Mechanism of in-stent restenosis after second-generation drug-eluting stents (DES): is it different from bare-metal stents and first-generation DES?

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First-generation drug-eluting stents (DES) have dramatically reduced the rate of in-stent restenosis (ISR) and subsequent target lesion revascularization (TLR) compared with bare-metal stents (BMS) (1). However, widespread use of first-generation DES has drawn attention to several unresolved, clinically relevant issues such as late stent thrombosis (ST) and late restenosis (2). Histopathological studies of first-generation DES have revealed that a chronic reaction to components of the permanent polymer reaction may lead to the delayed arterial healing, which is associated with increased risks of late DES failure (3,4). In addition, neoatherosclerosis is suggested as another cause of very late ST and late TLR (5). To overcome these limitations, biocompatible and biodegradable polymers have been developed and equipped with second-generation DES. Recent clinical trials demonstrated that second-generation DES has the improved efficacy and safety compared with those of first-generation DES (6,7). Nevertheless, second-generation DES, as well as first-generation DES, are not immune to ISR. In fact, Cassese *et al*. reported a large cohort of patients with angiographic surveillance that ISR rate of second-generation DES remains higher than 10% (8). Therefore, it is important to elucidate the mechanism of ISR after second-generation DES compared with that of BMS and first-generation DES, which may play a crucial role in the newly developed DES.

In recent issue of *American Journal of Cardiology*, Goto *et al*. retrospectively analyzed intravascular ultrasound (IVUS) data in 298 ISR lesions (52 BMS, 138 first-generation DES, and 108 second-generation DES) to compare the mechanisms of ISR after second-generation DES implantation with those of BMS and first-generation DES implantation (9). The main findings of this study was that (I) both neointimal hyperplasia (NIH) and stent underexpansion were the mechanisms of ISR even in the second-generation DES era; (II) NIH was dominant in 69% of BMS-ISR and 59% of DES-ISR; (III) stent underexpansion was greater in DES-ISR than BMS-ISR; (IV) stent fracture (SF) was found only in DES-ISR.

NIH has emerged as the main cause of ISR in both BMS and first-generation DES (9-11). However, histopathological studies demonstrated considerable differences in the tissue characteristics of ISR between BMS and first-generation DES. BMS-ISR is typically characterized by NIH consisting of a proteoglycan matrix and high proportion of vascular smooth muscle cells. Conversely, DES-ISR is typically characterized by a proteoglycan-rich NIH with relatively few smooth muscle cells. Furthermore, neoatherosclerotic change within the restenostic tissue is seen earlier and more frequently in DES-ISR (5). In fact, an optical coherence tomography (OCT) study demonstrated that homogeneous and lipid-laden neointima were frequently observed in the BMS early phase (≤1 year) and late phase (>1 year), respectively; heterogeneous neointima was observed more frequently in the DES early phase (≤1 year) compared with the BMS early phase (44% *vs*. 9%, P<0.05) (12). Habara *et al*. reported that homogeneous neointima was frequently observed in the early BMS-ISR (≤1 year) than in the late ISR (>5 years, without restenosis ≤1 year), whereas heterogeneous neointima was frequently observed in the late ISR (13). Furthermore, Habara also reported morphological differences of neointimal

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characteristics between early (<1 year), late (1–3 years), and very late (>3 years) restenosis after first-generation DES implantation using OCT that thin-cap fibroatheroma-like and heterogeneous neointima were increased from early to very late phase (14). These findings are consistent with pathological findings. Therefore, NIH is the main cause of ISR in both BMS and first-generation DES, but the detailed mechanism of NIH may be different according to stent type and restenotic phase.

Stent underexpansion is another mechanism of ISR in both BMS and first-generation DES. Previous IVUS studies showed that the cutoff of minimum stent area (MSA) to predict freedom from ISR was 6.5 mm^2 for the BMS, 5.0 mm^2 for sirolimus-eluting stent, and 5.7 mm^2 for the paclitaxel-eluting stent (15,16). Recently, Song *et al.* reported the cutoff of MSA for the second-generation DES, demonstrating 5.4 mm^2 for the everolimus-eluting stent and 5.3 mm^2 for the zotarolims-eluting stent (17). These findings suggested that the cutoff of MSA for the second-generation DES was similar to that for the first-generation DES. Interestingly, Kang *et al.* showed that NIH was the dominant mechanism of ISR, whereas stent underexpansion associated with longer stent length (>28 mm) remained an important mechanism of ISR (11). In previous studies, stent underexpansion (NIH <50% and MSA <5 mm^2) was seen in approximately 20-30%, which were consistent with the current study. Although NIH may be unavoidable mechanism of ISR in the second-generation DES, stent underexpantion is a preventable mechanism of ISR. Nevertheless, stent underexpansion still contributed to ISR even in the second-generation DES era. Therefore, we should recognize the clinical implication of stent underexpansion as a residual mechanism of ISR in the second-generation DES era. In addition, we should make effort to obtain an optimal final MSA in each DES using IVUS or OCT-guidance percutaneous coronary intervention (PCI) during the procedure.

SF after DES implantation has recently become an important concern because of its potential association with ISR, TLR, and ST. The incidence of SF in clinical setting has been reported to be 0.84% to 8.4% in first-generation DES (18). Recently, we reported the SF after second-generation DES implantation occurs in 1.7% to 4.1% of lesions and is associated with a higher incidence of major adverse cardiac events, mainly driven by higher rates of TLR or ST (19-21). These findings suggested that SF is still one of the causes of ISR in the second-generation DES. As reported previously, there are some differences in the predictors of SF among the second-generation DES (19-21). Therefore, we should make effort to learn the feature of stent platform and to select current DES appropriately on the basis of lesion characteristics.

In the second-generation DES era, the incidence of very late ST continued to be much lower up to 5 years after the index procedure, which was quite different from that of first-generation DES (8,22). These findings supported the improved safety of second-generation DES compared with first-generation DES. In contrast, late TLR beyond 1 year occurred constantly without attenuation up to 5 years, which was similar to first-generation DES (8,22). The reason why this discrepancy occurred remains unclear. In fact, there is limited data regarding the mechanism of ISR after second-generation DES implantation. Goto *et al.* confirmed the importance of NIH and stent underexpansion as the cause of ISR after second-generation DES, which were similar to BMS and first-generation DES (9). In addition, SF was seen only in DES-ISR. The authors should be congratulated for providing the IVUS data on mechanisms of ISR after second-generation DES implantation. However, a number of limitations need to be addressed. As authors mentioned in study limitations, grayscale IVUS could not identify the presence of neoatherosclerosis and thrombus within the stent. Recently, Otsuka *et al.* reported that the observed frequency of neoatherosclerosis did not differ significantly between first-generation DES and second-generation everolimus-eluting stent in human autopsy (23). Although these findings suggested that neoatherosclerosis was associated with ISR, TLR and ST after second-generation DES implantation, it remains unclear how often neoathersclerosis contribute to these events. In addition, the duration between index and stent failure was significantly shorter in the second-generation DES than in the BMS and first-generation DES. To date, the mechanism of late TLR after second-generation DES has not been fully evaluated. Compared with IVUS, OCT is a high resolution intravascular imaging modality to evaluate neointima tissue such as in-stent neoathersclerosis and thrombus adequately *in vivo*. Therefore, further long-term follow-up OCT studies are required to compare the mechanism between early and late ISR after second-generation DES implantation.

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Footnote

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