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SHORT REPORT
Interventional cardiology and cardiac surgery

Incidence and natural history of coronary evagination after implanted biodegradable polymer sirolimus-eluting stent

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Aims The incidence and temporal change in coronary evagination (CE) after first-generation drug-eluting stent implantation is well established, whereas that after biodegradable polymer sirolimus-eluting stent (BP-SES) implantation has not yet been evaluated. The aim of this study is to assess the incidence and natural history of CE after BP-SES implantation.

Methods and results In this multicenter registry, stable coronary lesions treated by Ultimaster BP-SES were evaluated by serial optical frequency domain imaging (OFDI) (at 0–1–12 or 0–3–12 months) and the incidence of CE was assessed. Coronary evagination was defined as the presence of an outward bulge in luminal vessel contour between apposed struts according to the following criteria: (i) evagination depth ≥10% of nominal stent diameter and (ii) evagination length ≥3.0 mm. Optical frequency domain imaging was obtained in 98, 47, 49, and 87 lesions at 0, 1, 3, and 12 months, respectively. Coronary evagination was observed in 20 (42.6%) and 12 (24.5%) lesions at 1 and 3 months, respectively, and all but one CE had resolved at 12 months. At 12 months, the mean CE area was almost zero and the mean malapposed stent area was also decreased. Comparison of the serial OFDI images indicated that CEs originated mostly from acute stent malapposition or coronary dissection behind the implanted stent.

Conclusions In stable lesions, CE was occasionally observed with Ultimaster BP-SES at 1–3 months but mostly resolved within 12 months, without late-acquired stent malapposition. These findings suggest the safety and feasibility of biodegradable polymer coating on DES.

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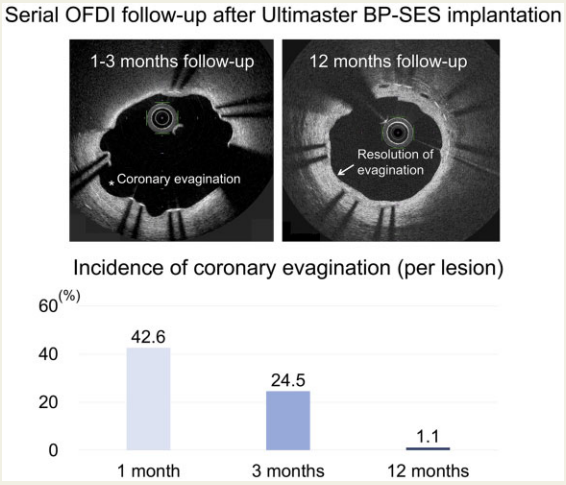
Graphical Abstract



Keywords Biodegradable polymer • Chronic coronary syndrome • Drug-eluting stent • Optical frequency domain imaging • Percutaneous coronary intervention

Introduction

Coronary evagination (CE), which is frequently and continuously observed in lesions after first-generation drug-eluting stent (DES) implantation, is known as a risk factor for late stent thrombosis.[1] However, the characteristics of CE in current-generation DES have yet to be investigated in detail. Recent study has reported low rates of stent thrombosis for the novel Ultimaster biodegradable polymer sirolimus-eluting stent (BP-SES) (Terumo Corporation, Tokyo, Japan), as well as for second-generation DES.[2] The polymer used with BP-SES is absorbed within 3–4 months after coronary artery implantation, resulting in decreased inflammatory action behind the BP-SES compared with first-generation DES,[2] and therefore the

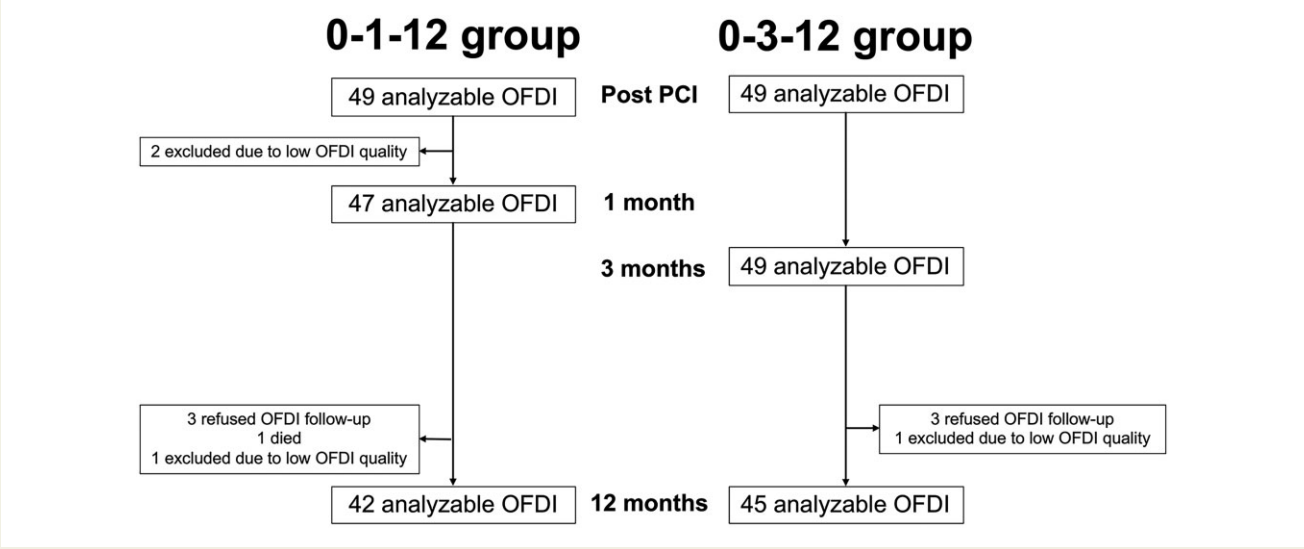


Figure 1 Study flow chart. OFDI, optical frequency domain imaging; PCI, percutaneous coronary intervention.

Table 1 **Baseline patient and lesion characteristics, procedural details, and results of post-percutaneous coronary intervention optical frequency domain imaging evaluations**

	Overall ($n = 98$)	0–1–12 group ($n = 49$)	0–3–12 group ($n = 49$)
Age	68.0 ± 9.4	69.6 ± 9.7	66.9 ± 9.0
Male sex	73 (72.3)	32 (65.3)	38 (77.6)
Hypertension	81 (81.3)	38 (77.6)	41 (83.7)
Hyperlipidaemia	81 (81.3)	38 (77.6)	41 (83.7)
Diabetes mellitus	47 (46.5)	23 (46.9)	22 (44.9)
Current smoking	46 (45.5)	14 (28.6)	31 (63.3)*
Renal insufficiency	32 (31.7)	16 (32.7)	14 (28.5)
Prior PCI	26 (25.7)	14 (28.6)	9 (18.4)
Target vessel: LAD/LCX/RCA	37 (36.6)/22 (21.8)/42 (41.6)	14 (28.6)/11 (22.4)/24 (49.0)	21 (42.9)/10 (20.4)/18 (36.7)
Minimum lumen diameter (mm)	2.58 ± 0.44	2.51 ± 0.39	2.66 ± 0.48
Reference diameter (mm)	2.91 ± 0.42	2.83 ± 0.39	2.98 ± 0.45
%Diameter stenosis	11.0 ± 10.2	11.2 ± 10.2	10.9 ± 10.3
Stented segment length (mm)	26.5 ± 12.9	28.0 ± 15.3	25.0 ± 9.9
Number of implanted stents	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.5
AHA type B2/C lesion	16/69 (32.9)	12/38 (31.6)	16/47 (32.7)
Implanted stent diameter (mm)	3.00 ± 0.41	2.85 ± 0.34	3.15 ± 0.43**
Total implanted stent length (mm)	30.3 ± 14.8	28.3 ± 12.2	32.4 ± 16.9
Maximum inflation pressure (atm)	16.5 ± 4.0	16.9 ± 4.0	16.1 ± 4.0
Post-dilation	62/97[a] (63.9)	31 (63.3)	31/48[a] (64.6)

	Post ($n = 98$)	12 months ($n = 87$)	Post ($n = 49$)	1 month ($n = 47$)	12 months ($n = 42$)	Post ($n = 49$)	3 months ($n = 49$)	12 months ($n = 45$)
Analyzed cross-sectional images	2777	2500	1408	1401	1258	1369	1312	1242
Mean stent length (mm)	26.9 ± 10.6	26.6 ± 10.6	26.9 ± 10.7	26.7 ± 10.7	26.4 ± 10.7	27.1 ± 10.7	26.9 ± 10.6	26.8 ± 10.6
Minimum stent area (mm^2)	5.67 ± 1.84	5.75 ± 1.82	5.67 ± 1.85	5.76 ± 1.86	5.74 ± 1.83	5.65 ± 1.85	5.74 ± 1.86	5.72 ± 1.83
Mean neointimal thickness (mm)	N/A	0.166 ± 0.099	N/A	0.047 ± 0.026	0.178 ± 0.105	N/A	0.051 ± 0.0337	0.155 ± 0.091
% uncovered struts	N/A	0.52 ± 0.93	N/A	9.11 ± 10.1	0.50 ± 0.91	N/A	8.82 ± 9.75	0.52 ± 0.94
Coronary evagination (per lesion)	N/A	1 (1.1)	N/A	20 (42.6)	1 (2.1)	N/A	12 (24.5)	0 (0.0)
Number of coronary evaginations (per lesion)	N/A	0.02 ± 0.21	N/A	0.46 ± 0.75	0.02 ± 0.22	N/A	0.12 ± 0.33	0 (0.0)
Mean area of coronary evagination (mm^2)	N/A	0.003 ± 0.080	N/A	0.056 ± 0.265	0.006 ± 0.113	N/A	0.032 ± 0.189	0
% length of coronary evagination (per lesion)	N/A	0.2 ± 1.7	N/A	7.5 ± 11.7	0.2 ± 1.6	N/A	4.4 ± 8.9	0 (0.0)
% malapposed struts	4.78 ± 4.66	0.19 ± 0.78	4.66 ± 4.57	2.41 ± 3.24	0.18 ± 0.79	4.78 ± 4.66	2.46 ± 3.24	0.19 ± 0.78
Stent malapposition (≥0.25 mm) (per lesion)	76 (87.4)	10 (11.5)	38 (90.1)	26 (61.9)	7 (16.7)	38 (84.4)	23 (51.1)	3 (6.7)
Intra-stent thrombus (≥0.25 mm) (per lesion)	39 (44.8)	7 (8.0)	18 (42.9)	17 (40.4)	4 (9.5)	21 (46.7)	9 (20)	3 (6.7)
Irregular protrusions (≥0.25 mm) (per lesion)	13 (14.9)	2 (1.1)	4 (9.5)	2 (8.5)	1 (2.4)	9 (20.0)	1 (2.2)	1 (2.2)
Any stent edge dissection (per lesion)	21 (24.1)	1 (1.1)	11 (26.2)	4 (9.5)	1 (2.4)	10 (22.2)	1 (2.2)	0 (0.0)

Renal insufficiency was defined by estimated glomerular filtration rate <60 mL/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease study equation.
AHA, American Heart Association; LAD, left anterior descending artery; LCX, left circumflex artery; N/A, not available; OFDI, optical frequency domain imaging; PCI, percutaneous coronary intervention; RCA, right coronary artery.
Data are presented as mean ± standard deviation, or *n* (%).
[a]One case was excluded from analysis due to missing data.
*$P < 0.005$,
**$P < 0.001$.

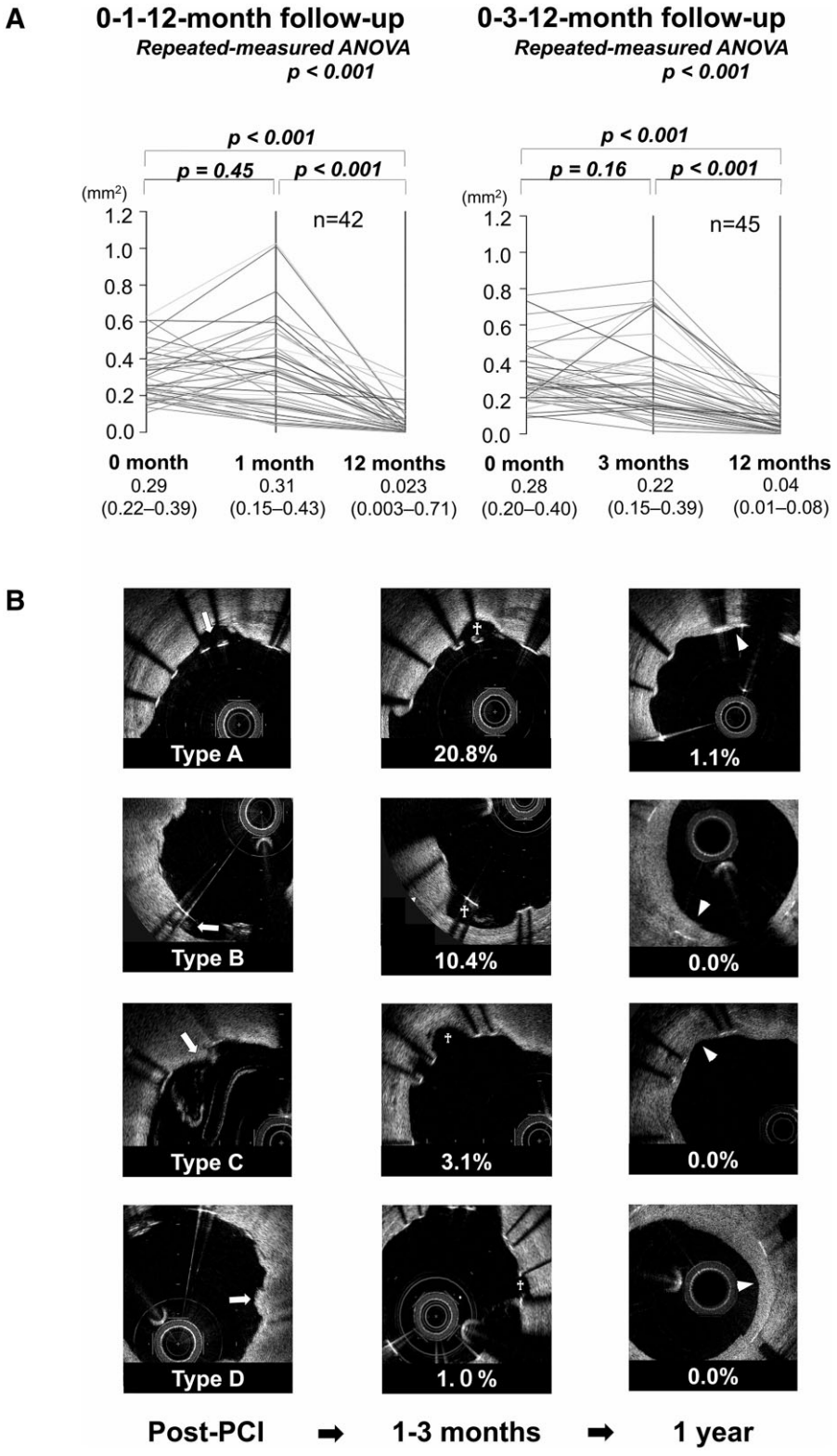


Figure 2 Serial change of mean malapposed area (*A*) and representative optical frequency domain imaging images showing relative factors and natural history of coronary evagination (*B*). Retrospective assessment of the post-percutaneous coronary intervention optical frequency domain imaging images could be classified as four types; acute stent malapposition (Type A, white arrow), coronary dissection behind implanted stent (Type B, white arrow), smooth tissue prolapse into the lumen between struts (Type C, white arrow), thrombus or irregular protrusion (Type D, white arrow). ANOVA, repeated-measures analysis of variance; PCI, percutaneous coronary intervention. †Coronary evagination (at 1–3 months follow-up), white arrowhead; resolution of coronary evagination (at 1-year follow-up).

incidence and natural history of CE after BP-SES implantation may differ to those after first-generation DES implantation. To clarify these characteristics, we analysed serial optical frequency domain imaging (OFDI) of coronary artery implantation after BP-SES.

Materials and methods

In this study, we used data from the MECHANISM-ULTIMASTER Elective study (UMIN 000021119), a prospective, multicenter registry that used OFDI to assess early vascular healing in chronic coronary syndrome (CCS) patients (*Figure 1*). The protocol and main results of the MECHANISM-elective study have been reported in detail.[3] All culprit lesions were treated with either one or two Ultimaster BP-SES in standard fashion. The endpoint was the presence of CE at either 1 or 3, and 12 months of the follow-up period. Coronary evagination was evaluated based on the previously reported definition.[4] To evaluate the aetiology of CE, we also retrospectively assessed early-term OFDI images corresponding to CE in the post-PCI OFDI images.

Statistical analysis

Statistical analysis was performed with SPSS software, version 21 (SPSS, Inc., Chicago, IL, USA). Continuous values are presented as the mean ± standard deviation or median (1st quartile–3rd quartile), and then compared between two groups using the Mann–Whitney *U* tests. Categorical variables are expressed as the number and percentage, and compared using the chi-square test or Fisher's exact test, as appropriate. To compare the mean malapposed area among the three time points, an analysis of variance was performed by the Friedman test. Post-hoc analysis was performed using the Bonferroni correction. *P*-values < 0.05 were considered statistically significant.

Results

The baseline patient and lesion characteristics and procedural details were similar between the two follow-up groups, with exception of current smoking and implanted stent diameter (*Table 1*). In terms of quantitative OFDI findings, mean neointimal thickness increased with time; and uncovered strut rates decreased with time. At early-term follow-up (1 or 3 months), 42.6% or 24.5% of lesions, respectively, had CE. However, CE had resolved in almost all lesions at 12 months of follow-up. Although there was variation in malapposed stent area at post-PCI, and also at early-term follow-up, OFDI at 12 months of follow-up showed a significant decrease in all malapposed areas ($P < 0.001$), with no late-acquired malapposition (*Figure 2A*).

Comparing the post-PCI and early-term OFDI images, we sought to identify and classify the relative factors of CE (*Figure 2B*). As a result, 20.8% of the lesion had CE related with acute stent malapposition (Type A) and 10.4% of the lesion had CE related with coronary dissection behind the implanted stent (Type B). Retrospective assessment of the post-PCI OFDI images revealed that CE was rarely caused by smooth tissue prolapse into the lumen between struts (Type C) or by resolution of thrombus and/or irregular protrusion (Type D). At 12 months follow-up, the incidences of CE became nearly zero regardless of the type of CE.

Discussion

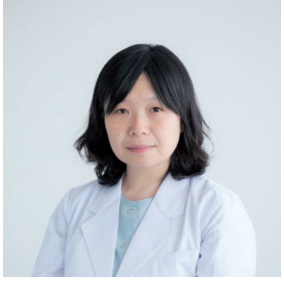
In lesions treated with Cypher SES, localized hypersensitivity was activated by coated durable polymer.[5] Accordingly, persistent inflammation led to delayed arterial healing and caused CE and late-acquired malapposition.[5,6] In contrast, Ultimaster BP-SES has a poly (DL-lactide-co-caprolactone) polymer that is absorbed within 3–4 months after implantation. Based on the product concept of Ultimaster BP-SES, it appears that inflammation caused by this biodegradable polymer occurs for only a limited time. Considering the pathological and clinical evidence, the present study indicates the safety and feasibility of polymer absorption for arterial healing after DES implantation. Another potential reason for the resolution of CE and malapposition is the relatively greater neointimal thickness following Ultimaster BP-SES implantation compared with Cypher SES (51 µm vs. 29 µm, respectively, at 3 months).[7] Thus, aggressive neointimal proliferation after Ultimaster BP-SES implantation might have filled in the hollowed space behind the stent strut within 1 year.

In the present study, the major aetiologies of CE were Type A and B. Based on the previous studies showing the vascular response to coronary stent,[8,9] a neointimal bridge formation and positive vessel remodelling could cause CE after Ultimaster BP-SES implantation. At early-term follow-up, Type C and D CE were rarely observed. This might be related to differences in the lesion morphology, the product features, and the early follow-up timing.

The present study has several limitations. First, selection bias should not be excluded, because of small sample size and non-randomized assignment to each group. Second, we did not assess lesions that had adverse clinical events. Third, the present study included only CCS lesions, and we did not assess thrombotic lesions causing acute coronary syndrome or complex lesions. Fourth, because we only used Ultimaster BP-SES, it is unknown whether the results would have been similar if another biodegradable polymer DES had been used.

In conclusion, early CEs were occasionally observed in CCS lesions treated with Ultimaster BP-SES, but most cases of CE resolved completely without the development of late-acquired stent malapposition. These findings suggest the safety and feasibility of biodegradable polymer coating on DES.

Lead author biography



Keiko Tsuji is a postgraduate student in Cardiology at Iwate Medical University, Japan. She started her medical studies at Iwate Medical University in 2010. After graduation in 2014, she conducted a medical internship at Iwate prefectural Kuji hospital and Iwate Medical University Hospital. In 2018, she admitted to an PhD Program at Iwate Medical University and is working as a cardiologist at university-affiliated hospital.

Conflict of interest: M.I. received lecture fees from Abbott Vascular Japan, Boston Scientific, Daiichi-Sankyo, Japan Lifeline, Kowa,

Medikit and Terumo Corporation. T.I. received lecture fees from Abbott Vascular Japan and Otsuka pharmacy. H.O. received lecture fees from Terumo Corporation. Toshiro Shinke received lecture fees from Terumo Corporation. Y.M. received grants from Terumo Corporation for this study, lecture fees from Daiichi-Sankyo, Medtronic and Terumo Corporation, and grants and lecture fees from Abbott Vascular Japan, Boston Scientific and Japan Lifeline. All other authors have no conflicts of interest.

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