The increased prevalence of type 2 diabetes mellitus (DM) is an important public health problem. The number of patients with DM worldwide is estimated to rise to 366 million by the year 2030. Furthermore, in recent Japanese large-scale registries and prospective randomized studies, approximately 45% of patients with coronary artery disease (CAD) who underwent percutaneous coronary intervention (PCI) had DM as a baseline characteristic.

In general, individuals with DM have more severe and diffuse atherosclerotic disease, which accounts for the significantly higher incidence of cardiovascular events in their native coronary, cerebrovascular, and peripheral arteries (Figure). In addition to aggravated atherosclerosis in native coronary arteries, DM is a well-known independent risk factor for worse outcomes after coronary stent implantation, such as angiographic restenosis, target lesion revascularization (TLR), late and very late stent thromboses, and even all-cause death.

In the era of bare metal stents (BMS), in-stent restenosis was the major limitation of PCI. The restenosis rate in patients with DM was almost 40%, and the odds ratio of restenosis associated with DM was reported to be 1.61 (95% confidence interval 1.21–2.14, P=0.004). Based on findings from both pathological and clinical studies, the main cause of excess restenosis in diabetic patients appears to be exaggerated neointimal hyperplasia.

At the present time, implantation of a drug-eluting stent (DES) is the standard of care for patients with CAD because of the considerably lower rate of restenosis compared with BMS. DES strongly inhibit neointimal growth by pharmacologically suppressing vascular smooth muscle cell proliferation and extracellular matrix production. In this regard, if enhanced neointimal proliferation is directly and strongly correlated with the occurrence of stent-related cardiovascular events, the adverse effects of DM on prognosis might be attenuated in patients treated with effective DES implantation. In fact, a recent meta-analysis comparing DES with BMS in 3,852 patients with DM showed that DES was associated with an approximately 65% relative risk reduction in TLR compared with BMS. However, this reduction in TLR did not affect the rate of myocardial infarction and overall mortality in the chronic phase. In addition, Park et al recently reported that the rates of both TLR (3.6% in DM vs. 1.9% in non-DM, P=0.008) and patient-oriented composite events (9.0% vs. 6.2%, P=0.005) were still significantly higher in diabetic patients with CAD treated with modern second-generation DES. Therefore, it seems likely that, even with the use of efficient second-generation DES, DM remains a strong risk factor for adverse outcomes.

There may be causes of stent-related adverse outcomes other than restenosis because of neointimal overgrowth, which may be classified into 2 categories: development of stent thrombosis related to impaired endothelial cell coverage of stent struts, and the development of neoatherosclerotic changes of the in-stent neointima.

In this issue of the Journal, Iwasaki et al report the influence of DM on the vascular healing process after implantation of second-generation everolimus-eluting stents in their study using both optical coherence tomography (OCT) and...
Intravascular ultrasound. In this study, non-significant higher restenosis rate was observed in patients with DM compared with those without (6.9% vs. 1.1%, P=0.09), but there were no significant differences between the 2 groups in the average neointimal thickness. On the contrary, uneven neointimal proliferation was evident in DM, and this phenomenon correlated with asymmetric stent expansion in patients with DM who had more complex coronary lesion morphology, higher plaque volume, and possibly increased arterial stiffness at baseline. Consistent with this finding, the proximal reference diameter was significantly smaller, and the prevalence of pre-procedural calcium deposition around culprit lesions was higher in patients with DM (45.8% vs. 21.7%, P=0.007). Interestingly, patients on insulin therapy showed greater asymmetric stent expansion and uneven neointimal distribution. In addition, subclinical thrombus formation within the stent lumen was more frequently observed in the diabetic patients. Although this study has several limitations, the observation that the baseline vascular characteristics of decreased compliance in DM results in the inadequate stent expansion that leads to uneven neointimal growth is meaningful. Further large-scale investigations would be necessary to elucidate whether uneven neointimal growth in second-generation DES is accompanied by impaired re-endothelialization and local thrombus formation because of disturbed rheological properties within the stent. In addition, it would be interesting to know whether neatherosclerosis occurs more frequently within the neointima of the DES in patients with DM.

In addition to more complex and advanced atherosclerotic disease, patients with DM often have systemic prothrombotic conditions that also play an important role in the occurrence of cardiovascular events. For example, a prothrombotic status in patients with DM is related to the activation of the platelet aggregation and coagulation systems, including the overexpression of glycoprotein IIb/IIIa receptors on platelets, increased plasma levels of fibrinogen, tissue factor, von Willebrand factor, and plasminogen activator-1. The current dual antiplatelet therapy regimen consists of aspirin plus clopidogrel, but resistance to both aspirin and clopidogrel occurs more commonly in patients with DM. Thus, it is also necessary to investigate whether the use of new antiplatelet agents, such as prasugrel and ticagrelor, as well as co-administration of novel oral anticoagulants, might improve prognosis in patients with DM who undergo second-generation DES implantation.

What should we learn from this study in the current PCI era? When a diabetic patient comes to the catheterization laboratory for PCI, we have to consider that he or she has developed not only focal stenosis but also has a substantially higher and more diffuse total plaque burden in the entire coronary tree, which cannot be fully treated with PCI. In addition, the efficacy of coronary stenting for dilating luminal stenosis is limited by both complex lesion morphology and systemic factors in patients with DM. A possible technical approach might be debulking the coronary plaque before stent implantation. In general, the interventional cardiologist should always consider not only local PCI treatment for angiographic stenosis, but a comprehensive systemic approach in order to improve prognosis, especially in patients with DM. The same approach could be considered even with the upcoming introduction of bioabsorbable vascular scaffolds.

References