FDA INSIGHTS

Evaluating Thoracic Endovascular Grafts

There has been recent progress in the evaluation of thoracic endovascular grafts—and not just for the treatment of aneurysms.

BY DOROTHY B. ABEL

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

THORACIC REGULATORY EXPERIENCE

The FDA has approved three endovascular grafts for the treatment of descending thoracic aortic aneurysms (TAAs) in contrast to six for the treatment of abdominal aortic aneurysms (AAAs). All of the approved thoracic endovascular grafts have similar indications, that is, for the treatment of aneurysms of the descending thoracic aorta in patients with suitable anatomy for endovascular repair. The more recently approved devices are also indicated for the treatment of saccular aneurysms and/or penetrating ulcers, because these indications were included in the clinical studies of these devices. Table 1 provides a list of the currently approved endovascular grafts with their respective general indications. Different levels of detail for the definition of suitable anatomy are included in the indications for use statements for these devices. These details are not included in the table because they are not significant for the purposes of this article.

In short, there has been less experience in regulating thoracic endovascular grafts as compared to AAA devices, and there have not been any devices approved for treatment of transections or dissections.

REPORTED PROBLEMS WITH THORACIC ENDOVASCULAR GRAFTS

Understandably, some of the types and incidence of problems reported for thoracic endovascular grafts in the literature and at conferences have been different from those reported for AAA devices. Some of the more common problems reported for thoracic devices have included the following:

- Poor apposition to the vessel wall
- Maldeployment (eg, stent flip)
- Aortic perforation
- Infolding
- Retrograde dissection
- Migration
- Type III endoleak

Many of these events tend to be associated with treatment of transections or dissections or implantation of the device in the aortic arch—all situations that would be considered off-label use in the United States.

OFF-LABEL USE

Information regarding off-label use was provided in previous issues of this publication.[1,2] Subsequently, an article coauthored by a group from the Center for Devices and Radiological Health at the FDA was published in the *Journal of Vascular and Interventional Radiology*.[3] This article defines off-label use as follows:

> A device's labeling (including the indications for use) is approved by the FDA on the basis of data submitted by the manufacturer. The use of a device for an indication other than that in the cleared or approved labeling is referred to as "off-label use."

We consider the labeling important to communicate information relevant to the specified indications for use. If a device is used off-label, the information in the label may or may not be relevant to the clinician in using the device to treat the patient. As such, it would be preferable to have sponsors conduct studies that could be used to support labeling their devices for the indications for which their devices are being used. For example, as the marketed thoracic endovascular grafts are indicated for treatment of aneurysms, but are being used to treat dis-

TABLE 1. APPROVED AORTIC ENDOVASCULAR GRAFTS

Graft	Indication
Abdominal	
Cook Zenith AAA Endovascular Graft (Cook Medical, Bloomington, IN)	Endovascular treatment of patients with abdominal aortic or aortoiliac aneurysms having morphology suitable for endovascular repair
Endologix Powerlink System for Abdominal Aortic Aneurysm (Endologix, Inc., Irvine, CA)	Endovascular treatment in patients with AAA for patients with suitable aneurysm morphology for endovascular repair
Guidant Ancure Endograft System (Guidant, Inc., Indianapolis, IN)	Endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms in patients having [appropriate anatomy]
Gore Excluder AAA Endoprosthesis (W. L. Gore & Associates, Flagstaff, AZ)	To exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal AAA disease and who have appropriate anatomy
Medtronic AneuRx Stent Graft System (Medtronic, Inc., Minneapolis, MN)	Endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms having [appropriate anatomy]
Medtronic Talent Abdominal Stent Graft System (Medtronic, Inc.)	Endovascular treatment of abdominal aortic aneurysms with or without iliac involvement having [appropriate anatomy]
Thoracic	
Cook Zenith TX2 TAA Endovascular Graft (Cook Medical)	Endovascular treatment of patients with aneurysms or ulcers of the descending thoracic aorta having vascular morphology suitable for endovascular repair
Gore Tag Thoracic Endoprosthesis (W. L. Gore & Associates)	Endovascular repair of aneurysms of the descending thoracic aorta in patients who have appropriate anatomy
Medtronic Talent Thoracic Stent Graft System (Medtronic, Inc.)	Endovascular repair of fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta in patients having appropriate anatomy

sections, manufacturers should consider conducting appropriate clinical studies to support changes in the labeling to include treatment of dissections.

CURRENT EFFORTS

In October 2008, the FDA provided the venue for a meeting hosted by the Society for Vascular Surgery and attended by manufacturers, clinicians, and FDA staff to discuss the challenges in evaluating nonaneurysmal indications. During this meeting, the participants discussed the possibility of using a performance goal, based on 30-day mortality, to serve as the primary endpoint for a study of endovascular grafts intended to treat acute complicated type B aortic dissections. Since this meeting, several societies (the Society for Vascular Surgery, the Society for Interventional Radiology, the Society for Thoracic Surgery, and the American Association for Thoracic Surgery) have been working together to capture previously collected investigational device exemption data for patients treated with endovascular grafts for an acute complicated type B aortic dissection. This registry may help the sponsor of a clinical study in establishing a reasonable performance goal for safety for this indication; however, the performance goal could also be supported by literature for medical and open surgical management. The goal would be established and justified by the clinical study sponsor by determining the reported rate(s) and setting a goal considering an acceptable difference from the reported rate(s) due to variability or anticipated differences in patient populations. This comparison to the 30-day mortality-based performance goal could be enhanced by monitoring the safety and effectiveness of the device over time in the clinical studies. Additional comparison information for these other outcomes of interest may also be captured in the registry.

A similar concept for capturing information for use in the design of clinical studies of the use of endovascular grafts for the treatment of traumatic transections has also been discussed. The registry may be expanded to include patients treated for traumatic transections, and this information may be helpful for comparison in clinical studies for this indication. The use of descriptive statistics if the device already has an aneurysm indication may be possible because the effectiveness of the device for treatment of a transection would likely be no worse than that for an

aneurysm, provided no device-related issues were identified.

This registry will not be expanded to capture information regarding patients treated for aneurysms as there are more data available in the literature for this indication as compared to the others.

Regarding the long list of other potential lesion types that could be treated using endovascular grafts, the participants at the October meeting indicated that each lesion type could not be evaluated in separate studies, but it may be beneficial for a sponsor to capture the treatment of other lesions in a separate study arm.

POSTAPPROVAL STUDIES AND POSTMARKET SURVEILLANCE

As a reminder, postapproval studies are an important mechanism for the continued evaluation of endovascular grafts after premarket approval. There have been postapproval study requirements for all of the devices listed in Table 1, including the need to collect and report 5-year clinical study data. In addition to planning to demonstrate the safety and effectiveness of an endovascular graft for the treatment of various thoracic lesions, a manufacturer should be prepared to work with the Epidemiology Branch in the Office of Surveillance and Biometrics at FDA to design an appropriate postapproval study.

Additionally, after a device is approved for any indication, a manufacturer is required per the conditions of approval for the device to:

> …, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:
>
> 1. May have caused or contributed to a death or serious injury; or
> 2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

This Medical Device Reporting (MDR) applies to use of the device both on- and off-label. As such, the system may be helpful in capturing information on problems associated with the real-world use of thoracic endovascular grafts. Physicians should help with this effort by providing event reports to manufacturers and FDA, when appropriate.

Additional information on MDR is available at: http://www.fda.gov/cdrh/devadvice/351.html.

AN ADDITIONAL ENDOVASCULAR GRAFT CHALLENGE

Regardless of the indication statement for an endovascular graft, there is a continuing problem with obtaining what has been considered adequate imaging over time to monitor these devices. In addition, this imaging is associated with radiation exposure. Although there have been several publications suggesting the use of alternative forms of imaging for follow-up, few prospectively designed analyses have been done to validate the alternative imaging protocols. Perhaps in future clinical studies of endovascular grafts, it would be helpful to incorporate concurrent evaluations of follow-up strategies. For example, it may be of benefit to attempt to prospectively identify patients for whom early or later follow-up computed tomography scans could be waived based on prior demonstrations of effective exclusion of the lesion and other favorable conditions, such as reasonably long and straight landing zone coverage by the endovascular graft. Although such analyses may not be necessary to demonstrate the safety and effectiveness of the device to support a marketing approval, this information may be of use to

the medical community in identifying appropriate follow-up plans.

FINAL COMMENTS

At FDA, our goal is to have properly labeled devices available to clinicians to provide reasonable treatment options for patients. At this time, there are no endovascular grafts with broad indications for the treatment of thoracic lesions in the United States. Since it may not be possible to conduct statistically based studies for each individual indication, it is unclear whether a broad indication may be supported for these devices, possibly using data available for the treatment of aneurysms, transection, and dissection. We are continuing to work with the medical community to identify appropriate strategies to evaluate thoracic endovascular grafts, which should lead to improved labeling for these devices. ■

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COMMENTARY

Alternative Approval Mechanisms

BY RODNEY WHITE, MD

Thoracic aortic endografts have been shown in preliminary investigations to treat indications beyond thoracic aortic aneurysms and have demonstrated a significant reduction in procedural morbidity and mortality, including paraplegia. Of particular interest is the role of these devices in redefining the treatment of aortic dissections and traumatic transections. Because of the apparent benefit in these critical indications, the Food and Drug Administration (FDA) has wisely agreed to the development of alternative study designs, avoiding the need for the collection of concurrent control data, to expedite broader-labeled indications for appropriately designed devices.

In response to the suggestion that the FDA would consider alternative approval mechanisms, the Society for Vascular Surgery (SVS) Outcomes Committee in collaboration with the Society for Vascular and Interventional Radiology (SIR), the Society for Thoracic Surgery (STS), and the American Association for Thoracic Society (AATS) have established a database that collects data using standardized definitions from studies that were performed using FDA-approved Investigational Device Exemption (IDE) protocols utilizing thoracic endografts to treat aortic dissections and traumatic transections. The data collection was funded solely by the academic societies. Extensive analysis of data from 5 institutions (Arizona Heart Institute, Cleveland Clinic Foundation, Harbor-UCLA Medical Center, Stanford University, and Union Memorial Hospital) that have FDA-approved single-center IDE protocols to evaluate the utility of thoracic endografts for these indications has been completed. The data collection and analysis was performed by the SVS administration and the New England Research Institutes, Inc. to create Master Access Files available through the SVS that has been submitted to the FDA and can be used to define a performance goal by manufacturers performing studies that broaden the indications for thoracic endografts.

The first Master Access File has been completed and includes approximately 100 patients who had acute thoracic aortic dissection with malperfusion syndromes, and a second file of approximately 60 patients with acute aortic transections is anticipated to be completed by the end of August.

Using this mechanism, the results of contemporary data using thoracic endografts for acute aortic dissections and traumatic transections from an IDE-level dataset can be complimented by other sources of available data regarding this therapy and potentially provide comparative information that can be used to expedite studies and provide approval for devices in a cost-effective and responsible manner in the current "off-label" environment. ■

For information regarding the Master Access Files, contact Sarah Murphy, Assistant Director, Socioeconomics and Professional Affairs, Society for Vascular Surgery, 633 North Saint Clair Street, 24th Floor, Chicago, Illinois 60611. Ms. Murphy may be reached at (312) 334-2305; smurphy@vascularsociety.org.

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