Late Failure of First-Generation Drug-Eluting Stents in Hemodialysis Patients

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Patients with end-stage renal disease (ESRD) on maintenance dialysis have extremely high morbidity and mortality from cardiovascular disease, especially coronary artery disease (CAD). Current progress in preventive medical treatment, including lowering low-density lipoprotein cholesterol with statins, enables us to significantly improve both primary and secondary outcomes in general patients with CAD. However, such medical approaches have failed to show similar benefit in hemodialysis (HD) patients, suggesting that ESRD as well as HD has different underlying mechanisms for the development and progression of CAD compared with patients with milder renal dysfunction or normal renal function, and that such clinical conditions are not easily modifiable even with modern medical strategies.

Figure. Schematic mechanism of late stent failure in ESRD patients on hemodialysis. ESRD, endstage renal disease.
Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has now gained worldwide acceptance for the treatment of CAD because it significantly reduces the rate of restenosis and improves outcome in the comparison with bare metal stents (BMS). However, renal impairment is also a well-known, independent risk factor for worse outcomes after coronary stenting. Sirolimus-eluting stents (SES), a 1st-generation DES, were recently shown to have progressive accumulation of late coronary events and worse clinical outcomes of CAD patients during mid- to long-term follow-up. The CREDO Kyoto Registry cohort 2 revealed that late target lesion revascularization (TLR) beyond 1 year after SES implantation occurred consistently and without decline for up to 7 years at annual rates of 2.0% per year, as compared with annual rates of 0.7% per year after BMS implantation.

In this issue of the Journal, Buronova et al report that ESRD patients on HD who were previously implanted with SES showed extremely worse long-term outcomes up to 7 years in their comparison with non-dialysis patients. In their study, the annual event rate of TLR and all-cause mortality beyond 1 year of the ESRD patients was 4.1% and 4.6%, respectively. These event rates were almost 4–5-fold higher than those observed in the non-dialysis patients. Notably, the MACE-free rate was only 24.7% in the HD patients, while 75.7% in the non-dialysis patients at 7 years after SES implantation.

What are the underlying mechanisms involved in the seriously poor outcomes in HD patients with SES implantation? The mechanism of late DES failure has not been elucidated, but it will be multifactorial, especially in the HD situation. First, baseline tissue characteristics of native coronary lesions in HD patients must account for this worse outcome. Calcium deposition and large plaque burden, which are frequently found in the coronary lesions of HD patients, prevent adequate stent expansion and strut apposition to the vascular wall during stent implantation. In addition, the relatively thick and rigid strut design of SES might aggravate the frequency and degree of such inadequate results at implantation. Both stent under-expansion and malapposition of struts to the vascular wall are the established procedure-related risk factors for restenosis and late stent failure. Accordingly, lesion preparation before stent implantation with rotational atherectomy, directional coronary atherectomy or scoring balloononing dilatation, might be useful for the optimal stent implantation in HD patients. In this regard, development of new coronary stents with thinner struts and higher conformability is necessary in the future.

In addition to the procedure-related factors, abnormal late vascular responses occurring within the stented segment should be considered. One of the most important factors is enhanced vascular smooth muscle cell (VSMC) activity in local coronary lesions in HD patients, which results in neointimal overgrowth and aggressive restenosis even with pharmacological suppression of VSMCs by sirolimus. Second, ESRD patients on HD are known to have multiple abnormalities of vascular and blood function, including endothelial cell dysfunction, decreased endothelial progenitor cells, activated function of platelets, resistant of platelets to antiplatelet agents, and so on. Because DES reduces restenosis by pharmacologically inhibiting neointimal proliferation, it carries the intrinsic risk of overly suppressing the normal vascular healing process, which would prevent regenerative tissue from covering the metal surface. Furthermore, the allergic reaction of the arterial wall to the polymers covering the metal struts also plays an important role in impaired vascular healing. These factors delay the normal vascular healing process, which results in a higher incidence of uncovered struts and late acquired malapposition, leading to late thrombotic events within the DES.

Thirdly, recent clinical studies using intravascular optical coherence tomography (OCT) have shown that neoatherosclerosis inside the coronary stent plays an important role in late adverse events after DES implantation. In an autopsy study, neoatherosclerosis was shown to be significantly more prevalent within SES than BMS (35% vs. 10%; P <0.001), and these changes were seen earlier with SES, with foamy macrophage infiltration observed as early as 4 months after implantation. Furthermore, unstable features of neoatherosclerosis, such as thin-cap fibroatheroma and ruptured plaque with thrombosis, are frequently observed in SES implanted ≥5 years previously. The predictive factors of neoatherosclerosis have not been established, but a recent OCT study revealed that renal dysfunction is an independent predictor. It is possible that neoatherosclerosis develops not only in 1st-generation DES, but also in 2nd-generation DES and even in those with a bioresorbable scaffold. These issues need to be confirmed in HD patients in future studies.

What should we learn from the study in the current PCI era with DES? When a HD patient is a candidate for PCI with coronary stenting, we have to consider that the patient has developed coronary lesions with a substantially higher calcium and larger plaque burden, not only in the local but also in the entire coronary tree, which may not be fully treated with PCI only. One possible technical approach might be adequate lesion preparation before stent implantation. In addition, we should always consider not only local PCI treatment for angiographic stenosis, but a comprehensive systemic approach in order to improve long-term secondary outcomes, especially in ESRD patients on HD.

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References
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