Leaving Nothing Is Leaving Unanswered Questions — Drug-Coated Balloon Angioplasty for Femoropopliteal Artery —

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The first transluminal revascularization of a lower extremity was performed in the superficial femoral artery (SFA) by Dr. Dotter in 1964.¹ Since then, advances in many devices have led to the introduction of drug-eluting stents (DES) and drug-coated balloons (DCB) to achieve lower restenosis rates. These technologies have become the standard in the contemporary treatment of coronary artery disease, but for peripheral artery diseases (PAD), evidence of the efficacy and safety of drug-associated devices is still insufficient.^{2,3} In such situations, DCBs are emerging as the new standard treatment for SFA lesions because of their potential advantages: (1) no permanent metallic scaffold, (2) drug delivery that inhibits vascular endothelial proliferation without the use of polymers, and (3) accelerated vascular healing after balloon angioplasty in the relatively short time of drug persistence in the vessel wall.⁴ Because patients with chronically advanced PAD may possibly undergo multiple endovascular treatments (EVT) in their lifetime,⁵ a scaffold-free approach that preserves subsequent treatment options has been warmly welcomed by physicians.

Efficacy of DCBs for SFA disease has been reported in large prospective trials,^{6–8} and a recent report even revealed comparable long-term patency rates between DCBs and DES in patients with SFA disease,⁹ supporting their consistent efficacy. However, unlike large trials with strict protocols, there are still concerns about whether the efficacy of DCBs can be maintained in real clinical practice for patients with more severe systemic profiles and vascular complexity. Additionally, the safety of DCBs with paclitaxel is controversial because of a reported increase in all-cause death.¹⁰ The U.S. Food and Drug Association and the Japan Pharmaceuticals and Medical Devices Agency (PMDA) have recently allayed concerns about the use of DCBs, but confirmation of their safety is still required. To this end, the study by Soga et al,¹¹ published in this issue of the Journal reports the efficacy and safety of the DCB from the mid-term observation period.

Briefly, the IN.PACT PMS Japan was a prospective, multicenter, non-randomized, single-arm, post-market surveillance study of IN.PACT Admiral DCB (Medtronic)

Article p2149

based on the indication approved by the Japan PMDA in real-world individuals with SFA disease. A total of 304 patients with symptomatic lower limb ischemia (Rutherford stage 1–6) and mean lesion length of 9.8 cm was examined. Primary patency at 6–12 months was defined as freedom from clinically driven target lesion revascularization and freedom from restenosis as determined by duplex-ultrasound. Overall, the 1-year primary patency rate was 82.6% (138/167), which is comparable to the results from DCB studies conducted in the USA or Europe.^{8,12} As for the clinical outcomes, 23 patients (9.6%) died, and 1 case of target limb amputation (0.4%) occurred within the 12-month follow-up. The authors should be congratulated for verifying the clinical benefit of a DCB-oriented strategy in SFA lesions in real-world contemporary practice.

However, to finalize EVT by DCB alone may select the patients, because the balloon is just a balloon. If aggressive predilation is performed to restore sufficient inner lumen, it is difficult to avoid major dissection, which requires bailout procedures with metal-scaffold placement. Conversely, if the angioplasty is terminated with a small balloon to avoid dissection, blood supply to the tip of the leg can be insufficient, and the restenosis rate will be higher. In other words, it is very difficult to achieve both “sufficient acute gain” and “no major dissection”. Evasive methods including very slow balloon inflation and long non-compliant balloon use have been attempted, but there is to date no established method. In fact, in prior large trials, randomization was generally executed after balloon dilatation and did not include data of patients with failed angioplasty.⁶ Therefore, general applicability of DCB to all patients is not possible at this point.

There are very few reports examining the efficacy of DCB in complex lesions (i.e., TASC C and D). Although both DES and DCB have shown better results than conventional percutaneous transluminal angioplasty (PTA) alone in randomized controlled trials, the studies frequently included small numbers of complex SFA diseases.^{8,13} The REAL

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PTX trial including 150 patients with SFA lesions randomly assigned to DES and DCB groups had longer lesion lengths (mean 15.2 cm), severely calcified lesions (54%) and total occlusions (53%).⁹ That study showed comparable 12-month primary patency for DES and DCB (79.3% vs. 79.9%), but showed a trend toward greater patency for DES than DCB at 36 months (56.7% vs. 42.4%). This result could translate to a promise of exacerbation and repeat EVT within 3 years, if patients are treated by DCB alone.

Furthermore, when treating long calcified lesions of the SFA, the modification of calcified plaques by atherectomy devices and scoring balloons may better achieve immediate luminal gain than PTA alone. However, it remains to be determined whether combining these strategies with DCB will provide any additional benefit in long-term patency. Additionally, there is the remaining issue of the efficacy of DCB in patients with chronic limb-threatening ischemia (CLTI).^{12,14} It is difficult to draw conclusions that DCBs enable finalization of EVT in patients with CLTI. Rather, scaffolding that can achieve greater luminal gain and improve blood flow as quickly as possible after revascularization may be preferred. A large prospective study comparing DCB and DES as treatment for patients with complex lesions and CLTI is expected. However, until a new drug-associated device is developed that can ensure long-term results in complex lesions, the DCB is an innovative device that leaves nothing in the vessel, and its effectiveness was demonstrated in this paper.

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