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EDITORIAL COMMENT

Percutaneous Revascularization for Peripheral Arterial Disease

Paclitaxel Saves the Day*

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Patients presenting with femoropopliteal (FP) disease often require revascularization for lifestyle-limiting claudication medical therapy that failed, or for critical limb ischemia. Percutaneous revascularization for FP disease has been fraught with challenges since the initial description of percutaneous transluminal balloon angioplasty (PTA) of the FP artery. Due to high rates of arterial dissection and restenosis after PTA, randomized comparisons of self-expanding stents and PTA for FP disease have been performed and have demonstrated the superiority of stenting (1,2). Nevertheless, restenosis rates with self-expanding nitinol stents are 19% to 37% at 1-year follow-up, and options for the treatment of FP restenosis are limited (1,2).

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Additionally, because this vessel undergoes significant torsion, extension, and flexion during daily activity, FP stent fractures have been reported that are associated with restenosis (3) and potential distal embolization of stent fragments. Self-expanding stent grafts covered with expanded polytetrafluoroethylene (ePTFE) (Viabahn, Gore Medical, Newark, Delaware) lead to comparable outcomes as surgical FP bypass using prosthetic conduits, (4) but can result in occlusion of collaterals and are not an appropriate initial treatment option for most patients with FP disease. Clinical outcomes from registries evaluating the use of extraction, rotational, and laser atherectomy for the treatment of FP disease have been encouraging but have not been compared in an adequately powered randomized clinical trial against PTA.

Drug-eluting stents were initially tested for use in FP disease with the sirolimus-eluting self-expanding SMART stent (Cordis, Miami, Florida) randomized against its bare-metal stent counterpart (SIRROCO I and II trials). The initial results from these trials were promising, with superior inhibition of neointimal proliferation and lower binary restenosis at 6 months with the sirolimus-eluting stent (5,6). However, at 18-month follow-up, the sirolimus-eluting stent group demonstrated a "catch-up" phenomenon resulting in comparable clinical and angiographic event rates in the 2 groups (5,6). Though sirolimus is highly effective in reducing coronary restenosis, its antiproliferative effect was inadequate in the FP segment. These trials highlighted the importance of longer term follow-up when evaluating revascularization techniques, drugs and devices in the peripheral as opposed to the coronary vasculature.

Paclitaxel is a highly lipophilic antimitotic drug that alters microtubule function. It inhibits vascular smooth muscle cell migration and proliferation (7), with pre-clinical data supporting its efficacy in reducing restenosis when coated on a balloon and delivered locally (8). Initial pilot studies demonstrated that use of a paclitaxel-eluting balloon (PEB) led to lower late luminal loss (0.4 ± 1.2 mm vs. 1.7 ± 1.8 mm; $p < 0.001$ and 0.5 ± 1.1 mm vs. 1.0 ± 1.1 mm; $p = 0.031$) and restenosis (4% vs. 37%; $p < 0.001$ and 19% vs. 47%; $p = 0.035$) (9,10) at 6-month follow-up as compared with an uncoated balloon for the treatment of symptomatic FP disease. Additionally, in a pivotal study enrolling patients with FP disease, at 1-year follow-up, the Zilver PTX randomized trial demonstrated superior primary patency (83.1% vs. 32.8%, $p < 0.001$) and event-free survival (90.4% vs. 82.6%; $p = 0.004$) for the polymer-free paclitaxel-eluting nitinol self-expanding stent compared with PTA. In a small subgroup in which PTA failed, the angiographic and clinical superiority of the paclitaxel drug-eluting stent was also shown compared with its bare-metal stent control (11).

In this issue of *JACC: Cardiovascular Interventions*, 2 studies addressing long-term outcomes after the treatment of native FP disease with a PEB, and FP in-stent restenosis with a nonpolymeric paclitaxel-eluting stent, respectively, are reported (12,13). In a multicenter registry of 105 patients (114 lesions), Micari et al. (12) treated FP lesions (76 ± 38 mm length; 5.2 ± 0.6 mm diameter reference vessels; 92.5 ± 8.2% stenosis) with the In.Pact Admiral PEB (Medtronic, Minneapolis, Minnesota) and bail-out stenting (12.3% lesions). Procedural success was achieved in all, and primary patency at 1 year was 83.7%. At 2-year follow-up, primary patency was maintained in 72.4%, whereas secondary patency was 84.7%. Importantly, for subjects without restenosis or target lesion revascularization at 1 year, primary patency was 85.1% with a target lesion revascularization rate of 7.1% at 2-year follow-up, demonstrating the absence of a catch-up phenomenon with the PEB. At 2-year follow-up, major adverse events were

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reported in 17.5% with significant improvements in ankle brachial index, claudication distance, Rutherford class, and quality of life functional measurements.

In the second study, Zeller et al. (13) report long-term outcomes for 108 subjects (119 lesions) enrolled with in-stent restenosis of FP disease (133.0 ± 91.7 mm length; 5.6 ± 0.7 mm reference vessel diameter; 87.0 ± 12.4% stenosis; total occlusion in 31.1%) and treated with the Zilver PTX drug-eluting stent (Cook Medical, Bloomington, Indiana). These data are reported from a larger multicenter registry (n = 787) evaluating this stent for FP disease. In the cohort of subjects with FP in-stent restenosis, procedural success was achieved in 98.2%, and primary patency at 1 year was reported to be 78.8%. At 2-year follow-up, freedom from major adverse events was 60.8% (all events due to clinically driven target lesion revascularization). No predictors of recurrent in-stent restenosis were identified. At 2-year follow-up, significant improvements in ankle brachial index, walking and climbing distance, and Rutherford class were observed.

Both of these studies demonstrate that a new paradigm for the treatment of FP disease involving local delivery of paclitaxel is emerging. These studies were multicenter, with broad inclusion criteria, inclusive of long lesions and evaluated both anatomic and clinical endpoints. However, both studies lacked control groups and had small sample sizes, so neither was adequately powered to identify predictors of failure. Micari et al. (12) report 2-year follow-up results, and it is reassuring that treatment of de novo FP disease with the PEB leads to no increase in late restenosis, and the early clinical benefit is maintained at longer term follow-up. By contrast, the treatment of FP in-stent restenosis remains challenging. Zeller et al. (13) evaluated the Zilver PTX stent in a recalcitrant group of patients who had long lesions with restenosis, occlusions in a third, and ≥2 previous interventions in half the cohort. Though procedural success and primary patency at 1 year were high, 2-year follow-up yielded less favorable results, with an almost 40% rate of target lesion revascularization.

Both the PEB and the Zilver PTX stent had polymer-free paclitaxel coated at a concentration of 3 $\mu g/mm^2$ of surface area. It is unclear whether the drug release kinetics are such that a short exposure of paclitaxel transferred from the PEB to the vessel wall leads to a different vascular response compared with the more sustained release of the drug from the stent. This is important because paclitaxel has a narrow therapeutic range, and at higher concentration, it can disrupt the internal elastic lamina and reduce intimal and medial smooth muscle cells and collagen content (14). Furthermore, in a murine model, transcriptional analysis by real-time reverse transcription-PCR showed an increase in proapoptotic mRNA transcripts (caspase 3, FAS, BAX) in paclitaxel-treated arteries (14). Therefore, though paclitaxel reduces restenosis in the peripheral vasculature, the timing of optimal drug delivery is critical in minimizing excessive vascular exposure to the drug and in reducing the risk of adverse vascular injury. Additionally, the exact mechanism of paclitaxel transfer and retention in the vessel wall is still unclear. The roles of drug concentration and carrier and diffusion kinetics also require additional understanding.

The long-term results of the currently reported studies appear to favor the treatment of de novo FP disease with the PEB, with the expectation of assisted patency of 84.7% in intermediate length lesions at 2-year follow-up. This is accompanied by favorable clinical endpoints, including low future rates of repeat revascularization and improved quality of life indexes. As opposed to other current treatment modalities for FP disease, including PTA, atherectomy, bare-metal stenting, and drug-eluting stenting, these data are extremely favorable. It is also clear that in-stent restenosis of the FP vascular territory remains difficult to treat. Though the Zilver PTX stent is an efficacious advance in the treatment of FP disease, using it for in-stent restenosis still results in high repeat revascularization at 2-year follow-up. However, the extremely low rate of stent fracture (1.2%) and improvements in other clinical parameters, including ankle brachial index and walking distance, are favorable at 2-year follow-up. By contrast, Stabile et al. (15) reported 1-year primary patency of 92.1% with the treatment of FP in-stent restenosis using a PEB. Longer term follow-up from that and other studies should shed light on the utility of PEB for the treatment of FP in-stent restenosis. Paclitaxel is a superior drug compared with sirolimus for the prevention of restenosis of lower extremity peripheral arterial disease, and the investigators of the current studies should be congratulated on prospectively collecting multicenter data with an adequate period of long-term follow-up. Future studies are required to evaluate the role of adjunctive debulking before the use of either the PEB or the paclitaxel-eluting stent in FP disease. These need to be appropriately powered randomized trials, and could also be an opportunity to better define the role of dual antiplatelet therapy in reducing long-term adverse events after peripheral arterial intervention.

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