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Clinical Research

Early and Mid-Term Vascular Responses to Optical Coherence Tomography–Guided Everolimus-Eluting Stent Implantation in Stable Coronary Artery Disease

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ABSTRACT

Background: Analysis of pooled clinical data has shown the safety of 3 months of dual antiplatelet therapy with everolimus-eluting cobalt–chromium stents (Co-Cr EESs). This study evaluated early and mid-term vascular responses to Co-Cr EESs in patients with stable coronary artery disease.

Methods: The **M**ulticenter Comparison of Early and Late Vascular Responses to **E**verolimus-Eluting Cobalt-**Ch**romium Stent and Platelet

RÉSUMÉ

Contexte : Une analyse de données cliniques groupées a démontré l'innocuité d'une bithérapie antiplaquettaire de 3 mois comprenant une endoprothèse en alliage cobalt-chrome à élution d'évérolimus. Cette étude visait à évaluer les réponses vasculaires à court et à moyen terme après l'implantation d'une endoprothèse en alliage cobalt-chrome à élution d'évérolimus chez des patients présentant une coronaropathie stable.

New-generation drug-eluting stents (DESs) have virtually eliminated the risk of stent thrombosis (ST) compared with first-generation DESs and are the standard of care for percutaneous coronary intervention (PCI). Everolimus-eluting cobalt–chromium stents (Co-Cr EESs) have shown improved clinical benefits and design, with antithrombogenic fluoropolymer coatings and safer drugs.[1] Meta-analyses have reported lower rates of definite ST using Co-Cr EESs than those using other DESs and, unexpectedly, even lower than those using bare metal stents.[2,3] In a recent paradigm shift, Co-Cr EESs allow a shortened duration of dual antiplatelet therapy (DAPT) in patients with stable coronary artery disease (CAD).[4] An updated analysis of pooled data indicated that the safety of Co-Cr EESs may

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Aggregation Studies in Patients With Stable Angina Managed as Elective Case (MECHANISM-Elective) study (NCT02014818) is a multicenter optical coherence tomography (OCT) registry. Enrolled patients were evaluated by OCT immediately after everolimus-eluting stent implantation were prospectively allocated to 1 month (n = 50) or 3 months (n = 50) OCT follow-up and then received a 12-month OCT evaluation. The incidences of intrastent thrombus (IS-Th) and irregular protrusion (IRP) were also assessed.

Results: The percentage of uncovered struts was 6.4% ± 10.3% at 1 month (*P* < 0.001 vs. postprocedure) and 0.5% ± 0.9% at 12 months (*P* < 0.001 vs. 1 month). The corresponding values in the 3-month cohort were 2.0% ± 2.5% (*P* < 0.001 vs. postprocedure) and 0.5% ± 1.5% (*P* < 0.001 vs. 3 months). The incidence of IS-Th was 32.7% at 1 month, 5.4% at 3 months, and 2.0% at 12 months. IRP was observed in 21.8% of patients post-EES but had totally resolved at 1, 3, and 12 months.

Conclusion: Early and mid-term vascular reactions after Co-Cr EES implantation in stable patients with coronary artery disease in the MECHANISM-Elective included dynamic resolution of IS-Th and IRP and rapid decrease in uncovered struts. Thus, EES may allow shortening of dual antiplatelet therapy duration less than 3 months in this patient subset.

Méthodologie : L'étude MECHANISM-Elective (*Multicenter Comparison of Early and Late Vascular Responses to Everolimus-Eluting Cobalt-Chromium Stent and Platelet Aggregation Studies in Patients With Stable Angina Managed as Elective Case*) (NCT02014818) porte sur un registre multicentrique des résultats d'examens par tomographie par cohérence optique (TCO). Les patients admis à l'étude ont été évalués par TCO immédiatement après l'implantation d'une endoprothèse à élution d'évérolimus, puis ont été répartis prospectivement pour faire l'objet d'un examen de suivi par TCO à 1 mois (n = 50) ou à 3 mois (n = 50) et à 12 mois. L'incidence des thromboses de l'endoprothèse et des saillies anormales a aussi été évaluée.

Résultats : La proportion d'entretoises à découvert s'établissait à 6,4 % ± 10,3 % à 1 mois (*p* < 0,001 par rapport à l'évaluation après l'implantation) et à 0,5 % ± 0,9 % à 12 mois (*p* < 0,001 par rapport à l'évaluation à 1 mois). Les valeurs correspondantes dans la cohorte des patients évalués à 3 mois s'établissaient à 2,0 % ± 2,5 % (*p* < 0,001 par rapport à l'évaluation après l'implantation) et à 0,5 % ± 1,5 % (*p* < 0,001 par rapport à l'évaluation à 3 mois). L'incidence des thromboses de l'endoprothèse était de 32,7 % à 1 mois, de 5,4 % à 3 mois et de 2,0 % à 12 mois. Une saillie anormale a été observée chez 21,8 % des patients après l'implantation d'une endoprothèse à élution d'évérolimus, mais elle s'était complètement résorbée dans tous les cas à 1, 3 et 12 mois.

Conclusion : Les réponses vasculaires à court et à moyen terme après l'implantation d'une endoprothèse en alliage cobalt-chrome à élution d'évérolimus chez des patients présentant une coronaropathie stable observées dans le cadre de l'étude MECHANISM-Elective comprenaient la résolution dynamique des thromboses de l'endoprothèse et des saillies anormales et la diminution rapide des entretoises à découvert. Ainsi, l'endoprothèse à élution d'évérolimus pourrait permettre de réduire la durée de la bithérapie antiplaquettaire à moins de 3 mois dans ce sous-groupe de patients.

allow shortening the duration of DAPT to 3 months.[5] A recent report even suggested the feasibility of 1-month DAPT.[6] However, early vascular responses from immediately after to 1 and 3 months after Co-Cr EES placement have not been fully elucidated.

Frequency domain-optical coherence tomography (FD-OCT) has emerged as an effective tool to assess vascular reactions to stent placement. It provides high-resolution cross-sectional images to evaluate vascular reactions to stent placement and expansion such as intrastent tissue protrusion and thrombus formation immediately after PCI, as well neointimal coverage and thrombus resolution in the chronic phase.[7] Previous serial optical coherence tomography (OCT) studies of Co-Cr EESs have investigated the vascular response at 6 and 24 months postprocedure.[8,9] Although recent OCT observations suggest that intrastent issues such as irregular protrusions (IRPs) influence the 1-year clinical end points, however, early vascular healing after Co-Cr EES placement has not been fully elucidated.[10] Theoretically, high residual platelet reactivity may hamper thrombus resolution and increase the risk of ST;[11,12] however, a direct relationship between the fate of intrastent thrombi and platelet reactivity has not been demonstrated. The study objective was to elucidate the early phase vascular responses after Co-Cr EES implantation at 1 or 3 months, focusing on serial changes of clinically relevant intravascular findings for culprit lesions of stable CAD and chronic phase healing using serial FD-OCT and point-of-care monitoring of residual platelet reactivity.

Methods

Study design and population

This was a **M**ulticenter Comparison of Early and Late Vascular Responses to **E**verolimus-Eluting Cobalt-**Ch**romium Stent and Platelet **A**ggregatio**n** Studies **i**n Patients With **Stable** Angina **M**anaged as **Elective** Case (MECHANISM-Elective) study (ClinicalTrials.gov, NCT02014818; UMINID, UMIN000012616). Patients with stable CAD receiving OCT-guided PCI using Co-Cr EES between February 2014 and March 2015 were screened in 20 Japanese institutions. Patients deemed to receive early and mid-term OCT evaluation for the implanted EES were enrolled in this study. OCT imaging (Dragonfly OPTIS; Abbott Vascular, St. Paul, MN) was performed immediately after PCI to confirm optimal stent expansion (first OCT)[13] and followed up at 1 or 3 months after the index PCI at the time of staged PCI for residual stenotic lesions or follow-up angiography (second OCT) and at 12 months (third OCT) (Fig. 1). Imaging was performed with an ILUMIEN or ILUMIEN OPTIS PCI Optimization System and an FD-OCT imaging catheter (Dragonfly/Dragonfly JP/Dragonfly OPTIS; Abbott Vascular). Digital images

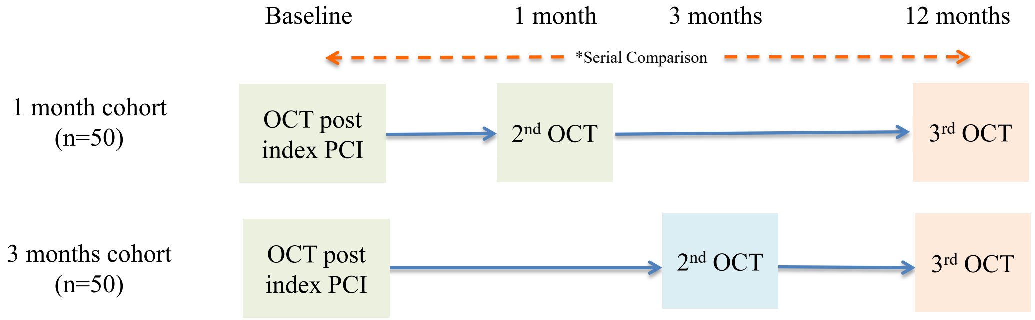

Figure 1. MECHANISM-Elective study flow chart. Optical coherence tomography (OCT) examination was performed immediately after index percutaneous coronary intervention (PCI) and at 1 or 3 months and at 12 months.

were analyzed offline. Exclusion criteria were acute myocardial infarction, overt heart failure, culprit lesion of the left main coronary artery or at a previously stented segment, reference vessel diameter < 2.0 mm or ≥ 4.5 mm, chronic kidney disease with serum creatinine > 2.0 mg/dL, maintenance hemodialysis, pregnancy, comorbid cancer with expected survival < 2 years, scheduled surgery within 3 months, history of adverse reactions to aspirin or clopidogrel, warfarin use before PCI, and age < 20 or > 85 years.

Culprit lesions were treated with Co-Cr EES (Xience Prime/Xpedition/Alpine, Abbott Vascular, Santa Clara, CA). Immediately after the procedure, FD-OCT imaging was performed throughout the stented segment, with a margin of ≥ 5 mm on either side of the lesion. Continual DAPT with aspirin and thienopyridine was recommended for 12 months after PCI.

All patients were taking clopidogrel at a dose of 75 mg/day for at least 14 days prior to index PCI or following a 300 mg loading dose, which was continued for at least 12 months in combination with aspirin after PCI. Platelet reactivity was assayed with the VerifyNow $P2Y_{12}$ test at the time of catheterization; values were reported in $P2Y_{12}$ reaction units (PRU).[14] All laboratory testing was performed by personnel blinded to patient information.

The study protocol was approved by the Ethics Committee at each participating institution. All patients provided written informed consent before inclusion.

Coronary FD-OCT image analysis and study end points

FD-OCT image analysis was performed at an independent core laboratory (Iwate Cardiovascular Analysis Laboratory, Morioka, Japan) using ILUMIEN proprietary software (Abbott Vascular). For quantitative assessment of stented segments, OCT images were analyzed at 1-mm intervals throughout the stented segment by independent observers, as previously described.[15] The lumen and stent areas were measured manually. Struts were recorded as uncovered if any part was visibly exposed in the lumen or covered if a layer of tissue covered all reflecting surfaces. The thickness of the intrastent tissue post-stent placement or the neointimal tissue at follow-up was measured from the center reflection of the stent strut to the vessel—lumen border for each stent strut. Struts with more than 108 μm between the center reflection and the adjacent vessel surface were recorded as malapposed (Fig. 2). The frequencies of uncovered and malapposed struts were calculated as a percentage of the total analyzed struts. On

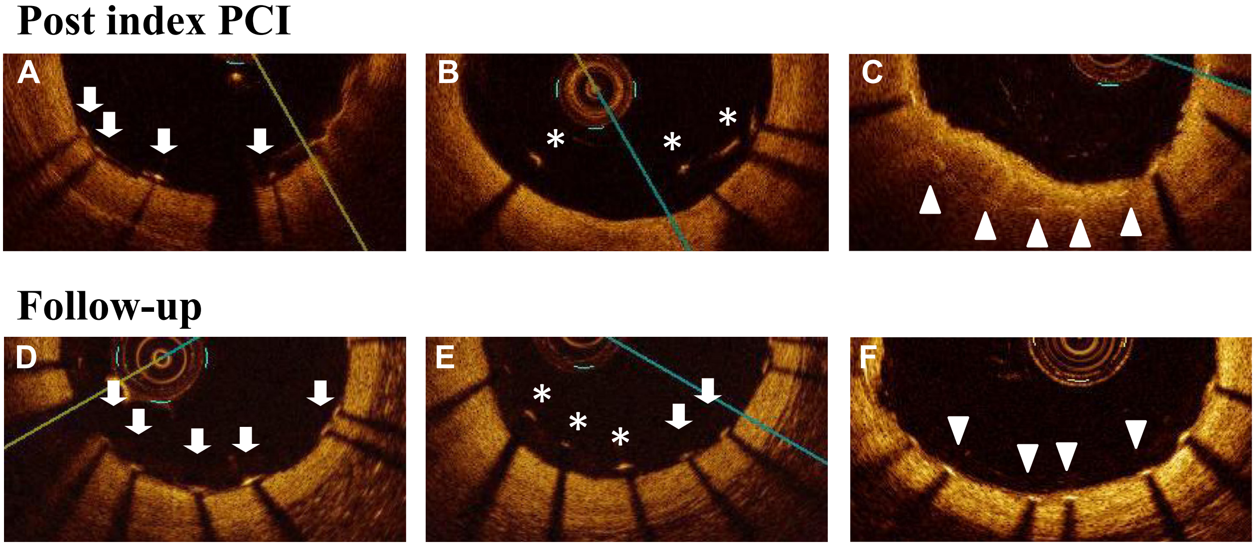

Figure 2. Frequency domain-optical coherence tomography (FD-OCT) evaluations were performed post-stent placement (**A-C**) and at follow-up (**D-F**). **Arrows** indicate uncovered struts (**A, B, E**), **asterisks** indicate malapposed struts (**B, E**), and arrowheads indicate embedded strut post-stenting (**C**) and neointimal coverage (**F**). PCI, percutaneous coronary intervention.

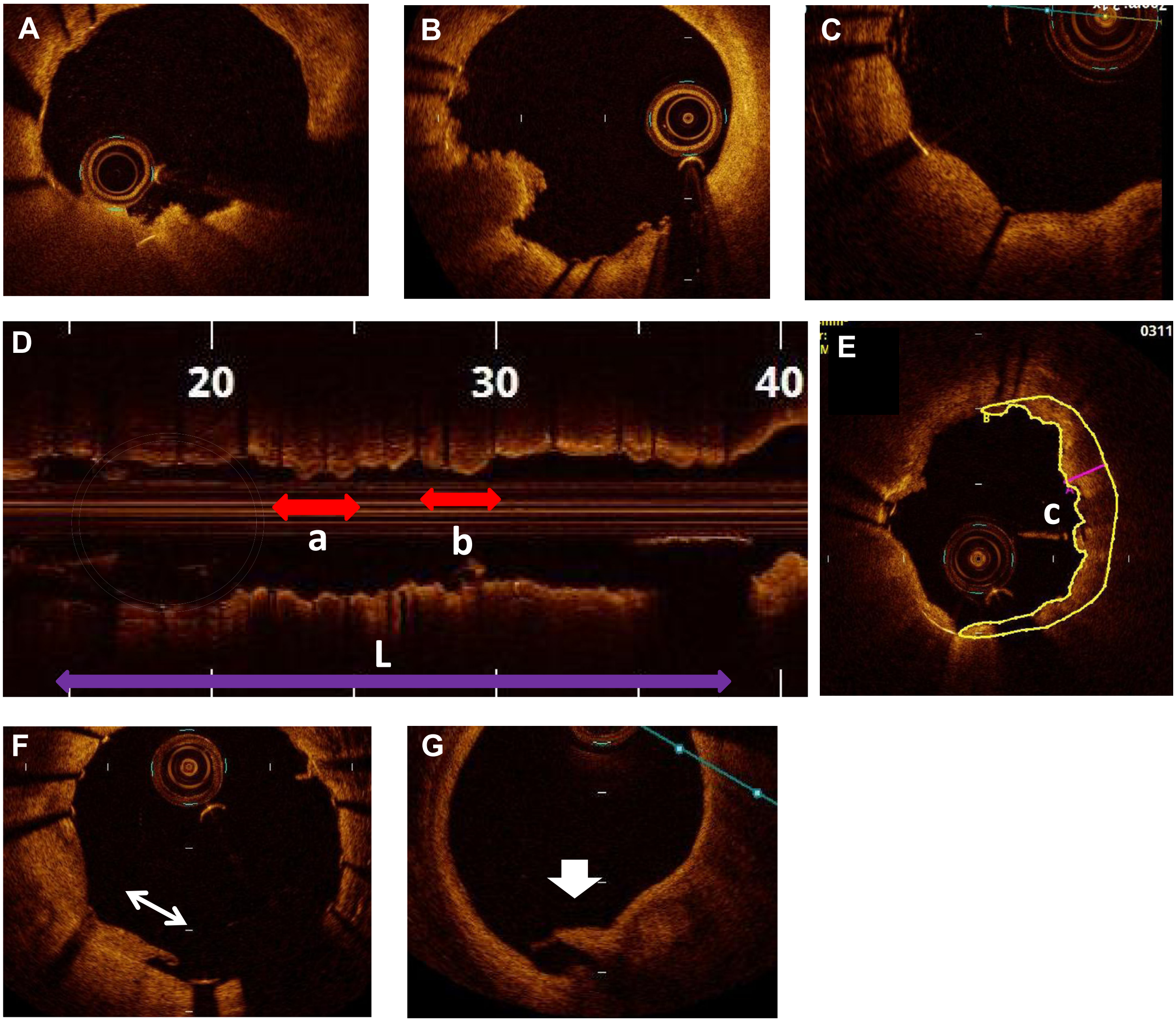

Figure 3. Quantitative classification of intrastent tissue post-stent placement. Quantitative classification of intrastent tissue (IST), including irregular protrusion (IRP) (**A**), thrombus (**B**), and smooth prolapse (SP) (**C**). Percentage length of each IST was measured as the sum of the length of IST divided by stent length (a + b/L) (**D**), quantitative measurement of IST area (**E**). Intrastent dissection (**F**) and edge dissection (**G**).

follow-up evaluations, neointimal area was calculated as stent area minus lumen area.[16]

Qualitative assessment of stented segments was performed in all cross-sections. Intrastent tissue with a height $\geq$ 250 μm was recorded as intrastent thrombus (IS-Th), IRPs, and smooth prolapses (SPs). IS-Th was defined as a mass with an irregular surface attached to the luminal surface, attached to the stent strut, or floating within the lumen, with signal attenuation behind it. IRP was defined as broad protrusion of material with an irregular surface into the lumen over stent struts.[10] SP was a signal-rich smooth tissue without attenuation protruding between the struts. Intraobserver and interobserver agreement for the discrimination of IS-Th, IRP, and SP were acceptable (intraobserver, $\kappa = 0.84$; interobserver $\kappa = 0.80$). IS-Th, IRP, and SP were manually traced for calculation of maximum area and % length (sum of the longitudinal distance/stent length, Fig. 3). Dissection, evidence of flaps $\geq$ 200 μm in height within the stent segment, and stent margins were also assessed. OCT images were analyzed independently by 2 investigators (T.I. and T.S.) who were blinded to the patient information. When there was a difference in the analysis of the 2 investigators, a consensus reading was obtained from a third independent investigator (Y.M.).

Clinical follow-up

Twelve-month follow-up data were available for all enrolled patients. Cardiac death, death from any cause, myocardial infarction by the third universal definition,[17] target lesion revascularization (TLR), non-TLR, and the composite major adverse cardiovascular events (MACE) end point, that is, cardiac death, myocardial infarction, TLR, non-TLR, and stent thrombosis based on the Academic Research Consortium definitions[18] were assessed. Thrombolysis in Myocardial Infarction major and minor bleeding events was

Table 1. Baseline patients and lesion characteristics

	1-month cohort	3-month cohort	
	Patients (n = 50)	Patients (n = 50)	*P* value
Age (y)	71 ± 8	70 ± 8	0.585
Male (n, %)	35 (70.0)	40 (80.0)	0.248
BMI (kg/m^2)	24.6 ± 3.6	24.5 ± 4.4	0.899
Diabetes mellitus (n, %)	28 (56.0)	30 (60.0)	0.685
Hypertension (n, %)	42 (84.0)	43 (86.0)	0.779
Dyslipidemia (n, %)	35 (70.0)	42 (84.0)	0.096
Smoker (n, %)	17 (34.0)	18 (36.0)	0.834
Clinical status			
Stable angina (n, %)	25 (50.0)	30 (60.0)	0.315
Silent myocardial ischemia (n, %)	25 (50.0)	20 (40.0)	
History of MI (n, %)	6 (12.0)	15 (30.0)	0.027
Medication at the index procedure			
Aspirin (n, %)	50 (100)	50 (100)	1.000
Clopidogrel/ticlopidine (n, %)	48 (96.0)/2(4.0)	49 (98.0)/1 (2.0)	0.71
Statin (n, %)	35 (70.0)	38 (76.0)	0.499
CYP2C19 genotype, EM/IM/PM (n, %)	16 (35)/22 (49)/7 (16)	9 (23)/21 (25)/10 (25)	0.141
Procedural characteristics			
Culprit vessel, LAD/RCA/LCx (n)	21/18/11	25/14/11	0.724
Implanted stent number (n)	1.2 ± 0.5	1.2 ± 0.4	0.651
Stent diameter (mm)	2.94 ± 0.39	2.88 ± 0.35	0.383
Stent length (mm)	24.8 ± 7.9	22.2 ± 7.5	0.145
PRU at PCI (first OCT)	216 ± 87	230 ± 74	0.388
PRU at the second OCT	215 ± 67	226 ± 81	0.455
PRU at 12 mo (third OCT)	209 ± 73	232 ± 72	0.121

BMI, body mass index; EM, extensive metabolizers; IM, intermediate metabolizers; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PM, poor metabolizers; PRU, P2Y12 reaction units; RCA, right coronary artery.

also assessed during the follow-up.[19] The primary end point was the frequency (%) of uncovered struts at 3 months. Secondary end points included the qualitative FD-OCT values, IS-Th, IRP, SP, and MACE at 12 months.[10]

Statistical analysis

Statistical analysis was performed with SPSS software, version 21 (SPSS, Inc, Chicago, IL). Normally distributed continuous variables were expressed as means ± standard deviation. Categorical variables were expressed as numbers and percentages. The significance of differences in the values of normally distributed variables following procedures and at the 1 or 3 months follow-up were tested by the pared *t* test. The chi-square test was used with categorical variables. Wilcoxon signed-rank test was used to compare differences in postprocedure and 1 and 3 months follow-up data. Friedman test was used to evaluate differences in repeated measurements and non-normally distributed postprocedure, 1, 3, and 12 months follow-up data. *P* values < 0.05 were considered statistically significant.

Results

Baseline characteristics and clinical outcomes

The baseline patients' lesions and procedural characteristics are shown in Table 1. A total of 100 patients were included in the 1- or 3-month follow-up cohort. There were no differences in patient, lesion, or procedural characteristics between the 2 groups, with an exception of history of myocardial infarction that was more frequent in the 3-month cohort. Patients in both groups were on DAPT, primarily with clopidogrel (97.0%). The CYP2C19 genotypes and PRU values at the time of the index PCI, second OCT at 1 or 3 months, and the third OCT at 12 months in the 2 groups were similar.

Qualitative and quantitative assessment of FD-OCT images

Post-PCI and second OCT pull-back images of 53 lesions in the 1-month cohort and 55 lesions in the 3 months cohort were evaluated at the central laboratory. The cases excluded from serial analysis because of patient refusal or poor image quality are summarized in Supplemental Figure S1. Serial OCT images obtained post-PCI and at the 1-month follow-up were independently analyzed in 51 lesions in 48 patients. OCT images obtained post-PCI and at the 3-month follow-up were analyzed in 51 lesions in 46 patients. The additional 12-month OCT follow-up was completed in 46 lesions in the 1-month cohort and 41 lesions in the 3-month cohort. Representative serial changes in strut coverage and intrastent tissue in the 1- and 3-month cohorts are shown in Figure 4.

The results of serial quantitative and qualitative OCT analysis are shown in Table 2. The post-PCI stent areas were 6.4 ± 1.9 mm^2 in the 1-month cohort and 6.4 ± 1.6 mm^2 in the 3-month cohort. The lumen area gradually decreased in both groups during the 12 months of follow-up. There were significant improvements in uncovered (87.0% ± 8.7% to

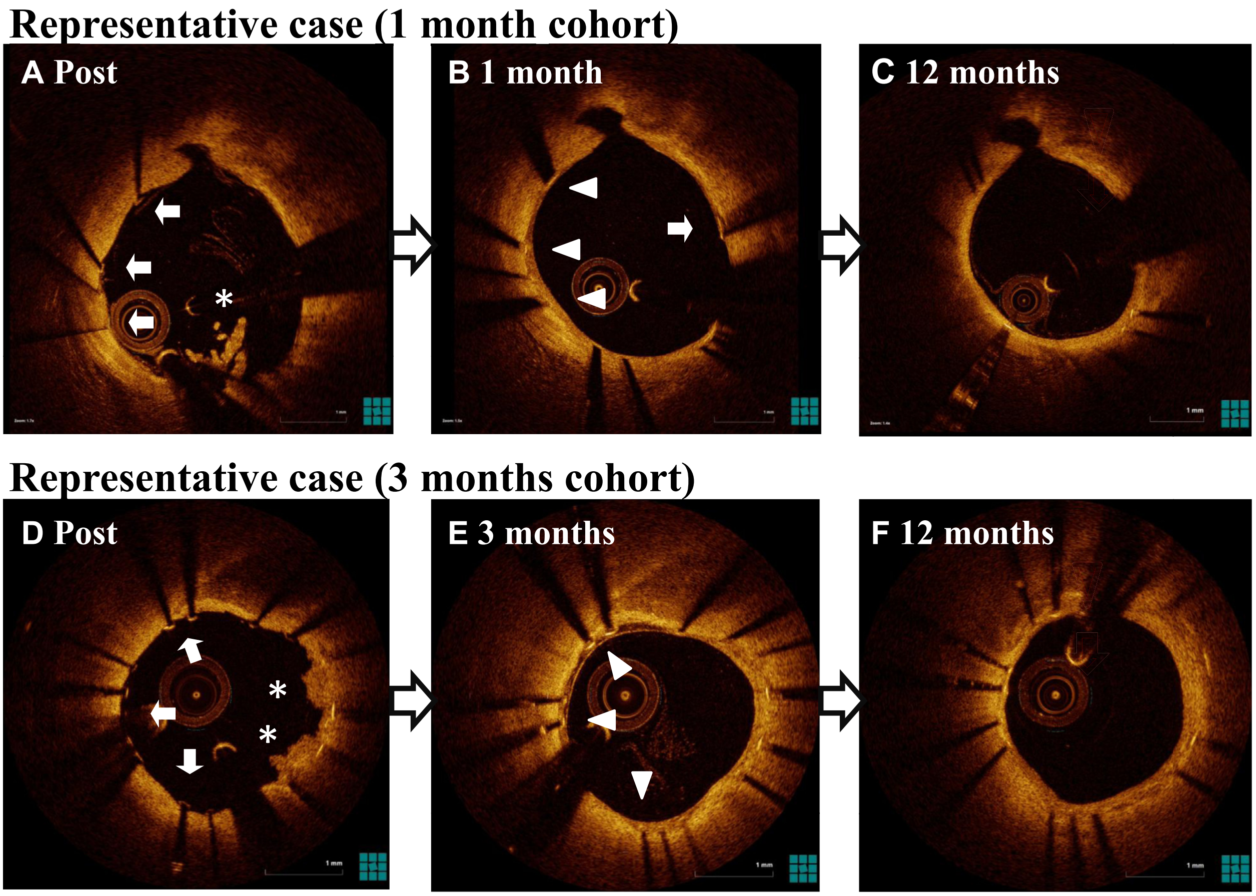

Figure 4. Representative serial OCT images at 1, 3, and 12 months in 1 month cohort (**A-C**) and 3 months cohort (**D-F**). **Arrows** indicate uncovered struts, **arrowheads** indicate covered struts, and **asterisks** indicate thrombi. Most uncovered struts became covered, and most thrombi were resolved at 1 or 3 months.

6.4% ± 10.3%, $P < 0.001$) and malapposed (7.0% ± 5.0% to 2.8% ± 3.4%, $P < 0.001$) struts from post-PCI to the 1-month follow-up. The improvements in uncovered and malapposed struts continued from post-PCI to the 3-month follow-up, with decreases from 79.3% ± 12.4% to 2.0% ± 2.5%, $P < 0.001$ and 7.3% ± 7.5% to 1.8% ± 4.1%, $P < 0.001$, respectively. Individual serial changes in the percentages of uncovered and malapposed struts are shown in Figure 5. The percentages of uncovered and malapposed struts were further improved at the 12 months follow-up to 0.5% ± 0.9% ($P < 0.001$) and 0.2% ± 0.7% ($P < 0.001$) in the 1 month and to 0.5% ± 1.5% ($P < 0.001$) and 0.3% ± 0.9% ($P < 0.001$) in the 3-month cohort, respectively.

The incidence of IS-Th was significantly decreased at 1 month from 65.4% to 34.6% ($P = 0.01$) and at 3 months from 74.5% to 11.8% ($P < 0.001$). At the 12-month follow-up, the incidence of IS-Th had decreased to 4.3% ($P < 0.001$) in the 1-month cohort and to 0% ($P < 0.001$) in the 3-month cohort. IRP was observed in 15.4% of the patients in the 1-month cohort and 25.5% in the 3-month cohort and had completely resolved in both cohorts at the 12-month follow-up (Fig. 6). The numbers of observed IS-Th, IRP, and SP and percentages of stent length and maximum area were significantly improved at the 1- or 3-month follow-up and were the least at 12 months (Table 2).

Relationship between IS-Th and residual platelet reactivity

The PRU values were not significantly different in cases with and without post-PCI IS-Th (225 ± 74 vs. 221 ± 85, $P = 0.828$). In cases with IS-Th at the 1-month follow-up, the PRU values at the index PCI (209 ± 63 vs. 225 ± 90, $P = 0.478$) and at 1 month (212 ± 57 vs. 219 ± 70, $P = 0.718$) were not different from those of cases without IS-Th. In cases with IS-Th at the 3-month follow-up, the PRU values at the index PCI (221 ± 44 vs. 229 ± 76, $P = 0.749$) and at 3 months (258 ± 66 vs. 219 ± 83, $P = 0.229$) were also not different from those in cases without IS-Th.

Clinical outcomes

Four cases of MACE occurred in both the 1-month and 3-month cohorts (Table 3). No cases of TLR occurred in the 1-month cohort, whereas 2 such cases occurred in the 3 months cohort. One occurred in a patient with ST 4 months after PCI during hospitalization for acute cholecystitis with discontinuation of antiplatelet therapy. The other occurred in a patient with PCI for stent edge restenosis at 12 months. One patient in the 3-month cohort experienced Thrombolysis in Myocardial Infarction minor bleeding event during an endovascular procedure to treat peripheral artery disease.

Table 2. Quantitative and qualitative FD-OCT analysis

	1-month cohort, 51 lesions					3-month cohort, 51 lesions				
	Post	1 mo	12 mo	*P* value (post vs. 1 month)	*P* value (among 3 points OCT)	Post	3 mo	12 mo	*P* value (post vs. 3 mo)	*P* value (among 3 points OCT)
Stent area (mm^2)	6.4 ± 1.9	6.5 ± 1.9	6.6 ± 1.9		0.15	6.4 ± 1.6	6.4 ± 1.7	6.3 ± 1.6		0.17
Lumen area (mm^2)	6.5 ± 1.9	6.4 ± 1.9	5.9 ± 1.8	0.147	< 0.001	6.6 ± 1.6	6.2 ± 1.8	5.7 ± 1.8	0.13	< 0.001
Thickness of neointima (μm)		40 ± 17	96 ± 41		< 0.001		47 ± 21	84 ± 50		< 0.001
Area of neointima (mm^2)		0.07 ± 0.29	0.72 ± 0.41		< 0.001		0.15 ± 0.32	0.58 ± 0.46		< 0.001
% Uncovered strut (%)	87.0 ± 8.7	6.4 ± 10.3	0.5 ± 0.9	< 0.001	< 0.001	79.3 ± 12.4	2.0 ± 2.5	0.5 ± 1.5	< 0.001	< 0.001
% Malapposed strut (%)	7.0 ± 5.0	2.8 ± 3.4	0.2 ± 0.7	< 0.001	< 0.001	7.3 ± 7.5	1.8 ± 4.1	0.3 ± 0.9	< 0.001	< 0.001
Intra-stent dissection (n, %)	39 (76.5%)	0 (0%)	0 (0%)	< 0.001	< 0.001	35 (68.6%)	0 (0%)	0 (0%)	< 0.001	< 0.001
Proximal edge dissection (n, %)	10 (19.6%)	4 (7.8%)	0 (0%)	0.15	0.27	11 (21.6%)	4 (7.1%)	0 (0%)	0.09	0.006
Distal edge dissection (n, %)	7 (13.7%)	3 (5.9%)	0 (0%)	0.31	0.58	8 (15.7%)	3 (5.4%)	0 (0%)	0.20	0.016
No. of Thrombi	1.2 ± 1.3	0.6 ± 1.3	0.04 ± 0.2	0.003	< 0.001	1.4 ± 1.5	0.1 ± 0.4	0.0 ± 0.0	<0.001	< 0.001
% Length of thrombus (%)	6.2 ± 8.8	2.6 ± 4.7	0.2 ± 0.8	0.006	< 0.001	9.3 ± 10.2	1.5 ± 6.3	0.0 ± 0.0	<0.001	< 0.001
Max area of thrombus (mm^2)	0.21 ± 0.23	0.17 ± 0.29	0.01 ± 0.03	0.262	< 0.001	0.31 ± 0.39	0.07 ± 0.35	0.0 ± 0.0	0.001	< 0.001
No. of IRPs	0.24 ± 0.62	0.0 ± 0.0	0.0 ± 0.0	0.009	<0.001	0.3 ± 0.6	0.0 ± 0.0	0.0 ± 0.0	0.001	< 0.001
% Length of IRP (%)	1.5 ± 4.7	0.0 ± 0.0	0.0 ± 0.0	0.026	0.007	2.5 ± 6.5	0.0 ± 0.0	0.0 ± 0.0	0.009	0.003
Max area of IRP (mm^2)	0.06 ± 0.18	0.00 ± 0.00	0.00 ± 0.00	0.024	0.006	0.10 ± 0.20	0.00 ± 0.00	0.00 ± 0.00	0.001	< 0.001
No. of SPs	1.4 ± 1.6	0.3 ± 0.8	0.1 ± 0.3	< 0.001	< 0.001	1.3 ± 1.4	0.3 ± 0.6	0.0 ± 0.2	< 0.001	< 0.001
% Length of SP (%)	5.6 ± 7.3	0.5 ± 2.1	0.1 ± 0.5	< 0.001	< 0.001	6.2 ± 7.5	1.8 ± 4.1	0.3 ± 1.5	< 0.001	< 0.001
Max area of SP (mm^2)	0.19 ± 0.17	0.06 ± 0.14	0.02 ± 0.10	< 0.001	< 0.001	0.16 ± 0.15	0.08 ± 0.20	0.02 ± 0.09	0.014	< 0.001

FD-OCT, frequency domain-optical coherence tomography; IRP, irregular protrusion; SP, smooth prolapse.

Discussion

The MECHANISM-Elective trial included early-phase OCT follow-up at 1 and 3 months followed by serial 12-month follow-ups after Co-Cr EES implantation in stable patients with CAD. The major findings were significant improvements in uncovered and malapposed struts from post-PCI to 1 month and from post-PCI to 3 months, which were further improved at 12 months. The incidence and number of thrombi and prolapses were significantly reduced at 1 month and decreased further at 12 months. IRPs were no longer observed at 1 month. Most intrastent and edge dissections had healed by 1 month. Although it was predictable that the vascular response to Co-Cr EES implantation was progressive, it seems that this study demonstrated the healing process has been achieved relatively sooner than those expected.

Early-phase vascular response to Co-Cr EES in stable CAD

This is the first report of systematically conducted early phase OCT follow-up of Co-Cr EES placement in stable patients with CAD. Human autopsy studies and in vivo OCT follow-up evaluations have confirmed improved vessel healing in Co-Cr EESs compared with first-generation DESs.[9,20] In most previous studies using OCT, the interval between stent placement and follow-up evaluation varied from 4 months to 2 years, focusing on the chronic phase of vascular healing. The characteristics of Co-Cr EESs, such as thin struts, antithrombotic polymer coating, and the dose of everolimus, are expected to promote rapid healing; however, there is a lack of OCT data describing early response to implantation. The neointimal coverage of Co-Cr EESs at 1 month, with 6.4% uncovered and 2.8% malapposed struts, was far better than that of first-generation DESs at 6 months.[21] The longitudinal extension of malapposed and uncovered stents was the most important correlate of thrombus formation in cases of late ST even in new-generation DESs.[22] The study observations support the safety of Co-Cr EES at early postimplantation phase of 1 and 3 months.

Optimal duration of DAPT after Co-Cr EES implantation in stable patients with CAD

Updated guidelines recommend shortening the duration of DAPT to less than 6 months when new-generation DESs are used in stable patients with CAD.[4] Recently, Natsuaki et al.[23] reported that stopping DAPT at 3 months after Co-Cr EES implantation in selected patients was at least as safe as a prolonged DAPT regimen. Especially for the elderly patients, such as ≥ 75 years, using DES with 1-month DAPT would be a better choice for stable CAD in terms of reducing both ischemic and bleeding events.[6] Several ongoing prospective, multicenter, and randomized controlled clinical trials, including **Sho**r**t** and **Op**timal Duration of **D**ual **A**nti**p**latelet **T**herapy (STOPDAPT)-2 study, in which DAPT is discontinued at 1 month irrespective of age, are expected to provide comprehensive data on the optimal duration of DAPT.

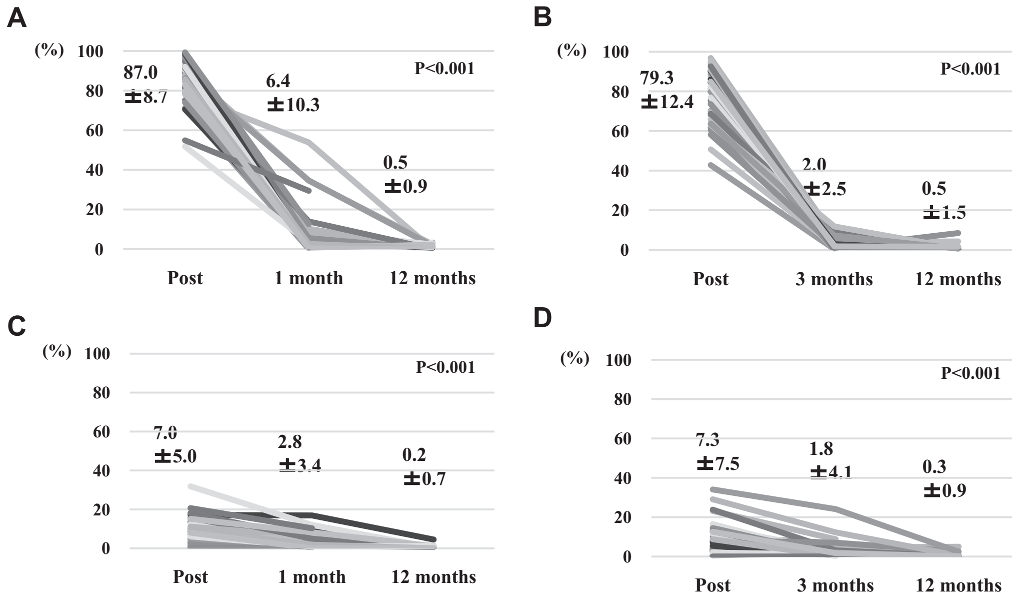

Figure 5. Serial changes in percentages of uncovered struts at 1 month (**A**) and at 3 months (**B**). Serial changes in percentages of malapposed struts at 1 month (**C**) and at 3 months (**D**).

Impact of abnormal intrastent findings immediately after PCI

OCT can image post-stent abnormal findings, such as tissue protrusion or thrombi. Soeda et al.[10] described the impact of OCT imaging of IRPs on the incidence of device-associated clinical end points, especially TLR. Sugiyama et al.[24] found a weak correlation of the area of tissue protrusion at the index PCI and the extent of neointima development at a 9-month follow-up. In both studies, tissue protrusion, including thrombus, was more prominent in patients with acute coronary syndrome than in patients with stable CAD. In this study, IRP was not observed at 1 month and thrombi were minimized at 3 months. There was no difference in neointimal area at 12 months between IRP(+) and IRP(−) lesions.

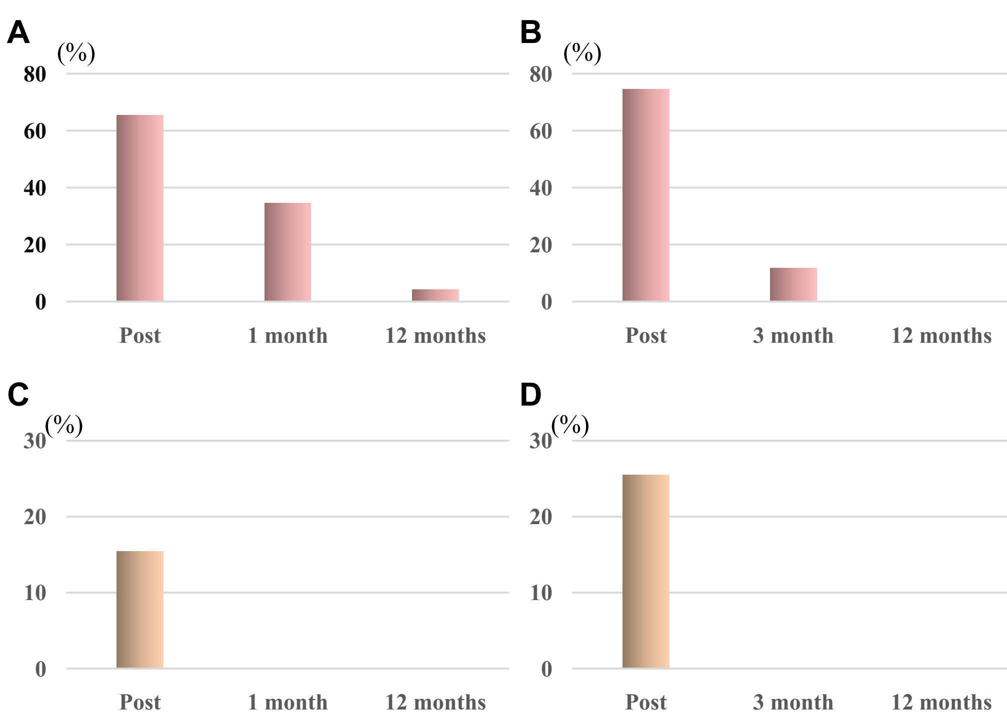

Figure 6. Serial changes in the incidence of intrastent thrombus (IS-Th) at 1 month (**A**) and 3 months (**B**). Serial changes in the incidence of IRPs at 1 month (**C**) and 3 months (**D**).

Table 3. Clinical events

	1-mo cohort	3-mo cohort
	Patients (n = 50)	Patients (n = 50)
MACE	4	4
Cardiac death (n)	0	0
Total death (n)	1	0
Myocardial infarction (n)	1	1
TLR (n)	0	2
Non-TLR (n)	4	2
Stent thrombosis (n)	0	1
Bleeding event (n)	0	1

MACE, major adverse cardiovascular events; TLR, target lesion revascularization.

Clinical relevance of residual platelet reactivity in stable CAD

A recent meta-analysis reported that high on-treatment platelet reactivity using the $P2Y_{12}$ assay was associated with long-term cardiovascular events after PCI,[12] and the impact of residual platelet reactivity on adverse cardiovascular outcome was found to be greater in ACS than in stable CAD.[11] The impact of on-treatment platelet activity seems to be associated with the generation of DESs. The association of in-stent thrombus attachment at 9 months and residual platelet reactivity was weaker with Co-Cr EESs compared with first-generation DESs. In this study, no association between in-stent thrombus and PRU was observed at 1, 3, or 12 months. The results suggest routine platelet function testing is not necessary in stable CAD.

Clinical implications

Clinical decisions for continuation or discontinuation of DAPT may depend on several systemic factors, such as the Precise DAPT score.[25] The study results suggest the possible shortening of DAPT duration up to 1 month and warrant testing through comprehensive clinical trials of the optimal use of antiplatelet regimens.

Study limitations

Patient selection bias might have occurred because the study mainly evaluated patients with multivessel disease and scheduled FD-OCT assessments during staged PCI in 88% of the patients or regular follow-up angiography in 12%. The study included a relatively small sample size with cases of unavailable third OCT (5 lesions in 1-month cohort and 10 lesions in 3-month cohort), but serial FD-OCT analysis in each patient provided detailed data on the vascular responses to Co-Cr EESs. Several definitions of OCT parameters have been reported,[26] and OCT images were evaluated using pre-specified criteria. The results of clinical studies are influenced by differences in definition, but the serial dataset evaluated in this study substantially minimized such influences on the comprehensive assessment of the vascular healing process.

Conclusions

Early and mid-term vascular reactions after Co-Cr EES implantation in stable patients with CAD in the MECHANISM-Elective trial included dynamic resolution of IS-Th, IRP, dissections, and rapid decrease in uncovered struts. EES may allow shortening DAPT duration in patients with CAD.

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Disclosures

Drs Shinke, Morino, and Otake have served as members of advisory boards of Abbott Vascular. There are no other potential conflicts to disclose that are associated with this manuscript.

References

1. Planer D, Smits PC, Kereiakes DJ, et al. Comparison of everolimus- and paclitaxel-eluting stents in patients with acute and stable coronary syndromes: pooled results from the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) Trials. JACC Cardiovasc Interv 2011;4:1104-15.
2. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting stents: is the paradigm shifting? J Am Coll Cardiol 2013;62:1915-21.
3. Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011;58:1569-77.
4. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.
5. Genereux P, Rutledge DR, Palmerini T, et al. Stent thrombosis and dual antiplatelet therapy interruption with everolimus-eluting stents: insights from the Xience V Coronary Stent System Trials. Circ Cardiovasc Interv 2015;8:001362.
6. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet 2018;391:41-50.
7. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;59:1058-72.
8. Iannaccone M, D'Ascenzo F, Templin C, et al. Optical coherence tomography evaluation of intermediate-term healing of different stent types: systemic review and meta-analysis. Eur Heart J Cardiovasc Imaging 2017;18:159-66.
9. Taniguchi Y, Otake H, Shinke T, et al. Two-year vessel healing after everolimus-eluting stent implantation: serial assessment by optical coherence tomography. J Cardiol 2015;65:298-304.
10. Soeda T, Uemura S, Park SJ, et al. Incidence and clinical significance of poststent optical coherence tomography findings: one-year follow-up study from a multicenter registry. Circulation 2015;132:1020-9.
11. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents

(ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382:614-23.

12. Brar SS, ten Berg J, Marcucci R, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. J Am Coll Cardiol 2011;58:1945-54.

13. Kubo T, Shinke T, Okamura T, et al. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): one-year angiographic and clinical results. Eur Heart J 2017;38:3139-47.

14. Malinin A, Pokov A, Spergling M, et al. Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12(R) rapid analyzer: the VERIfy Thrombosis risk ASsessment (VERITAS) study. Thromb Res 2007;119:277-84.

15. Otake H, Shite J, Ako J, et al. Local determinants of thrombus formation following sirolimus-eluting stent implantation assessed by optical coherence tomography. JACC Cardiovasc Interv 2009;2:459-66.

16. Terashita D, Otake H, Shinke T, et al. Differences in vessel healing between sirolimus- and everolimus-eluting stent implantation for bifurcation lesions: the J-REVERSE Optical Coherence Tomography Substudy. Can J Cardiol 2016;32:384-90.

17. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.

18. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015-26.

19. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.

20. Otsuka F, Vorpahl M, Nakano M, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation 2014;129:211-23.

21. Miyoshi N, Shite J, Shinke T, et al. Comparison by optical coherence tomography of paclitaxel-eluting stents with sirolimus-eluting stents implanted in one coronary artery in one procedure. Circ J 2010;74:903-8.

22. Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. Circulation 2016;133:650-60.

23. Natsuaki M, Morimoto T, Yamamoto E, et al. One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. Cardiovasc Interv Ther 2016;31:196-209.

24. Sugiyama T, Kimura S, Ohtani H, et al. Relationship between quantities of tissue prolapse after percutaneous coronary intervention and neointimal hyperplasia at follow-up on serial optical coherence tomography examination. Int J Cardiol 2017;241:470-7.

25. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025-34.

26. Souteyrand G, Amabile N, Mangin L, et al. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. Eur Heart J 2016;37:1208-16.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.07.633.