.387 |
| Lumen volume, $mm^3$ | 35.13 [25.61-47.81] | 35.75 [24.49-46.38] | 0.928 |
| Mean lumen area*, $mm^2$ | 8.20 (7.32-9.07) | 8.17 (7.27-9.08) | 0.969 |
| Minimum lumen area, $mm^2$ | 6.23 [4.60-8.56] | 6.73 [3.84-7.88] | 0.759 |
| Dissection | 1 (1.6) | 0 (0) | 1.000 |
| **Distal reference segment** | | | |
| Length, mm | 5.06 [5.06-5.06] | 5.06 [5.06-5.06] | 0.148 |
| Lumen volume, $mm^3$ | 26.08 [20.13-40.02] | 27.60 [20.63-41.29] | 0.629 |
| Mean lumen area*, $mm^2$ | 5.96 (5.33-6.59) | 6.16 (5.51-6.81) | 0.664 |
| Minimum lumen area, $mm^2$ | 4.56 [3.52-6.63] | 4.74 [3.11-6.99] | 0.711 |
| Dissection | 0 (0) | 1 (1.8) | 0.466 |

Data are n (%) or median [interquartile range] for crude analysis and mean (95% confidence interval) for multilevel analysis. *assessed by multilevel analysis. Volume index indicates volume/length. 3D: three-dimensional; IVUS: intravascular ultrasound; OFDI: optical frequency domain imaging

intracoronary contrast medium injections, raising concerns about potential periprocedural adverse events. However, in this study, the rate of procedure-related complications in OFDI-guided PCI was notably low and comparable to that in IVUS-guided PCI. Although the OFDI-guided PCI group used greater amounts of contrast for PCI, the incidence of contrast-induced nephropathy post-PCI was similar between the 2 groups. Interestingly, the total fluoroscopic time was significantly shorter in the OFDI-guided PCI group than in the IVUS-guided PCI group. Although speculative, a faster OFDI pullback speed and angiographic coregistration with automatic measurement may have contributed to simplifying the PCI procedure, resulting in a shorter procedural time.

Post-PCI MSA is a robust predictor of TLR and stent thrombosis following stent implantation. Previous studies consistently highlighted that intravascular imaging-guided PCI using OCT or IVUS achieves a significantly larger MSA than angiography-guided PCI. However, the relationship between stent expansion and imaging modalities such as OCT and IVUS has been controversial. In our prior OPINION trial, we reported that the selected stent diameter was slightly but significantly smaller in the OFDI-guided PCI group than in the IVUS-guided PCI group, resulting in a smaller post-PCI MSA in the OFDI-guided PCI group[11]. The OCTIVUS trial echoed these results, demonstrating that the selected maximum stent and balloon sizes were notably larger in the IVUS group than in the OCT group[4]. Conversely, the ILUMIEN III trial, which employed an alternative OCT algorithm for optimal stent selection based on the external elastic lamina diameter, showed similar post-PCI MSA between OCT and

IVUS guidance[12]. In the current study, operators were guided to determine the stent diameter based on the distal lumen diameter for the OFDI-guided PCI group and the vessel diameter for the IVUS-guided PCI group. Consequently, the OFDI-guided PCI group exhibited a slightly smaller stent and maximum balloon diameter than the IVUS-guided PCI group, leading to a trend toward a smaller MSA post-PCI. However, these subtle differences did not translate into significant variations in MLA in the stented segment at 8-month follow-up OFDI, in angiographic parameters, or in binary restenosis rates at 8-month follow-up, probably due to less neointimal proliferation in the OFDI-guided PCI group.

Attaining a large MSA can have inherent complexities. The recent OCTIVUS randomised clinical trial reported a lower incidence of major procedural complications (e.g., major dissection, coronary perforation, vasospasm, thrombus formation, air embolisation, slow flow or no reflow, distal embolisation, acute closure, ventricular arrhythmia, cardiac tamponade, or cardiogenic shock) in the OCT-guided PCI group than in the IVUS-guided PCI group[4]. Although the precise reasons for these differences remain unclear, speculation points to a potentially more aggressive interventional approach in the IVUS arm, including larger stents and balloon sizing. Consistently, OFDI-guided PCI in our current study utilised smaller stent sizing and selected smaller maximum balloon sizes; this approach was associated with a lower incidence of stent edge dissection at the proximal edge, a higher incidence of cases achieving TIMI grade 3 flow with a better corrected TIMI frame count, and a numerically decreased occurrence of distal embolisation compared with IVUS-guided PCI.

Regarding the stent edge dissection, the OFDI-guided PCI group had significantly fewer proximal stent edge dissections than the IVUS-guided PCI group. Previous investigations, such as the ILUMIEN III trial[12], observed a significantly lower prevalence of post-PCI dissection in the OCT-guided PCI group than in the IVUS- and angiography-guided PCI groups. In our previous OPINION imaging substudy[11], the incidence of stent edge dissection with haematoma, a more severe form of stent edge dissection, was notably higher in the IVUS-guided PCI group than in the OFDI-guided PCI group, particularly at the proximal stent edges. Although still speculative, the differences in stent and post-balloon sizing may have contributed to the lower prevalence of stent edge dissections observed in the OFDI-guided PCI group. Considering the potential impact of stent edge-related issues, particularly in patients with haemodynamically unstable ACS, a smooth stent landing facilitated by OFDI guidance emerges as a positive aspect of OFDI-guided PCI.

In our study, the OFDI-guided PCI group demonstrated a significantly lower corrected TIMI frame count after PCI than the IVUS-guided PCI group. Amano et al reported a higher incidence of slow flow after stent implantation in lesions with irregular protrusions[13]; our study results align with this finding. We also found a statistically significant association between the volume of irregular protrusions and corrected TIMI frame count post-PCI. In our study, we observed a significantly lower incidence of irregular protrusions in the OFDI-guided PCI group than in the IVUS-guided PCI group post-PCI. Larger stent sizing with a selection of larger maximum balloon sizes might accelerate the development of irregular protrusions through the stent struts, potentially leading to distal embolisation during PCI. These results are particularly noteworthy in PCI for ACS patients, where no-reflow/slow-flow phenomena are more likely to occur.

In our study, despite a smaller post-PCI MSA in the OFDI-guided PCI group, we found comparable 8-month MLAs between the 2 groups. We attribute this to potential factors such as greater in-stent protrusion post-PCI and differences in neointimal progression. In addition, the OFDI-guided PCI group exhibited smaller neointima proliferation than the IVUS-guided PCI group. Similar trends were observed in a previous OPINION imaging substudy involving patients with CCS[11]. Previous studies in animals and humans have consistently demonstrated a positive relationship between vascular injury severity and increased neointimal proliferation[14-16]. This relationship has been observed not only in lesions treated with bare metal stents[17] but also in those treated with DES[16]. We speculate that the inflammatory reaction triggered to repair local arterial injury induced by IVUS-guided large stent and balloon sizing might have led to accelerated reactive neointimal growth within the stents. These findings support our speculation that IVUS-guided PCI may contribute to increased neointimal hyperplasia due to more aggressive stent sizing compared to OFDI-guided PCI. Considering the lower prevalence of stent edge dissection and the lower corrected TIMI frame count with comparable 8-month MLAs, opting for a smooth stent landing by adjusting the stent expansion to the lumen size under OFDI guidance might emerge as a potential option for guiding PCI in patients with ACS.

## Limitations

First, the small sample size may have increased the possibility of selection bias, and the study was not sufficiently powered to evaluate the clinical impact of imaging-guided PCI. Additionally, 19 patients were excluded from the analysis due to registration errors related to the process of obtaining informed consent. Following this incident, we have implemented proactive measures to prevent similar occurrences in the future, and such errors have not recurred. Second, although the incidence of contrast-induced nephropathy after PCI was extremely low and comparable between the 2 groups, patients at high risk of contrast-induced nephropathy (i.e., severe renal dysfunction at baseline) were not included in the study. Third, the rate of recruitment in our study was low (5.2%), primarily because of the onset of the COVID-19 pandemic, which imposed significant restrictions on hospital admissions and patient care. Our patient enrolment period coincided with the initial phase of the pandemic, leading to challenges in recruiting eligible patients. Despite the protocol requiring rehospitalisation for follow-up OFDI, the restrictions imposed during the pandemic made it difficult to adhere to the study protocol and enrol patients as planned. Fourth, in our study, each clinical event was adjudicated by the respective institution rather than by an independent committee. Finally, the follow-up period was limited to 12 months. Further studies with longer follow-up periods are required to address the long-term impact of these imaging-guided procedures.

## Conclusions

Detailed IVUS and OFDI analyses with a blinded comparison confirmed several differences in local findings between OFDI- and IVUS-guided PCI in patients with ACS. The MLA on 8-month follow-up OFDI was comparable between the 2 groups, suggesting that both OFDI- and IVUS-guided PCI are similarly feasible for coronary intervention using current-generation DES. Given the post-PCI findings, OFDI guidance may be a potential option for PCI in ACS.

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## Conflict of interest statement

T. Akasaka is a medical advisor of Terumo Corporation (employee). The other authors have no conflicts of interest relevant to the contents of this paper to declare.

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## Supplementary data

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**Supplementary Appendix 2.** Participating institutions and OPINION ACS investigators.
**Supplementary Appendix 3.** Supplementary methods.
**Supplementary Appendix 4.** Definitions.
**Supplementary Table 1.** Baseline patient and lesion characteristics (per protocol set).
**Supplementary Table 2.** Quantitative angiographic findings (modified intention-to-treat).
**Supplementary Table 3.** Quantitative angiographic findings (per protocol set).
**Supplementary Table 4.** Procedural characteristics (per protocol set).
**Supplementary Table 5.** Antithrombotic therapy (safety analysis set).
**Supplementary Table 6.** IVUS results post-PCI.
**Supplementary Table 7.** Non-inferiority analysis of MLA by 8-month follow-up OFDI (per protocol set).
**Supplementary Table 8.** Sensitivity analysis of MLA using 8-month follow-up OFDI (modified intention-to-treat).
**Supplementary Table 9.** Clinical outcomes.
**Supplementary Figure 1.** OPINION ACS study flow.
**Supplementary Figure 2.** Representative OFDI images.
**Supplementary Figure 3.** Cases with target vessel revascularisation.

*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00314*

**Supplementary data**

**Supplementary Appendix 1. Study organisation.**

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**Supplementary Appendix 3. Supplementary methods.**

***3-1. Use of distal protection***

In the OFDI-guided PCI group, the use of distal protection could be considered if the culprit lesion had one of the following: 1) multiple thrombi; 2) a thin-cap fibroatheroma, defined as a plaque with a minimal fibrous cap thickness < 65 mm; and/or 3) a maximum lipid arc >180 degrees.

In the IVUS-guided PCI group, the use of distal protection could be considered if the culprit lesion had an attenuated plaque (defined as a hypoechoic or mixed atheroma with ultrasound attenuation but without calcification) > 5 mm in longitudinal length.

***3-2. OFDI and IVUS procedure***

An OFDI examination was performed using LUNAWAVE® (Terumo Corporation, Tokyo, Japan) as previously described[3]. A bolus intracoronary injection of nitroglycerin or isosorbide dinitrate was performed before OFDI. After manual calibration, the OFDI catheter was advanced > 5 mm distal to the target lesion over a 0.014-inch conventional angioplasty guidewire. Following catheter placement, the preheated contrast medium was flushed through the guiding catheter at a rate of 2–4 mL/s for approximately 3–6 s, using an injector pump. When a blood-free image was obtained, the OFDI imaging core was pulled back over a longitudinal distance of up to 150 mm at a rate of 20–40 mm/s using the standalone electronic control of the pullback motor.

IVUS procedures were planned for all patients assigned to the imaging study following the index procedure (post-stent) using an intravascular ultrasound catheter (ViewIT®: Terumo Corporation, Tokyo, Japan) and an ultrasound diagnostic imaging system (VISIWAVE®: Terumo Corporation, Tokyo, Japan). A bolus intracoronary injection of

nitroglycerin or isosorbide dinitrate was performed before IVUS imaging. The IVUS catheter was advanced > 5 mm distal to the target lesion over a 0.014-inch conventional angioplasty guidewire. The IVUS procedure was then performed in a standard fashion using an automated motorized 1.0 mm/s pullback with commercially available imaging systems (Terumo Corporation, Tokyo, Japan).

### *3-3. OFDI and IVUS analysis*

Offline OFDI analysis was performed using a dedicated software (Terumo Corporation, Japan) in an independent core laboratory at Kobe University Graduate School of Medicine (Kobe Cardiovascular Core Analysis Laboratory, Kobe, Japan) blinded to the clinical presentation, lesions, procedural characteristics, and randomization. For the quantitative OFDI analysis, cross-sectional OFDI images were analysed at 1-mm intervals in stented segments and in adjacent reference segments (≤5 mm long). The stent and lumen areas were measured manually for every 1 mm, and the neointima area was calculated as the stent area minus the lumen area on the 8-month follow-up OFDI images. The stent expansion index was calculated as the minimum stent area (MSA)/average of the proximal and distal reference luminal areas. A case with a stent expansion index of >0.8 was regarded as a case with optimal stent expansion[19]. Using Simpson's method, the lumen, stent, malapposed, and neointima volumes were computed, and the volume index was calculated as volume data divided by length to adjust for different segment lengths. Neointima thickness was measured as the distance from the centre reflection of the stent strut to the vessel-lumen border for each stent strut. An uncovered strut was defined as that with a neointima thickness equal to 0 μm. A malapposed strut was defined as the maximum distance > the thickness of the strut and polymer[20] between the centre reflection

of the strut and the adjacent vessel surface. For the quantitative evaluation of malapposition, the malapposed area was measured for each cross section and averaged for the entire stented segments.

A qualitative assessment was performed for every frame to evaluate stent-edge dissection, in-stent dissection, haematoma, plaque protrusion, thin-cap fibroatheroma at the reference segment, and thrombus. Stent-edge dissection was defined as the disruption of the vessel luminal surface with a visible flap at the stent edge or 5 mm proximal and distal reference segments (Supplementary Figure 1A)[19]. When a dissection flap was visualized, the maximal flap length on the cross-sectional view was measured as the maximum dissection length. The dissection length (mm) on the longitudinal view was also measured. Stent edge dissection with haematoma was defined as a hypo-backscattering area related to stent-edge dissection (Supplementary Figure 1B)(7). Thin-cap fibroatheroma was defined as a plaque presenting with a fibrous-cap thickness of <65 μm and a lipid arc of ≥90 degrees (Supplementary Figure 1C)[7]. In-stent dissection was defined as the disruption of the luminal vessel surface within the stented segment. In-stent tissue protrusion was divided into three categories: smooth protrusion, disrupted fibrous tissue protrusion, and irregular protrusion (Supplementary Figure 1D–F)[8]. Smooth protrusion was defined as the bowing of the plaque into the lumen between stent struts, without intimal disruption, and appeared as a smooth semicircular arc connecting adjacent struts, which is likely to represent compression of the soft plaque by the stent. Disrupted fibrous tissue protrusion was defined as the disruption of the underlying fibrous tissue protruding in between the stent struts into the lumen. Irregular protrusion was defined as the protrusion of a material with an irregular surface into the lumen between the stent struts. As struts are sometimes buried within the intima, we only included in-stent protrusions with a maximal height of

≥100 μm for analysis in the current study. For quantitative assessment of plaque protrusion, the longitudinal length was measured, and the maximum thickness, average area, and volume were calculated.

Volumetric IVUS measurements were performed using planimetry software (echoPlaque, Indec Systems Inc., Santa Clara, CA, USA), as previously described[9]. Briefly, lumen, stent, and vessel areas were traced manually at every 1.0-mm interval in stented segments and in adjacent reference segments (≤5 mm long). Using Simpson's method, the lumen, vessel, peri-stent plaque (vessel minus stent), and neointima volumes were computed, and the volume index was calculated as volume data divided by length to adjust for different segment lengths. Plaque protrusion was defined as protruding material into the lumen.

### *3-4. Antithrombotic therapy*

Procedural anticoagulation was achieved with heparin according to local site protocols. At the index procedure, a loading dose of aspirin (81–200 mg) plus clopidogrel (loading dose, 300 mg) or prasugrel (loading dose, 20 mg) was administered before PCI in patients who were not on chronic antiplatelet treatment. The recommended duration of dual antiplatelet therapy (aspirin >81 mg daily and clopidogrel 75 mg or prasugrel 3.75 mg) was until 8-month follow-up; however, a shorter dual antiplatelet therapy duration was allowed if the operator deemed it appropriate.

### *3-5. Study outcomes*

The primary endpoint of the OPINION ACS study was the MLA in the stented segment, as determined by the 8-month follow-up OFDI. The secondary endpoints included: (1) the minimum stent and lumen areas assessed by OFDI post-PCI; (2) the frequency of

irregular protrusions, edge dissection, and haematomas assessed by OFDI post-PCI; (3) the percentage of uncovered and malapposed struts by 8-month follow-up OFDI; and (4) the average neointimal thickness, average neointimal area, and average lumen area by 8-month follow-up OFDI

### *3-6. Statistical analysis*

The primary endpoint of this study was to confirm the non-inferiority of OFDI-guided PCI to IVUS-guided PCI with regard to the MLA at 8 months post-PCI in patients with ACS. Based on the OPINION imaging study (11), we assumed the following: 1) a 0 $mm^2$ between-group difference in the mean MLA 8 months after PCI, 2) a non-inferiority margin of 1.3 $mm^2$, and 3) a standard deviation of 2.3 $mm^2$. With these assumptions, we calculated that 60 patients per group would be required for the study to provide 90% power to detect the non-inferiority of OFDI-guidance to IVUS-guidance, with a one-sided alpha level of 0.05. Assuming a dropout rate of 30%, we planned to enrol 158 patients (n = 79 per group).

The primary endpoint was analysed in the per-protocol set (PPS) population that underwent OFDI-guided PCI or IVUS-guided PCI with no major protocol deviations. Non-inferiority was tested using an analysis of covariance (ANCOVA) model with the treatment group, reference vessel diameter, STEMI, and diabetes as covariates. The criterion for non-inferiority was that the lower limit of the one-sided 95% confidence interval of the difference in least square means estimated by the ANCOVA model was above the non-inferiority margin of -1.3. We also performed sensitivity analyses for the primary endpoint in the modified intention-to-treat (mITT) population of all randomized patients who underwent stenting.

The baseline characteristics, angiographic findings, lesion characteristics, and other efficacy endpoints were evaluated in the mITT population. Categorical data were compared using Fisher's exact test. Continuous variables were presented as medians with interquartile ranges and were compared using the Wilcoxon rank-sum test. A multilevel random effects model was used to compare several OCT findings (Supplementary Material). The correlation between the irregular protrusion volume and corrected TIMI frame count was examined using Spearman's correlation.

Except for the non-inferiority test of the primary endpoint, all reported p-values are two-sided, with values less than 0.05 considered significant. All statistical analyses were conducted using the SAS software (version 9.4; SAS Institute, Cary, NC, USA).

**Supplementary Appendix 4. Definitions.**

| **Inclusion/exclusion criteria** | **Definition** |
|---|---|
| Acute coronary syndrome | Acute ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina |
| Cardiogenic shock | Cardiac death according to MIRU definition<br>Clinical condition of inadequate tissue (end-organ) perfusion* due to sustained low blood pressure†<br>……<br>* Impaired organ perfusion<br>Oliguria with urine output <20 mL/h<br>Consciousness disturbance<br>Peripheral vasoconstriction<br>† Systolic blood pressure < 90 mmHg or 30 mmHg below the basal value<br>(Exclusion: low blood pressure due to vasovagal reflex or arrhythmias) |
| Chronic kidney disease | Estimated glomerular filtration rate <30 mL/min/1.73 $m^2$ or serum creatinine level >1.5 mg/dL |
| **Clinical presentation** | **Definition** |
| Unstable angina pectoris | Any one of the following criteria meets the diagnosis for unstable angina pectoris.<br>(1) New onset (within the recent month) angina<br>(2) Increasing angina within the recent month: angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previous<br>(3) Resting angina: angina at rest or angina by which daily living is significantly restricted. The symptoms appear after walking for several dozen meters or walking up a flight of stairs.<br>(4) Post-infarction unstable angina: angina within the first month after a documented acute myocardial infarction (ST elevation on electrocardiogram and/or increases of serum level of cardiac markers are not accompanied. If accompanied, clinical diagnosis is ST-segment elevated or non-ST-segment elevated myocardial infarction.) |
| ST-elevation myocardial infarction (STEMI) | New ST-segment elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V1–V3 where the following cut-points apply: ≥ 0.2 mV |
| Non-ST-elevation myocardial infarction (NSTEMI) | Non-ST-segment elevation myocardial infarction<br>Myocardial infarction other than ST-segment elevation myocardial infarction |

| Coronary angiography | Definition |
|---|---|
| ACC/AHA lesion type | (1) Type A Lesions<br>Discrete (<10 mm length)<br>Concentric<br>Readily accessible<br>Non-angulated segment (<45 degrees)<br>Smooth contour<br>Little or no calcification<br>Less than totally occlusive<br>Not ostial in location<br>No major branch involvement<br>Absence of thrombus<br>(2) Type B Lesions *<br>Tubular (10–20 mm length)<br>Eccentric<br>Moderate tortuosity of proximal segment<br>Moderately angulated segment (>45 degrees <90 degrees)<br>Moderate to heavy calcification<br>Total occlusion <3 months old<br>Ostial in location<br>Bifurcation lesions requiring double guidewires<br>Irregular contour<br>Some thrombi present<br>* B1 (one adverse characteristic) and B2 (>two adverse characteristics)<br>(3) Type C lesions<br>Diffuse (>2 cm length)<br>Excessive tortuosity of proximal segment<br>Extremely angulated segments (>90 degrees)<br>Total occlusion >3 months old<br>Inability to protect major side branches<br>Degenerated vein grafts with friable lesions |
| Percent diameter stenosis | (Reference vessel diameter – minimum lumen diameter) x 100 / reference vessel diameter |
| Thrombolysis In Myocardial Infarction (TIMI) flow grade | |
| Acute gain | Minimum lumen diameter at post-PCI – minimum lumen diameter at pre-PCI |
| Late loss | Minimum lumen diameter at post-PCI – minimum lumen diameter at 8-month follow-up |
| In-stent | Coronary segment implanted stent |
| In-segment | Coronary segment involving the implanted stent and the 5-mm proximal and distal edges adjacent to the stent |
| Binary restenosis | Percent diameter stenosis at follow-up >50% |

| **Percutaneous coronary intervention (PCI)** | **Definition** |
|---|---|
| PCI procedure success | Successful stent implantation in target lesion with residual diameter stenosis <50% without any major in-hospital complications including death, myocardial infarction, or stroke |
| **Procedure-related complications** | **Definition** |
| Optical frequency domain imaging (OFDI)/intravascular ultrasound (IVUS) and PCI procedure-related complications | Composite of acute coronary occlusion, air embolization, slow flow, distal embolization, side branch occlusion, coronary dissection, thrombus formation, vasospasm, and ventricular arrhythmia<br>……<br>Note: Assessment of the procedure related complications are based on angiography during PCI. Individual components of the procedure related complications are defined below |
| Acute coronary occlusion | Abrupt closure in the target coronary artery during PCI |
| Air embolism | Embolism caused by one or more air bubbles |
| Slow flow | TIMI flow grade <3 without evidence of dissection, stenosis, or vasospasm during PCI in the target coronary artery with previously normal anterograde flow (TIMI 3) |
| Distal embolization | A distal filling defect with an abrupt 'cut-off' in the main target coronary artery or one of the peripheral coronary branches, distal to the site of angioplasty |
| Side branch occlusion | TIMI flow grade <3 in side branch (diameter of ≥2.3 mm) immediately after PCI |
| Coronary dissection | Coronary dissection is defined according to the National Heart Lung and Blood Institute (NHLBI) criteria<br>(1) Minor radiolucent areas within the coronary lumen during contrast injection, with little or no persistence of contrast after the dye has cleared<br>(2) Parallel tracts or a double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance<br>(3) Contrast outside the coronary lumen with persistence of contrast after dye has cleared from the lumen<br>(4) Spiral luminal filling defects<br>(5) Appearance of a new, persistent filling defects within the coronary lumen<br>(6) Dissections leading to total occlusion of the coronary lumen without distal antegrade flow<br>……<br>Note: Coronary dissection includes residual final dissection (occurring proximally or distally to the deployed stent; and persisting after the last balloon |

| | |
|---|---|
| | inflation) and non-persistent dissection (sealed with additional stents or balloon inflations) |
| Thrombus formation | Intraluminal filling defect or haze seen in multiple angiographic projections |
| Vasospasm | Sudden, intense vasoconstriction of an epicardial coronary artery that causes vessel occlusion or near occlusion |
| Ventricular arrhythmia | Sustained ventricular tachycardia (defined as a regular wide-complex tachycardia of ventricular origin lasting >30 s and/or accompanied by haemodynamic compromise requiring electrical cardioversion or anti-arrhythmic therapy) and ventricular fibrillation (defined as irregular undulations of varying contour and amplitude on the electrocardiography, with absent distinct QRS and T waves and haemodynamic compromise requiring direct-current defibrillation) occurring in the cardiac catheterization laboratory during PC |
| **OFDI** | **Definition** |
| Stent expansion index | Minimum stent area/ average of proximal and distal reference lumen area |
| Uncovered struts | Struts with measured neointima thickness equal to 0 mm |
| Stent malapposition | Stents with the maximum distance > the thickness of stent strut plus polymer between the centre reflection of the strut and the adjacent vessel surface. |
| Stent-edge dissection | The disruption of the vessel luminal surface with a visible flap at the stent edge or 5 mm proximal and distal reference segments (Supplementary Figure 1A) |
| Stent-edge dissection with haematoma | Hypo-backscattering area related to stent-edge dissection (Supplementary Figure 1B) |
| In-stent dissection | In-stent dissection was defined as disruption of the luminal vessel surface within the stented segment |
| Thin-cap fibroatheroma | A plaque presenting with a fibrous-cap thickness <65 μm and a lipid arc ≥90 degrees[7] (Supplementary Figure 1C) |
| Tissue protrusion | Protruding material into the lumen with maximal height ≥100 μm[8] |
| Smooth protrusion | The bowing of plaque into the lumen between stent struts, without intimal disruption, appearing as a smooth semicircular arc connecting adjacent struts (Supplementary Figure 1D)[8] |
| Disrupted fibrous tissue protrusion | Disruption of underlying fibrous tissue protruding in between stent struts (Supplementary Figure 1E)[8] |
| Irregular protrusion | Protrusion of material with an irregular surface into the lumen between stent struts (Supplementary Figure 1F)[8] |
| In-stent segment | Coronary segment implanted stent |
| Reference segment | Within 5 mm segment adjacent to the implanted stent |

| IVUS | Definition |
|---|---|
| Volume index | Volume data divided by length |
| Peri-stent plaque | Vessel minus stent |
| Percent peri-stent plaque volume | Peri-stent plaque volume divided by stent volume |
| Tissue protrusion | Protruding material into the lumen |
| **Clinical endpoints** | **Definition** |
| Cardiac death | Cardiac death according to ARC definition[18]<br>Any death due to proximate cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment<br>……<br>Note: Unexpected death even in patients with coexisting and potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac unless the history related to the non-cardiac diagnosis suggests death was imminent |
| Myocardial infarction | Myocardial infarction includes acute myocardial infarction and prior myocardial infarction<br>(1) Acute myocardial infarction<br>Symptom of ischaemia with serum creatinine kinase MB fraction<br>≥2 times upper limit of normal or serum troponin ≥ the 99th percentile<br>(2) Prior myocardial infarction<br>Any one of the following criteria meets the diagnosis for prior myocardial infarction<br>(i) Abnormal Q wave in any two leads of a contiguous lead (grouping I, aVL; V1–V6; II, III, aVF) without symptom of ischaemia within 1 month<br>(ii) Imaging evidence of a region of loss of variable myocardium that thinned and fails to contract without symptom of ischaemia within 1 month<br>……<br>Electrocardiographic detection of myocardial infarction: Q wave<br>(1) Q wave myocardial infarction<br>Abnormal Q wave in any two leads of a contiguous lead (grouping I, aVL; V1–V6; II, III, aVF) with or without serum creatinine kinase MB fraction ≥2 times upper limit of normal or serum troponin<br>≥ the 99th percentile<br>(2) Non-Q wave myocardial infarction<br>Myocardial infarction other than Q wave myocardial infarction |

| | |
|---|---|
| | ……<br>Electrocardiographic detection of myocardial infarction: ST-segment<br>(1) ST-segment elevation myocardial infarction<br>New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V1–V3, where the following cut-points apply: ≥0.2 mV<br>(2) Non-ST-segment elevation myocardial infarction<br>Myocardial infarction other than ST-segment elevation myocardial infarction |
| Target-vessel related myocardial infarction | Myocardial infarction in the vessel treated at the index PCI |
| Target vessel failure | Composite of cardiac death, target-vessel related myocardial infarction, and ischaemia-driven target vessel revascularization<br>……<br>Note: Individual components of the primary endpoint are defined in the secondary endpoints |
| Ischaemia-driven target lesion revascularization | Repeat PCI or bypass graft placement for restenosis or other complications at the lesion treated during index PCI or occurring within 5 mm of the PCI site<br>……<br>Note: Target lesion revascularization is considered ischaemia-driven if the target lesion was >70% diameter stenosis by quantitative coronary angiography analysis at the independent angiography core laboratory or for diameter stenosis between ≥50% and ≤70% if the event assessment committee determined there was objective evidence of recurrent angina pectoris or objective signs of ischaemia in any diagnostic test |
| Ischaemia-driven target vessel revascularization | Unplanned repeat PCI or bypass graft placement for a stenosis in another part of the vessel treated at the index PCI<br>……<br>Note: Target vessel revascularization is considered ischaemia-driven if the lesion in the vessel treated at the index PCI was >70% diameter stenosis by quantitative coronary angiography analysis at the independent angiography core laboratory or for diameter stenosis between ≥50% and ≤70% if the event assessment committee determined there was objective evidence of recurrent angina pectoris or objective signs of ischaemia in any diagnostic test. Target vessel revascularization includes target lesion revascularization. Target vessel revascularization does not include planned, staged PCI |

| | |
|---|---|
| | for a stenosis in another part of the vessel treated at the index PCI |
| Major adverse cardiac event | Composite of cardiac death, myocardial infarction, or ischaemia-driven target lesion revascularization<br>Note: Individual components of the major adverse cardiac event are defined in the secondary endpoints |
| Stent thrombosis | Stent thrombosis per ARC definition[18]<br>(1) Definite stent thrombosis*<br>Angiographic confirmation of stent thrombosis†<br>The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-h time window:<br>Acute onset of ischaemic symptoms at rest<br>New ischaemic ECG changes that suggest acute ischaemia<br>Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)<br>Non-occlusive thrombus<br>Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream<br>Occlusive thrombus<br>TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).<br>(2) Pathological confirmation of stent thrombosis<br>Evidence of a recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy<br>(3) Probable stent thrombosis<br>Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:<br>Any unexplained death within the first 30 days<br>Irrespective of the time after the index procedure, any myocardial infarction that is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause<br>Possible stent thrombosis |

| | |
|---|---|
| | Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up<br>……<br>* Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation<br>† The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)<br>‡ Intracoronary thrombus |
| Stroke | Ischaemic or haemorrhagic stroke requiring hospitalization with symptoms lasting >24 h<br>……<br>Note: Transient ischaemic attack (TIA) (defined as a neurological event with the signs and symptoms of a stroke, but which go away within a short period of time [<24 h]) is excluded |
| Contrast-induced nephropathy | Increase of serum creatinine level of $\geq$ 25% or $\geq$0.5 mg/dL within 72 h after PCI |

ACC=American College of Cardiology. AHA=American Heart Association. ARC=Australian Resuscitation Council. IVUS=intravascular ultrasound. MIRU= myocardial intervention research unit. OFDI= Optical frequency domain imaging. PCI=percutaneous coronary intervention. TIMI=Thrombolysis In Myocardial Infarction.

**Supplementary Table 1. Baseline patient and lesion characteristics (per protocol set).**

| | OPINION ACS per protocol set (n=120) | | |
|---|---|---|---|
| | OFDI-guided (n=64) | IVUS-guided (n=56) | p value |
| Age, yrs | 65.2 ± 11.9 | 66.0 ± 9.4 | 0.981 |
| Men | 48 (75.0) | 50 (89.3) | 0.058 |
| Obesity | 18 (28.1) | 16 (28.6) | 1.000 |
| Coronary risk factor | | | |
| Hypertension | 45 (70.3) | 32 (57.1) | 0.181 |
| Dyslipidaemia | 43 (67.2) | 36 (64.3) | 0.847 |
| Diabetes mellitus | 41 (64.1) | 37 (66.1) | 0.849 |
| Current smoker | 9 (14.1) | 3 (5.4) | 0.163 |
| Family history of coronary artery disease | 6 (9.4) | 7 (12.5) | 0.769 |
| Prior myocardial infarction | 1 (1.6) | 4 (7.1) | 0.183 |
| Prior PCI | 3 (4.7) | 8 (14.3) | 0.110 |
| Prior CABG | 0 (0.0) | 1 (1.8) | 0.466 |
| Clinical presentation | | | 1.00 |
| STEMI | 37 (57.8) | 31 (55.4) | 0.819 |
| NSTEMI | 16 (25.0) | 17 (30.4) | |
| Unstable angina pectoris | 11 (17.2) | 8 (14.3) | |
| Lesion characteristics | | | |
| Target coronary artery | | | 0.002 |

| | | | |
|---|---|---|---|
| LAD | 39 (60.9) | 18 (32.1) | |
| LCX | 9 (14.1) | 8 (14.3) | |
| RCA | 16 (25.0) | 30 (53.6) | |
| Location: proximal/mid/distal | 23 (35.9) /33 (51.6)/8 (12.5) | 19 (33.9)/ 29 (51.8)/8 (14.3) | 0.967 |
| ACC/AHA lesion type A, B1/ B2, C | 40 (62.5) / 24 (37.5) | 41 (73.2)/15 (26.8) | 0.244 |
| Total occlusion | 26 (40.6) | 22 (39.3) | 1.000 |
| Ulceration | 3 (4.7) | 3 (5.4) | 1.000 |
| Moderate or heavy calcification | 4 (6.3) | 3 (5.4) | 1.000 |
| Thrombus | 24 (37.5) | 25 (44.6) | 0.460 |

Data are n (%) or mean ± SD. SD=standard deviation; PCI=percutaneous coronary intervention; CABG= coronary artery bypass Graft; STEMI=ST-elevation myocardial infarction, NTEMI=non-ST-elevation myocardial infarction; LAD=left anterior descending artery; LCX= left circumflex artery; right coronary artery; IVUS=intravascular ultrasound; OFDI=optical frequency domain imaging.

**Supplementary Table 2. Quantitative angiographic findings (modified intention-to-treat).**

| | OPINION ACS (modified intention to treat: n=134) | | |
|---|---|---|---|
| | OFDI-guided (n=68) | IVUS-guided (n=66) | p-value |
| ***In-stent analysis*** | | | |
| ***Pre-PCI*** | | | |
| Reference vessel diameter, mm | 2.65 (2.22–3.12) | 2.71 (2.38–3.00) | 0.629 |
| Minimum lumen diameter, mm | 0.29 (0.00–0.45) | 0.31 (0.00–0.63) | 0.178 |
| Diameter stenosis, % | 88.12 (82.66–100) | 89.98 (74.46–100) | 0.226 |
| **TIMI flow grade** | | | 0.603 |
| TIMI 0 | 28 (41.2) | 25 (37.9) | |
| TIMI 1 | 5 (7.4) | 5 (7.6) | |
| TIMI 2 | 13 (19.1) | 19 (28.8) | |
| TIMI 3 | 22 (32.4) | 17 (25.8) | |
| ***Post-PCI*** | | | |
| Reference vessel diameter, mm | 2.93 (2.61–3.31) | 3.08 (2.68–3.33) | 0.202 |
| Minimum lumen diameter, mm | 2.44 (2.08–2.85) | 2.64 (2.20–2.92) | 0.395 |
| Diameter stenosis, % | 13.83 (10.29–18.38) | 14.65 (11.00–19.10) | 0.649 |
| Acute gain, mm | 2.29 (1.87–2.52) | 2.26 (1.62–2.80) | 0.987 |
| **TIMI flow grade** | | | 0.024 |
| TIMI 0 | 0 (0) | 0 (0) | |
| TIMI 1 | 0 (0) | 0 (0) | |

| | | | |
|---|---|---|---|
| TIMI 2 | 7 (10.3) | 17 (25.8) | |
| TIMI 3 | 61 (89.7) | 49 (74.2) | |
| TIMI frame count | 23.50 (20.00–31.00) | 29.50 (23.00–43.00) | <0.001 |
| Corrected TIMI frame count | 18.10 (13.20–23.80) | 24.00 (20.00–33.00) | <0.001 |
| ***8-month follow-up*** | | | |
| Reference vessel diameter, mm | 2.79 (2.51–3.13) | 2.90 (2.53–3.19) | 0.521 |
| Minimum lumen diameter, mm | 2.68 (2.39–3.02) | 2.85 (2.59–3.12) | 0.180 |
| Diameter stenosis, % | 15.16 (11.44–22.43) | 17.17 (13.79–24.47) | 0.204 |
| Late loss, mm | 0.18 (-0.05–0.50) | 0.27 (-0.02–0.43) | 0.679 |
| Binary restenosis | 2 (3.1) | 1 (1.8) | 1.000 |
| Stent fracture | 0 (0) | 0 (0) | NA |
| Peri-stent contrast staining | 0 (0) | 0 (0) | NA |
| **TIMI flow grade** | | | 0.704 |
| TIMI 0 | 0 (0) | 0 (0) | |
| TIMI 1 | 0 (0) | 0 (0) | |
| TIMI 2 | 3 (4.6) | 4 (7.0) | |
| TIMI 3 | 62 (95.4) | 53 (93.0) | |
| ***In-segment analysis*** | | | |
| ***Post-PCI*** | | | |
| Reference vessel diameter, mm | 2.92 (2.42–3.27) | 3.06 (2.61–3.36) | 0.200 |
| Minimum lumen diameter, mm | 2.80 (2.56–3.23) | 2.99 (2.65–3.22) | 0.189 |
| Diameter stenosis, % | 20.34 (14.54–30.75) | 20.01 (15.11–29.19) | 0.936 |
| Acute gain, mm | 1.90 (1.50–2.30) | 2.00 (1.40–2.60) | 0.801 |

| | | | |
|---|---|---|---|
| ***8-month follow-up*** | | | |
| Reference vessel diameter, mm | 2.79 (2.40–3.24) | 2.93 (2.62–3.23) | 0.334 |
| Minimum lumen diameter, mm | 2.15 (1.80–2.53) | 2.24 (1.87–2.54) | 0.420 |
| Diameter stenosis, % | 22.34 (16.57–1.04) | 21.64 (16.86–28.87) | 0.891 |
| Late loss, mm | 0.17 (-0.26–0.41) | 0.08 (-0.11–0.27) | 0.707 |

Data are n (%) or medians (interquartile range).
IVUS=intravascular ultrasound; OFDI=optical frequency domain imaging; PCI=percutaneous coronary intervention; TIMI=Thrombolysis In Myocardial Infarction.

**Supplementary Table 3. Quantitative angiographic findings (per protocol set).**

| | OPINION ACS (per protocol set; n=120) | | |
|---|---|---|---|
| | OFDI-guided (n=64) | IVUS-guided (n=56) | p value |
| ***In-stent analysis*** | | | |
| ***Pre-PCI*** | | | |
| Lesion length, mm | 15.95 (12.10–18.55) | 15.33 (11.36–20.96) | 0.692 |
| Reference vessel diameter, mm | 2.61 (2.20–3.16) | 2.71 (2.34–3.00) | 0.710 |
| Minimum lumen diameter, mm | 0.29 (0.00–0.45) | 0.23 (0.00–0.59) | 0.422 |
| Diameter stenosis, % | 88.12 (82.66–100.00) | 91.77 (75.82–100.00) | 0.546 |
| **TIMI flow grade** | | | 0.620 |
| TIMI 0 | 26 (40.6) | 22 (39.3) | |
| TIMI 1 | 5 (7.8) | 4 (7.1) | |
| TIMI 2 | 12 (18.8) | 16 (28.6) | |
| TIMI 3 | 21 (32.8) | 14 (25.0) | |
| ***Post-PCI*** | | | |
| Reference vessel diameter, mm | 2.95 (2.64–3.31) | 3.10 (2.66–3.32) | 0.303 |
| Minimum lumen diameter, mm | 2.46 (2.09–2.85) | 2.64 (2.20–2.92) | 0.566 |
| Diameter stenosis, % | 13.67 (10.29–17.80) | 14.69 (11.28–19.16) | 0.417 |
| Acute gain, mm | 2.31 (1.92–2.52) | 2.31 (1.69–2.81) | 0.687 |
| **TIMI flow grade** | | | 0.024 |

| | | | |
|---|---|---|---|
| TIMI 0 | 0 (0.0) | 0 (0.0) | |
| TIMI 1 | 0 (0.0) | 0 (0.0) | |
| TIMI 2 | 7 (10.9) | 14 (25.0) | |
| TIMI 3 | 57 (89.1) | 42 (75.0) | |
| TIMI Frame Count | 23.00 (20.00–31.50) | 28.50 (23.00–42.50) | 0.001 |
| Corrected TIMI Frame Count | 18.10 (12.90–23.50) | 24.00 (20.20–35.05) | <0.001 |
| ***8-month follow-up*** | | | |
| Reference vessel diameter, mm | 2.79 (2.48–3.14) | 2.87 (2.52–3.18) | 0.671 |
| Minimum lumen diameter, mm | 2.33 (1.98–2.63) | 2.32 ± 0.52 | 1.000 |
| Diameter stenosis, % | 14.51 (11.35–22.39) | 17.22 (13.81–25.22) | 0.110 |
| Late loss, mm | 0.18 (-0.07–0.50) | 0.27 (-0.02–0.44) | 0.494 |
| Binary restenosis | 1 (1.6) | 1 (1.8) | 1.000 |
| Stent fracture | 0 (0.0) | 0 (0.0) | NA |
| Peri-stent contrast staining | 0 (0.0) | 0 (0.0) | NA |
| **TIMI flow grade** | | | 0.703 |
| TIMI 0 | 0 (0.0) | 0 (0.0) | |
| TIMI 1 | 0 (0.0) | 0 (0.0) | |
| TIMI 2 | 3 (4.7) | 4 (7.1) | |
| TIMI 3 | 62 (95.3) | 53 (2.9) | |
| ***In-segment analysis*** | | | |
| ***Post-PCI*** | | | |
| Reference vessel diameter, mm | 2.96 (2.46–3.27) | 3.07 (2.53–3.34) | 0.263 |

| | | | |
|---|---|---|---|
| Minimum lumen diameter, mm | 2.17 (1.77–2.54) | 2.43 (1.82–2.83) | 0.284 |
| Diameter stenosis, % | 20.80 (14.54–31.22) | 20.94 (15.01–28.96) | 0.987 |
| Acute gain, mm | 1.90 (1.50–2.30) | 2.10 (1.44–2.62) | 0.499 |
| ***8-month follow-up*** | | | |
| Reference vessel diameter, mm | 2.80 (2.40–3.25) | 2.93 (2.60–3.19) | 0.456 |
| Minimum lumen diameter, mm | 2.17 (1.80–2.53) | 2.24 (1.84–2.53) | 0.611 |
| Diameter stenosis, % | 22.32 (16.54–30.01) | 21.68 (17.01–29.06) | 0.862 |
| Late loss, mm | 0.14 (-0.27–0.40) | 0.08 (-0.11–0.27) | 0.939 |

Data are n (%) or medians (interquartile range). PCI=percutaneous coronary intervention; TIMI=Thrombolysis In Myocardial Infarction; IVUS=intravascular ultrasound; OFDI=optical frequency domain imaging.

**Supplementary Table 4. Procedural characteristics (per protocol set).**

| | OPINION ACS (per protocol set; n=120) | | |
|---|---|---|---|
| | OFDI-guided (n=64) | IVUS-guided (n=56) | p value |
| ***Stent and procedures*** | | | |
| Stent diameter, mm | 3.0 (2.8–3.5) | 3.0 (3.0–3.5) | 0.174 |
| Total stent length, mm | 24.0 (21.0–33.0) | 28.0 (24.0–38.0) | 0.053 |
| Number of stents per patient | 1.0 (1.0-1.0) | 1.0 (1.0-1.0) | 0.574 |
| Stent type | | | 0.687 |
| Ultimaster Sirolimus-eluting stent | 59 (92.2) | 49 (87.5) | |
| Everolimus-eluting stent | 4 (6.3) | 4 (7.1) | |
| Resolute | 0 (0.0) | 1 (1.8) | |
| Osiro | 1 (1.6) | 2 (3.6) | |
| Others | 0 (0.0) | 0 (0.0) | |
| Thrombus aspiration | 24 (37.5) | 19 (33.9) | 0.706 |
| Rotablation | 0 (0.0) | 2 (3.6) | 0.215 |
| Distal protection | 3 (4.7) | 10 (17.9) | 0.036 |
| Post-dilation | 44 (68.8) | 34 (60.7) | 0.443 |
| Maximum balloon diameter, mm | 3.3 (3.0–3.5) | 3.5 (3.0–4.0) | 0.045 |
| Maximum inflation pressure, atmosphere | 14.0 (12.0–16.0) | 14.0 (12.0–18.0) | 0.695 |
| **Further intervention after imaging** | | | |
| Pre-dilation balloon size up | 16 (25.0) | 17 (30.4) | 0.544 |

| | | | |
|---|---|---|---|
| Pre-dilation pressure up | 8 (12.5) | 4 (7.1) | 0.376 |
| Pre-dilation with Cutting balloon | 6 (9.4) | 4 (7.1) | 0.749 |
| Rotablation | 0 | 0 | NC |
| Post-dilation | 21 (32.8) | 18 (32.1) | 1.000 |
| Additional stenting | 1 (1.6) | 2 (3.6) | 0.598 |
| PCI procedure success | 64 (100) | 56 (100.0) | NA |
| Total fluoroscopic time | 26.5 (19.5–37.0) | 35.0 (22.5–47.0) | 0.031 |

Data are n (%) or medians (interquartile range). IVUS=intravascular ultrasound; OFDI=optical frequency domain imaging.

**Supplementary Table 5. Antithrombotic therapy (safety analysis set).**

| | OPINION ACS (safety analysis set; n=139) | | |
|---|---|---|---|
| | OFDI-guided (n=70) | IVUS-guided (n=69) | p value |
| At discharge | | | |
| Aspirin | 69 (100.0) | 64 (97) | 0.237 |
| Thienopyridine | 68 (98.6) | 34 (97.0) | 0.613 |
| Anticoagulation | 7 (10.1) | 7 (10.6) | 1.000 |
| Therapies at 8-months | | | |
| Aspirin | 56 (83.6) | 43 (68.3) | 0.062 |
| Thienopyridine | 58 (86.6) | 54 (85.7) | 1.000 |
| Anticoagulation | 3 (4.5) | 9 (14.3) | 0.070 |

Data are n (%). p values were calculated with the use of two-sided Fisher's exact test or chi-square test.
IVUS=intravascular ultrasound; OFDI=optical frequency domain imaging.

**Supplementary Table 6. IVUS results post-PCI.**

| | OFDI-guided (n=62) | IVUS-guided (n=56) | p value |
|---|---|---|---|
| ***In-stent segment*** | | | |
| Length, mm | 26.35 (19.60–33.30) | 28.72 (23.53–38.25) | 0.088 |
| Lumen volume, $mm^3$ | 185.65 (139.49–227.20) | 201.92 (160.77–259.21) | 0.049 |
| Lumen volume index, $mm^3/mm$ | 6.46 (5.48–8.21) | 7.26 (5.69–8.54) | 0.203 |
| Minimum lumen area, $mm^2$ | 5.05 (4.08–6.87) | 5.84 (4.63–6.87) | 0.253 |
| Stent volume, $mm^3$ | 185.94 (139.00–227.09) | 205.35 (161.04–272.95) | 0.046 |
| Stent volume index, $mm^3/mm$ | 6.53 (5.50–8.21) | 7.24 (5.73–8.59) | 0.159 |
| Minimum stent area, $mm^2$ | 5.35 (4.16–7.28) | 5.92 (4.63–7.23) | 0.235 |
| Peri-stent plaque volume, $mm^3$ | 95.29 (141.39–277.05) | 237.99 (167.68–324.31) | 0.079 |
| Peri-stent plaque volume index, $mm^3/mm$ | 7.84 (5.79–9.44) | 9.04 (6.34–10.13) | 0.304 |
| Percent peri-stent plaque volume, % | 54.23 (49.04–57.88) | 53.73 (48.47–56.54) | 0.457 |
| Vessel volume, $mm^3$ | 370.50 (300.54–503.11) | 442.49 (327.57–598.59) | 0.066 |
| Vessel volume index, $mm^3/mm$ | 14.07 (12.04–17.44) | 16.25 (12.11–19.15) | 0.237 |
| Tissue protrusion volume, $mm^3$ | 0.03 (0.00–1.52) | 0.39 (0.00–4.05) | 0.08 |
| Tissue protrusion volume index, $mm^3/mm$ | 0.00 (0.00–0.07) | 0.02 (0.00–0.10) | 0.097 |
| ***Proximal reference segment*** | | | |
| Length, mm | 5.00 (5.00–5.00) | 5.00 (5.00–5.00) | 0.064 |
| Lumen volume, $mm^3$ | 40.86 (28.45–52.09) | 40.47 (28.06–51.07) | 0.739 |
| Lumen volume index, $mm^3/mm$ | 8.32 (5.74–10.54) | 8.23 (5.61–10.95) | 0.815 |
| Minimum lumen area, $mm^2$ | 6.65 (4.82–8.45) | 6.84 (4.76–8.19) | 0.972 |

| | | | |
|---|---|---|---|
| Plaque volume, $mm^3$ | 43.02 (29.69–55.96) | 42.00 (32.79–51.13) | 0.810 |
| Plaque volume index, $mm^3/mm$ | 8.80 (5.94–11.22) | 8.40 (6.64–11.68) | 0.893 |
| Percent plaque volume, % | 52.22 (43.03–58.84) | 51.17 (42.08–59.83) | 0.944 |
| Residual stent-edge plaque burden >50% | 33 (53.2) | 30 (53.6) | 0.601 |
| Vessel volume, $mm^3$ | 86.74 (65.08–102.20) | 82.99 (66.44–97.76) | 0.624 |
| Vessel volume index, $mm^3/mm$ | 17.52 (13.66–20.91) | 16.96 (13.33–19.86 | 0.711 |
| Calcification | 42 (70.0) | 27 (51.9) | 0.054 |
| Dissection | 0 (0.0) | 2 (3.9) | 0.213 |
| Dissection with haematoma | 0 (0.0) | 0 (0.0) | NA |
| ***Distal reference segment*** | | | |
| Length, mm | 5.00 (5.00–5.00) | 5.00 (5.00–5.00) | 0.568 |
| Lumen volume, $mm^3$ | 25.03 (21.13–37.72) | 29.20 (20.89–41.15) | 0.397 |
| Lumen volume index, $mm^3/mm$ | 5.09 (4.25–7.55) | 5.93 (4.45–8.23) | 0.138 |
| Minimum lumen area, $mm^2$ | 4.25 (3.26–6.64) | 4.89 (3.45–7.05) | 0.190 |
| Plaque volume, $mm^3$ | 19.59 (12.02–39.55) | 26.85 (9.99–37.60) | 0.548 |
| Plaque volume index, $mm^3/mm$ | 3.92 (2.54–7.91) | 5.56 (2.37–7.95) | 0.344 |
| Percent plaque volume, % | 44.03 (27.39–52.04) | 45.53 (28.93–54.54) | 0.588 |
| Residual stent-edge plaque burden >50% | 23 (37.1) | 24 (42.9) | 0.442 |
| Vessel volume, $mm^3$ | 47.39 (31.11–69.47) | 58.76 (34.28–80.17) | 0.474 |
| Vessel volume index, $mm^3/mm$ | 9.57 (6.22–13.89) | 12.14 (7.53–16.04) | 0.185 |
| Calcification | 33 (53.2) 22 (40.0) | 22 (40.0) | 0.194 |
| Dissection | 2 (3.2) | 2 (3.6) | 1.000 |
| Dissection with haematoma | 1 (1.6) | 1 (1.8) | 1.000 |

Data are n (%) or median (interquartile range).
OFDI=optical frequency domain imaging; IVUS=intravascular ultrasound.

**Supplementary Table 7. Non-inferiority analysis of MLA by 8-month follow-up OFDI (per protocol set).**

| | OPINION ACS (per protocol set: n=120) | | | |
|---|---|---|---|---|
| | OFDI-guided (n=64) | IVUS-guided (n=56) | Difference (OFDI – IVUS) | p-value for noninferiority |
| MLA, $mm^2$, LS means (95% CI) | 4.91 (4.53–5.30) | 4.76 (4.35–5.17) | 0.16 (-0.31–Inf) | <0.001 |

CI=confidence interval; IVUS=intravascular ultrasound; LS=least square; MLA=minimum lumen area; OFDI=optical frequency domain imaging.

**Supplementary Table 8. Sensitivity analysis of MLA using 8-month follow-up OFDI (modified intention-to-treat).**

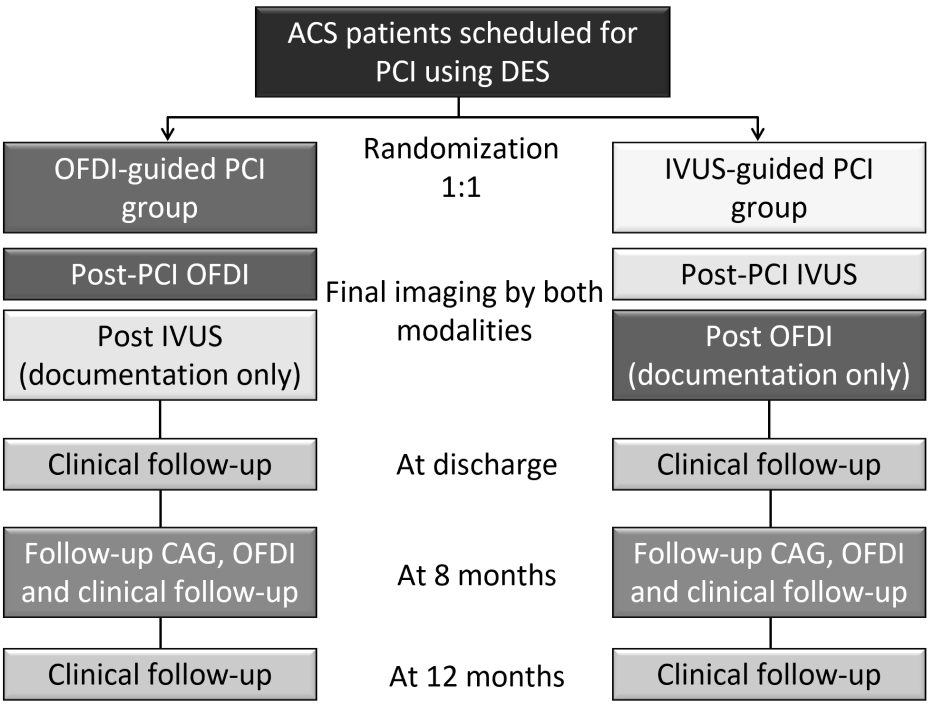
| | OPINION ACS (modified intention to treat; n=134) | | | |
|---|---|---|---|---|
| | OFDI-guided (n=68) | IVUS-guided (n=66) | Difference (OFDI–IVUS) | p value for non-inferiority |
| MLA ($mm^2$), LS means (95% CI) | 4.91 (4.53, 5.30) | 4.76 (4.35, 5.17) | 0.16 (-0.31, Inf) | <0.001 |

Data were similar to those presented in Supplementary Table 7 because the patient population is similar to that of PPS.
MLA=minimum lumen area; LS means = least square means; OFDI=optical frequency domain imaging; IVUS=intravascular ultrasound.

**Supplementary Table 9. Clinical outcomes.**

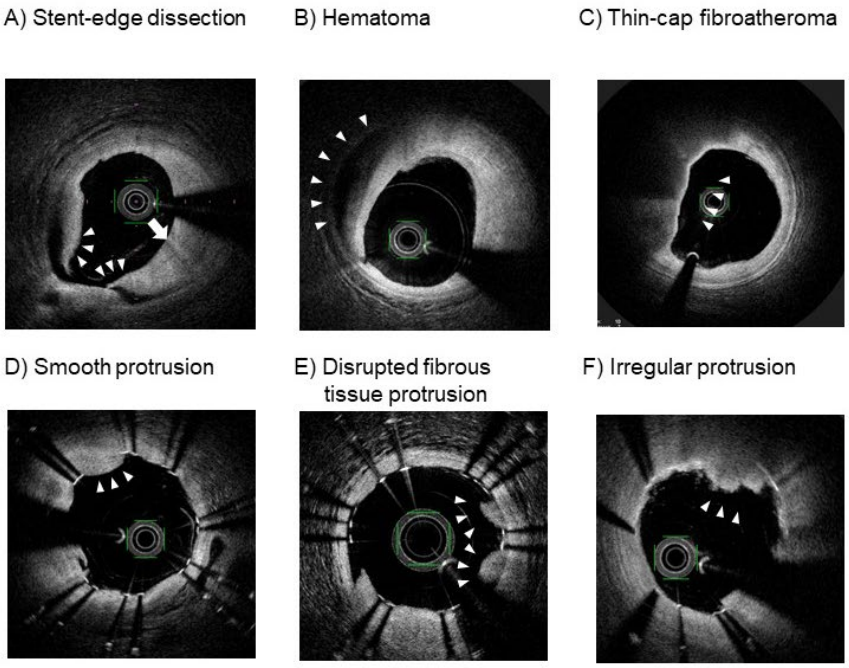
| | OPINION ACS (safety analysis set; n=139) | | |
|---|---|---|---|
| | OFDI-guided | IVUS-guided | p value |
| All cause death | 0 (0.0) | 1 (1.4) | 0.496 |
| Cardiac death | 0 (0.0) | 0 (0.0) | NA |
| Myocardial infarction | 1 (1.4) | 0 (0.0) | 1.000 |
| Myocardial infarction attributed to the target vessel | 0 (0.0) | 0 (0.0) | NA |
| Target vessel failure | 3 (4.3) | 0 (0.0) | 0.245 |
| Target vessel revascularization | 3 (4.3) | 0 (0.0) | 0.245 |
| Target lesion revascularization | 2 (2.9) | 0 (0.0) | 0.496 |
| Non- Target lesion revascularization TVR | 1 (1.4) | 0 (0.0) | 1.000 |
| Major adverse cardiac event | 2 (2.9) | 0 (0.0) | 0.496 |
| Stent thrombosis | 0 (0.0) | 0 (0.0) | NA |
| Stroke | 1 (1.4) | 0 (0.0) | 1.000 |
| Contrast-induced nephropathy | 1 (1.4) | 2 (2.9) | 0.620 |

Data are n (%).
OFDI=optical frequency domain imaging. IVUS=intravascular ultrasound.




**Supplementary Figure 1.** OPINION ACS study flow.

In addition to the allocated imaging modality, the OFDI-guided PCI group also underwent post-PCI IVUS, whereas the IVUS-guided PCI group underwent post-PCI OFDI. Both groups underwent follow-up angiography with OFDI eight months after the index procedure. ACS, acute coronary syndrome; CAG, coronary angiography; DES, drug-eluting stent; IVUS, intravascular ultrasound; OFDI, optical frequency domain imaging; PCI, percutaneous coronary intervention.

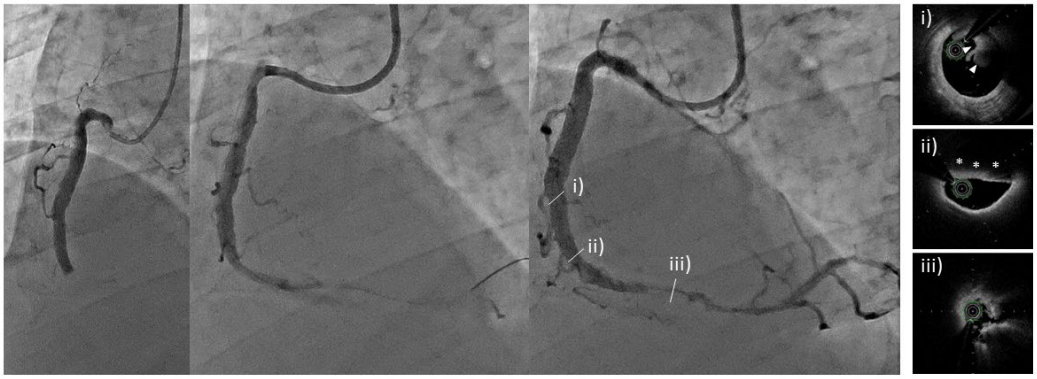



**Supplementary Figure 2.** Representative OFDI images.

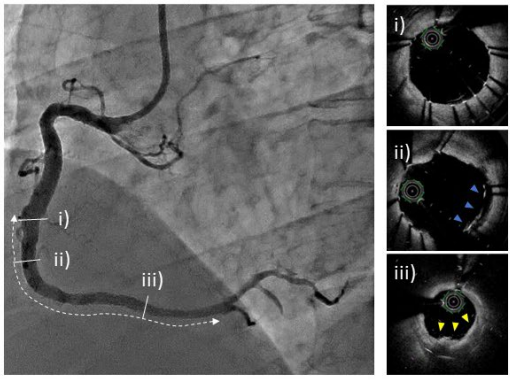
**(**A) Stent edge dissection, (B) haematoma, (C) thin-cap fibroatheroma, (D) smooth protrusion, (E) disrupted fibrous tissue protrusion, and (F) irregular protrusion

A) Case 1: RCA STEMI TLR

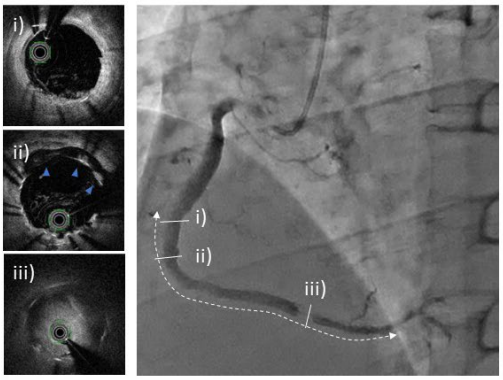
a) Pre and during PCI




b) Post PCI

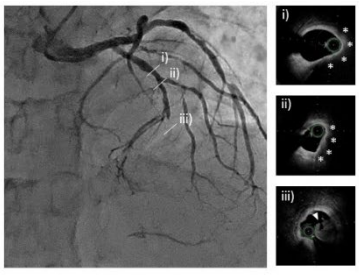



c) 8-month follow-up

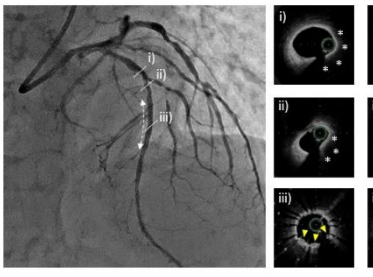



B) Case 2: LAD STEMI non-TLR TVR

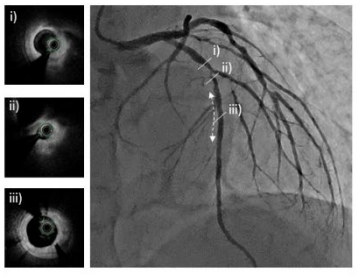
a) Pre PCI

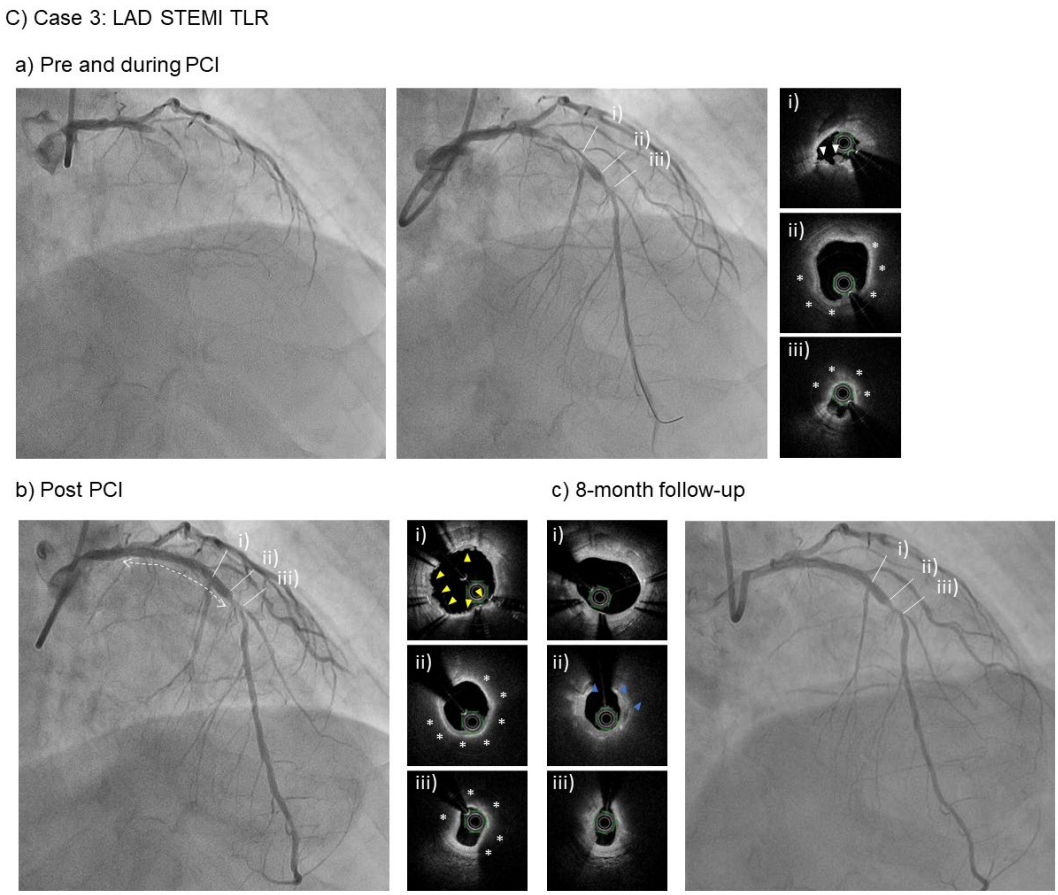



b) Post PCI




c) 8-month follow-up






**Supplementary Figure 3. Cases with target vessel revascularisation.**

(A) RCA-STEMI . a) Thrombus aspiration and POBA with a 2.0 mm balloon resulted in no reflow. After intracoronary glyceryl trinitrate injection and additional balloon dilatation, TIMI grade 2 flow was achieved, followed by OFDI. Thrombus (white arrowhead) and lipid-rich plaque with thin-cap fibroatheroma (*) are revealed by OFDI. b) Ultimaster$^{TM}$ sirolimus-eluting stents (Terumo, Japan. 3.5 mm*21 mm, 3.0 mm*28 mm) were used. Due to the presence of large intra-stent thrombus, post-dilatation was performed with a 3.0 mm Ryusei Perfusion Balloon (Kaneka Medix Corp, Japan 3.0*20 mm) for 3 min. Post-PCI OFDI displayed a small malapposition (blue arrowhead) and a large protrusion (yellow arrowhead) inside the stent. Final coronary angiography revealed TIMI 2 flow. c) Eight-month follow-up angiography revealed significant stenosis inside the stent at the site where a notable plaque protrusion was observed. This lesion underwent PCI. The white dotted arrows indicate the stented segment.

B) LAD STEMI . a) Thrombus aspiration and POBA with a 2.0 mm balloon were conducted. OFDI shows a thrombus (white arrowhead) and a lipid-rich plaque with thin-cap fibroatheroma (*). b) After additional

balloon dilatation with a 2.5 mm cutting balloon, a Xience$^{TM}$ everolimus-eluting stent (Abbott Vascular: 2.5 mm*18 mm) was deployed. Post-PCI OFDI displayed appropriate stent expansion with a small in-stent protrusion (yellow arrowheads). An intermediate stenotic lesion with TCFA was detected at the proximal site of the stented segment using post-PCI OFDI (*). c) Eight-month follow-up angiography revealed significant stenosis progression at the proximal site of the stented segment, where TCFA was observed on post-PCI OFDI. This lesion underwent PCI. The white dotted arrows indicate the stented segment.

C) LAD STEMI . a) Thrombus aspiration and POBA with a 2.5 mm balloon were conducted. OFDI shows a thrombus (white arrowhead) and a lipid-rich plaque with thin-cap fibroatheroma (*). b) An Ultimaster$^{TM}$ sirolimus-eluting stent (2.5 mm*18 mm) was deployed, and post-dilatation was performed. Post-PCI OFDI displayed appropriate stent expansion with a small in-stent protrusion (yellow arrowheads). At the distal site of the stented segment, a significant stenotic lesion with TCFA was detected using post-PCI OFDI. However, this lesion was not treated during primary PCI. c) Eight-month follow-up angiography revealed significant stenosis at the distal site of the stented segment, where TCFA was observed on post-PCI OFDI. This lesion underwent PCI.
The white dotted arrow indicates stented segment