Peripheral Drug Elution Enters the US

Vascular specialists with experience using Cook Medical's Zilver PTX paclitaxel-eluting peripheral stent share thoughts on its potential impact in the United States.

In November 2012, the US Food and Drug Administration (FDA) announced the approval of the first drug-eluting stent with a peripheral indication in the United States. Designed for use in the superficial femoral artery, the Zilver PTX paclitaxel-eluting stent by Cook Medical (Bloomington, IN) has been studied extensively in both a pivotal randomized trial and a large-scale international registry, showing superiority to balloon angioplasty and its bare-metal counterpart. The device has gained approval in more than 50 markets worldwide, and an FDA panel unanimously recommended approval for the device in October 2011, but American physicians did not have access to it until starting in December 2012, when Cook initiated the first phase of the Zilver PTX commercial launch in the US.

The first commercial use of the Zilver PTX came in experienced hands, when Gary M. Ansel, MD, treated a patient using the platform at Riverside Methodist Hospital in Columbus, Ohio, as he had many times during the clinical trial. Along with Michael D. Dake, MD, Dr. Ansel served as a principal investigator in the global Zilver PTX randomized trial, which enrolled patients on three continents and ultimately provided the data that led to US approval.

With the device becoming increasingly available in early 2013 and more US physicians beginning to incorporate drug-eluting stents into their practices, Endovascular Today *asked a few interventionists who have already been using the Zilver PTX, either as part of a clinical trial or commercially in Europe, for their perspectives on how the device might be used in the US. Drs. Nicholas Morrissey, Nicolas Diehm, and Nelson Bernardo discussed optimal applications, current and future areas of study, and the questions that remain.*

Nicholas Morrissey, MD

Associate Professor of Clinical Surgery
Columbia University College of Physicians and Surgeons
The New York Presbyterian Hospital
New York, New York

Dr. Morrissey has disclosed that he is on the speakers' bureau for Cook Medical.

The Zilver PTX has shown favorable results in its randomized controlled trial as well as a single-arm study. What kinds of studies are coming in the near future for this drug-eluting stent?

As with many newly approved devices, the Zilver PTX stent will be further studied in a postmarket trial. The exact design is still being established; however, the postmarket study should provide important information on the use of the stent. For example, the use of the device in lesions that are longer than those studied in the randomized trial will certainly be investigated. There will also be additional data on the drug effect, as the postmarket study will provide more real-world data on the patency of the Zilver PTX. The registry that was performed alongside the randomized controlled trial provides a large amount of real-world data that support the role of Zilver PTX in complex lesions, and postmarket studies in the US should reinforce these results.

In your experiences as a Zilver PTX trialist, what did you learn about patient selection for peripheral drug-eluting stent use? Are there any special considerations for particular patient populations?

During the trial, we selected patients based on symptoms and found that symptom relief was quite durable. Patients were typically very compliant with follow-up and showed an enthusiasm for participating in a study of new technology. We had noted prior to the Zilver PTX trial that many of our heart transplant patients, who were on immunosuppressive drugs to prevent rejection, had stent patency rates greater than non–immunosuppressed patients. This finding increased our enthusiasm for participating in the trial and for providing the first advanced technology that actually demonstrates benefit in SFA disease. There appears to be greater benefit on the diabetic


(Courtesy of Cook Medical)

population as well, so this may be a group that particularly responds to DES. Also, in the Zilver PTX trial, the pattern of restenosis in the patients treated with the DES was much less diffuse than those who had bare stents, so one could argue that patients with a history of aggressive restenosis in their peripheral or other arteries are better off receiving Zilver PTX stents for their SFA disease.

When placing a peripheral DES, do you anticipate doing so primarily in most cases, or will you often use adjunctive therapies beyond angioplasty?

As far as primary DES use is concerned, I believe that postmarket data will be helpful in defining the populations and lesions best treated with the Zilver PTX. We all have to be cognizant of cost issues and ensure that we use technology where it is indicated. The strength of the Zilver PTX trial is in the quality of its design and execution. Based on these criteria, the data are very strong and support the use of this DES in SFA disease. When dealing with long lesions, especially long total occlusions, the question will be raised as to how many DES to use. Unfortunately, we are not yet able to determine which parts of the artery will be more likely to experience failure, so we have to choose our tools wisely. Having said that, using two DES in a long lesion may be initially more expensive, but if reintervention is prevented, then it is worth the cost. As far as adjunctive procedures are concerned, we don't anticipate any change in our use of atherectomy, plaque remodeling, etc., with the advent of DES availability. It will be interesting to see how the Zilver PTX performs in postatherectomy lesions and whether there is a difference in long-term results. Of course, in the absence of compelling data, it may be difficult to justify the expense of such combined therapy.

What do you think we can learn from the long FDA approval timeline for the Zilver PTX?

I believe the FDA was demonstrating due diligence in its evaluation of the Zilver PTX. Given the history of DES technology in other vascular beds, the government has a responsibility to ensure that all aspects of a device's safety and efficacy are thoroughly adjudicated prior to release. The FDA has been under criticism for both too tough and too loose criteria for approval of technology. I believe that as a health care system, we should be doing our part to assist the FDA in coming to the decisions in these approval cases by providing excellent data, which Cook did in the case of the Zilver PTX trial. But as practitioners, we need to demonstrate responsible use of technology once it is approved. We have to pick our patients properly for each specific technology and not overuse expensive devices in lesions and patients where they do not belong. In the area of vascular intervention, I believe there is a lot we can do to assist the FDA in timely, appropriate approval of devices. Companies and practitioners that perform good-quality studies and demonstrate safety and efficacy should be rewarded with efficient delivery of technology to the marketplace. The best lesson is that the approval process is multifaceted, and we can all do our part.

Prof. Dr. med. Nicolas Diehm

Senior Consultant and Director of Vascular Research
Clinical and Interventional Angiology
Inselspital, University Hospital Bern
Prof. Diehm states that he has no financial interest related to this discussion.

How has the Zilver PTX been incorporated into your practice?

The Zilver PTX is an excellent solution for patients with midlength lesions of the femoropopliteal arteries. Given that we have appropriate reimbursement for this technology, we use it primarily in patients with unsatisfying angiographic angioplasty results.

What is your impression regarding its penetration in European practices overall?

My impression is that given the availability of clear data from the Zilver PTX study, the penetration will largely depend on reimbursement of this technology in individual countries. It is likely that the use of the Zilver PTX is cost-effective in many European health care scenarios, but this has to be shown in individual countries.

After more than 3 years of experience with the Zilver PTX, what do you think will be the greatest benefit to US-based interventionists just now gaining access to this device?

Although there are no dedicated studies comparing

different stents, the Zilver PTX stent is the one with the most promising patency performance for femoropopliteal use at present.

What advice would you give US doctors who are not sure if they're ready to switch to DES? What should they know before making the decision and before adding DES to their peripheral practice if they decide to?

This depends on their personal clinical practice so far. In Bern, we avoid implanting stents in the femoropopliteal arteries for as long as possible, because we feel that if implantation of a foreign body can be avoided, both the patient and the interventionist will have more options down the line. However, if a stent is used, based on data from the Zilver PTX study, the Zilver PTX is currently the best stent on the market.

The FDA gave the Zilver PTX approval based on the results of the randomized controlled trial. What are some key points from the Zilver PTX single-arm study that US physicians might miss?

Primarily that the Zilver PTX stents seem to work well in longer lesions than those included in the randomized trial.

Nelson L. Bernardo, MD

Director of the Peripheral Vascular Laboratory
Medstar Heart Institute at the Washington Hospital Center
Washington, DC

Dr. Bernardo has disclosed that he hosts a Retrograde Pedal Access Training Course for Cook Medical and is involved in the Tibiopedal Access for Crossing of Infrainguinal Artery Occlusions Registry conducted by Cook Medical.

Are there any differences in using a drug-eluting stent in the periphery versus a bare-metal device that US clinicians should know about before placing their first one?

The deployment of the drug-eluting Zilver PTX stent is not significantly different from the delivery of any bare-metal nitinol self-expanding stent. Attention may need to be paid on the selection of guidewire being used in the delivery and deployment of the Zilver PTX stent. A more supportive wire is recommended to ensure adequate support of the system during the "pin-and-pull" deployment of the drug-coated nitinol self-expanding stent. In addition to the mechanical support (ie, imparting an outward radial force upon the inner lumen of the vessel to establish patency) provided by the Zilver Flex stent platform, the Zilver PTX drug-eluting stent also provides the vehicle for the delivery of the drug paclitaxel coated on the stent struts. As such, the important issue of implanting it in women needs to be addressed prior to using the stent: Its use is contraindicated in women who are pregnant, breastfeeding, or plan to become pregnant in the next 5 years. It is not known whether paclitaxel is excreted in human milk, and there is a potential for adverse reaction in nursing infants from paclitaxel exposure. In addition, the safety of implanting more than four Zilver PTX drug-eluting stents (with a maximum drug coating quantity of approximately 3 mg of paclitaxel) has not been clinically evaluated. This needs to be taken into consideration when treating very long lesions. Lastly, previous allergic reactions to nitinol, nickel, titanium, and paclitaxel need to be taken into account prior to the implantation of the Zilver PTX stent.

Now that the Zilver PTX has gained approval in the US, are there any other "combination therapy" devices on the horizon in the foreseeable future? Where are there areas of need, and when might these be met?

Treatment of infrainguinal arterial occlusive disease has been the Achilles' heel for interventionists involved in the management of peripheral arterial disease using the percutaneous endovascular approach. Although use of adjunctive therapeutic modalities such as "debulking" and the development of new stent technologies have shown encouraging results, significant room for improvement remains in our endovascular treatment of femoropopliteal arterial occlusive disease. This is especially true in the recanalization and treatment of "long" lesions (ie, > 14 cm in length), which is not usually included in studies. The pending release of the approved Zilver PTX drug-eluting peripheral stent is widely anticipated. The remarkable primary patency rate of 75% at 24 months is definitely encouraging notwithstanding the limitations of the study. Parallel to this has been the development of the drug-coated balloon technologies also delivering paclitaxel into the tissue of the treated segment. Preliminary data have been very encouraging, and the results of randomized trials are awaited. Conceptually, "combination therapy" with adjunctive use of atherectomy devices prior to drug delivery by drug-coated balloon makes logical sense. However, this approach will need to be validated by randomized trials. Finally, the use of Viabahn ePTFE-covered nitinol self-expanding stents (Gore & Associates, Flagstaff, AZ) to "line" long occlusive segments is hampered with "edge stenosis." Theoretically, deployment of Zilver PTX drug-eluting stents at the proximal and distal edges of the Viabahn as "combination therapy" could potentially mitigate this issue. New studies comparing the relative

efficacy of these different modalities will be necessary to determine the best treatment approach in this challenging patient population.

In which ways do you feel the peripheral experience with drug-eluting stents will be similar to that in the coronaries in terms of adoption and use? How might the experiences be different?

The encouraging results from both the Zilver PTX randomized study and the Zilver PTX registry suggest that drug-eluting peripheral stents may have renewed application in the treatment of femoropopliteal arterial occlusive disease. However, the lower restenosis rate does not equal the long-term patency seen in stenting in the coronary bed. This could certainly hamper the widespread adoption of this technology, especially in the subgroup of interventionists who only do bailout stenting for suboptimal results. Expectations for a single-digit restenosis rate from coronary stenting data will certainly slow down adoption and cloud the experience. In addition, we await the long-term 3- to 5-year poststenting data. Although the primary patency has been superior in the 12- to 36-month data when compared to balloon angioplasty plus bare-metal stenting, the question of long-term tissue response to the implanted Zilver Flex stent remains to be answered at 4 years and beyond. One needs to bear in mind that the implanted stent will be subjected to the same physical-mechanical forces as a bare-metal stent.

How will you implement the Zilver PTX into your daily practice?

In the percutaneous endovascular treatment of infrainguinal femoropopliteal artery segment, an interventionist can be classified either as a "stenter" or a "nonstenter." The former routinely deploys an intravascular stent as definitive therapy for the revascularization procedure. The nonstenters make use of the strategy of bailout stenting for suboptimal balloon angioplasty results. Those of us who have taken the latter approach have been driven by the fact that overall restenosis rates, easily > 50% in "long" lesions, remain unacceptably high despite the introduction of newer-generation stents. The Zilver PTX paclitaxel-eluting stent has certainly improved on this with a real-world registry showing 50% reduction in the 24-month restenosis rate, albeit not the single-digit rate that we see with stenting in the coronary bed. Use of the Zilver PTX drug-eluting stent would certainly be preferred in the instance of bailout stenting in our daily practice. The threshold for stenting could easily be lowered driven by the reduction in the restenosis rate by half. ■