Drug-Eluting Stents in the Periphery

A summary of the barriers, unanswered questions, and potential benefits of this technology.

BY H. BOB SMOUSE, MD

Indications for drug-eluting stents (DESs), as approved by the US FDA, are limited to short, *de novo* lesions in coronary arteries measuring between 2.5 mm and 3.5 mm (sirolimus-eluting stents) or ≤3.75 mm (paclitaxel-eluting stents) in diameter. In these standard indications, the use of DESs has shown excellent outcomes with low rates of target lesion revascularization at long-term follow-up.[1-3]

IRRATIONAL EXUBERANCE

This success was greeted with a great deal of excitement, and within a short period of time, the use of DESs spread quickly to a diverse and more complicated patient population. In the CRUSADE registry,[4] the average use of DESs was 50% within 6 months of approval and increased to 82% within 1 year, and was used in mostly high-risk patients. Win et al[5] and Beohar et al[6] noted a high frequency of off-label use of stents between 2004 and 2005. In the study by Win et al, 55% of patients had at least one off-label characteristic, whereas in the study by Beohar et al, 47% of patients received DESs for off-label or untested indications.

The initial excitement also spilled into the peripheral market, and interest grew in using DESs elsewhere in the body—especially in arteries of the legs and kidneys. This enthusiasm would come with a price when the first reports of unexpected late stent thrombosis, myocardial infarction, and even death occurred more than 1 year after the initial procedures involving DESs.[7] Initially, this coronary report did not significantly hamper the potential for DES use in the periphery. However, this report and other concerns about late DES adverse events resulted in added vigilance by the FDA and also concern by device manufacturers that DESs in peripheral arteries might encounter similar problems.

PERIPHERAL APPLICATIONS

On the peripheral front, the SIROCCO trials were poised to open the door for DES use in peripheral arteries, a potential huge market of more than 3 million patients in the US alone. The SIROCCO results were released intermittently over a 2-year period as data became available and were followed keenly by industry, investors, and medical professionals, stimulating a fair amount of armchair quarterbacking. Discussions centered on patency rates and revolved around elution curves, drug type, polymer, target dosing, and length of elution.

The initial hypothesis was simple—add a drug that has been proven to retard or prevent neointimal hyperplasia in coronary arteries to a stent that has been used routinely in the superficial femoral artery (SFA), and patency rates will improve. Unfortunately, encouraging early results were once again followed by disappointing results at 3 months and longer. Although patency rates were not terrible, they were no better than bare-metal stents alone—again, an outcome unexpected by most investigators. At 24 months, the restenosis rate in the sirolimus group was 22.9% versus 21.1% in the bare-stent group ($P>.05$).[8] Unfortunately, the SIROCCO trial results were a wake-up call to peripheral device manufacturers and users alike.

COST AND GAMBLE

With no apparent difference between bare-metal stents and DES, industry leaders were forced to gamble and make difficult decisions. At least one large device company put its peripheral DES program on hold after spending hundreds of millions of dollars on research and development. The decision, although controversial, is understandable given that the cost of a new medical product is staggering. The average cost of a new prescription drug is $879 million, almost four times the cost in the early 1990s,

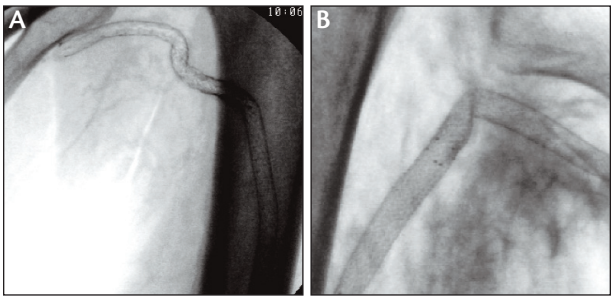

Figure 1. Deformation of flexible (A) and rigid (B) stents implanted behind the knee.

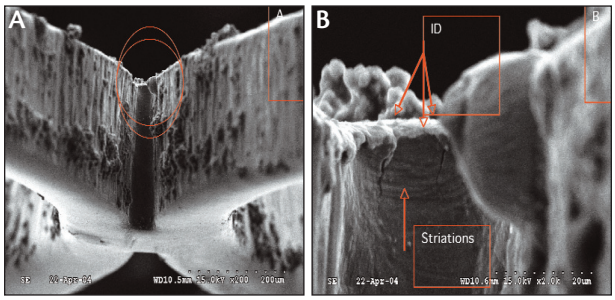

Figure 2. Scanning electron micrograph of a commercially available stent showing cracks, striations, and retained slag.

according to a study by the Tufts Center for the Study of Drug Development.[9] Similar expenses are necessary in the development of a DES, with estimates of costs from one researcher at a large device company in excess of $100 million and time to market of nearly 10 years.

HURDLES WITH THE FDA

The FDA has repeatedly stated that it wishes to help make innovative technologies available sooner and to reduce the costs of developing safe and effective medical products while maintaining the FDA's traditional high standards of consumer protection. As part of the application process, all new devices and drugs must go through one or more review cycles. A review cycle for a priority drug takes 6 months; for a nonpriority drug, it takes 10 months for new drug application.[10] Usually, more than a few review cycles are needed to complete the process.

Furthermore, a new medical product that is both a device and a drug requires a doubling of effort in the form of communication, explanation, and presentation of the product to the FDA panel. A different panel reviews peripheral products than that which reviews coronary products, and at present, the confidence level in DES in peripheral arterial use is less than in coronary arterial use. More data are required on engineering, quality assurance, safety, and animal studies to convince the panel. In addition, the "gold standard" for percutaneous treatment of the SFA is angioplasty and not bare-metal stents; jumping from angioplasty to DESs in the SFA skips the essential step of bare-metal stent validation as a viable and at least equal treatment alternative to angioplasty. This is a very different dynamic than in cardiology, where the use of bare-metal stenting was the undisputed "gold standard" and where DES trials were allowed to compare bare-metal stents against DESs.

Peripheral panel members are reluctant to approve new devices without randomizing against the impractical yet scientifically correct controls, such as medication for renal artery stenosis, surgery for carotid artery disease, and bypass surgery or angioplasty for intermittent claudication. Randomizing bare-metal stents to DESs would be much more practical yet scientifically incorrect.

As a national coprincipal investigator of a peripheral DES trial, I was involved with the FDA application process, especially as it pertained to animal and engineering components. Although this is not a criticism, the better part of 3 years was spent working our way through the review process, without success, and ultimately requiring a move into Europe for phase 1 data gathering.

On the other hand, Cook Medical (Bloomington, IN) successfully navigated the FDA review process and received approval for clinical testing of their DES for the SFA, the Zilver PTX stent. This is the first such peripheral trial in the US, and Cook Medical has recently finished phase 1 testing after enrolling 60 patients. Phase 2 testing is expected to begin shortly and will enroll 420 patients at 50 sites. One industry researcher speculated that FDA approval was based on three factors: the Cook Medical DES uses no polymer (and therefore, there are no delamination issues from repeated cyclic stress), one stent per leg is allowed (reducing the risk of stent fracture), and relatively short target lesions are treated (reducing host-toxicity risk from the drug). However, enrollment has been slower than expected. The Zilver PTX stent is coated with paclitaxel, a drug approved for clinical use as an anticancer agent. Full patient disclosure requires listing of all potential side effects of this agent including anemia, infection, hair loss, numbness, tiredness and feeling weak, allergic reaction, and others,[11] although the amount of drug on a stent is magnitudes lower than that used for cancer therapy. At our institution, we had patients balk at enrolling in the trial because of perceived side effects. The time necessary to enroll 420 patients is unknown but will certainly take several years or longer.

SCIENTIFIC DATA NEEDED

As we move from coronary arteries into peripheral arteries, we are encountering different challenges, most of which are unexpected. These developments have

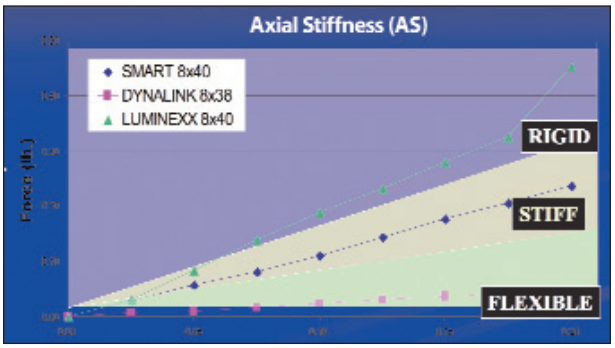

Figure 3. Three commercially available stents with different axial rigidities.

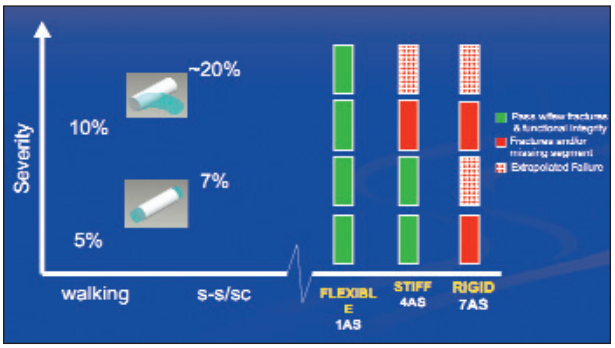

Figure 4. Fatigue resistance is significantly better with axially flexible stents.

slowed peripheral DES development and FDA approval. For example, there is no clear evidence from animal data to say how much and how long a drug should be in the tissue until the vessel-stent complex develops a thin neointimal layer and becomes biomechanically stable. It may never become stable, so perhaps a small amount of drug eluted over a long time period will retard tissue growth, improving stent durability, but never stabilizing the vessel-stent complex. In addition, the stent itself is subjected to mechanical forces within the femoropopliteal arterial segment that threaten the integrity of the stent and disrupt the uniformity of drug delivery (Figure 1). Various studies, including SIROCCO and FESTO,[12,13] suggest that stent fracture rates increase with a higher number of stents used, and can be as high as 37%.[13] Stent stress testing based on cadaver data resulted in somewhat predictable and high fracture rates for nitinol stents with poor surface finish and high axial rigidity (Figures 2 through 4).[14] Stent manufacturers are having to prove their "metal" and are tasked with developing bench tests that accurately model extremity movement allowing for *in vitro* testing, with the ultimate goal of proving stent fatigue resistance—a time-consuming project.

CONCLUSION

There are many factors delaying peripheral DES use in the US, including, but not limited to, developing fracture-resistant stents, divining successful drug-elution formulas, stabilizing drug coating, obtaining FDA clinical testing approval, enrolling patients, and ultimately proving stent durability and superior vessel patency. Device manufacturers entered the market enthusiastically based on early coronary DES success, not expecting to encounter the multitude of challenges listed previously. However, advancements in endovascular medicine come in spits and spurts, requiring tenacity, single-mindedness, and perseverance. Given the incredible expense of product development, some peripheral device manufacturers are adopting a wait-and-see attitude, while others are gambling on the success of DES in the periphery. Hopefully, the winners of this gamble will be the patients. ■

H. Bob Smouse, MD, is with the Central Illinois Radiological Associates, and Clinical Assistant Professor of Radiology and Surgery at University of Illinois College of Medicine at Peoria. He has disclosed that he is a paid consultant to Abbott, Cook Medical, ev3, Cordis, and Bard, and that he receives research funding from Abbott and Cordis. Dr. Smouse may be reached at bsmouse@cirarad.com.

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-1323.
2. Stone GW, Ellis SG, Cox DA, et al. TAXUS-IV investigators. One-year clinical results with slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation. 2004;109:1942-1947.
3. Fajadet J, Morice MC, Bode C, et al. Long-term suppression of restenosis by sirolimus-eluting coronary stents: three-year results of the RAVEL trial. Circulation. 2005;111:1040-1044.
4. Kandzari DE, Roe MT, Ohman EM, et al. Frequency, predictors, and outcomes of drug-eluting stent utilization in patients with high-risk non-ST-segment elevation acute coronary syndromes. Am J Cardiol. 2005;96:750-755.
5. Win HK, Caldera AE, Maresh K, et al. EVENT Registry Investigators. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA. 2007;297:2001-2009.
6. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA. 2007;297:1992-2000.
7. Mcfadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004;364:1519-1521.
8. Duda SH, Bosiers M, Lammers J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. J Endovasc Ther. 2006 Dec;13:701-710.
9. Prescription drugs/costs of new drug development reaches $879 million, study says. Daily Health Policy Reports. May 15, 2003.
10. Improving innovation in medical technology: beyond 2002 executive summary [press release]. US Food and Drug Administration; January 30, 2003.
11. Perry MC, ed. The Chemotherapy Source Book. 3rd ed. Lippincott Williams and Wilkins; 2001.
12. Duda SH, Bosiers m, Lammers J, et al. Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease: The SIROCCO II trial. J Vasc Interv Radiol 2005;16:331-338.
13. Scheinert D, Scheiner S, Sax J, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol. 2005;45:312-315.
14. Smouse HB, Nikanorov A, LaFlash D. Biomechanical forces in the femoropopliteal arterial segment. Presented at: International Symposium on Endovascular Therapies; January 2006; Miami, FL.