

EDITORIAL COMMENT

Drug-Eluting Stents in the Superficial Femoral Artery

Real-World Versus Randomized Clinical Trials; You Choose, But Caveat Emptor!*



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Randomized clinical trials (RCT) are considered the pinnacle of the research pyramid, but they often include patients and/or lesion subsets that are not found as commonly in the “real world.” In this issue of *JACC: Cardiovascular Interventions*, Yokoi et al. (1) report the “real-world” results from a post-market surveillance study of the Zilver drug-eluting stent (DES; Cook Medical, Bloomington, Indiana) for the treatment of obstructive atherosclerotic disease of the superficial femoral artery (SFA). This Japanese study of 907 patients

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provides a glimpse of how these stents respond in nontrial patients who often have more diffuse disease and more comorbidities than most trial patients do. However, we must recognize that stenting the SFA is very different from stenting the left anterior descending coronary artery and that the DES data in the SFA vascular bed is very small in comparison to the coronary bed; although these results at first glance are impressive, they must be seen in the context of the general literature—may the buyer beware!

The movement in the periphery from percutaneous transluminal angioplasty (PTA) to bare-metal stents (BMS) to potential drug-eluting technologies mirrors what was seen over the past 3 decades in the coronary realm. Similarly, stenting has been shown to be superior to PTA alone in the femoropopliteal arterial

bed (2,3), except when lesions are short (<50 mm) (4). These trials, published in high-profile journals, led many to assume a stent-first strategy given the ease of deployment and the small residual stenosis often seen with stenting. Interventionalists, used to the 0% residual stenosis seen with coronary stents, often desire similar results in the peripheral vessels. However, the restenosis rates of BMS in the femoropopliteal artery far exceed those seen in the coronary realm. These high rates are likely secondary to the diffuse, calcific, and often occlusive nature of the disease found in this arterial bed, as well as the well-documented complex biophysical forces exerted on these vessels with daily movement (5). These forces manifest themselves in stent fracture, which has been associated with in-stent restenosis and is more common with older stent designs (6). Contemporary stent designs show lower rates of stent fracture, but neointimal hyperplasia leading to restenosis and reocclusion has remained the Achilles heel of endovascular therapy of this vascular bed, underscoring that one treatment does not fit all when it comes to arterial beds. As in the coronary vasculature, there has been a movement toward drug-eluting technologies to preclude neointimal hyperplasia. Initial studies with DES, however, have yielded less than optimal results. In the SIRROCO (Sirolimus-Coated Cordis Self-Expandable Stent) trial (7), the drug sirolimus was mounted on a S.M.A.R.T. stent (Cordis Corp., Fremont, California) and failed to show any difference in restenosis at 12 months when compared with the non-drug-coated S.M.A.R.T. stent. Similarly, the STRIDES (Superficial Femoral Artery Treatment with Drug-Eluting Stents) study (8), a single-arm study of an everolimus stent with no comparative group in short lesions (mean lesion length was 9 cm)

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demonstrated a disappointing 12-month restenosis rate of 32%.

Despite these initial disappointing results, the pursuit of an effective DES for the femoropopliteal segment continued. The Zilver PTX trial (9), published in 2011, was an RCT of a mere 236 patients randomized to either PTA or a Zilver DES for treatment of the SFA. In the 120 patients (50%) who failed PTA alone, a second randomization was performed between a Zilver BMS and a Zilver DES. Compared with PTA alone, the DES group showed a dramatic primary patency rate of 74.8% versus 26.5% at 24 months. Although these absolute percentages are impressive, astute readers have underscored that the high crossover rate of this RCT essentially means that 25% of the control group had the intervention tested, which dilutes the benefit as well as any risks of the DES (10). The lesions included in this RCT also were short with an average length of 65 mm and are generally considered easy to treat; most would be categorized as TASC (TransAtlantic Inter-Society Consensus) A/B (11) and as such, it is not surprising that these lesions did well with endovascular therapy.

In this study by Yokoi et al. (1), we see how the Zilver DES responds in a real-world Japanese cohort study of 907 patients (58.8% diabetic, 43.8% chronic kidney disease, and 21.5% with critical limb ischemia), wherein Zilver DES were used to treat various conditions (41.6% occlusions, 18.6% restenosis of BMS). In this cohort, a total of 1,861 stents were placed to treat 1,075 lesions, demonstrating a freedom from target lesion revascularization rate of 91.0% and a primary patency rate of 86.4% at 1 year. Although these numbers are impressive, delving deeper into who these patients are reveals that many of them had only Rutherford class I or II claudication, which naturally will dampen the number of patients needing clinically driven target vessel revascularization, because these patients approximately one-third of the cohort had mild symptoms at baseline. Thus, the astute reader will cautiously interpret the “post-treatment clinical benefit” outcome measure and focus more on those patients who had an ultrasound. Duplex surveillance was performed in 65% of patients and demonstrated an ultrasound-based patency of

86% at 12 months. Such an endpoint, although common in femoral trials, has been questioned because its validity for predicting symptoms of impending occlusion is not certain (10). The investigators also relate that their study stands in contrast to another “real-world” clinical study from Japan called the ZEPHYR (Zilver PTX for the Femoral Artery and Proximal Popliteal Artery) study (12). Zephyr included slightly more diabetics and critical limb ischemia patients, but it demonstrated a 1-year patency rate of 68% using the Zilver DES, a major adverse limb event rate of 22%, and a stent thrombosis rate of 2% in 690 patients with 831 femoropopliteal lesions. So which study is correct? Is the 1-year patency 86% or 68%? Caveat emptor indeed!

The other major issue that plagues operators, insurance companies, and patients is the cost of these devices that must be weighed against the cost of repeat procedures. To date, there are no U.S. cost-effectiveness studies nor any comparative effectiveness studies of DES versus drug-eluting balloon. Although the rate of stent fracture is very low, the long-term impact of a permanent metal scaffold is unknown, and whether there will be a late catch-up phase of these technologies or the development of new atheroma within these stents is also uncertain. No matter what treatment is chosen, both we and the patient enter into a long-term contract of surveillance by clinical assessment, functional testing, and imaging when any intervention to the femoropopliteal bed is performed, which mirrors what is demanded of our colleagues in vascular surgery when they perform lower-extremity bypass grafting (10). We must be constantly vigilant and weary of all data from peripheral vascular trials, as the numbers of both the RCT and “real-world” studies are small in comparison to the coronary realm, and enthusiasm for new devices must be tempered with the realism that the SFA is not the left anterior descending coronary artery: caveat emptor!

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