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Restenosis patterns after percutaneous coronary intervention with drug-coated balloons for *de novo* coronary lesions

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Drug-coated balloons (DCBs) are currently used to treat *de novo* coronary artery lesions. Although controversial, previous studies have suggested the possibility that DCB treatment for *de novo* coronary artery disease is non-inferior to drug-eluting stent implantation, including small vessel disease[1]. However, the morphological changes in lesions with target lesion revascularisation (TLR) following DCB treatment have not been fully clarified. Thus, this study examined TLR lesions treated with DCBs using serial optical coherence tomography (OCT) to explore the mechanism of restenosis.

This retrospective observational study was conducted at the Japanese Red Cross Musashino Hospital (Tokyo, Japan). Between April 2018 and April 2024, 408 patients with *de novo* coronary lesions were subjected to OCT-guided percutaneous coronary intervention (PCI) using paclitaxel-coated balloons (SeQuent Please [B. Braun] or AGENT [Boston Scientific]). Among them, 26 TLR lesions in 24 patients with serial OCT examinations (at index PCI [pre- and post-PCI] and at TLR) were enrolled **(Supplementary Figure 1)**. All TLR were ischaemic or clinically driven (presence of chest symptom or evidence of physiological ischaemia).

OCT images at pre-PCI, post-PCI and at TLR were assessed. Suboptimal lumen expansion (SLE) is defined as lesions with both a post-PCI minimum lumen area (MLA) <3.00 mm^2 and an expansion ratio (defined as MLA/mean reference lumen area) <0.50 at index PCI. Layered plaque (LP) was defined as a different optical intensity with clear demarcation from the underlying plaque[2]. Calcified nodule protrusion (CNP) was defined as a calcified nodule (CN) protruding into the lumen. A CN was defined as the accumulation of small calcium deposits underlying the calcified plate, including pathological eruptive CNs and nodular calcification[3]. Representative cases are shown in **Central illustration A**.

The baseline patient characteristics and procedural details of the index PCI are summarised in **Supplementary Table 1** and **Supplementary Table 2**, respectively. The median period between the index PCI and TLR was 309 (interquartile range 239-462) days.

Based on the OCT findings at TLR, LP was the most frequent lesion type (76.9%), followed by CNP (38.5%) and erosion (3.8%) **(Table 1)**. These OCT findings were not significantly different in lesions with early (<1 year from index PCI) or late TLR (≥1 year). All post-PCI coronary dissections that occurred at index PCI disappeared at TLR. When the pre- and post-PCI OCT findings at index PCI were retrospectively assessed and compared to those at TLR, the absence of post-PCI medial dissection (50.0%), post-PCI SLE (23.1%), and pre-PCI CN (26.9%) was more frequently observed in the future TLR segment. After excluding one lesion with erosion, 25 lesions that underwent TLR were divided into three groups based on the predominant restenosis type: LP (53.8%, n=14), SLE (23.1%, n=6), and CNP (19.2%, n=5). The largest lipid arc was found in lesions with LP (median lipid arc: LP 159°, SLE 76°, CNP 0°; p=0.004), while the most severely calcified plaque was seen in lesions with CNP (median calcium thickness: LP 730 µm, SLE 1,130 µm, CNP 1,180 µm; p=0.014) at index PCI **(Central illustration B, Central illustration C)**.

To the best of our knowledge, this is the first study to assess serial OCT imaging at index PCI and TLR with DCBs for *de novo* coronary lesions. In the present study,

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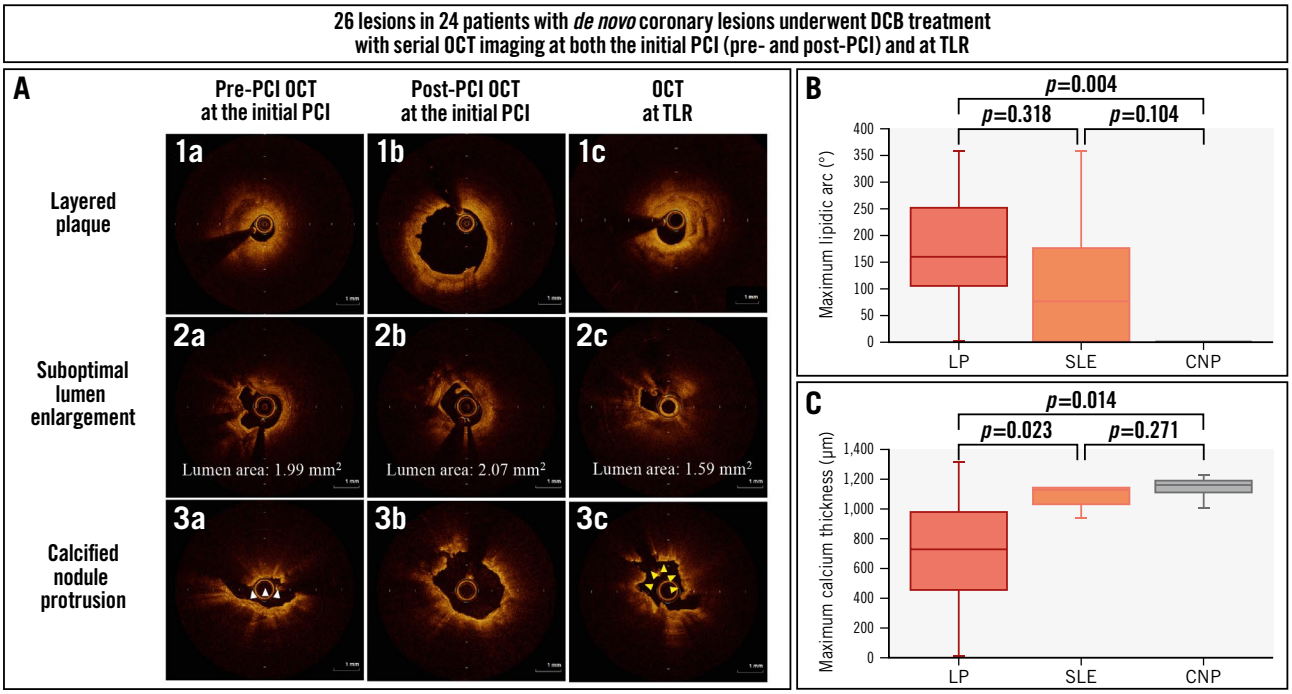
EuroIntervention — Central Illustration

Representative images of serial OCT imaging and comparison of OCT findings among lesions with layered plaque, suboptimal lumen enlargement, and calcified nodule protrusions.



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A) Representative serial OCT images (at index PCI [pre- and post-PCI] and at TLR) revealed three main reasons for restenosis. A1a, A1b) Pre- and post-PCI OCT images of the culprit lesion at initial PCI. A1c) OCT images of the LP at the culprit TLR lesion. LP, defined as a different optical intensity with a clear demarcation from the underlying plaque, was observed. A2a, A2b) Pre- and post-PCI OCT images of the culprit lesion at the initial PCI. SLE was observed during the initial PCI (post-PCI lumen area 2.07 mm²). A2c) OCT image of the SLE of the culprit TLR lesion. A3a, A3b) Pre- and post-PCI OCT images of the culprit lesion with a CN (white arrowheads) at the initial PCI. CN is defined as the accumulation of small calcium deposits on a calcified plate. A3c) OCT image of the CNP culprit lesion at TLR. CNP was observed in the lumen (yellow arrowheads). B) Comparison of the maximum lipidic arc among three TLR morphologies. The maximum lipidic arc was largest in lesions with LP (158° vs [SLE] 76° vs [CNP] 0°; p=0.017) at index PCI. C) Comparison of maximum calcium thickness among three types of TLR morphologies. The highest maximum calcium thickness was noted in lesions with CNP (720 μm vs [SLE] 1,130 μm vs [CNP] 1,180 μm; p=0.010) at index PCI. CN: calcified nodule; CNP: calcified nodule protrusion; DCB: drug-coated balloon; LP: layered plaque; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; SLE: suboptimal lumen expansion; TLR: target lesion revascularisation

TLR lesions treated with DCBs were classified into three groups (LP, SLE, and CNP) based on the stent failure type, such as neoatherosclerosis, neointimal hyperplasia, and stent underexpansion, as reported in previous studies of coronary stents.

In TLR lesions with LP, the lipid arc at index PCI was larger than in the other types. According to previous OCT studies, LP is considered a healed phenotype of vulnerable plaque[2]. Thus, the development of LP during the follow-up period after DCB treatment is considered an excessive healing process, resulting in restenosis and the need for TLR.

Conversely, thick calcification and CNs were observed at index PCI in lesions with CNP at TLR, suggesting that calcium may hinder optimal drug absorption[4] and that the CN may eventually protrude, even after DCB treatment for severe calcification.

Previous studies have reported that post-PCI coronary artery dissection is positively associated with late lumen enlargement and fewer target lesion failure events[5]. Considering the optimal PCI strategies for stenting, more research is needed to determine whether the same strategies are appropriate for DCB treatment.

This study had several limitations. First, this hypothesis-generating study was retrospective and observational. Therefore, selection bias was inevitable. Second, the sample size was small. Third, only paclitaxel-coated balloons were used. Fourth, because of the limited penetration depth of OCT imaging, we were unable to demonstrate whether remodelling

Table 1. OCT findings.

Pre-PCI OCT findings	Vessels with TLR (n=26)
Pre-PCI OCT findings	
Pre-PCI minimum lumen area, mm²	1.22 (0.91-2.01)
Maximum lipid arc, °	109 (0-193)
Maximum calcium angle, °	199 (81-313)
Maximum calcium thickness, μm	1,050 (888-1,173)
Calcium length, mm	11 (4-26)
Calcified nodule	7 (26.9)
Post-PCI OCT findings	
Post-PCI minimum lumen area, mm²	3.37 (2.54-4.64)
Post-PCI area stenosis, %	42.1 (29.9-54.4)
Post-PCI suboptimal lumen expansion	6 (23.1)
Post-PCI dissection	
None or intimal dissection	13 (50.0)
Medial involvement	3 (11.5)
Adventitial involvement	10 (38.5)
Maximum dissection angle, °	103 (67-159)
Longitudinal dissection length, mm	9.5 (5.6-13.0)
OCT findings at TLR	
Minimum lumen area at TLR, mm²	1.30 (1.06-2.24)
Residual dissection	4 (15.4)
Calcified nodule protrusion	5 (19.2)
Layered plaque	20 (76.9)
Erosion	1 (3.8)

Values are n (%) or median (interquartile range). OCT: optical coherence tomography; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation

occurred. Fifth, the classification of TLR morphology was not supported pathologically. Sixth, relatively severely calcified plaques were included in this study, which may have affected lipid content parameters, including the maximum lipidic arc.

In conclusion, after treatment with DCBs for *de novo* coronary lesions, unique underlying morphological findings were observed in lesions treated with TLR.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Patient characteristics at the index PCI.

Supplementary Table 2. Angiographic and procedural results at the index PCI.

Supplementary Figure 1. Study flowchart.

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Supplementary data

Supplementary Table 1. Patient characteristics at the index PCI.

	Patients with TLR (n=24)
Age (years)	71 (62-75)
Male, n (%)	20 (83.3%)
Hypertension, n (%)	21 (87.5%)
Diabetes mellitus, n (%)	11 (45.8%)
Dyslipidemia, n (%)	14 (58.3%)
Current smoker, n (%)	8 (33.3%)
Hemodialysis, n (%)	4 (16.7%)
Prior MI, n (%)	9 (37.5%)
Prior PCI, n (%)	15 (62.5%)
Prior CABG, n (%)	3 (12.5%)
Stable CAD, n (%)	17 (70.8%)
Acute coronary syndrome, n (%)	7 (29.2%)
ST elevation MI	1 (4.2%)
Non-ST elevation MI	6 (25.0%)
EF (%)	61.9 (45.8-68.1)
LDL-chol (mg/dL)	93.2 (68.3-121.7)
HbA1c (%)	5.9 (5.6-7.2)
eGFR (ml/min/1.73m^2)	62.0 (51.6-69.4)

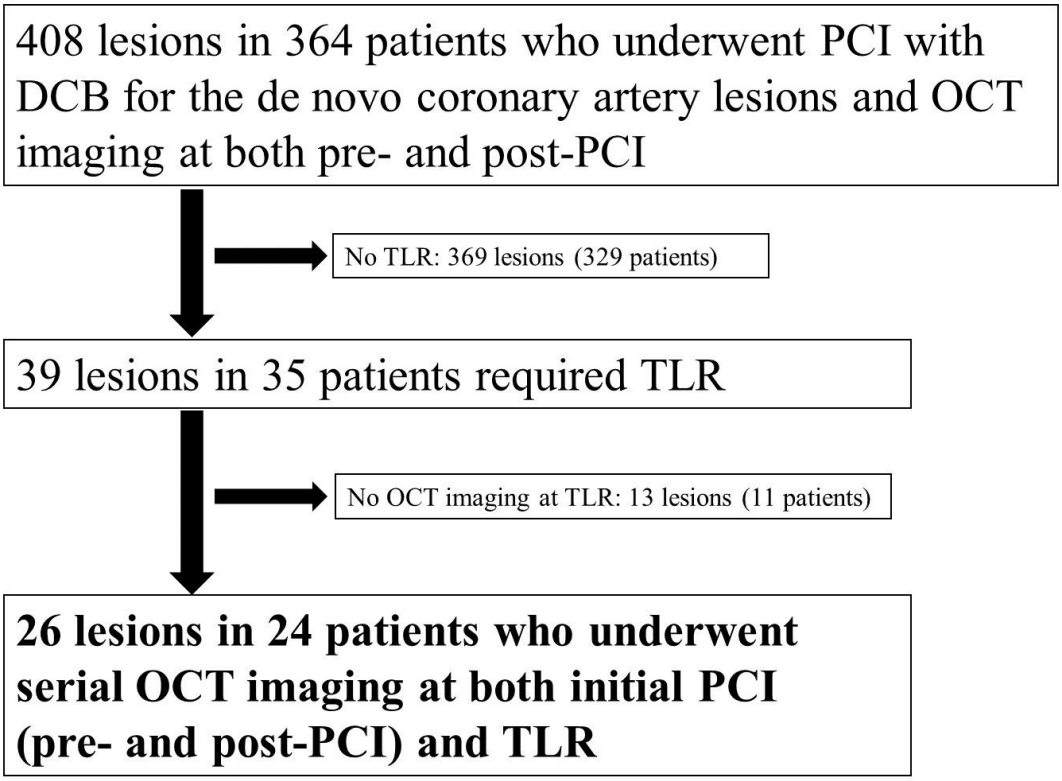
Abbreviations: PCI, percutaneous coronary intervention; TLR, target lesion revascularization; MI, myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; EF, ejection fraction; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate.

Supplementary Table 2. Angiographic and procedural results at the index PCI.

	Vessels with TLR (n=26)
Target Vessel, n (%)	
RCA	6 (23.1%)
LAD	17 (65.4%)
LCX	3 (11.5%)
Calcification, n (%)	
None or mild	10 (38.5%)
Moderate	2 (7.7%)
Severe	14 (53.8%)
Pre-PCI QCA	
Minimum lumen diameter, mm	0.78 (0.58-1.11)
Reference vessel diameter, mm	2.59 (2.21-3.19)
Diameter stenosis, %	67.1 (61.4-77.8)
Lesion length, mm	13.3 (9.9-23.4)
Post-PCI Angiography findings	
Minimum lumen diameter, mm	1.92 (1.50-2.07)
Diameter stenosis, %	34.2 (27.7-39.3)
Acute Gain, mm	0.93 (0.74-1.38)
Post-PCI dissection classification (NHLBI classification), n (%)	
Type A	1 (3.8%)
Type B	9 (34.6%)
Type C	1 (3.8%)
PCI procedure results	
Cutting balloon, n (%)	10 (38.5%)
Scoring balloon, n (%)	15 (57.7%)
Maximum balloon size, mm	2.75 (2.5-3.25)
Maximum inflation pressure, mmHg	14 (12-20)
Rotational atherectomy, n (%)	1 (3.8%)
Orbital atherectomy, n (%)	10 (38.5%)
Excimer laser, n (%)	6 (23.1%)
Intravascular lithotripsy, n (%)	2 (7.7%)

Total DCB length, mm	20 (20-30)
Maximum DCB diameter, mm	3.0 (2.75-3.5)
Maximum inflation pressure of DCB, mmHg	7 (6-8)

Abbreviations: PCI, percutaneous coronary intervention; TLR, target lesion revascularization; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; QCA; quantitative coronary angiography; NHLBI, National Heart, Lung, and Blood Institute; DCB, drug-coated balloon.



Supplementary Figure 1. Study flowchart.

Of the 408 de novo coronary lesions that underwent OCT-guided PCI with DCB, we enrolled 26 TLR lesions in 24 patients with serial OCT examinations (pre-and post-PCI at the index PCI and at TLR). Abbreviations: PCI, percutaneous coronary intervention; DCB, drug-coated balloon; OCT, optical coherence tomography; TLR, target lesion revascularization.