The DURABILITY II Trial

Krishna Rocha-Singh, MD, FACC, FSCAI, discusses the current status of the DURABILITY II trial, a challenging landmark study of patency and fracture resistance of stenting in the superficial femoral and popliteal arteries.

What are the goals of the DURABILITY II trial, and how would you summarize its study design?

There are three important goals of the DURABILITY II trial, which represent three very significant "firsts" for trials of nitinol stents in the superficial femoral artery (SFA). It is the first trial to hypothesize that placement of a single nitinol stent, potentially up to 200 mm in length, may translate into a reduced incidence in stent fractures and, therefore, a reduced 12-month target lesion revascularization (TLR) rate. Previous data have suggested that multiple overlapping stents—particularly three or more—are associated with a high rate of fracture and restenosis.

Another "first" is that DURABILITY II is the first trial to engage in a new study design, which has been proposed by VIVA Physicians, Inc., and endorsed by the FDA. It is very important to realize that previous premarket approval (PMA) trial designs—including the most recent RESILIENT trial design—randomized patients between balloon angioplasty and nitinol stenting. Approximately 18 months ago, VIVA Physicians, in collaboration with the FDA, proposed a single-arm trial design with a point estimate for PTA restenosis in the SFA; the nitinol stent would have to be superior in its 12-month patency rate to the PTA point estimate. This is the first trial to engage this performance goal, and importantly, I understand that at least four other clinical trials are engaging or will soon be enrolling trials using this performance goal, specifically trials sponsored by Cordis Corporation (Warren, NJ), Medtronic Vascular (Santa Rosa, CA), and IDev Technologies (Houston, TX). It is our hope that manufacturers of non-stent technologies will also use this performance goal to establish superiority to PTA in the SFA.

The other important "first," and very relevant to clinicians and regulators, is that this is the first PMA trial that will engage a "therapeutic endpoint." Patients with moderate-to-severe claudication enrolled in the DURABILITY II trial will undergo both a preprocedure and 12-month objective assessment of walking distance using a claudication treadmill to document the potential clinical improvement. This is important because CMS is now requesting physicians and industry members to demonstrate that these procedures actually have benefit to patients—not just improve a surrogate endpoint. This is the first trial to challenge the endovascular field to enroll patients, put them on a treadmill, perform an intervention, and establish the improvement in that therapeutic endpoint. These are three very important "firsts" for the DURABILITY II trial.

What are the inclusion criteria, specifically pertaining to lesion lengths and the severity of disease?

DURABILITY II is investigating lesion lengths that are a little outside of the described performance goals in that it will enroll patients with slightly longer lesion lengths—up to 18 cm; the performance goals include lesion length up to 15 cm. This allows for the use of the 20-cm Protégé EverFlex Self-Expanding Stent (ev3 Inc.,

Plymouth, MN). These are patients with moderate-to-severe claudication on the Rutherford scale. These patients will be given a preprocedure claudication treadmill test and then followed-up with a postprocedure 12-month claudication treadmill assessment of their clinical improvement. There will be a complete analysis of stent fractures. The DURABILITY II trial is very significant with these distinguishing features.

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Aside from incorporating the performance goal design, what differentiates DURABILITY II from previous and other ongoing SFA stenting trials?

This is definitely a challenging trial. Right now, stent manufacturers are very much under scrutiny. Several of them have already received subpoenas from Attorney Generals asking them to provide their promotional materials, questioning their "off-label" promotion of nitinol "biliary stents." There is a shadow over the field, and companies are challenged to get on-label. These trials are very important in that regard, and DURABILITY II is showing the way.

Despite there not being randomization in the trial, has enrollment been difficult?

There have been challenges, but we must evolve. Several years ago, PTA was—at least from the FDA's point of view—believed to be the gold standard for endovascular therapy in the SFA. We now know, with fairly good assurance, that angioplasty, particularly in lesions >5 cm, has associated restenosis and TLR rates that are inferior to nitinol stenting. These data come from randomized trials: the RESILIENT trial (level 1 data); the ABSOLUTE trial (level 1 data); and more recently, the FAST trial (level 1 data). If you put those three randomized trials together and look at the PTA-arm patency rates, and then look at the data pulled together from the VIVA Performance Goals looking at angioplasty, we now realize that clearly we do not have to revisit a procedure (balloon angioplasty) that does not perform well—angioplasty in long lesions. We can say this with some certainty, which is why the Performance Goals represent a point of evolution: it is a single-arm trial design in which superiority to a 12-month angioplasty patency point estimate must be shown. This represents an incremental step forward; the next incremental step is to get everyone on board and evolve beyond the surrogate for patency (duplex Doppler, peak systolic velocity) and looking at what it means to the patient. Does the patient who undergoes this procedure realize a clinical benefit? This should be our next focus.

How would you summarize the Performance Goal design, developed by VIVA Physicians? What is its role in the trial?

The Performance Goals are rooted in the desire of VIVA Physicians to advance the endovascular field forward. We understand that randomized trials are expensive, take a long time to enroll patients, and to an extent, have created a barrier to entry for small companies. We actually collaborated with both the FDA and with industry members; VIVA Physicians obtained appropriate nondisclosure agreements and was subsequently given access to the companies' blinded PTA data from previous PMA trials. We went to Gore & Associates (Flagstaff, AZ), Spectranetics Corporation (Colorado Springs, CO), and ev3, and they were gracious enough to provide us with that data. Based on several hundred patients with moderate-to-severe claudication and SFA lesion lengths between 4 and 15 cm, in which we were able to look at specific safety and patency endpoints, we were able to come up with a number. We then examined the literature, and we were able to make similar estimates from the angioplasty-arm from four randomized trials performed in Europe. We joined those two segments of data—the patient-level data from PMA trials and the angioplasty from randomized control trials in the literature, and we came up with a 12-month patency estimate of patients undergoing SFA angioplasty. It is to this estimate that nitinol stenting must establish its superiority.

VIVA Physicians felt that—as opposed to angioplasty—stenting had several distinguishing factors. One, it uses an implantable device. Two, stenting carries safety concerns—specifically, stent fractures—and the possibility that these fractures could be associated with higher TLR rates. Three, stenting is more expensive, and that burden to society should be associated with some superior benefit (ie, patency). All three aspects were considered in the Performance Goal design; we came up with an approximate restenosis patency rate at 12 months for angioplasty of 33%, which is fairly low. A nitinol stent should be substantially superior to that; therefore, we suggested that the 12-month nitinol stent patency rate would be approximately 66%. The FDA agreed with this proposal, and we went through the peer-review process, and it was published in May 2007 in *Catheterization and Cardiac Intervention*. This represents an important vision

of VIVA Physicians—to move the vascular field forward, and I believe that we have.

What is the current state of enrollment in the DURABILITY II trial, and when is completion anticipated?

The trial is ramping up right now. There will ultimately be 40 sites involved. This is a challenging protocol in that we are asking physicians to perform a claudication treadmill assessment. That has challenged enrollment because it is something many physicians do not do routinely, but we have regrouped. We have made amendments that will foster more brisk enrollment. The hope is that we will be able to enroll approximately 250 patients by early 2010. Enrollment began approximately 9 months ago.

In several ways, DURABILITY II is setting a new bar. The real issue here is the evolution in the clinical science. Recall that CMS came very close to not reimbursing renal stenting because they concluded that the clinical data supporting its use as being "reasonable and necessary" were not available. Importantly, CMS said that although they would continue to reimburse renal stenting but revisit the issue, and if the clinical science had evolved, they may not continue to reimburse it. The CMS decision not to reimburse carotid stenting in asymptomatic patients has had a significant impact on the carotid stent procedure, and CMS has announced that they have contracted with the Agency for Healthcare Research and Quality (AHRQ), and peripheral artery stenting and the data supporting its use are under evaluation now. We need to invest in trial designs that establish clinical benefit, and, unfortunately, some companies have not done that. The announcements by CMS and several recent editorials in both *Circulation* and the *New England Journal of Medicine* have challenged physicians, as well as industry, to engage in more clinically relevant trial designs.

One of the difficulties with modern clinical trials is the duration needed to show meaningful outcomes. With 5-year follow-up originally planned, is there concern over the effect of new technologies that could emerge while the trial is ongoing?

You may see study amendments forthcoming, and the follow-up may be shortened to 3 years. There will be long-term telephone follow-up. There have been expressions of concern that, given the considerable amount of "off-label" stent use, long-term safety issues have avoided thorough evaluation. This reflects the times in which we live; without appropriate longer-term postmarket surveillance, certain potential safety issues may not become evident to us. I agree that the follow-up is arduous and expensive, but that is balanced by safety issues. How can we do this more uniformly and at a lower cost? CMS has very huge databases, and physicians have not engaged those databases to look at potential safety megatrends in this population; it is about time that this option is considered.

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The 20-cm stent is not yet available on the market. There are 15-cm stents that have been made available through the 510(k) regulatory pathway; they are used "off-label" in the vasculature by physicians. These stents are manufactured by IDev, Cordis, Medtronic, and ev3. However, we need to evolve beyond this 510(k) biliary stent paradigm; this is a regulatory pathway, used by industry, in order to provide doctors with these technologies. The unintended consequence is that we now have millions of stents being placed in patients without a thorough understanding of the clinical effectiveness or the long-term safety profile of these devices in the various vascular beds in which they are being deployed. Industry, physicians, and the FDA must work together to investigate ways to obtain such data without stifling trial execution and innovation. The present regulatory environment will cause industry members to invest resources elsewhere, much to the determinant of our society. They must work together to answer these questions sooner rather than later.

VIVA Physicians wants to be part of the solution and not the problem by setting out the Performance Goals and encouraging industry's involvement. The DURABILITY II investigators and ev3 are to be congratulated for taking on the risk and challenges associated with this trial. When we look back, this will be a landmark trial in many ways. ■

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