Setting the Stage for Future Lower-Extremity Device Trials

Krishna Rocha-Singh, MD, of VIVA Physicians, Inc., discusses their effort to determine nitinol stenting performance goals, collaboration with the FDA and industry, and how clinicians can apply these standards to their practices.

Endovascular Today: What was the impetus for the effort by VIVA Physicians, Inc. (VPI) to draw up the performance goals and endpoint assessments?

Dr. Rocha-Singh: This project evolved as a result of VPI's interest in assisting the FDA in promoting relevant industry-sponsored clinical trials in the SFA. As you know, the off-label use of devices in the superficial femoral artery (SFA) is rampant. VPI and the FDA developed a collaborative relationship outside of the spectrum of the device industry. The FDA is very open to this relationship in an effort to understand what is relevant to physicians in the care of patients. Importantly, VPI, as a group of independent physicians, was able to access industry's confidential device data, which had been used to support their own device submissions; the FDA was not able to evaluate these data to develop vascular device performance goals. We employed our own statisticians in the 15-month process to develop and publish the SFA percutaneous transluminal angioplasty (PTA) performance goals.

Endovascular Today: How would you summarize the recommendations that VPI has put forth?

Dr. Rocha-Singh: The performance goals provide a general blueprint whereby any individual or device company could go to the FDA and address the question of the efficacy and safety of its nitinol stent compared to specific clinical endpoints in a single-armed, nonrandomized trial design. The FDA was very open to this because of its regulatory language, which states the FDA must provide a "least-burdensome" regulatory pathway whereby industry can establish the safety and efficacy of a device. The FDA also understood that randomized trials with PTA and stents in the SFA were extremely difficult to execute.

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We proposed criteria regarding PTA to act as a reference when performing a nitinol stent device trial. We chose to develop angioplasty performance goals because the FDA considered angioplasty, which was approved for that vascular bed, to be the established gold standard. Cryoplasty, laser, and atherectomy were not specifically approved by showing superiority to angioplasty; they are adjuncts to angioplasty. These devices have established their safety in improving luminal vessel diameter but not their superiority to angioplasty.

For the first time, there is now a regulatory pathway whereby, in a cost-efficient and expeditious manner, the FDA can say to industry, "We believe these goals are reasonable, and here is an regulatory pathway for you to potentially establish the efficacy of your technology."

This raises all boats. It is a win, win, win: it shows that the FDA is engaged; it gives industry a clear pathway; and it provides physicians and patients safety and efficacy data to support clinical decision making.

Endovascular Today: Does VPI plan to publish any other guidelines?

Dr. Rocha-Singh: This was an interesting perfect storm that came together in February 2007. The FDA met with industry and stated, "You must stop promoting the off-label use of your devices." At the same time, it said, "Here is a regulatory pathway to get 'on label' using the VPI PTA performance goals." We now are planning to do the same in the below-the-knee vasculature. The FDA believes, as many people do, that surgery is the therapeutic gold standard in patients with critical limb ischemia. Endovascular therapies are presently challenging that paradigm, particularly in debilitated and elderly patients who have this problem.

At the SVMB meeting in Baltimore, we will have our first meeting of a writing group of VPI and non-VPI physicians to collaborate with the FDA to develop a below-the-knee surgical objective performance criteria (OPC). We plan to develop safety and efficacy criteria, and whoever has a device ready to deal specifically with these critical limb ischemia patients can hopefully use this regulatory pathway to get their device approved.

Endovascular Today: Do you have an opinion regarding the FDA's editorial of the VPI criteria?

Dr. Rocha-Singh: Understanding the incredible hurricane that the FDA always finds itself in, I think what they said was positive yet tempered. More important, however, was the fact that this was a collaborative process with the FDA. There were multiple conference calls and face-to-face meetings over the 15-month period. In that respect, the FDA was very engaging and went above and beyond the measured words of their editorial.

Endovascular Today: How were the data gathered to draft the criteria?

Dr. Rocha-Singh: These endpoints were termed *performance goals* as opposed to *OPC* because the quantity of the SFA PTA data was, frankly, suboptimal. However, we agreed that we needed the best quality data available. Therefore, we went to three device companies and asked to see their de-identified PTA data from the control arms of their randomized device trials. We also reviewed the medical literature from the last 15 years and combed it for randomized trials, looking for data from the control PTA arms. We had two statisticians assist us in analyzing this patient-level data from the industry trials and medical literature review. After obtaining and analyzing these data, we focused on developing specific parameters, such as lesion length, to create finite and specific performance goals, which encompass SFA lesion lengths from 4 cm to 15 cm in severe claudicants, and not patients who have critical limb ischemia. It is as circumscribed as we could make it.

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Endovascular Today: How have the challenges associated with randomized clinical trials of PTA versus stenting made gathering these data difficult?

Dr. Rocha-Singh: Physicians are human, and we all carry our own prejudices with regard to what we think is appropriate. I applaud some industry individuals who took on randomized trials. Unfortunately, because PTA fails so frequently, those randomized trials ended up being trials of failed PTA versus stenting. I think we have moved beyond the challenges of SFA PTA randomized trials with these performance goals.

I now strongly believe that it borders on unethical to subject a patient with long SFA disease to angioplasty alone; our data suggest that angioplasty will fail in two-thirds of the cases, and important safety issues are associated with that failure rate. Angioplasty should be avoided in patients with long lesions.

Endovascular Today: Were you particularly surprised by any of the trends you observed?

Dr. Rocha-Singh: I think all VPI investigators, as well as the FDA, were surprised that the PTA patency rates were so poor. However, we were reassured because the data from industry and the peer-review medical literature were both in the same ballpark. The PTA control-arm data from the medical literature suggested that the 12-month duplex Doppler-defined SFA patency rate was 37%; the industry data from a similar cohort of patients with similar SFA lesion lengths noted a 12-month patency rate of 28%. The fact that these two different data sets yielded similar results was a reassuring internal control.

This is an incremental process. We have gotten over angioplasty; next we must better define the safety and efficacy of nitinol stenting. Perhaps, in the future, nitinol stenting will be challenged by bioabsorbable drug-eluting stents. Our next goal is to work with industry to develop an SFA nitinol stent OPC to establish its efficacy and safety and to understand the design differences among nitinol stents. As we move toward bioabsorbable stents, we can reference nitinol stent data.

Developing the criteria was a 15-month process, but this was an important evolution. I have had personal handshakes from three industry presidents and vice presidents who have said to me, "Yes, Krishna, you guys have done this, we appreciate that, and we look forward to lending our de-identified nitinol stent data so you can continue to do this type of work together."

Endovascular Today: Do you anticipate that these goals and endpoints will be re-evaluated at a later date as data are gathered and the technology progresses?

Dr. Rocha-Singh: Absolutely. It is a living document because technologies change so quickly. When we started thinking about the SFA PTA performance goals, that fact was appreciated. Several industry representatives have come to us and said that they would like to use these performance goals to request a label change from the FDA for their vascular device. They have a 510(k) label as an "adjunct to angioplasty" and now want to say that their device is superior to angioplasty through trial designs using our PTA performance goals. I support that. Although it was not our initial intent as we specifically referred to nitinol stenting, at least it establishes a basis for dialogue between the FDA and industry members. Rather than continually promoting off-label device use through marketing registries, we helped give industry the mechanism to put some clinical rigor into device development and sales.

Endovascular Today: What can clinicians learn from these criteria, and how can they apply the standards to their practices outside of clinical trials?

Dr. Rocha-Singh: Physicians are human and are swayed by marketing. The criteria, first and foremost, tell them that other physicians are very interested in bringing rigor to the decision-making process in the SFA. Right now, PTA is something that should be avoided for this type of cohort with this type of morphology. I suspect that a lot of doctors were avoiding stand-alone PTA in the SFA because they had the same inkling, for which we have now provided confirmatory data. My hope is that at least three stent manufacturers will use these goals to put out quality data in the next year to 18 months that show how good or how bad nitinol stenting is. The next hurdle will be deciding what to do for diffuse in-stent restenosis.

Endovascular Today: What inconsistencies did you notice among the three data pools, along with differing definitions of in-stent restenosis?

Dr. Rocha-Singh: The three manufacturers provided data from slightly different patient cohorts; however, definitions of patency and time-point assessments were similar. These manufacturers did not provide data regarding in-stent restenosis. Likewise, procedural safety was defined slightly differently; however, because we had patient-level data, we were able to go back and extrapolate safety issues to develop our own definitions of safety—for example, 30-day total lesion revascularization.

Endovascular Today: How do the standards proposed by VPI compare to other guidelines, such as those of the ACC/AHA or TASC II? Are there areas of convergence or disagreement, or do the various publications differ too much in their focus to draw comparisons?

Dr. Rocha-Singh: Because we couched our PTA data as part of a regulatory pathway paradigm in the SFA, comparison with the clinical practice guidelines from TASC II is not applicable. The TASC guidelines provide general recommendations for the use of endovascular or surgical therapies in specific patients with a variety of lesion morphologies. The VPI performance goals provide specific safety and efficacy targets for nitinol stenting in comparison to PTA in specific lesions between 4 cm and 15 cm in length. We make or infer no clinical recommendations in our document.

With regard to the ACC/AHA guidelines for SFA therapies, these guidelines only suggested that stenting be pursued in the event of a suboptimal or failed PTA result. Because these guidelines are based on clinical data, they are appropriately limited because the available clinical data are poor. We are attempting to provide a mechanism through which solid clinical data will become available.

Endovascular Today: Are there any trials underway that will apply these guidelines?

Dr. Rocha-Singh: Yes, three companies have verbally contacted us and said they plan to use our guidelines to

(Continued on page 61)

(Continued from page 60)

support premarket approvals; they have requested our help to answer questions about how we derived certain endpoints. I strongly believe that, based on our collaborative experience with the FDA in developing these performance goals, a press release announcing FDA approval of this study design as part of a premarket approval trial design is imminent. There are other companies that do not make nitinol stents that want to use these goals for nonstent technologies. It establishes a basis for dialogue with the FDA. Some of the other nonstent companies now realize that they need rigorous clinical data to support their marketing.

I am very concerned about the evolving disconnect between the FDA and CMS, such as when the FDA approves a device as "safe and efficacious," but CMS does not reimburse its use because it believes it is not "reasonable and necessary." This occurred with carotid stenting, and it may happen with renal stenting. As physicians, we must challenge industry and ourselves to stop doing these expensive procedures that have no clinical value for our patients. The FDA will approve these devices; however, CMS will not pay for them because we have not shown that it is reasonable and necessary with a meaningful impact on the quality of our patients' lives. This is just one step on the road to challenge ourselves and industry to provide meaningful and relevant data. If a device does not show clinical value, it should not be approved. Industry should be challenged to prove the value of their products to society.

Endovascular Today: In the conclusion of the performance goals you state that, "The development of these performance goals is an important first step in the design and implementation of single-arm registry trials." What is the next step?

Dr. Rocha-Singh: The next step is below the knee. This group of patients is sorely neglected, and the development of a surgical OPC for comparison in single-armed device trials will hopefully invite much-needed clinical trial investigation. VPI will also consider the development of a renal stent OPC. As a not-for-profit group, that is a lot for right now; we run on our own passion. ■

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