Drug-eluting stents (DES) have made innovative success in suppressing neointimal proliferation with reduced target lesion revascularization. Long term safety, however, becomes the major concern due to persistent incidence of very late stent thrombosis. By intravascular ultrasound (IVUS) examinations, most DES appears uncovered by neointima at a chronic stage, even though it is difficult to evaluate the extent or thickness of neointimal coverage due to its limited resolution. Since 2004, optical coherence tomography (OCT), which has almost 10 times higher resolution than IVUS, became available for coronary evaluation and its image acquisition method is in progress.1 Matsumoto et al reported that when using OCT for a 6-month follow-up period, 89% of the sirolimus-eluting stents (SES) lesion were covered by thin neointima and 64% of neointima covering the struts were less than 100μm thickness, which was undetectable by IVUS. Thus, most of the SES lesions appeared to be covered by thin neointima. However, the frequency of full covered SES was only 16% at 6 months.2 Thus, most of the SES are supposed to have partial uncovered struts at 6 months. As a result, the more important question was proposed; when will most of SES be fully covered by neointima?

Delayed Neointimalization on Drug-Eluting Stents
— Speculation From Optical Coherence Tomography —

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Ishigami et al evaluated the time course of neointimal growth in SES.3 OCT examinations were fulfilled in 3 intervals after SES implantation in different patients: G1, after 7.1±0.8 months, 27 patients; G2, after 13.8±3.6 months, 18 patients; and G3, after 32.6±5.6 months, 15 patients. They suggested significant increase in neointimal thickness (G1: 53.4±23.9μm, G2: 70.1±40.6μm, G3: 98.6±40.2μm) and significant decrease in the frequency of uncovered struts (G1 14.8%, G2 11.7%, G3 4.1%). Katoh et al also reported previously a comparison of OCT findings at 6 months and 12 months in identical SES. The neointimal thickness increased from 112±123μm to 120±130μm and the frequency of uncovered struts decreased from 10.4% to 5.7%.4 Although these 2 studies showed different values, these indicated clearly that long term delayed neointimalization exists in SES. Frequency of full-covered SES, however, was only 17.6% at G3 in Ishigami’s study and 24% at 12 months in Kato’s study. These results still lead us to speculate when the majority of SES will be fully covered by neointima. There is a possibility that partially uncovered struts remain long term, probably more than 5 years in SES. Therefore antiplatelet therapy might not be discontinued in patients implanted SES for a long term.

But this suggestion is based on the hypothesis that partially uncovered struts are thrombogenic. Otake et al examined whether uncovered struts had an effect on the presence of mural thrombus in SES using OCT. They reported that the frequency of mural thrombus, which was detected by OCT was 26% (14/53 lesions) in SES at 6 months and subclinical thrombus was associated with a larger number of uncovered struts, uneven neointimal thickness, larger stent eccentricity and longer SES.5 Thus, uncovered stent struts might be thrombogenic. Pathological findings indeed suggest that the ratio of uncovered struts to total struts per cross-section was the best morphometric predictor of late stent thrombosis, and mural thrombus might be one of the risk factors for thrombosis.6 In Otake’s study, mural thrombus in SES seems not to be a rare phenomenon, however, none of the cases suffered major adverse cardiac events thereafter (median follow-up 485 days). I speculate that, to result in complete obstruction (thrombosis), additional specific factors such as blood flow stasis or increased coagulability might be required.

There is another speculation proposed by Murakami et al. They suggested that neointimal coverage might not always prevent thrombus formation.7 Yet this brings up another important issue to be discussed: is the neointima covering DES has physiological function and is it anti-thrombogenic? According to the pathological study, the tissue covering DES might not always consist of endothelium covering smooth muscle cell, and sometimes be filled with fibrin, proteoglican or inflammatory cells.8 According to our OCT studies, neointima covering DES is not homogeneous in image intensity, some lesions show low intensity or medium intensity with granular pattern (Figure). These findings might be related to the atypical tissue growth in neointima. Also even if endothelium exists, its vasomotor function might be impaired.9 These issues remain to be clarified with further histological or physiological studies. Also, the future progress in OCT tissue characterization will enable us to address pathological neointimal features.

In conclusion, we can at least state that physiological neointimal coverage should be obtained as much as possible to prevent thrombosis. As for analysis factors for neointi-
neointimal coverage on SES, Ishigamin et al reported that small vessel, complex coronary lesions with lipid and calcium content adjacent to stent and diabetes were thought to be the risk factors for delayed neointimal coverage. Matsumoto et al have reported that SES implanted in chronic total occluded lesions and SES overlapped lesion were more likely to have malapposition and uncovered struts. I speculate that wall apposition to the vessel is important to promote neointimal coverage, because OCT findings suggest that neointima generally climbs up from the vessel wall. Whether several factors such as small vessel, complex lesions, chronic total occluded lesion, stent overlapping area or diabetes are the important factors for disturbed neointimal coverage remains to be clarified with larger number of individuals.

By Ishigami’s study with OCT, we understand that there is a delayed neointimalization in SES and we do not have to be too worried about stent thrombosis in DES. However, we should still work with DES neointima using functional assessment and tissue characterization with larger number of individuals and longer follow-up period. This effort will guide us for the indication of DES implantation and dual antiplatelet therapy.

References

Figure. Different image intensities in drug-eluting stents neointima.