FDA Perspectives on Aortic Reinterventions

What is the gold standard for follow-up, and what makes good follow-up practices?

With Rohini Retarekar, PhD; Robert Lee, MD; Ronald Fairman, MD; and Carmen Gacchina Johnson, PhD

One question we are exploring in this edition of *Endovascular Today* is the shift in the discussion surrounding reintervention after abdominal aortic aneurysm (AAA) repair given that recent data suggest reinterventions improve survival long term and may just be a marker of adequate follow-up. What is the FDA's current view on reinterventions? Does the agency consider the need for reintervention a failure, or does it largely imply that higher follow-up compliance equating to a larger number of reinterventions could be due to factors that go beyond device effectiveness failure? Are there any notable changes in the Agency's thinking regarding reinterventions?

Aortic disease is complex and dynamic, and it warrants lifelong surveillance regardless of the treatment method. Longer-term follow-up of aortic endovascular stent grafts shows that reinterventions continue to occur over time, and oftentimes, they are deemed necessary by the treating physician to ensure that the benefit of the medical device is not lost.[1] Reinterventions performed after AAA repair are one consideration of many that the Agency evaluates when assessing the benefits and risks of a given device. Of particular interest to FDA is the reintervention reason and type.[2] The overall rate of reinterventions and their outcomes can help inform the overall benefit/risk profile of the device.

In all FDA premarket approval (PMA) application decisions, the benefits and risks of the device are carefully considered,[3] including information pertaining to reintervention. For instance, for novel technology that fulfills an unmet need, an elevated rate of reinterventions may be considered an acceptable risk if the benefits of using the device are profound (eg, reduction in morbidity and mortality compared to other available treatment options, device meets an unmet need). For other scenarios wherein there may be several established treatment options available that do not require reinterventions and a new device does not provide notable benefit, there may be less tolerance for accepting the risk of reinterventions. In making this benefit/risk evaluation, the reason and timepoint for reintervention are also important. For example, reinterventions performed to address device integrity events or failures of the device to function as intended are viewed differently than reinterventions associated with disease progression. Other factors also come into play, such as the nature of reinterventions. A treatment approach wherein the majority of reinterventions are outpatient procedures using minimally invasive techniques with good outcomes would be viewed more favorably by all stakeholders (physicians, patients, and FDA) as compared with those that are associated with increased morbidity and mortality risks and need inpatient care. The outcome of reinterventions is also critical (eg, successful resolution of issue, acknowledgment if the problem remains unresolved after multiple reintervention attempts, morbidity and mortality associated with the reinterventions). It is also important to consider patient perspectives, such as desire for minimally invasive treatment options, need for lifelong follow-up, and awareness of the potential need for reinterventions. A key part of FDA's role in reviewing PMAs for aortic devices is ensuring that physicians and patients are provided clear device-specific safety and effectiveness data to inform them of both expected outcomes and need for reinterventions (eg, via patient labeling and instructions for use [IFU]).

What are FDA's views on the importance of clearly defining reinterventions, the need for reintervention, and reintervention rates?

Use of standardized definitions for reinterventions and clear documentation of the reason, timepoint, type, frequency, and outcome of each reintervention is helpful

to all stakeholders. For example, it can allow FDA to evaluate outcomes across different treatment options while assessing the benefit/risk profile of a device, it can allow physicians to make informed treatment decisions for their patients, and it can allow patients to have a balanced understanding of the device-specific risks and benefits. FDA acknowledges that the Society for Vascular Surgery (SVS) publications on reporting standards for endovascular aneurysm repair (EVAR),[4] thoracic endovascular aortic repair,[5] and complex EVAR involving the renal and mesenteric vessels[6] have helped lead to a more uniform adoption of definitions for reporting.

From a regulatory perspective, what is the current gold standard for follow-up after EVAR? What are some of the essential elements?

Pivotal study designs intended to support regulatory approval typically include 5-year follow-up of study patients with imaging at appropriate intervals (eg, CT scans at 30 days, 6 months, 1 year, and annually thereafter through 5 years). To support PMA approval of endovascular aortic stent grafts, complete 1-year follow-up with adequate imaging to evaluate all critical parameters is generally provided. If the 1-year data support a favorable benefit/risk profile of the device, 5-year follow-up data on pivotal study patients has been collected postmarket, and the results are shared in annual clinical updates and an IFU update once the study is complete.[7]

When the postmarket surveillance of EVAR devices was discussed at the 2021 Circulatory System Devices Panel meeting, the panel members recommended postmarket follow-up through 10 years.[2] The recommendation has been adopted by the medical device industry, as noted through new postapproval enrollment studies of recently approved endovascular and hybrid stent grafts,[8-10] which are intended to address questions about the real-world performance of novel medical devices or when there are specific questions about the performance of approved devices in the longer term.

FDA continues to emphasize to physicians and other health care providers the critical importance of lifelong surveillance, including imaging, for patients with EVAR.[11] In real-world use of EVAR devices, physicians may find device-specific recommendations (eg, IFU recommendations, FDA safety communications) and the SVS clinical practice guidelines helpful for follow-up of patients.

What efforts might result in improved patient compliance in follow-up?

Maintaining patient follow-up compliance is a known challenge especially evident in postmarket studies and real-world surveillance of medical devices.[7] As discussed at the 2021 panel meeting,[2] improved follow-up compliance for EVAR starts with appropriate patient selection and clear communication from physicians that regular clinical follow-up and imaging are critical if EVAR is performed. This essential element is typically reflected in patient labeling and would benefit if clearly reinforced as part of the informed consent process.

Successful long-term follow-up has been achieved by committed device manufacturers and physicians working together, engaged study coordinators, and use of optimized follow-up strategies (eg, telemedicine, remote imaging). For example, data published on mid- and long-term outcomes from some manufacturer-sponsored investigational device exemptions (IDEs)[12] and postapproval studies[13] show that high rates of follow-up compliance can be maintained in the longer term (eg, 5 years) when there are focused efforts to achieve this goal.

FDA is not committed to any one approach in terms of maximizing postmarket follow-up compliance and is ready to engage with all stakeholders regarding strategies to improve follow-up and data collection over the longer term.

What are important considerations for regulatory use of clinical data?

When clinical data are used for regulatory decision-making, the relevance and reliability of that data are considered carefully by FDA. As it relates to real-world evidence, the FDA guidance document "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices"[14] outlines important considerations. Data quality control is essential for providing confidence in the reliability of data, and there are several important factors outlined in the guidance to consider, including standardizing procedures to ensure the use of uniform and systematic methods for collecting and cleaning data.

At the 2021 panel meeting, potential plans for long-term EVAR postmarket surveillance studies were discussed. Are there any updates regarding these studies and what they will comprise?

Since the panel meeting, FDA has participated in collaborative efforts led by industry, with engagement from multidisciplinary professional societies, and representatives from existing EVAR data collection infrastructure (eg, SVS Vascular Quality Initiative and Kaiser Permanente) regarding the development/strengthening of infrastructure that would allow for robust postmarket surveillance of EVAR devices.[15,16] This collaboration has aligned on specific elements that are critical for this effort. These include collection of device-specific clinical and imaging (site-reported)

outcomes of interest through 10 years with an ability for further assessment on an as-needed basis (eg, core laboratory evaluation of imaging in case of a safety signal). Data collection will focus on including a diverse patient population (particularly underrepresented groups), various institution types (eg, urban, rural, academic, private), a wide geographic distribution, disparities in health care utilization, and physicians with a range of EVAR experience.[16,17] FDA is enthusiastic about reaching alignment on the protocol and looks forward to continued collaboration as the improved surveillance is implemented, incorporating learnings from prior surveillance efforts.

How might the extensive sponsor-investigator experience in the endovascular graft space be used to shed light on the issues around reinterventions and patient follow-up? How might new models in real-world evidence collection be incorporated?

There have been several published reports from sponsor-investigator IDEs, particularly those evaluating endovascular devices for treatment of thoracoabdominal aortic disease.[17] The follow-up compliance and treatment outcomes in these IDEs have been exceptional in many cases.[18] Sustaining the longer-term treatment benefit often involves reinterventions. With complex multibranch devices, the potential for device or treatment failure increases, making the need for rigorous follow-up of patients and indicated reinterventions even more critical. The FDA remains committed to working with all stakeholders to translate the enormous learnings from the sponsor-investigator IDE experience to safe and effective commercially available devices for all patients with complex aortic pathology in the United States.

FDA and other stakeholders are interested in obtaining real-world long-term outcomes data. However, it is acknowledged that intensive resources are involved in this type of postmarket data collection, particularly in maintaining a high level of follow-up compliance and collection of imaging data. Therefore, FDA is open to targeted strategies to engage select, yet diverse, sites (eg, in terms of geography, patient demographics, physician experience) committed to the long-term data collection for certain endpoints that may otherwise be challenging to obtain (eg, imaging-based outcomes).

Does FDA have any patient engagement data that provide perspectives on potential need for reintervention versus feelings regarding open surgery?

When making a benefit/risk determination, FDA recognizes that patient perspectives on benefits and risks may include tolerance of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life. FDA acknowledges that patients with aortic pathology may desire less invasive treatment options, even when that means more frequent follow-up and greater need for reinterventions as compared with open repair.[19]

FDA encourages sponsors to include patient preference information in marketing submissions, as noted in the 2016 guidance document, "Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling."[20] FDA also works with industry to develop transparent documents (eg, IFU, patient labeling, Summary of Safety and Effectiveness Data) so that the risks and benefits of a device are clear and can be carefully considered for individual patient circumstances. It remains key that the informed consent process incorporates clear communication from physicians regarding the importance of lifelong surveillance with appropriate imaging and potential need for long-term reinterventions as their patients decide between endovascular or open aortic repair. ■

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Rohini Retarekar, PhD
Team Lead, Vascular and Endovascular Devices Team (VEDT)
Division of Circulatory Support, Structural and Vascular Devices
Office of Cardiovascular Devices
Office of Product Evaluation and Quality
CDRH, US Food and Drug Administration
Silver Spring, Maryland
Disclosures: None.

Ronald Fairman, MD
Medical Officer, Vascular and Endovascular Devices Team (VEDT)
Division of Circulatory Support, Structural and Vascular Devices
Office of Cardiovascular Devices
Office of Product Evaluation and Quality
CDRH, US Food and Drug Administration
Silver Spring, Maryland
Disclosures: None.

Robert Lee, MD
Medical Officer, Vascular and Endovascular Devices Team (VEDT)
Division of Circulatory Support, Structural and Vascular Devices
Office of Cardiovascular Devices
CDRH, US Food and Drug Administration
Silver Spring, Maryland
Disclosures: None.

Carmen Gacchina Johnson, PhD
Assistant Director, Vascular and Endovascular Devices Team (VEDT)
Division of Circulatory Support, Structural and Vascular Devices
Office of Cardiovascular Devices
Office of Product Evaluation and Quality
CDRH, US Food and Drug Administration
Silver Spring, Maryland
carmen.gacchina@fda.hhs.gov
Disclosures: None.