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EDITORIAL COMMENT

Paclitaxel-Eluting Devices for Femoropopliteal Disease

Drastic Advance in Therapy or a Danger to Our Patients?*

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Increasing the safety and durability of interventional therapies for femoropopliteal disease has long been the "holy grail" for endovascular specialists. The superficial femoral artery (SFA) and popliteal artery have proved challenging due to the extensive plaque burden that is encountered in these arteries. Diffuse disease, severe calcification, and long occlusion are common. In addition, there are a variety of complex mechanical forces (flexion, torsion, elongation, shortening) during bending of the leg that contribute to mechanical fatigue of endovascular prostheses implanted in the SFA or popliteal artery (1).

A variety of techniques and devices have been developed to try and better deal with the challenges faced in this vascular bed. Chronic total occlusion devices, specialty balloons, atherectomy devices, nitinol stents, and covered stents have expanded treatment options (2,3). While the quality of data supporting the use of some of these devices is often disappointingly poor, numerous randomized trials of peripheral vascular devices have been completed, and much has been learned. It has become clearer over time that standard percutaneous transluminal angioplasty (PTA) is ineffective for femoropopliteal disease. The PTA arms of recent randomized trials have revealed 1-year primary patency rates of around 50% for relatively simple lesions (4,5). Standard laser cut nitinol stents provide better patency than PTA in randomized trials, but restenosis rates are unacceptably high when used for long lesions (6,7). Plaque modification techniques (cutting/scoring balloons, atherectomy) have become popular; however, there are limited comparative data demonstrating superior effectiveness of these devices compared with other modalities (2).

The introduction of drug-eluting devices for peripheral vascular use heralded a sea change in the treatment of femoropopliteal disease. Paclitaxel-eluting stents (DES) and paclitaxel-coated balloons (DCBs) have been shown to be effective in the SFA, with superior primary patency and freedom from clinically driven target lesion revascularization (CDTLR) at 1 year and beyond compared with PTA (4,5,8,9). The long-term durability of DES and DCB has now been demonstrated out to 5 years in randomized trials (10–12). With the advent of effective drug-eluting therapies, questions have arisen regarding the optimal strategy: a drug-eluting scaffold or "leave nothing behind" DCB?

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In this issue of the *Journal*, Liistro et al. (13) compare 12-month outcomes between a commercially available DES (Zilver PTX, Cook Medical, Bloomington, Indiana) and DCB (In.Pact Admiral, Medtronic, Santa Rosa, California). The investigators randomized 192 patients with 240 lesions in 225 limbs to treatment with the 2 drug-eluting therapies. The DRASTICO (Paclitaxel-Eluting Balloon Angioplasty With Provisional Use of Nitinol Stent Versus Systematic Implantation of Paclitaxel-Eluting Stent for the Treatment of Femoropopliteal De Novo Lesions) study differed from typical Investigational Device Exemption trials as lesion lengths were longer (mean

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lesion length 14 cm) and the study included a mixture of patients with claudication and critical limb ischemia (CLI). The authors demonstrated that there were no significant differences between DES and DCB with regard to primary patency (21% vs. 22%; p = 0.90) or freedom from CDTLR (17% vs. 14%; p = 0.50). There were no major amputations in either arm of the trial, despite the inclusion of a high percentage of CLI patients.

The authors are to be congratulated for the completion of this well-done trial and for the excellent procedural outcomes that were obtained. There was 100% procedural success despite the inclusion of complex lesions, with excellent 1-year primary patency and freedom from CDTLR. The fact that there were no major amputations in either treatment arm despite the high percentage of CLI patients was a great achievement. Limitations of the DRASTICO study include the relatively small sample size, imbalance in baseline patient characteristics, lack of independent angiographic and ultrasound core laboratories, lack of independent adjudication of outcomes, and relatively short-term (12-month) follow-up. The findings of the DRASTICO trial may also have been already made obsolete by the introduction of a newer, polymer-based DES with prolonged and controlled paclitaxel elution (Eluvia, Boston Scientific, Natick, Massachusetts). The Eluvia DES was found to provide superior 1-year outcomes compared with Zilver PTX in a recently published randomized trial (14).

The results of the DRASTICO trial come on the heels of the publication of the 36-month results of the REAL PTX (Randomized Evaluation of the Zilver PTX Stent vs. Paclitaxel-Eluting Balloons for Treatment of Symptomatic Peripheral Artery Disease of the Femoropopliteal Artery) trial (15). In REAL PTX, 150 patients were randomized to DES or DCB after stratification for lesion length (≤10, >10 to 20, and >20 to 30 cm). Similar primary patency rates were seen at 12 months between DES and DCB (79% vs. 80%; p = 0.96); however, there was significant drop off in patency at 36 months, with a trend toward better outcomes with DES (54% vs. 38%; p = 0.17). Freedom from CDTLR was initially high for both DES and DCB at 12 months (90.0% vs. 92.5%; p = 0.34) but dropped to around 70% at 36 months (68.9% vs. 71.3%; p = 0.74).

The superior and seemingly durable results seen with paclitaxel-eluting devices have had a significant effect on the endovascular approach to femoropopliteal disease around the world. The recent publication by Katsanos et al. (16) of a meta-analysis that suggested an increased risk of late mortality in patients treated with paclitaxel-eluting devices has thus been a source of great consternation and chagrin for many. Concern in the endovascular community lead to the rapid organization of a Vascular Leaders Forum in Washington, DC, to further investigate this important issue. Recent publication of patient-level data from industry-sponsored randomized trials, an updated meta-analysis, and outcomes from a large nationwide study of Medicare beneficiaries, which failed to show excess mortality for paclitaxel-eluting devices, has allayed some of these concerns (17–20). Nonetheless, a recent Letter to Health Care Providers from the Food and Drug Administration urged caution regarding the use of paclitaxel-eluting devices, going so far as to recommend use of alternative treatment options for most patients until additional analysis of the safety signal has been performed (21).

It will take time for questions regarding the safety of paclitaxel-eluting devices to be definitively answered. What is not in question is the effectiveness of paclitaxel-eluting stents and paclitaxel-coated balloons in reducing restenosis and lowering the need for additional interventions. Based on the results of the DRASTICO and REAL PTX trials, DES and DCB would appear to be similarly effective in the short-term. Additional data will be required to compare the long-term effectiveness of these alternative modalities. In the meantime, it is my hope that paclitaxel-eluting devices will be confirmed to be safe, so that we can continue to offer these promising therapies to our patients.

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