Sustaining long-term patency in the femoral-popliteal segment is particularly challenging because of extensive plaque burden and characteristically long segments of stenosis or occlusion. Complex mechanical forces such as elongation, compression, torsion, and flexion place significant stress on stents implanted in this vascular bed. A number of factors may impact the results of DES in this location. The time course of femoropopliteal restenosis is more delayed than coronary restenosis, and, thus, the drug dose and elution kinetics for a successful femoropopliteal DES likely need to be different than for coronary DES. In addition, nonresorbable polymers on peripheral artery DES may induce inflammatory and thrombotic reactions after elimination of the drug, leading to late stenosis and thrombosis.\(^9\)

Zilver PTX (Cook Medical, Bloomington, IN) is the only DES to date that has demonstrated superior and sustained patency in comparison with its bare metal counterpart. Zilver PTX is unique in its design with direct application of paclitaxel to the stent without the use of a polymeric coating. Paclitaxel’s unique properties make it well suited as an antirestenosis agent for peripheral vascular interventions. Paclitaxel is lipophilic and avidly binds intracellular target proteins, which allows for drug uptake in the target artery with detectable retention for up to 2 months, despite being cleared from the circulation within 10 hours.\(^10\) This ability to rapidly bind to the arterial wall made it possible for the Zilver PTX stent to deliver paclitaxel from the abluminal surface of the stent without the aid of polymers, bindings, or carriers.\(^11\) Once incorporated in the target artery and locally circulating macrophages, paclitaxel interferes with the normal turnover of microtubules, and inhibits the proliferation and migration of smooth muscle cells, which are the key drivers of neointimal hyperplasia after vessel injury.\(^12\)

The Zilver PTX DES has been investigated in a randomized clinical trial, and large prospective multicenter registries, as well. In the randomized clinical trial design, as approved by the Food and Drug Administration, the Zilver PTX stent was compared with percutaneous transluminal angioplasty (PTA) for lesions up to 14 cm in length in the SFA and proximal popliteal artery. For those subjects who needed a provisional (bailout) stent because of suboptimal PTA or flow-limiting dissection, there was a secondary randomization to Zilver PTX versus bare metal Zilver stent. Importantly, provisional stenting was considered a failed PTA with loss of primary patency. At 1 year, primary stenting with Zilver PTX was (not surprisingly) superior to PTA (83\% versus 33\% primary patency), because provisional stenting was required in 50\% of the PTA group. Provisional DES was superior to provisional BMS, confirming a treatment effect from the paclitaxel.\(^11\)

One-year primary patency was 89.9\% for provisional DES.
in comparison with 73.0% for provisional BMS. The 2-year results demonstrated sustained superiority of DES over BMS with a 2-year primary patency of 83.4% versus 61.1%.13

In the current issue of Circulation, Dake and colleagues14 present the 5-year results of the Zilver PTX randomized trial, building on the previous 1- and 2-year results. The authors and the sponsor are to be congratulated for continuing long-term follow-up in this trial, with annual duplex ultrasound evaluation of stents out to 5 years, allowing for continued assessments of patency at the treatment site. This trial is unique among industry-sponsored medical device trials for peripheral artery disease. The 5-year results confirm the findings of the earlier publications and demonstrate sustained and durable treatment effect with the Zilver PTX DES. Primary patency at 5 years was 64.9% for the primary DES group in comparison with 19% for the PTA group. Sustained efficacy was demonstrated in the head-to-head comparison of provisional DES with provisional BMS with primary patency of 72.4% versus 53.0%. The investigators also performed a subanalysis comparing the entire DES group (both primary and provisional) with a so-called standard care group, which consisted of those with PTA alone or PTA with provisional bare metal stenting. The benefit of DES was again demonstrated at the 5-year mark, with superiority demonstrated in both lesion-specific (primary patency 66.4% versus 43.4%) and symptom-specific end points (freedom from persistent or worsening symptoms of ischemia at 79.8% versus 59.3%). The long-term safety of the Zilver PTX stent was also confirmed. Stent fracture rate was 0.9% at 1 year and 1.9% at 5 years. There were no reports of adverse reactions to paclitaxel.

There are a few limitations of this study that are worthy of mention. There was a high provisional or bailout stent rate in the PTA arm of the trial, and treating these provisional stents as a loss of primary patency tilts the results in favor of DES. The comparison of the entire DES group with the standard-of-care group in the current study was not a prespecified or randomized comparison. Also, it is important to note that, although duplex ultrasound was performed on all stented patients out to 5 years, only a subgroup of the PTA patients underwent duplex ultrasound during longer-term follow-up.

The widespread applicability of the Zilver PTX randomized clinical trial results is also limited by several factors. First, 90% of the treated patients initially presented with claudication. Second, 92% of the lesions were confined to the superficial femoral artery. Finally, the mean lesion length was short (≈6.6 cm). The results of the Zilver PTX randomized clinical trial are supplemented by a single-arm study and a Japanese Zilver PTX registry involving a patient population much more aligned with real-world clinical practice. In the single-arm study, 787 patients received primary drug-eluting stenting. A TASC C/D (Trans-Atlantic Inter-Society Consensus [TASC II]) subset in this single-arm analysis was separately reviewed. This group had a substantial average lesion length of 22.6 cm, yet had a favorable 12-month primary patency of 77.6%.14,15 In the Japanese postmarket study, 907 patients from 95 Japanese institutions were enrolled and 20% of patients had critical limb ischemia. The lesions were much more complex than in the original randomized, controlled trial, with an average lesion length of 14.7 cm. Chronic total occlusions were present in 41%, and 18.6% of patients were treated for in-stent restenosis. At 12 months, freedom from target lesion revascularization was 91%, and the primary patency rate was 86.4%.

Despite these positive results with Zilver PTX, there remains no evidence-based standard of care for the SFA. Although the benefit of Zilver PTX over PTA and Zilver BMS were clearly demonstrated in this trial, the superiority of Zilver PTX over other well-designed nitinol BMS has not been established.16 In addition, there have been promising results with drug-coated balloons.17,18 Recent publication of the 2-year results from the IN.PACT SFA trial demonstrated sustained benefit of drug-coated balloons over PTA with a 2-year primary patency of 78.9% for drug-coated balloons.18 Atherectomy devices remain popular because of favorable reimbursement and the viewpoint that avoidance of a permanent metal implant is desirable.19 Future investigation will likely be directed at evaluation of the combination of atherectomy and drug-coated balloons. There are also promising results from a preliminary study of a new paclitaxel-eluting nitinol DES that is polymer based.20

Many questions remain unanswered; however, after a long and winding journey, we have strong evidence that DES improve outcomes in the SFA. Much as in the coronary arteries, the combination of antiproliferative drugs and devices is here to stay and will likely become a mainstay of treatment for SFA disease in the years to come.

Disclosures
Dr Laird is a consultant or advisory board member for Bard Peripheral Vascular, Boston Scientific, Cordis, Medtronic, and Abbott Vascular. He receives research support from WL Gore. Dr Hong has no disclosures to report.

References

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