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BRIEF REPORT

OCT–Verified Neoatherosclerosis in BMS Restenosis at 10 Years

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Neoatherosclerosis (1) is characterized by infiltration of foamy macrophage clusters within neoimtima, and thin-capped neoatheroma (TCNA) and neointimal rupture has been demonstrated during an extended period as a contributor to late stent failure (2–4). Using intravascular ultrasound (IVUS) and optical coherence tomography (OCT), we characterized in-stent restenosis (ISR) in patients who underwent clinically driven target lesion revascularization late after bare-metal stent (BMS) placement. From March 2009 to August 2011, 51 patients with BMS-ISR underwent target lesion revascularization; 30 patients presented with stable and 21 with unstable angina. Of the 30 patients with stable angina, 26 (87%) had demonstrated thallium scan perfusion defects of target vessel territories, and 4 (13%) showed resting or exercise-induced ST-segment–T-wave changes on electrocardiography. Pre-procedure OCT was performed in 22 of 51 patients, using a 0.019-inch ImageWire (LightLab Imaging, Westford, Massachusetts). OCT findings were classified as calcific intima, lipid-rich intima, TCNA, neointimal rupture, and thrombi, and were defined as previously described (4). IVUS imaging was performed after OCT imaging; lesions were stented, and reference segments were analyzed.

In the 22 patients undergoing OCT imaging (Table 1), unstable angina patients showed a trend of a thinner fibrous cap compared with stable angina patients (50 μm [interquartile range (IQR): 40 to 60 μm] vs. 60 μm [IQR: 50 to 120 μm], p = 0.056). Overall, 15 (68%) lesions had at least 1 TCNA; multiple TCNA were seen in 7 (32%) lesions. Neointimal rupture was identified in 13 (59%) lesions, and multiple neointimal ruptures were present in 5 (23%) lesions. At the site of the minimal lumen area (MLA), the frequency of TCNA and neointimal rupture was 55% and 46%, respectively. The frequency of these findings was 46% and 32% at the proximal segment to the MLA site, and 18% and 5% at the distal segment of the MLA site, respectively. Red thrombi were more frequent in patients with unstable angina compared with stable angina (75% vs. 30%, p = 0.035). All lesions but 1 (95%) showed at least 1 of the 3 OCT findings, that is, TCNA, neointimal rupture, and neointimal thrombi; 11 (50%) patients had all 3, and 19 (86%) had 2 of these features. All but 1 lesion (92%) with OCT-defined rupture had thrombi near the rupture site. The rate of agreement between grayscale IVUS and OCT for detecting neointimal rupture was 59% and for detecting thrombus was 41%.

Therefore, the present study demonstrates OCT-verified neointimal thrombi in 80%, TCNA in 70%, and neointimal rupture in 60% ISR, and suggests that advanced neoatherosclerosis is a common mechanism of very late BMS-ISR. Takano et al. (3) reported different OCT findings of BMS-ISR between late ISR beyond 5 years and early ISR within 6 months. The frequency of lipid-rich neointima (67% vs. 0%), neointimal disruption (38% vs. 0%), and TCNA (29% vs. 0%) was substantially higher in the late-phase ISR. Habara et al. (5) also suggested that the frequency of neointimal rupture with cavity formation and intraluminal material was only 19% and 21%, respectively, in the very late BMS-ISR ≥5 years. We observed a higher frequency of TCNA (68%), neointimal rupture (59%), and neointimal thrombi (77%). Nakazawa et al. (1) suggested that the earliest atherosclerotic change in BMS remained rare until 4 years, and necrotic core formation began from 5 years after implantation. Because the incidence and severity of neoatherosclerosis is time dependent, the difference

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Table 1. IVUS-OCT Analysis

Variable	Total (N = 51)	OCT Subgroup (n = 22)
IVUS data		
IVUS-measured MSA, mm^2	6.6 (5.2–8.2)	7.0 (5.4–7.6)
IVUS-measured MLA, mm^2	2.0 (1.4–2.5)	1.5 (1.3–2.5)
Stent area at the MLA site, mm^2	8.1 (6.2–10.0)	8.5 (7.0–9.5)
Vessel area at the MLA site, mm^2	15.9 (13.3–18.7)	16.2 (13.0–18.4)
IH, %	74.3 (64.7–81.5)	77.1 (70.2–84.3)
Significant IH at the MLA site	45 (88%)	22 (100%)
Underexpansion at the MLA site	17 (33%)	5 (23%)
Underexpansion in entire segment	27 (53%)	10 (46%)
IVUS-defined intimal rupture	22 (43%)	12 (55%)
IVUS-defined thrombi	13 (26%)	8 (36%)
OCT data		
Strut coverage		
Completely embedded at all frames		20 (90%)
Malapposition seen at ≥1 frame		1 (5%)
OCT-measured MLA, mm^2		1.6 (1.0–2.4)
Stent area at the MLA site, mm^2		9.0 (7.9–11.2)
Lipidic neointima		22 (100%)
Calcium-containing		7 (32%)
Thickness of fibrous cap, μm		50 (50–60)
OCT-defined intimal rupture		13 (59%)
TCFA-containing neointima		15 (68%)
OCT-defined thrombi		17 (77%)
OCT-defined red thrombi		12 (55%)

Values are median (interquartile range [IQR]) or n (%). Continuous variables were compared using nonparametric Mann-Whitney test, and categorical variables were compared by chi-square statistics or Fisher exact test. Significant IH is defined as %IH/stent area >50%. Underexpansion is defined as MSA <7.0 mm^2.

IH = intimal hyperplasia; IVUS = intravascular ultrasound; MLA = minimal lumen area; MSA = minimal stent area; OCT = optical coherence tomography; TCFA = thin-cap fibroatheroma.

in stent duration and characteristics of the patient population may explain the discrepancy in neointimal composition among the studies. Most reports have included lesions without ISR or lesions with incidentally detected ISR during routine angiographic surveillance. Stent duration of our study was 132.0 ± 31.2 months, which is longer than that in the studies by Takano et al. (3) (91.5 ± 25.9 months) and Habara et al. (5) (113.8 ± 29.6 months) (3,5). Moreover, target lesion revascularization was performed in only 62% of patients in the former and 72% of patients in the latter study, wherein 40% of patients were asymptomatic. Our study only included symptomatic patients with clinically driven target lesion revascularization. Furthermore, in our case, the patients presented either with unstable angina or stable angina with objective evidence of myocardial ischemia. Frequent calcium-containing neointima (32%) supported our contention that the patients were at more advanced stages of neoatherosclerosis and restenotic progression. Unstable neointima including TCNA, neointimal rupture, and neointimal thrombi were common even in patients with stable presentation. The neoatherosclerotic process may promote further luminal narrowing or develop an unstable substrate during the delayed phase.

The data in this paper does have certain distinct limitations. First, because this study included only patients with clinically driven target lesion revascularization, it is difficult to determine the incidence of major findings in an unselected population. Second, by not performing serial imaging follow-up, we could not determine the natural course of BMS-treated lesions and predictors of neoatherosclerosis. Third, because attenuation caused by red thrombi obscured underlying morphology, we may have underestimated the frequency of some OCT findings. In conclusion, OCT findings of vulnerable neointima were frequent in patients with very late BMS-ISR, suggesting that neoatherosclerosis is a general mechanism of late BMS failure.

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Key Words: bare-metal stent ■ neoatherosclerosis ■ optical coherence tomography.