

Evaluation of Renal Artery Stenting

Clinical study design, nonclinical testing, and regulatory considerations for appropriate use of this technology.

BY KENNETH J. CAVANAUGH, JR, PhD

The views and opinions presented in this article are those of the author and do not necessarily reflect those of the US FDA, the US Department of Health and Human Services, or the Public Health Service.

Stenosis of one or both renal arteries can lead to hypoperfusion of the downstream kidney(s), which is believed to exacerbate pre-existing conditions such as hypertension, left ventricular dysfunction, and renal dysfunction, or lead to the onset of new comorbidities.¹ Depending on several factors, including the etiology of the stenosis, the location of the lesion, and the comorbidities of the patient, the available treatment options may include medical therapy, surgical bypass, balloon angioplasty, and renal artery stenting (RAS). The last option has been aggressively adopted by many interventional physicians, and the clinical community is becoming increasingly interested in learning more about the specific risks and benefits of RAS. This article presents an overview of the current regulatory and clinical environment for renal artery stent systems and identifies some of the key challenges that must be overcome to maximize our understanding of the safety and effectiveness of these potentially life-saving devices.

REGULATION OF RENAL ARTERY STENTS

As with all coronary and peripheral vascular stent systems, the FDA has classified renal stents as Class III devices due to their relative complexity and the high level of risk they pose to the patient. Marketing of a renal stent system in the US requires FDA approval of a pre-market approval (PMA) application, in which the applicant must demonstrate reasonable assurance of safety and effectiveness for their device when used to treat the indicated patient population. Both clinical and nonclinical (using benchtop and animal models) evaluations are typically used to support a safety and effectiveness claim for these devices. Because

renal artery stents are significant-risk devices, clinical data are obtained under an investigational device exemption (IDE) application, which allows a clinical study to be conducted using a device that is not approved for marketing in the US or a device that has been approved for a different indication.² If the clinical study is conducted outside the US, an IDE is not needed. Regardless of where the study is conducted, any clinical data used to support a marketing application should be of a sufficiently high level of evidence such that valid conclusions can be drawn from the results; anecdotal evidence or case studies generally are not adequate.

There are currently two vascular stents approved for RAS—the Cordis Palmaz Balloon Expandable Stent (Cordis Corporation, a Johnson & Johnson Company, Miami, FL) and the Medtronic Bridge Extra Support Stent (Medtronic, Inc., Minneapolis, MN). Both of these systems were approved in 2002 for the treatment of patients who had previously undergone failed or suboptimal balloon angioplasty of atherosclerotic renal artery lesions located within 1 cm of the aortorenal border. Although the results of some published studies suggest that RAS may ameliorate hypertension and retard the decline in renal function in some patients,³ no renal stents have been approved as a primary treatment option for atherosclerotic lesions.

No renal stents have yet been approved for the treatment of renal artery stenosis resulting from fibromuscular dysplasia. These cases account for approximately 10% of all instances of renal artery stenosis, typically occurring in a younger, female population and are more often located distally within the renal artery than are atherosclerotic lesions.⁴ Treatment of these stenoses is usually performed using balloon angioplasty or surgery, if necessary.

CURRENT CHALLENGES FOR RENAL ARTERY STENT REGULATION

As with most complex medical devices used to treat a complicated disease state, the evaluation of the safety and

effectiveness of renal artery stents can be challenging. The following paragraphs describe some of the key challenges, clinical and nonclinical, involved in evaluating these devices.

Off-Label Use

A recent search of the FDA's publicly available Manufacturer and User Facility Device Experience (MAUDE) database for medical device adverse event reporting suggests that virtually all of the renal stenting procedures currently conducted in the US are performed using stents not indicated for use in the renal vasculature, most commonly including biliary stents. Biliary stents are Class II devices under the FDA's risk-based classification system⁵ and are marketed under the premarket notification (510[k]) pathway. Biliary stents are not indicated for use in any part of the vasculature (unless a separate PMA has been approved for such use) and are typically indicated only for palliative treatment of malignant neoplasms in the biliary trees of patients with terminal cancer. As a result of the risk/benefit profile for these patients, marketing clearance under 510(k) requires minimal evaluation of long-term performance characteristics such as stent durability. Clinical data are only provided in unusual cases and, for a biliary stent, would be unrelated to renal artery stenosis.

Because the FDA regulates the marketing of medical devices, manufacturers or study sponsors who promote a device to be safe and effective for an unapproved use can be subject to regulatory and/or legal action. However, the FDA does not regulate the practice of medicine and therefore generally does not penalize clinicians for treating patients in an off-label manner when they are acting in accordance with what they believe is best for the patient.⁶ Nevertheless, off-label use of devices for RAS can subject the patient to unknown risks because the safety and effectiveness of the devices, when used to treat renal artery stenosis, have not been adequately evaluated. Potential procedural adverse events that can result from such use are vascular trauma, such as dissections and perforations, and embolization of air bubbles from the delivery system or particulates from the lesion. Longer-term adverse effects may include stent fracture, additional particulate embolization, and restenosis. The incidence and clinical impact of these events is difficult to fully appreciate due to the lack of well-designed clinical studies intended to evaluate RAS. In addition, enrollment in such studies is hindered by the large amount of off-label use, creating a cycle that must be broken if we are to learn more about the safety and effectiveness of RAS.

It is important to keep in mind that every patient treated in an off-label manner is one less patient available for enrollment in a renal stenting study. Although physi-

cians must treat patients with the best interests of the patients in mind, it is also important to emphasize that both clinicians and patients would benefit from learning more about the safety and effectiveness of these devices and of RAS in general because very little is known and much is assumed. One way to accomplish both goals is to conduct an appropriately designed clinical study.

Clinical Study Design

A RAS clinical study should be designed to ensure that it will result in valid conclusions regarding the performance of the device studied. Based on the principles of evidence-based medicine, a randomized, controlled trial (RCT) comparing clinical outcomes from RAS to those resulting from optimal medical therapy is well-suited to support a new indication, such as primary RAS. Although this type of study has associated enrollment challenges as described in the preceding section, the design of such a study could inherently minimize the influence of potentially confounding factors, such as treatment bias. Depending on the study size and the enrolled patient population, an RCT would also facilitate the identification by subgroup analyses of patient populations who would benefit most from RAS. Completion of RCTs with sufficient statistical power would help to address many of the unanswered questions regarding the clinical outcomes and appropriateness of RAS.

Single-arm clinical studies are also feasible and may be easier to conduct, although the clinical indications supported by such a study may be narrower than those obtained with an RCT. For example, single-arm, premarket clinical studies were used to support the PMAs for both renal artery stents approved by the FDA for adjunctive use in the event of failed or suboptimal balloon angioplasty, although such provisional stenting is not currently representative of real-world RAS. The use of single-arm studies to support a more clinically relevant primary stenting indication is hindered by several factors. The main challenge is the need to identify an appropriate control population or objective performance criteria for comparisons of safety and effectiveness. A related concern is the need to account for the progress of the underlying disease, which, in a double-arm study, would presumably affect both groups equally and therefore be inherently accounted for. In addition, the specific patient population to be studied would need to be selected carefully due to the narrow indication such a study would support. Potential study sponsors should work interactively with the FDA to establish an appropriate single-arm study designed to support a clinically meaningful indication.

An additional level of complexity is provided by the growing interest in the use of embolic protection devices

during renal intervention. No devices are currently marketed with this indication, although currently available embolic protection devices indicated for use in carotid arteries and saphenous vein bypass grafts are used off-label in this manner. Potential study sponsors are encouraged to consult with the FDA regarding the design of studies using embolic protection devices until further recommendations are available.

Nonclinical Testing

Clinical data are not the only predictors of RAS performance. Nonclinical assessments provide valuable information regarding device safety and performance limits without many of the constraints and variability associated with human studies. This is especially true of stent durability assessment, by which an implanted stent is subjected to repetitive forces of known physiological relevance to determine whether the stent will fracture during its anticipated implant life. The FDA 2005 guidance document on nonclinical testing for intravascular stents provides recommendations on how such an evaluation might be most appropriately conducted.⁷

Meaningful data may be obtained by modeling not only the magnitude of the clinically anticipated loads, but also the direction, orientation, and location of these applied loads. All target arteries for stenting are subject to various degrees of cyclic radial deformation due to pulsatile blood flow, but individual arteries may also be subject to specific nonradial loads due to significant internal movements or external deformations. For the renal arteries, it has been previously shown that respiration-induced displacement of the kidneys results in significant arterial bending,⁸ and other types of loads may also be present. According to the embolic protection devices FDA 2005 guidance document on nonclinical testing for intravascular stents, a valid durability assessment should incorporate all possible loading conditions present in the indicated arterial bed, and the results of this test and of any associated fatigue analyses should demonstrate an acceptable safety factor for the durability of the device based on its anticipated clinical use.⁷

Animal studies provide a similarly unique opportunity for device evaluation due to their ability to permit safety assessment prior to human implantation and to provide gross pathology and histopathology data not available from living patients. Because of the known morphological differences among vessels and their effects on the vascular tissue response to stent placement,⁹ the most compelling safety data for renal artery stents might be obtained from animal studies conducted in the renal artery, even if safety data from other vascular beds using the same device are available. In such studies, it would be beneficial to exam-

ine the stented region for evidence of injury and healing. In addition, the kidney downstream of the stented region could be assessed using pathological methods, *in situ* imaging, and/or metabolic markers to determine whether stent delivery or implantation results in renal dysfunction. For all assessments, appropriate time points would best be identified prospectively. A persuasive and comprehensive animal study regimen might incorporate a long-term assessment period, such as 6 months. Although *in vivo* data gathered over a shorter period may be sufficient to indicate an acceptable device safety profile, it is nearly impossible to know this ahead of time; therefore, conducting a longer study is a more conservative option in case the shorter-term data show inadequate tissue healing that resolves acceptably at a later time point. A long-term study may also identify delayed chronic effects such as materials-mediated nephritis or other undesirable outcomes, which can require up to 1 year to fully assess in some animal models.^{10,11}

SUMMARY

RAS offers the opportunity for improved outcomes and quality of life for many patients. However, in order for this technology to be used most appropriately, we must work to better characterize the performance of the device and identify the patient populations that would benefit from its use. Consideration of the issues presented in this article may assist device manufacturers and study sponsors with proper formulation and completion of these evaluations. Those working in this field are encouraged to consult with the FDA throughout device development and clinical investigation. ■

Kenneth J. Cavanaugh, Jr, PhD, is a Regulatory Review Scientist with the US FDA Center for Devices and Radiological Health in Rockville, Maryland. He may be reached at (301) 443-8517, ext. 170; kenneth.cavanaugh@fda.hhs.gov.

1. Zeller T. Renal artery stenosis: epidemiology, clinical manifestation, and percutaneous endovascular therapy. *J Interv Cardiol.* 2005;18:497-506.
2. Abel DB. Investigational device exemptions. *Endovasc Today.* 2003;2:51-52.
3. White CJ. Catheter-based therapy for atherosclerotic renal artery stenosis. *Circulation.* 2006;113:1464-1473.
4. Cheung CM, Hegarty J, Kalra PA. Dilemmas in the management of renal artery stenosis. *Br Med Bull.* 2005;73:35-55.
5. Abel DB. Premarket approval and premarket notification. *Endovasc Today.* 2004;3:53-54.
6. Abel DB. Off-label medical device use. *Endovasc Today.* 2003;2:60-61.
7. Guidance for industry and FDA staff: non-clinical tests and recommended labeling for intravascular stents and associated delivery systems. January 13, 2005. <http://www.fda.gov/cdrh/ode/guidance/1545.pdf>.
8. Draney MT, Zarins CK, Taylor CA. Three-dimensional analysis of renal artery bending motion during respiration. *J Endovasc Ther.* 2005;12:380-386.
9. Fawcett DW. *A Textbook of Histology*, 11th ed. Philadelphia, PA: W.B. Saunders Company; 1986:367-380.
10. Koch M, Joosten SA, Mengel M, et al. Adoptive transfer of primed CD4+ T-lymphocytes induces pattern of chronic allograft nephropathy in a nude rat model. *Transplantation.* 2005;79:753-761.
11. Goluszko P, Moseley SL, Truong LD, et al. Development of experimental model of chronic pyelonephritis with *Escherichia coli* O75:K5:H-bearing Dr fimbriae: mutation in the dra region prevented tubulointerstitial nephritis. *J Clin Invest.* 1997;99:1662-1672.