Objective Performance Goals for Renal Artery Stenting Trials

Krishna J. Rocha-Singh, MD, discusses what led to the creation of OPG for renal stenting and how these goals can be applied to new research endeavors.

In 2011, representatives of VIVA Physicians Inc. published an article entitled "Objective Performance Goals of Safety and Blood Pressure Efficacy For Clinical Trials of Renal Artery Bare Metal Stents in Hypertensive Patients with Atherosclerotic Renal Artery Stenosis."[1] The purpose of establishing these objective performance goals (OPG) was to provide benchmarks for safe and effective single-arm trials evaluating stenting for the treatment of patients with resistant hypertension related to highly stenosed renal arteries. Endovascular Today *sat down with lead author Krishna J. Rocha-Singh, MD, for a closer look at the process by which these goals were arrived upon, the parties that were consulted, and how they might affect future renal stenting trials.*

What initially prompted VIVA Physicians to establish OPG for renal stenting trials?

Our primary goal was to evolve the clinical space away from using an angiographic endpoint (ie, suboptimal/failed renal angioplasty) and define success in renal stenting based on a clinical endpoint—namely, improvement in hypertension control. The previous paradigm for evaluating renal stenting in regulatory trials was in comparison to a renal angioplasty performance goal. The initial renal stenting trials were randomized versus renal balloon angioplasty; however, many clinicians came to realize that restenosis rates with angioplasty alone were so high that to continue to randomize against this PTA control was unethical. So, what did it really mean to be better than angioplasty? With no clinical endpoint (eg, hypertension control), these trials did little to show us which patients are most likely to benefit from renal stenting and what exactly the benefits of the renal stent procedure were, if any.

Our primary goal was to evolve the clinical space away from using an angiographic endpoint and define success in renal stenting based on a clinical endpoint …

How did your team determine which criteria should be included?

We began speaking to interested physicians, industry representatives, and the FDA. While each group agreed that a clinical endpoint should be pursued, each had its own viewpoint as to what was relevant, so it took quite a bit of time to even get started. Eventually, we determined that we needed access to the data collected as part of the previously completed premarket approval (PMA) renal stent trials with devices that were on label for "suboptimal/failed renal PTA," namely that of Cordis Corporation (Bridgewater, NJ), ev3 Inc. (now part of Covidien, Mansfield, MA), and Medtronic, Inc. (Minneapolis, MN).

We were granted that access to patient line item data, and we culled through data from more than 600 patients. Of particular interest to us were patients who had experienced improvement in blood pressure after stenting, so much of our evaluation focused on these patients. We had access to the patients' blood

pressures before and after the procedure, and through 1-year follow-up.

How would you summarize the primary endpoints that were ultimately proposed?

We determined there should be two coprimary endpoints—one for safety and one for effectiveness. Safety would evaluate duplex ultrasound-defined restenosis rates at 9 months, and effectiveness would focus on reduction of systolic blood pressure at 9 months. We proposed these to the FDA, at which point it was discussed that if a trial were to meet or beat the hypertension performance goal, the device would be eligible for treatment of hypertension labeling. If the hypertension endpoint were not met, but the safety endpoint was, the device could not be associated with claims of improving hypertension. But, it could be stated that it was at least noninferior to renal bare-metal stenting in a previous cohort of patients.

As such, we proposed the necessary benchmark for hypertension claims, without, we believe, adding risk to industry if they elected to take on this clinical endpoint.

What brought about your initial interest in seeking blood pressure response as an individual endpoint and labeling indication?

The way in which doctors viewed the need for stenting in the renal arteries had begun to evolve from more than just the treatment of an unspecified renal artery stenosis to an increased focus on resistant hypertension in the presence of a high-grade stenosis. Some parties in industry began to rethink the way a renal artery trial should be conducted, and physicians became introspective as to how they should ideally participate. We saw this increased focus on hypertension in the recently reported HERCULES trial (Abbott Vascular, Santa Clara, CA), which included many patients who were truly hypertensive. Importantly, this evolutionary thinking seemed to be accelerated by emerging trials in the renal denervation arena, which included extremely hypertensive patients on multiple medications.

American interventionists are now appreciating the global buzz surrounding renal denervation. The focus is increasingly on appropriate patient selection and appropriate aggressive medical therapy and the importance of collaboration with hypertension specialists and nephrologists. Ultimately, the renal OPG is clearly more than just a statistical tool and a single-arm trial comparator to establish superiority in blood pressure control. Understanding that in 2009, the Centers for Medicare & Medicaid Services (CMS) strongly considered *not* reimbursing for the procedure due to a lack of compelling data establishing its effectiveness, this OPG will hopefully focus the efforts of the physician community and industry to provide relevant patient-centric metrics, improve patient care, and continue reimbursement.

Did your review of the data turn up anything particularly surprising, either positively or negatively, about these patients?

We found that many of the patients enrolled in these trials were not particularly hypertensive, and some had only moderate stenoses measuring little more than 50%. They were also on a wide variety of medications on suboptimal doses. After evaluating 600 study patients to determine who would meet what we felt was an appropriate endpoint for blood pressure (≥ 155 mm Hg on three medications of maximum tolerable doses, one being an ACE inhibitor), we were left with just 286 patients. This was not entirely surprising because in these PMA trials, blood pressure was a secondary endpoint. But, for renal stenting to be on-label for a blood pressure improvement endpoint, we believed that this was the population that should included.

Please tell us about the decision to require a medical documentation period before establishing baseline values.

The OPG requires the inclusion of a 2-week medical observational period before intervention to ensure that patients are truly hypertensive, and excluding factors such as patient noncompliance and the "White Coat Syndrome," which is the possibility of a patient's blood pressure heightening due to any anxiety or aggravation associated with being in a doctor's office. Patients may also experience regression to the mean by virtue of participation in such trials where multiple blood pressures are taken. There is, of course, also variability in blood pressure measurement methods.

Although the variability is that all these factors may not be completely eliminated by requiring this observation period, we believed that ensuring patient medical compliance, standardizing the blood pressure assessment method (three readings on two separate occasions), and meeting the minimal definition of resistant hypertension, would greatly improve the rigor of the trial and assist in identifying the patient most likely to benefit from the stent procedure. All of this gets back to the point of refocusing physicians on the question of who really are the best patients, while also emphasizing the aggressive treatment of resistant hypertension.

To what degree does the application of these OPG make it more difficult to enroll patients, as well as to show favorable safety and efficacy of a renal stent than a trial conducted without them?

I don't necessarily think it makes it more difficult, and I'll explain why. This OPG does challenge doctors and industry

(Continued on page 97)

(Rocha-Singh, continued from page 66)
to apply more rigor to the execution of these trials, particularly with regard to appropriate patient selection criteria. Renal stenting is, for the most part, associated with a low complication rate. But, it is nonetheless an expensive procedure, the efficacy of which should be justified. Insurers and CMS are looking at renal stenting with increased scrutiny, and reimbursement is already being limited in some cases. Most clinicians agree that this procedure does have value; it is up to us to continue to prove it, and in which patients.

Some may initially feel that this will cause higher screening failure rates and therefore make these trials more difficult and expensive to complete. But, in the larger picture of the goals of the trial and the procedure itself, the OPG facilitate appropriate identification of patients and accurate assessment of outcomes. The majority of patients who do not meet these criteria should not be enrolled in stenting trials. The choice is to classify the patient as a medical screen failure rather than place a renal stent inappropriately, only to see no improvement in blood pressure control.

How have the OPG been received by physicians and industry?

Atrium Medical Corporation (Hudson, NH) will be the first company to adopt the OPG, applying it to their ARTISAN trial evaluating their covered renal stent in the renal arteries. That trial should be getting underway soon. Industry overall may feel that the OPG is challenging, but they have listened with interest. On the physician side, I think many will embrace the opportunity to produce more meaningful data. Again, the OPG reflect a certain evolution in our overall understanding of renovascular hypertension, resistant hypertension, and the clinical trial setting needed to evaluate and validate this procedure—both in our eyes and the eyes of the insurers and Medicare. Rather than threaten the practice of renal stenting, the OPG may actually help to save it. ■

Krishna J. Rocha-Singh, MD, FACC, FAHA, FSCAI, FSVM, is Medical Director, Prairie Research and Education Cooperative, St. John's Hospital in Springfield, Illinois. He has disclosed that he is a consultant to Medtronic, Inc., Vessix Vascular, Inc., ev3 Inc., and CardioSonic Ltd.. Dr. Rocha-Singh may be reached at ksingh@prairieheart.com.

1. Rocha-Singh KJ, Novack V, Pencina M, et al. Objective performance goals of safety and blood pressure efficacy for clinical trials of renal artery bare metal stents in hypertensive patients with atherosclerotic renal artery stenosis. Catheter Cardiovasc Interv. 2011;78:779-789.