FDA Executive Summary

Circulatory System Devices Advisory Committee Meeting

November 2, 2021

Endologix AFX

Risk of Type III Endoleaks

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1 Introduction

This is FDA's Executive Summary for the Circulatory System Devices Advisory Committee Meeting on the post-market Type III endoleak risk associated with the Endologix AFX Endovascular AAA System (AFX) used for treatment of abdominal aortic aneurysms (AAA). This meeting is being held to review the available information and obtain Advisory Committee input on:

- The totality of data as it relates to the Type III endoleak risk with the Endologix AFX Endovascular AAA System device iterations (AFX with Strata, AFX with Duraply, and AFX2).
- Strategies to mitigate or treat Type III endoleaks in patients with AFX devices.
- Whether the benefits continue to outweigh the risks for the currently available AFX product (AFX2), and whether additional mitigation strategies should be implemented.

The Executive Summary discusses the clinical condition and AAA treatment options, the regulatory history of the Endologix AFX Stent Graft System, a summary of the Type III Endoleak safety signal and the currently available data, current treatment recommendations for managing patients when AAA repair with AFX devices is not successful (i.e., due to Type III endoleak), and options for additional risk mitigations measures. The Advisory Committee's review and discussion of the information will inform the Agency's future actions with regard to this post-market safety concern.

2 Overview of Abdominal Aortic Aneurysms

2.1 Abdominal Aortic Aneurysms

Aneurysmal disease is characterized by structural deterioration of the aortic wall and gradual expansion of the aneurysm sac. As the aneurysm enlarges, the risk of rupture increases, making detection and treatment of aneurysms essential to minimize the risk of mortality.[1]

AAAs (Figure 1A) are the most common aneurysms of the aorta, with more than 90% occurring inferior to the renal arteries (infrarenal AAAs).[2] Risk factors for AAA include obesity, coronary artery disease, hypertension, previous myocardial infarction, and a family history of AAA.[1]

AAAs result in an estimated 10,000 deaths each year in the US, most of which occur in people over the age of 65.[3,4] AAAs are four to six-fold more common in males than in females.[5] The risk of AAA rupture

[1] Hirsch AT, Haskal ZJ, Hertzer NR, et al. "ACC/AHA 2005 Practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines." *Circulation*. 2006, 113(11).
[2] Clouse WD, Cambria, R. P. Complex Aortic Aneurysm: Pararenal, Suprarenal, and Thoracoabdominal. In: Hallett JR, JW. Comprehensive Vascular and Endovascular Surgery: Expert Consult. 2 ed. Philadelphia: Mosby; 2009.
[3] Gillum, Richard F. "Epidemiology of aortic aneurysm in the United States". *Journal of Clinical Epidemiology*. 1995, Vol 48(11).
[4] Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2019 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2019, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/ucd-icd10.html
[5] Christina Villard, Rebecka Hultgren, Abdominal aortic aneurysm: Sex differences, Maturitas, Volume 109, 2018, Pages 63-69, ISSN 0378-5122, https://doi.org/10.1016/j.maturitas.2017.12.012.

is proportional to aneurysm size.[6] Once rupture occurs, death may occur rapidly, with mortality rates as high as 80% to 90%.[7]

2.2 Current Therapies for Abdominal Aortic Aneurysms

There are three treatment options for AAAs: medical management, open surgical repair, and endovascular repair. Selection of the appropriate treatment depends on several factors including aneurysm size, location, and patient risk factors.[8]

2.2.1 Medical Management

Medical management is preferred for patients who are not at high risk of rupture.[6] Patients should be treated to normalize blood pressure and address other atherosclerotic risk factors, such tobacco use, hyperlipidemia and diabetes. Patients with small, asymptomatic aneurysms are monitored for symptoms and periodic imaging studies are performed (most often ultrasound exams) to determine whether sac expansion has progressed to a stage where intervention is indicated.[6]

2.2.2 Open Surgical Repair

Open surgical repair may be offered to patients who are at high risk of aneurysm rupture. The surgical procedure involves aortic exposure via laparotomy or a left retroperitoneal exposure and replacing the aneurysmal section of the aorta with a prosthetic vascular graft, which is usually made of a durable synthetic polymer. The vascular graft is sutured to the native aorta (Figure 1B).

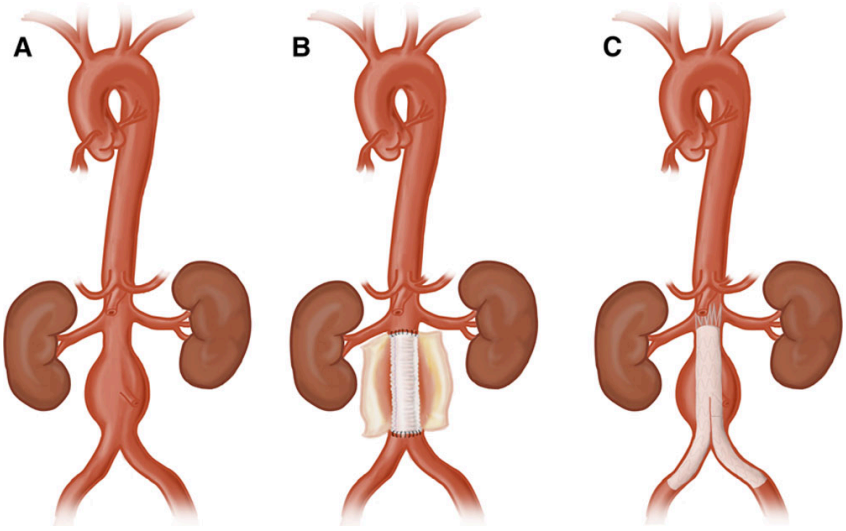


Figure 1: Open and Endovascular Abdominal Aortic Aneurysm (AAA) Repair. A, Unrepaired Infrarenal AAA. B, Open Repair with Tube Graft. C, Endovascular Repair[8]

[6] Chaikof EL, Halman RL, Eskandari MK, et al. "The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm." Journal of Vascular Surgery. 2018, Vol 67(1).
[7] Kent, CK. "Abdominal Aortic Aneurysms". *New England Journal of Medicine*. 2014; 371:2101-2108
[8] Swerdlow NJ, Wu WW, Schermerhorn ML. "Open and Endovascular Management of Aortic Aneurysms." Circulation Research. Vol 124 Issue 4. 2019

2.2.3 Endovascular Aneurysm Repair

Endovascular aneurysm repair (EVAR) is a less invasive alternative to open surgery and may be offered to patients with appropriate anatomic characteristics, such as adequate landing zones proximally in the aorta and distally in the iliac arteries. During the procedure, a catheter is used to deliver a stent-graft system to the desired location. The stent-graft is expanded to provide a conduit to exclude the aneurysm from blood flow (Figure 1C).[8] The objective of EVAR is to depressurize the aneurysm sac, and by excluding aortic blood flow into the aneurysm sac, the pressure in the aneurysm is reduced. Improved long-term mortality is associated with patients who experienced aneurysm sac regression after EVAR compared with those patients that have stabilization or expansion. Continued aneurysm growth after EVAR due to endoleaks is discussed below.

Over the past three decades, EVAR technology advances and the availability of multiple endograft systems, many now in their 3rd or 4th generation, have led to a shift in the elective management of AAAs. By 2015, 83% of elective AAA repairs in the US were performed with EVAR, and EVAR continues to be the most common treatment for AAA repair in the US.[9]

Commercially Available Endovascular Grafts

The endovascular stent graft systems currently approved and marketed in the US for the treatment of infrarenal AAA are shown in Table 1.

*Table 1: AAA endovascular grafts currently marketed in the US**

Sponsor	Device Name in Original PMA	Year of Original PMA Approval	Currently Marketed Iteration[10]
W. L. Gore and Associates, Inc	Excluder AAA Endoprosthesis	2002	Excluder AAA Endoprosthesis
Cook, Inc	Zenith AAA Endovascular Graft	2003	Zenith Flex AAA Endovascular Graft & Zenith Fenestrated AAA Endovascular Graft**
Endologix, LLC	Endologix Powerlink System	2004	AFX2 Endovascular AAA System
Medtronic Vascular	Endurant Stent Graft System	2010	Endurant II & IIs Stent Graft System**
Trivascular, Inc / Endologix, LLC	Ovation Abdominal Stent Graft System**	2013	Alto Abdominal Stent Graft System**
W. L. Gore and Associates, Inc	Excluder Conformable AAA Endoprosthesis	2020	Excluder Conformable AAA Endoprosthesis
Bolton Medical Inc (dba Terumo Aortic)	TREO Abdominal Stent Graft System	2020	TREO Abdominal Stent Graft System

**The Cordis US Corporation Incraft AAA Stent Graft System is PMA approved (2018) but is not yet marketed in the US.*
***These devices have unique device designs and approved indications to treat more challenging proximal anatomies.*

[9] Epidemiology of endovascular and open repair for abdominal aortic aneurysms in the United States from 2004 to 2015 and implications for screening. Dansing KD, Varkevisser RRB, et al. J Vasc Surg 2021;74:414-24.)
[10] US Device Guide: Main Body Grafts. *Endovascular Today*. 2021.

Although the currently available EVAR devices have some similarity in being multicomponent systems constructed using a fabric graft material and a supportive stent framework or skeleton, the specific materials and device designs are unique to each endograft platform. Materials used to fabricate these devices include polytetrafluoroethylene (PTFE) that is manufactured using different processes, polyester (Dacron), stainless steel, nitinol, and cobalt chromium alloy.

Most designs employ stents, barbs, or hooks to help achieve secure active fixation of the bifurcate components. Supporting stents or framework stents may be internal, external, or encased by the graft material. Aortic endografts can be categorized by whether they are designed to deploy and provide a proximal seal in the aorta below or above the level of the renal arteries (infrarenal or suprarenal aorta, respectively). The Cook Zenith Fenestrated endovascular graft is the only marketed device designed to achieve a seal above the renal arteries. Most of the other devices have proximal bare stents to provide transrenal or suprarenal fixation, with the seal zone remaining in the infrarenal aorta. Figure 2 shows the endovascular grafts commercially available to treat AAAs in the US.

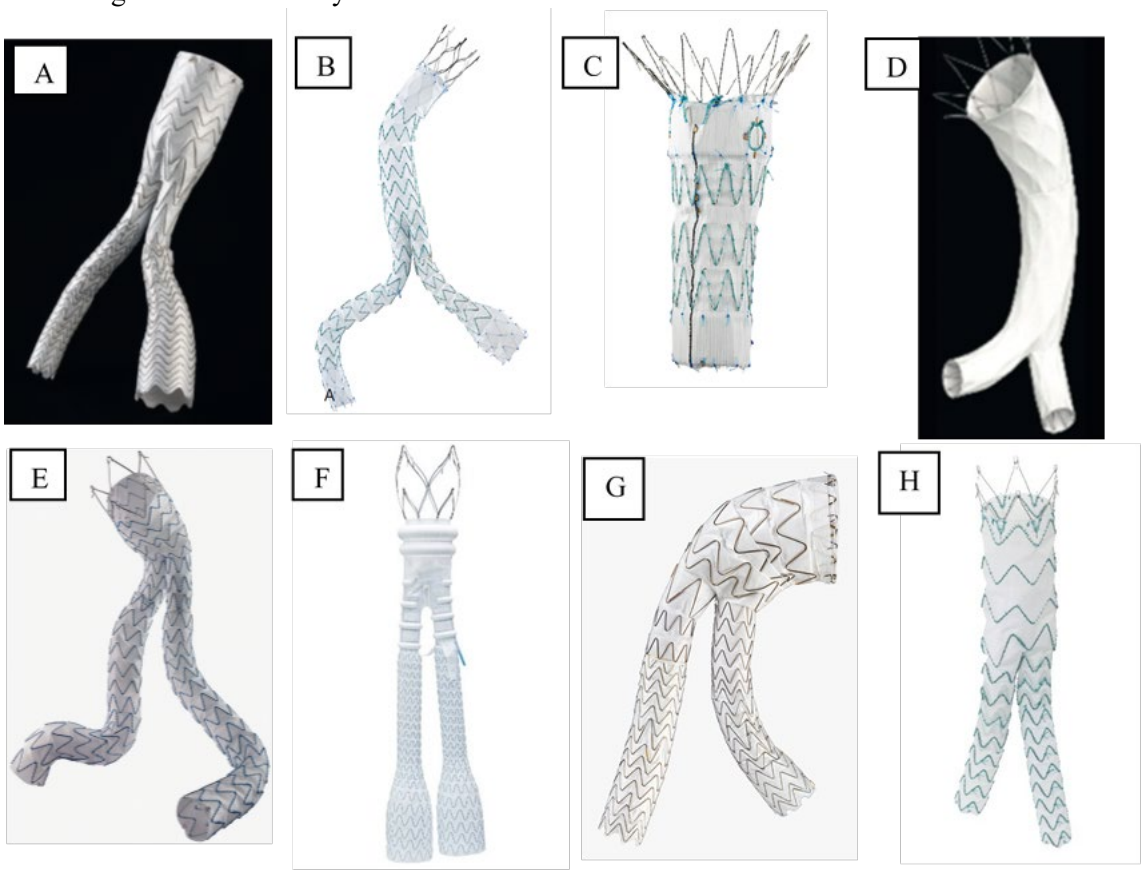


Figure 2: Commercially Available Devices: A, Gore Excluder. B, Cook Zenith Flex. C, Cook Zenith Fenestrated. D, Endologix AFX2. E, Medtronic Endurant II. F, Endologix Alto. G, Gore Excluder Conformable. H, Bolton TREO.

Understanding specific endovascular design features provides insight into the potential failure modes for these devices. The unique aspects of the Endologix AFX design are discussed in Section 2.4.

AAA Endovascular Graft Tracking
EVAR devices manufacturers are required to track their devices from the device manufacturing facility to the patient for whom the device is intended.[11] The purpose of device tracking is to ensure that EVAR device manufacturers are able to promptly locate devices in commercial distribution. Tracking information is used to facilitate notifications and recalls ordered by FDA in the case of serious risks to health associated with device use.[12]

2.3 Trends in AAA Management

In literature reports on the outcomes of the open surgical and endovascular approaches, both from randomized clinical trials and from US Medicare data, EVAR provided important short-term mortality benefits over open repair in anatomically eligible candidates.[13] [14] The early survival benefit favoring EVAR vs. open surgery is not sustained long-term due to an increased rate of aneurysm rupture post-EVAR. The endovascular mode of treatment requires careful lifelong surveillance because of this greater potential for late AAA rupture and the need for secondary interventions to lower the risk of AAA-related events.[15] For a further discussion of trends in AAA management, including a more detailed discussion of open surgical repair vs. EVAR, please see Appendix 1.

2.3.1 Device Failures Associated with Endovascular AAA Repair

After EVAR, there are a number of failure modes that can lead to loss of device effectiveness and serious adverse events. Failure mode examples include delivery system failures resulting in the inability to deploy the device as intended, iliac limb stenosis or occlusion, stent graft migration, fabric tears caused by stent or plaque wear against the graft material, excess fabric porosity, stent or barb fractures, loss of proximal or distal seal, and modular stent graft separations. These failure modes are associated with various clinical sequalae (e.g., vascular injury, tissue ischemia, branch vessel coverage or thrombosis, arterial dissection, endoleak) and many result in the need for additional interventions. If not treated, endoleaks can lead to re-pressurization of the AAA, which is associated with an increased rupture risk and death.

Aneurysm expansion (>5.0 mm) after EVAR indicates that aneurysm sac re-pressurization has likely occurred, and the sac is no longer effectively excluded by the endovascular graft and is at risk of rupture. Endoleaks are the most common cause of aneurysm expansion.

[11] 21 CFR 821 Medical Device Tracking Requirements
[12] Center for Devices and Radiological Health. Medical Device Tracking. U.S. Food and Drug Administration. https://www.fda.gov/medical-devices/postmarket-requirements-devices/medical-device-tracking.
[13] Hertzer NH. A Primer on Infrarenal Aortic Aneurysms, F1000 Research, 2017 Aug 23;6:1549. doi: 10.12688/f1000research.11860.1
[14] Schermerhorn ML, Buck DB, O'Malley AJ, Curran T, McCallum JC, Darling J, et al. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. N Engl J Med 2015;373:328-38.
[15] The EVAR 1 Investigators, Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1: a randomised controlled trial. The EVAR 1 Investigators, Lancet 2016; 388: 2366–74

2.3.2 Endoleaks and Endoleak Management

Endoleaks arising at the time of or subsequent to EVAR are categorized by the source of blood flow into the aneurysm sac (Table 2).[16]

Table 2: Types of Endoleaks[16]

Type	Definition
Type I	Persistent filling of the aneurysm sac due to incomplete seal or ineffective seal at the proximal (Type Ia) or distal (Type Ib) end of the stent graft
Type II	Persistent filling of the aneurysm sac due to retrograde branch flow from collateral vessels
Type III	Blood flow into the aneurysm sac due to inadequate or ineffective sealing of overlapping graft joints (Type IIIa) or tear of the graft fabric (Type IIIb)
Type IV	Blood flow into the aneurysm sac due to the porosity of the graft fabric, causing blood to pass through the graft and into the aneurysm sac
Type V	Aneurysm sac expansion without clear evidence of endoleak origin

The types of endoleaks with the sources of sac blood flow are illustrated in Figure 3.

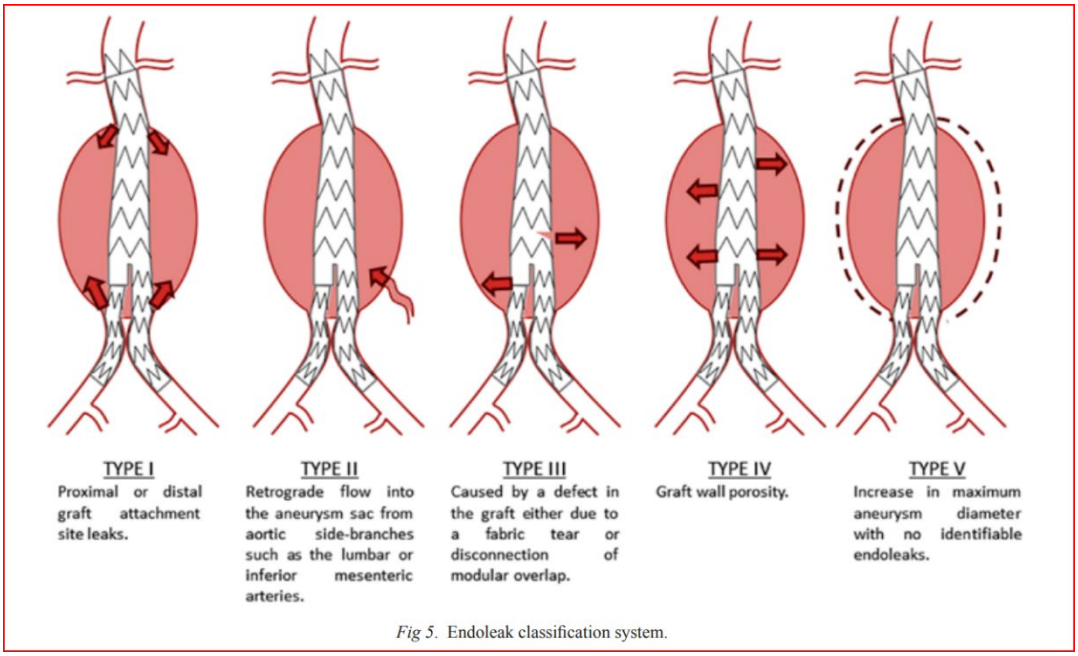


Figure 3: Endoleak Classification System[17]

The post-market safety concern for the Endologix AFX is related specifically to Type III endoleaks, which are discussed below.

[16] Guimaraes G, Yamada R, Schonhloz C. Endoleak and the Role of Embolization, Endovascular Today, 2015(4)68-74.
[17] England A, Mc Williams R. Endovascular aortic aneurysm repair (EVAR). Ulster Med J. 2013;82(1):3-10.

Type III Endoleaks

Type III endoleaks occur when the components of the endograft system separate (Type IIIa) or when a fabric tear or perforation develops (Type IIIb). Type IIIa endoleaks usually can be treated with an endovascular approach, bridging the area of separation with a new device that provides sufficient overlap. Figure 4 shows a CT image of a patient treated for Type IIIa endoleak in which the proximal cuff of an early generation Endologix device disconnected from the main bifurcate component (arrow).

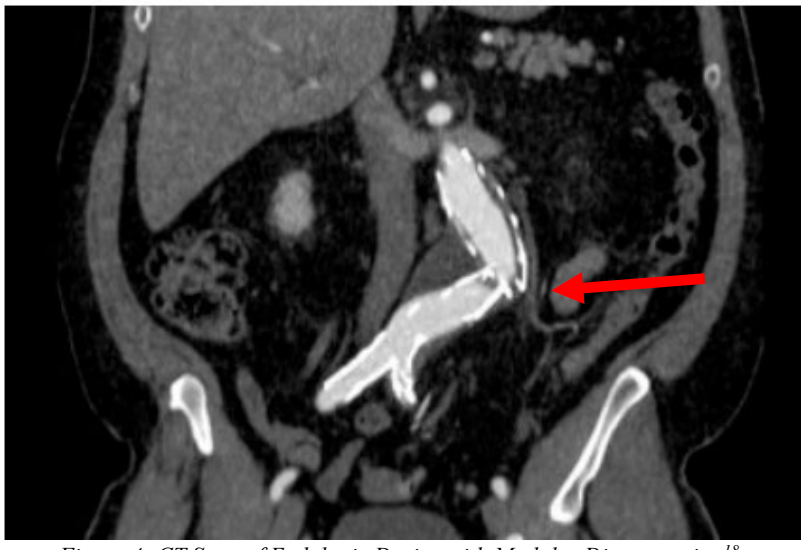


Figure 4: CT Scan of Endologix Device with Modular Disconnection[18]

For Type IIIb endoleaks caused by a fabric tear or holes, relining the endograft may be possible if there is enough room to place the proximal cuff below the renal arteries. Complete relining for Type IIIb leaks may be preferable if the fabric defects tend to occur in the area of the bifurcation. Other areas of the endoprosthesis may also be at risk of perforation. Alternatively, stent graft explantation via open surgical repair may be required to manage Type IIIb leaks when relining is not an option.

All Type III endoleaks represent serious device related events and should be promptly repaired when recognized to lower the risk of progressive aneurysm sac expansion, rupture, and death.[17] While it may be possible to anticipate the development of Type IIIa endoleaks when progressive device migration or separation is noted on radiographic imaging, Type IIIb endoleaks from fabric perforation cannot be anticipated and may occur at any time. Thus, it is particularly challenging to prospectively predict this device failure mode.

2.4 Endologix AFX Stent Graft System

There have been multiple Endologix AAA stent graft system design iterations following initial approval in 2004. These are described below along with unique design features compared to other marketed AAA endovascular grafts.

[18] Skibba AA, Evans JR, Greenfield DT, Yoon HR, Katras T, Ouriel K, Rush DS. Management of late main-body aortic endograft component uncoupling and type IIIa endoleak encountered with the Endologix Powerlink and AFX platforms. J Vasc Surg. 2015 Oct;62(4):868-75.

2.4.1 Powerlink System Stent Graft

The Endologix Powerlink System Stent Graft was approved in 2004. To support the marketing application, in addition to non-clinical and animal testing, a prospective, multicenter, non-randomized, concurrently controlled clinical study was conducted to compare standard risk endovascular patients having anatomy suitable for the Powerlink System Graft to a control group of standard risk surgical patients. Fifteen sites enrolled 192 EVAR patients and 66 surgical control patients. Follow-up evaluations were conducted pre-discharge and at 1 month, 6 months, 12 months and annually thereafter though 5-years. At the time of approval, clinical data showed that the Powerlink System Stent Graft could be placed with a high level of technical success, which was maintained over 12 months and was comparable to a surgical control. The trial showed that the Powerlink System Stent Graft compared to open surgical repair (control) had a comparable risk of serious treatment-related complications, reduction in the number of ICU and hospital days, reduction in procedural blood loss, reduction in procedural and anesthesia time, and reduction in the need for general anesthesia. Most aneurysms either decreased in size or remained unchanged (98%) at 12 months.

After approval of the Powerlink System Graft, Endologix conducted clinical studies to support approval of various extensions and an expansion of the indication.[19]

In March of 2015, the Powerlink System Stent Graft was discontinued by Endologix who indicated that the discontinuation was a result of a business decision to transfer customers to the AFX System. Distribution of the Powerlink System ceased globally in January 2016.

2.4.2 AFX System with Strata

The AFX System with Strata was a line extension of the existing Powerlink System and was approved in 2011. In comparison to the Powerlink System, the AFX System featured a different ePTFE (expanded polytetrafluoroethylene) graft processing method (known as Strata) with a change from a tube extrusion process to a sheet extrusion process. Although the new AFX with Strata manufacturing method employed a different process, the starting materials were the same. The new method also produced a thinner nominal wall thickness, while continuing to meet Endologix's mechanical and strength specifications. The AFX System also introduced a reduced bifurcated delivery system profile (19 Fr profile) and a standalone 17 Fr (19 Fr profile) AFX Introducer.

To support the new graft material processing method, Endologix submitted a PMA Supplement without clinical data. The graft process changes were supported by the following non-clinical tests:

- Structural Characterization and Biocompatibility
- In Vivo Healing Characteristics (animal model)
- Stent Graft In Vitro Performance
- Stent Graft Fatigue Resistance
- Graft Mechanical, Strength and Performance Comparisons
- Stent Graft Migration Resistance
- Performance Qualification

[19] Endologix 2016-2019 Clinical Update for AFX Endovascular AAA System. https://endologix.com/wp-content/uploads/2019/10/MM2165-Rev-01-Endologix-2016-2019-AFX-Clinical-Update.pdf

Endologix ceased distribution of AFX with Strata in November of 2016and removed the device from shelves in December of 2016 as part of recall activities (see Section 3.2). The last implantation in the US was in November of 2016.

2.4.3 AFX System with Duraply

In 2014, Endologix proposed graft material process changes; the graft material made with the new manufacturing process was referred to as Duraply. The changes were intended to optimize the ePTFE graft material (i.e., improve suture retention strength and tear propagation resistance) without changing wall thickness. The Strata manufacturing method wrapped the ePTFE membrane around a mandrel at the same orientation throughout the process. The new ePTFE wrapping process impacted the orientation of the middle layers of the graft. The Duraply manufacturing method involved helical wrapping in the middle layers of the same ePTFE material, meaning that the middle layers of the material were wrapped around the mandrel at a 45° bias with a shorter length of the same ePTFE material. Endologix stated that these changes would improve suture retention strength and tear propagation resistance

To support the new graft material processing method, Endologix conducted the following bench tests:

- Visual Inspections
- Dimensional Verification
- Suture Retention Test (Longitudinal and Radial)
- Longitudinal Tensile Test
- Static Pressure Dilation
- Water Entry Pressure
- Burst Pressure
- Internodal Distance
- Installation and Operational Qualification

Information provided by Endologix was supportive that the Duraply graft material would be expected to have a similar or potentially improved safety and effectiveness profile vs. the previous Strata graft material. Like the Strata graft material process change, approval was based upon bench testing, and clinical data were not deemed necessary.

Endologix utilized Duraply graft material rather than Strata graft material on all newly manufactured AFX System grafts starting in mid-2014. Endologix also made minor adjustments to the design of the device during this time, including a change in the graft thickness manufacturing tolerances in 2016 in alignment with those implemented in the AFX2 System (described further in Section 2.4.4). Endologix stopped US distribution of the AFX System with Duraply in August 2018 and worldwide distribution in May 2020.

2.4.4 AFX2 System

Figure 5: Illustration of AFX2 System[20]

In 2015, Endologix proposed a line extension for the AFX System with Duraply referred to as AFX2. In the submission, Endologix included changes to the delivery system and provided bench testing to support the changes to the system. Endologix described these changes as intended to improve useability of the device. The original proposal did not include changes to the stent design or ePTFE graft material.

Before commercialization of the AFX2 System, Endologix also implemented a change in the graft material manufacturing tolerances (reported in a PMA Annual Report). Specifically, Endologix tightened the production window within the approved manufacturing specification for graft thickness which resulted in an increase the average thickness of the graft material. Endologix indicated that they implemented the change to improve the final loading manufacturing process, and the change was not expected to impact device safety or effectiveness. Endologix also noted that the production parameters remained the same, and that the tighter specifications did not introduce new clinical risks. This change was coupled with a change to the graft loading process to protect the ePTFE graft from damage during loading onto the delivery system.

AFX2 was approved in October 2015 and commercially released in February 2016. It is the only AFX device iteration currently marketed in the US.

2.4.5 Unique Design Characteristics of the AFX System

The AFX system and the prior Powerlink design are unique compared to other marketed endovascular grafts as they provide passive anatomic fixation by device deployment on the native aortic bifurcation, preventing distal migration of the main component. The bifurcate component of the AFX system is placed

[20] "AFX® - Abdominal AORTA Stent GRAFT BY Endologix: MedicalExpo." The B2B Marketplace for Medical Equipment, www.medicalexpo.com/prod/endologix/product-94533-588647.html

first, and then an aortic cuff (with or without a suprarenal stent) is docked into the bifurcate component superiorly to achieve a proximal seal (Figure 6).

The AFX device also has two other unique design features. The self-expanding metal endoskeleton of the device is on the inside of the PTFE graft fabric. In addition, the ePTFE fabric is fixed to the device only at the superior and inferior ends, which can allow the fabric to billow outward from the endoskeleton under arterial pressure. This design feature was intended to provide enhanced seal at the AAA neck and the aortic bifurcation.

The components of the current AFX2 system are shown in Figure 6.[19]

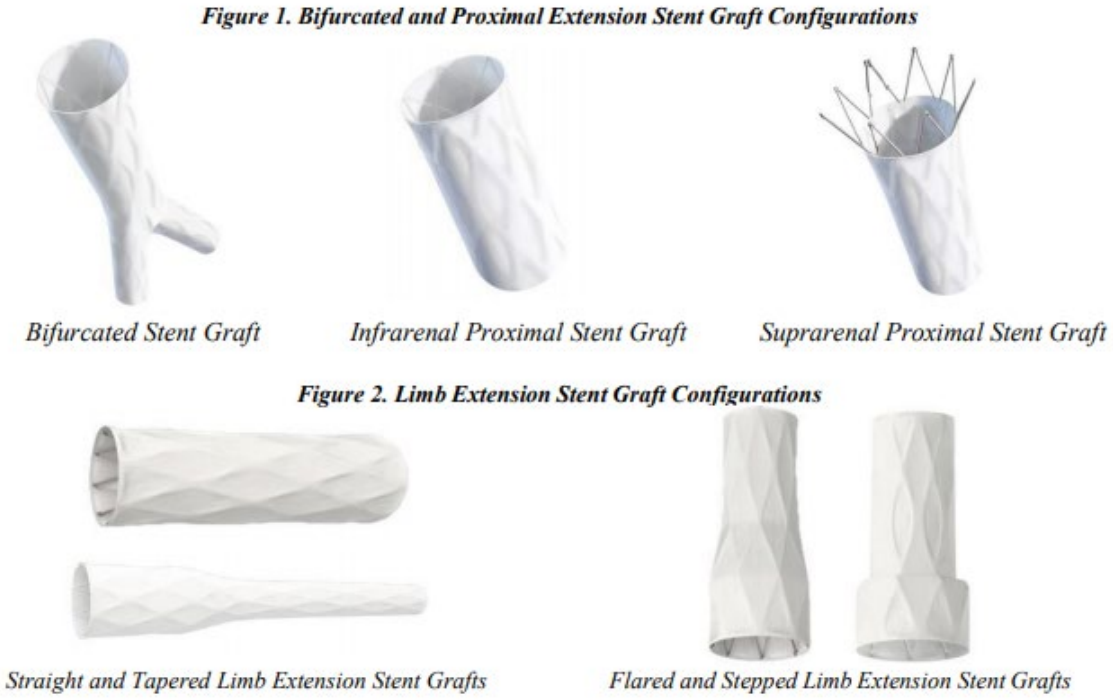


Figure 6: AFX2 Components[19]

The schematic in Figure 7 shows how the unattached PTFE fabric can billow outward from the area in which the stent frame does not follow the aortic contour. This can occur in a tapered neck or in a dilated common iliac artery. Some literature reports describe billowing as a normal radiographic phenomenon, but others suggest that this finding may indicate an increased risk of aneurysm rupture.[21, 22]

[21] Chang H, Hadro NC, Norris MA, Rhee SW, Morris ME. The Progression of Billowing of Endologix AFX2® Abdominal Aortic Aneurysm Device as a Precursor for the Rupture of an Abdominal Aortic Aneurysm. Ann Vasc Surg. 2019 Jan;54:335.e11-335.e14.

[22] Mara Fanelli, Claudio Bianchini Massoni, Alberto Bramucci, Paolo Perini, Antonio Freyrie, Complete Relining in Type 3 Endoleak with AFX Endograft Billowing and Severe Kinking: A Case Report, Annals of Vascular Surgery, Volume 69, 2020, Pages 451.e11-451.e16, ISSN 0890-5096,

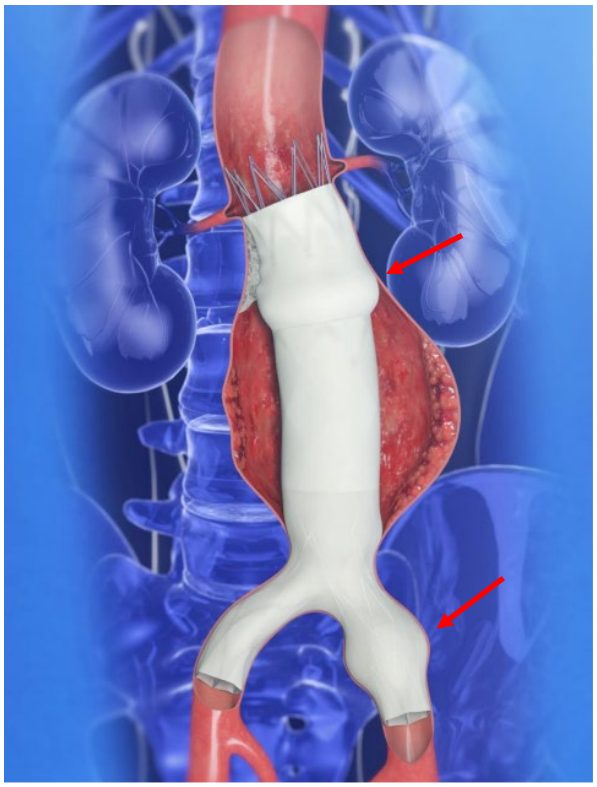


Figure 7: Graphic of Fully Deployed AFX2 with Arrows Pointing to Fabric Billowing[19]

The unique design characteristics of AFX have been postulated to have contributed to an increased Type III endoleak risk observed in clinical reports (see Section 3.1).

Endologix has provided the following potential benefits of the AFX2 system from their analysis of clinical experience, physician opinion and clinical data:

- AFX2 may provide an option for a shorter operative procedure time and a reduction in fluoroscopy use and contrast volume in comparison to proximally fixated endografts.
- AFX2 may demonstrate a lower peri-operative Type Ia endoleak rate than comparator grafts.
- AFX2 provides a low-profile solution with a small contralateral access requirement (7F).
- AFX2 preserves the native aortic bifurcation, which may be useful in patients with downstream peripheral vascular access in whom it may be desirable to preserve the option for retrograde "up and over" contralateral access.

- AFX2 may provide benefits in patients with a narrowed aortic bifurcation, as unibody endografts may navigate a narrowed aortic bifurcation without compromise of graft diameter. In contrast, proximally fixated endografts may be compromised by having to traverse two iliac limbs through this narrowed space.

FDA Comment: In summary:

- **AFX with Strata** – This iteration was introduced in 2011. In comparison to the Powerlink System, the AFX with Strata utilized a sheet extrusion process to manufacture the graft material. Although the new manufacturing method of the AFX with Strata employed a different process than the Powerlink, the starting materials were the same. The new method also produced a thinner nominal wall thickness. There were no differences to the stent design. Distribution of AFX with Strata stopped in November 2016, and all Strata devices taken off the shelf in December 2016.
- **AFX with Duraply** – This iteration was introduced in 2014. In comparison to AFX with Strata, the AFX with Duraply utilized a new manufacturing method with helical wrapping in the middle layers of the same ePTFE material. The thickness of the graft material also increased due to manufacturing tolerance changes that were introduced in 2016. The stent design remained the same. Endologix stopped US distribution in August 2018 and worldwide in May 2020.
- **AFX2** – This iteration was introduced in 2015. The manufacturing process of the graft material is the same as AFX with Duraply, including the increased graft thickness vs. Strata. The stent design is also the same as AFX with Duraply and AFX with Strata. There are differences in the delivery system, which were implemented to improve device useability.

AFX2 is the latest iteration of the AFX family of devices and is the only Endologix device still in distribution. Although there was a change in the graft material manufacturing processes between AFX with Strata and AFX with Duraply, the material and manufacturing process is largely the same between AFX with Duraply and AFX2. As such, FDA expects that the AFX2 to have a similar safety and effectiveness profile with AFX with Duraply. Endologix has presented several potential AFX System benefits; the panel will be asked to consider these benefits in assessing the overall benefit-risk of the AFX System.

3 Endologix AFX Type III Endoleak Risk

3.1 AFX Type III Endoleak Risk Clinical Reports

FDA monitors post-market data sources for device safety and effectiveness. Key peer reviewed publications that have detected an AFX Type III endoleak safety risk are in Appendix 2 and summarized below and the findings are consistent with the device failure mode that is of concern to CDRH.

3.1.1 Lemmon GW, Motaganahalli RL, et al. Failure mode analysis of the Endologix endograft Publication (Powerlink and AFX with Strata), 2016

The authors reviewed all patients at their center undergoing EVAR with FDA-approved endovascular grafts. They treated 151 patients between April 2011 until August 2014, 83 treated with an Endologix

device (Powerlink or AFX with Strata) and 68 patients treated with a Cook, Gore, or Medtronic device.[23] Significant differences were noted with higher rates of post-implant rupture and AAA related reinterventions in the Endologix Group (Table 3). Seven of 8 AAA ruptures and 20 of 24 AAA reinterventions in the Endologix Group were associated with Type III endoleaks. No ruptures or Type III endoleaks were noted in patients treated with non-Endologix devices.

Table 3: Major Adverse Events in Endologix Powerlink or AFX with Strata vs. Comparator Devices (Cook, Gore, Medtronic)

Event Type	Endologix Powerlink or AFX with Strata	Comparator Devices (Cook, Gore, Medtronic)
Type III Endoleak	16.8% (14/83)	0% (0/68)
Type IIIa	7.3% (6/83)	
Type IIIb	9.6% (8/83)	
Reintervention Rate	28.9% (24/83)*	7.4% (5/68)
Device-related mortality	4.8% (4/83)	0% (0/68)
Aneurysm rupture	9.6% (8/83)**	0% (0/68)
Open Conversion	2.4% (2/83)	0% (0/68)

**20 of the 24 interventions were for patients with Type III endoleaks*
***7 of the 8 ruptures were in patients with Type III endoleaks*

The incidence of Type IIIa endoleaks and Type IIIb endoleaks in the Endologix Group was 7.3% (6/83) and 9.6% (8/83), respectively. No type III endoleaks at all were noted in the 68 patients with comparator grafts. Repeated interventions (n=20) were necessary for patients with Endologix endografts with Type III endoleaks to prevent aneurysm rupture while no such additional procedures were necessary in patients in the comparator group. Another observation was that patients with an AAA diameter >65 mm appeared to be at an increased risk for Type III endoleak complications with the Endologix devices.

The authors noted the AFX Type IIIa endoleaks involved proximal migration of the aortic cuff rather than disconnection of an iliac limb due to distal migration, which is the more common Type IIIa endoleak failure mode seen with other device systems. The authors hypothesized that the billowing of the proximal aortic extension may provide a reverse windsock effect that can cause an uncoupling of the two components that was more pronounced with larger size aneurysms. In addition, the authors reported that the AFX Type IIIb endoleaks tended to occur in proximity to the aortic bifurcation. They stated that Type IIIb endoleaks were unrelated to AAA morphology but appeared linked to AAA size and the device design.

Study strengths and limitations

Strengths

- Focused outcomes analysis where number of treated patients and number of events are known with a reasonable degree of certainty
- Peer-reviewed publication
- Collected outcomes in patients treated with Endologix Powerlink and AFX with Strata as compared to other commercial AAA devices (Cook, Gore, or Medtronic) used in the same time period by an academic vascular surgical practice group

[23] Lemmon GW, Motaganahalli RL, et al. Failure mode analysis of the Endologix endograft. J Vasc Surg. 2016 Sep; 64(3):571-6

- The authors provided perspectives on type III endoleaks to the unique design features of the AFX platform

Limitations

- Single center retrospective study
- Low sample size
- Follow-up patient visit and CT compliance were not stated
- No data was presented on AFX with Duraply or AFX2 device iterations

3.1.2 Barleben A, Mogannam A, et al. *Lessons Learned from the Largest Cohort of Type III Endoleaks With the Endologix AFX Stent Graft.* Abstract, 2018 (AFX Strata)

The authors noted a rise in the incidence of Type III endoleaks with "early generation" Endologix AFX grafts.[24] Through a targeted effort to improve follow-up of 107 patients treated with AFX devices and clinical follow-up before 2018, the Type III endoleak rate was 24.3% (26/107). Complete endograft relining was performed in 22 patients; indications were type IIIa (4) and type IIIb (18) endoleaks.

Study strengths and limitations

Strengths

- Focused review of outcomes where number of treated patients and number of events are known with a reasonable degree of certainty
- Extensive experience with treating AFX failures (discussed further in Treatment of Endologix AFX Devices That Have Experienced a Failure Mode)

Limitations

- Single center retrospective study
- Abstract publication
- No comparator group
- CT follow-up obtained in only 63.1% of subjects
- Limited to AFX with Strata; no data on AFX with Duraply or AFX2 device iterations

3.1.3 Chang, RW, Rothenberg KA, et al., *Midterm outcomes for 605 patients receiving Endologix AFX or AFX2 Endovascular AAA Systems in an integrated healthcare system.* Publication, 2019 (AFX with Strata, AFX with Duraply, AFX2)

Chang et al. published an analysis of midterm outcomes for 605 patients receiving Endologix AFX or AFX2 Endovascular AAA Systems who were followed prospectively in the Kaiser Permanente (KP) endovascular stent graft registry.[25] The outcomes evaluated included endoleak, major reintervention, aneurysm rupture, and mortality (Table 4). Of the 605 patients, 375 received AFX with Strata (AFX-S), 197 received AFX with Duraply (AFX-D), and 33 received AFX2. EVAR procedures included in the study sample were performed by 60 surgeons at 23 healthcare centers.

[24] Barleben A, Mogannam A, et al. Lessons Learned from the Largest Cohort of Type III Endoleaks With the Endologix AFX Stent Graft. J Vasc Surg 2018, 68(3) p. e37

[25] Midterm outcomes for 605 patients receiving Endologix AFX or AFX2 Endovascular AAA Systems in an integrated healthcare system. Chang, RW, Rothenberg KA, et al. J Vasc Surg 2021;73:856-66.

The median postoperative follow-up was 3.9 years (interquartile range (IQR), 2.5 to 5.1 years) with a maximum follow-up of 7.3 years. There were 45 patients (7.4%) lost to follow-up through healthcare membership termination at a median follow-up time of 1.6 years (IQR, 0.6-2.6 years).

Table 4 summarizes the outcomes reported as both an overall incidence and 2-year cumulative probability. The freedom from Type III endoleak is shown in Figure 8. Given that the follow-up period varies among patients, 2-year cumulative probability (incidence at 2 years of follow-up) for each event type is a more interpretable analysis than overall incidence. The 2-year cumulative probability of Type III endoleak were similar between AFX with Strata and AFX with Duraply (4.0% vs. 5.1%, respectively). While the number of patients treated with AFX2 was small, the cumulative probability of Type III endoleak was 14.1%. The authors also emphasized that the 2-year cumulative probability of aneurysm rupture for the AFX2 was notable (7.3%).

Table 4: Rates of Adverse Events of AFX Iterations Reported in KP Review[25]

Event Type	AFX with Strata (n=375)	AFX with Duraply (n=197)	AFX2 (n=33)
Type III Endoleak			
Overall Incidence*	16.5% (62)	9.6% (19)	9.1% (3)
Incidence at 2-years of follow-up**	4.0% (2.4 - 6.7)	5.1% (2.7 - 9.7)	14.1% (4.7 - 38.2)
Intervention Rate			
Overall Incidence*	28.3% (106)	14.7% (29)	12.1% (4)
Incidence at 2-years of follow-up**	12.3% (9.3 - 16.2)	9.5% (6.0 - 14.8)	16.2% (6.4 - 37.7)
Aneurysm-related mortality			
Overall Incidence*	4.0% (15)	3.1% (6)	6.1% (2)
Incidence at 2-years of follow-up**	1.6% (0.7 - 3.6)	2.6% (1.1 - 6.0)	6.1% (1.6 - 22.1)
Aneurysm rupture			
Incidence at 2-years of follow-up**	0.6% (0.2 - 2.4)	0.6% (0.1 - 4.0)	7.3% (1.8 - 26.5)
Open Conversion			
Overall Incidence*	3.2% (12)	1.0% (2)	0.0%
Incidence at 2-years of follow-up**	0.3% (0.0 - 2.0)	1.2% (0.3 - 4.6)	0.0%

**Overall incidence is calculated as the total number of patients with the event of interest divided by the number of patients in the cohort.*

***Cumulative incidence probability is presented with 95% confidence interval. Cumulative incidence probability is calculated as one minus the Kaplan-Meier estimator at 2 years. This represents the incidence at 2 years of follow-up.*

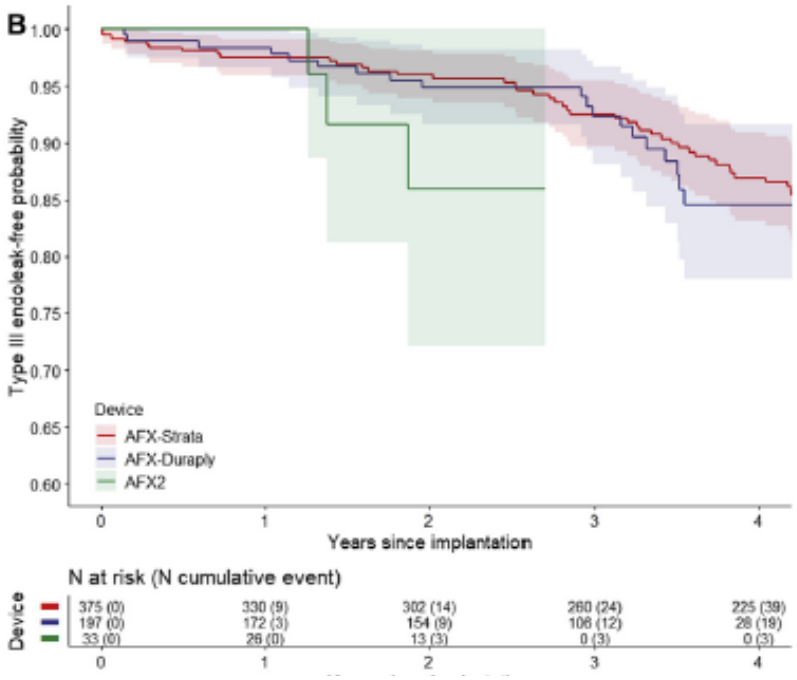


Figure 8: Postoperative endoleak-free probability (solid) and 95% confidence interval (CI) (shaded area)

The authors compared the Type III endoleak risk to a 3.0% to 4.5% long-term estimated risk after EVAR, per the authors' literature review. The authors believe these rates may increase as surveillance continues over the longer-term. They concluded that despite the changes in the AFX systems, continued close monitoring of patients with AFX devices is needed to ensure device integrity and patient safety. The authors believe further study is needed to confirm their findings and identify underlying mechanisms, which may not be limited to aneurysm size, fabric, or Instructions for Use.

Study strengths and limitations

Strengths

- Peer-reviewed study
- Prospective collection of data from a nationally recognized device registry from an integrated health system
- Longitudinal follow-up of a large sample size of patients treated relevant AFX device versions
- Low rates of missing data (7.4% of subjects)

Limitations

- Number of patients with AFX2 implants is small (n=33) with limited long-term follow-up
- No comparator group of non-AFX devices
- CT follow-up compliance was not reported

3.1.4 Wanken ZJ, Anderson P, et al. *Comparison of Endologix Endografts Made With Strata Fabric Versus IntuiTrak and Duraply Fabrics.* Abstract, 2019 (AFX with Strata, AFX with Duraply)

Wanken et al. from the Dartmouth Hitchcock Medical Center presented a comparison of Endologix endografts made with Strata fabric vs. IntuiTrak and Duraply fabrics.[26] The authors conducted a retrospective single-center chart review of patients treated for infrarenal aneurysm with Endologix AFX devices from 2011 to 2015.

They grouped patients on the basis of the fabric type of the endograft, Strata vs non-Strata. Major adverse events (MAEs) were defined as reintervention related to the endograft, aneurysm-related death, and aneurysm rupture. The authors identified 118 patients (67 Strata, 51 non-Strata) with median follow-up of 4.07 years. Kaplan-Meier analysis demonstrated that 25% of patients suffered MAEs within 4 years of repair with no significant difference between groups (log-rank P=0.76). Reintervention procedures were required in 26 patients (Strata, n=15, 22.4%; non-Strata, n=11, 21.6%):

- Primary reinterventions
    - Relining (n = 10)
    - Type I endoleak (n = 6)
    - Limb thrombosis or kinking (n = 5)
    - Type II endoleak (n = 3)
- Secondary reinterventions
    - Relining (n = 2)

FDA confirmed with the authors that relinings were performed to treat Type III endoleaks. In total, relining was needed in 10 Strata and 2 non-Strata subjects. Kaplan-Meier analysis demonstrated that most relining procedures occurred between 2 and 5 years after initial repair.

The authors concluded that a quarter of patients treated with Endologix devices suffer MAEs within 4 years, and relining procedures may be required 2 to 5 years out. They recommended that patients receive close follow-up surveillance for type III endoleaks.

Study strengths and limitations

Strengths

- Focused review of outcomes where number of treated patients and number of events are known with a reasonable degree of certainty
- Median follow-up of 4 years for 118 patients

Limitations

- Single center retrospective study
- Abstract publication
- No comparator group
- Non-Strata devices probably AFX with Duraply (not AFX2), but detailed device description not provided
- CT follow-up rate not provided

[26] Wanken ZJ, Anderson P, et al. Comparison of Endologix Endografts Made With Strata Fabric Versus IntuiTrak and Duraply Fabrics. J Vasc Surg, 2019. 70(3) pp.e44.

3.1.5 Ta TM, Aranson NJ, et al., *Six-Year Outcomes of the Endologix AFX1 Endovascular AAA System: A Single-Center Experience.* Abstract, 2020 (AFX with Strata)

Aranson et al. from the Maine Medical Center (MMC) performed a retrospective review of their single tertiary center's experience comparing first generation AFX with Strata grafts (n=122) with a control EVAR Device cohort (Medtronic, Gore, Cook; n=101) placed between December 2012 and April 2019.[27] The primary study endpoint was freedom from AAA-related major complications (endoleak excluding Type II, graft relining, or graft explantation). Secondary endpoints were 5-year survival, freedom from endoleak, and freedom from reintervention. Median follow-up was longer for the AFX with Strata cohort compared with the control cohort (4.6 years vs 1.8 years; p=0.001).

Five-year survival was similar between AFX with Strata and control (79% vs 71%; p=0.61). The AFX with Strata cohort had significantly lower rates of freedom from graft-related endoleaks, reinterventions, and AAA-related major complications at 5-years (Table 5).

Table 5[+]: Freedom from Adverse Events Presented in Maine Medical Center Review[27]

Freedom from *X*	**AFX with Strata (n=122)**	**Control (Cook, Gore, Medtronic) (n=101)**	**p value**
Any Endoleak	62% (	85%	p=0.006
Reintervention	63%	87%	p=0.001
AAA-related Major Complications	69%	95%	p=0.001

[+]Follow-up periods are inconsistent between the AFX with Strata group and the control group
[*]The MMC publication presents freedom as percentages. Numerator is extrapolated for the purpose of this table.

The authors noted that most complications in the control group occurred within the first year post-procedure, whereas AFX with Strata-related complication rates increased beyond 3 years and approached 50% at 6 years (Figure 9).

[27] Ta TM, Aranson NJ, et al., J Vasc Surg , 2020, Six-Year Outcomes of the Endologix AFX1 Endovascular AAA System: A Single-Center Experience 72(3) pp.e291.

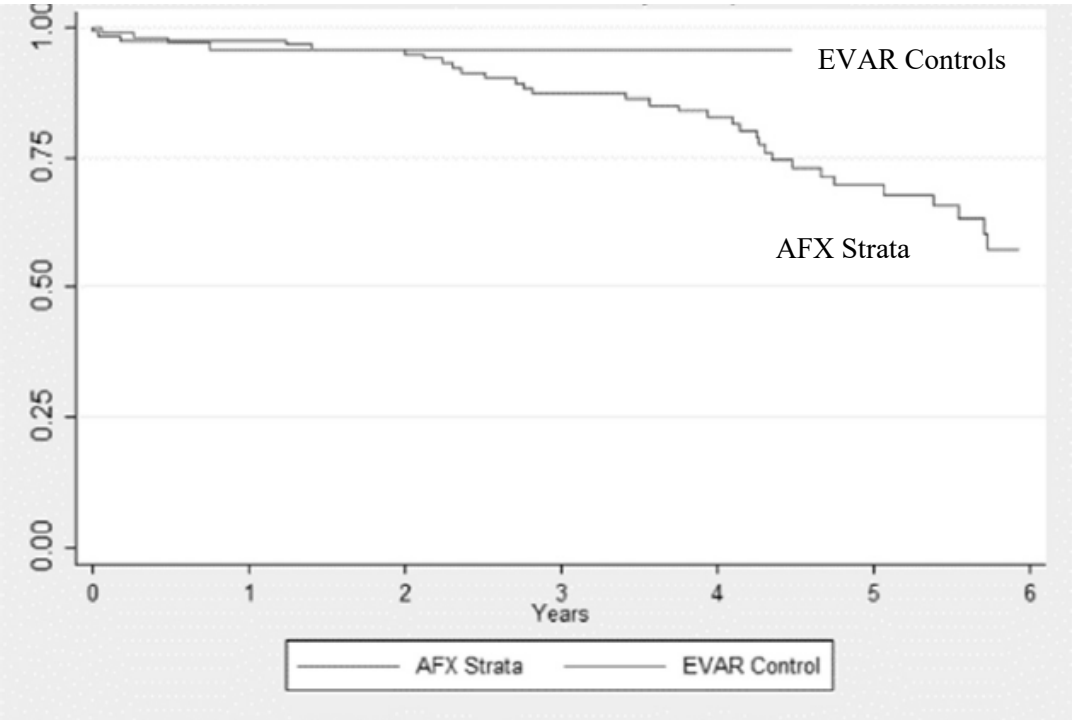


Figure 9: Freedom from AAA-related major complications between AFX Strata and EVAR Control
**The abstract did not provide the life table to go with this Kaplan Meier plot*

The authors concluded that the long-term AAA-related complication rate is higher in patients treated with an AFX with Strata graft, and late complications highlights the need for lifelong surveillance for all treated patients. The authors advised patients treated with an AFX with Strata graft should be observed closely and potentially considered for prophylactic relining or explantation and that outcomes of the reinterventions for AFX failures should be further analyzed.

Study strengths and limitations

Strengths

- Focused review of outcomes where number of treated patients and number of events are known with a reasonable degree of certainty
- Includes a comparator group of other marketed endograft devices

Limitations

- Single center study
- Abstract publication
- Retrospective analysis
- Duration of follow-up information longer for AFX with Strata vs. the comparator devices group, and the number of subjects available for follow-up at later time points not provided
- CT follow-up rate not provided
- No data on with AFX with Duraply or AFX2

FDA Comment: Acknowledging the strengths and limitations of the clinical studies, key findings are as follows:

- **Type III Endoleak Rate**
  - AFX with Strata
    - Type III endoleak rate reported to be as high as 24%
    - Type III endoleak rate (Type IIIa and Type IIIb) reported to be statistically significantly higher for AFX with Strata as compared to other marketed AAA endovascular devices (pooled data)
  - AFX with Duraply: KP data showed a generally similar Type III endoleak rate between the Strata and Duraply cohorts
  - AFX2: Sample size too small to draw meaningful conclusions
- **Clinical Outcomes of Interest**
  - AFX with Strata
    - Reintervention rate as high as 37% (Ta, et al.)
    - Aneurysm rupture rate 9.6% (Lemmon, et al.).
    - AAA-related major complications reported in 25% of patients (Wanken, et al.) and 31% of patients (Ta, et al.).
    - Device-related mortality 4.8% (Lemmon, et al.).
  - AFX with Duraply
    - The rates of reinterventions and aneurysm-related mortality generally similar to patients treated with Strata (Chang, et al.).
    - MAE and reintervention rates generally similar between the Stata and the non-Strata groups (Wanken, et al.)
  - AFX2: The rates of reintervention (16.2%), aneurysm-related mortality (6.1%), and rupture (7.3%) exceeded the rates observed for the earlier iterations of the AFX platform, but the sample size (n=33) was too small to draw meaningful conclusions (Chang, et al.).

Table 6: Summary of Type III Endoleaks from Clinical Reports

Publication	Overall Type III endoleak			Type IIIa endoleak		Type IIIb endoleak		Median Follow-Up
	Strata	Duraply	AFX2	Strata	Duraply	Strata	Duraply	
Lemmon et. al.	16.9% (14/83)	--	--	7.3% (6/83)	--	9.6% (8/83)	--	2.1 ± 1.2 Years[a]
Barleben et al.	24.3% (26/107)[b]	--	--	3.7% (4/107)	--	16.8% (18/107)	--	3.8 years[c]
Chang et al.	16.5% (62/375)	9.6% (19/197)	9.1% (3/33)	--	--	--	--	3.9 years
Wanken et al.	14.9% (10/67)	7.1% (2/28)	--	3.0% (2/67)	0.0% (0/28)	12.0% (8/67)[d]	7.10% (2/28)[d]	4.07 years
Aranson et al.	38%[e] (n=122)	--	--	--	--	--	--	4.6 years

[a]Mean follow-up
[b]Abstract did not stratify 4 Type III endoleaks
[c]Average time to relining procedure
[d]Presumed Type IIIB Endoleak
[e]One minus calculated freedom from any endoleak

Most data available in published clinical reports are on the AFX with Strata device, which has been removed from the market due to high Type III endoleak rates. There is less information available on AFX with Duraply and very limited AFX2 information on Type III endoleak rate and other clinical outcomes. Comparator device outcomes help put the AFX data information into context. Additionally, in the single-center reports, Type III endoleaks were observed at 4 and 5-years post EVAR for AFX with Strata or Duraply.

In FDA's opinion, it is unclear whether AFX design/manufacturing changes incorporated into the current generation AFX2 device are sufficient to address the Type III endoleak concerns. Based on device design, the AFX2 may be expected to have a similar performance profile as the AFX with Duraply.

3.2 Summary of AFX Type III Endoleak Recalls and Associated Risk Mitigation

To mitigate the Type IIIa and IIIb endoleak concerns, Endologix has implemented various corrections across the different AFX iterations. Figure 10 from Endologix shows the timeline of corrective actions and the devices impacted by the actions. The IFU changes were included in the device recalls described in the following sections.

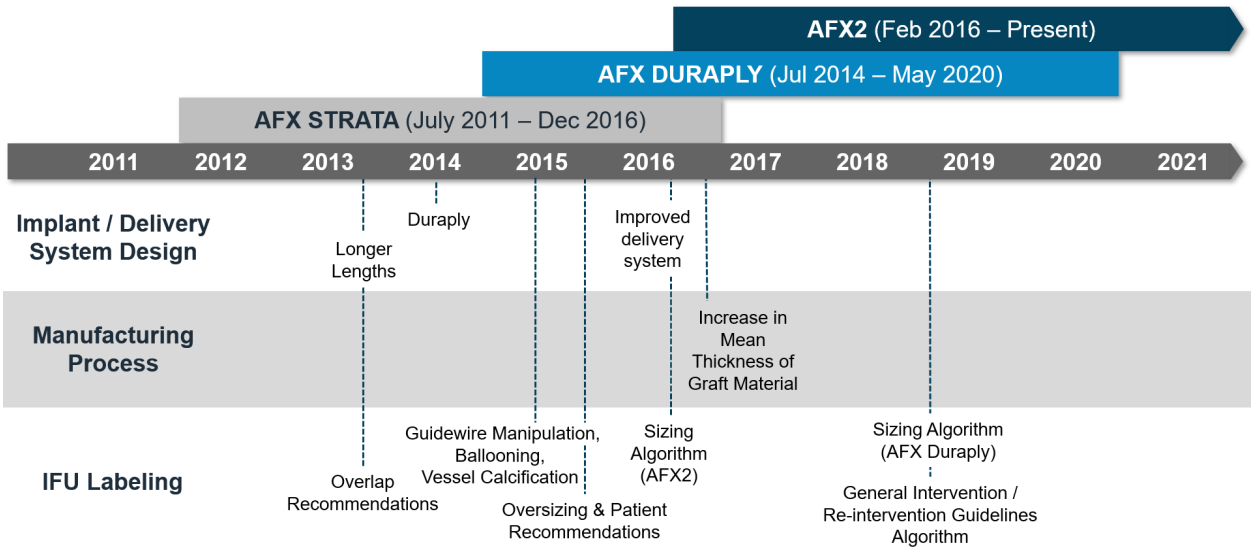


Figure 10: Timeline of Type III Endoleak Mitigation Actions

Under 21 CFR 806, Medical Device Correction and Removals, manufacturers and importers are required to make a report to FDA of any correction or removal of a medical device(s) if the correction or removal

was initiated to reduce a risk to health posed by the device or to remedy a violation of the Act caused by the device which may present a risk to health. Correction refers to repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a product without its physical removal to some other location. Removal refers to the physical removal of a device from its point of use to some other location for repair, modification, adjustment, relabeling, destruction, or inspection. Recalls are classified into a numerical designation (I, II, or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled.[28]

- Class I - a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
- Class II - a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
- Class III - a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

3.2.1 2016/2017 Class II Recall

In 2016, Endologix reported to FDA the existence of a Corrective and Preventative Action (CAPA) initiated in 2013 to address Type IIIa and Type IIIb endoleak complaints for the AFX with Strata. **Error! Reference source not found.Error! Reference source not found.** show the Type IIIa and Type IIIb complaint rates, respectively, at the time of the recall. At the time of the recall, Endologix stated that they do not "have long term data on the effectiveness of these changes as the time to event may exceed the amount of follow-up currently available." In addition, they stated that "the rates are calculated based on voluntary reporting and units sold, which may underestimate the true event rate occurring on a per patient basis. This underestimate may be greater for the more recent versions (i.e., AFX with Duraply and AFX2 System), which may have a larger hospital inventory as compared to the AFX with Strata."

From August 2011 to December 2016, a total of 259 Type IIIa endoleaks and a total of 186 Type IIIb endoleaks were identified. The following related clinical sequalae were reported:

- Type IIIa endoleaks: 18 deaths, 28 ruptures, 8 open surgeries, 173 secondary procedures, 7 increased procedure time
- Type IIIb endoleaks: 17 deaths, 30 ruptures, 17 open surgeries, 97 secondary procedures

The firm subsequently submitted a recall for the corrections initiated as a result of the 2013 CAPA, which is further described below. The recall was classified as Class II (Recall Event IDs: 76110, 76112, 76075, 76086, 76113, 76106, 76256).

[28]Center for Devices and Radiological Health, "Recalls, Corrections and Removals (Devices)." *U.S. Food and Drug Administration.* https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices

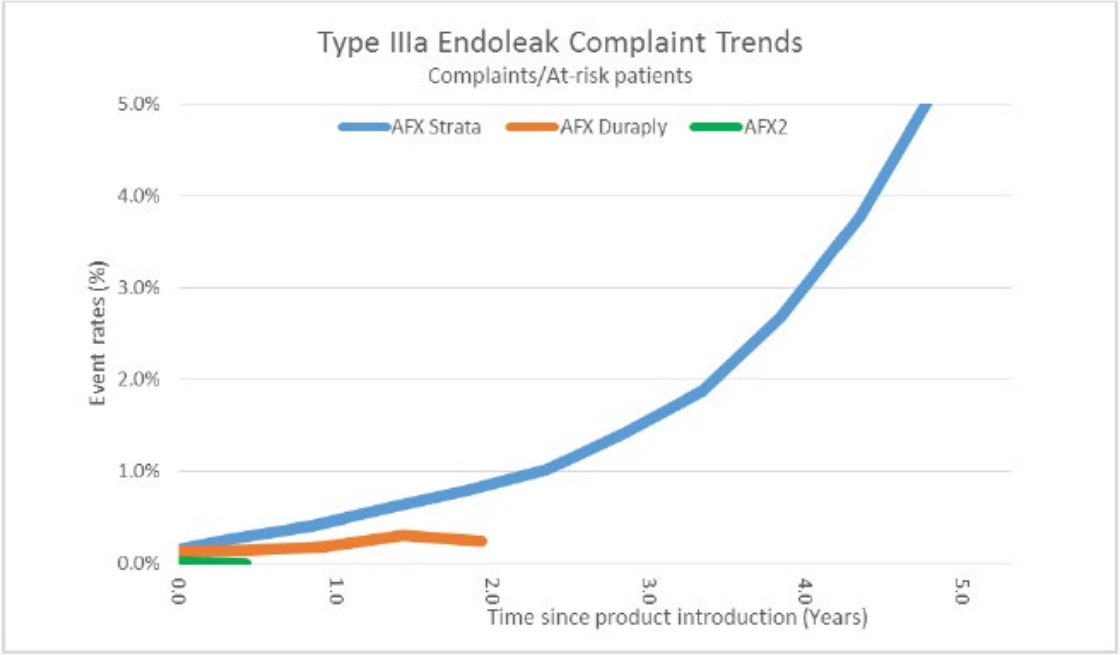


Figure 11: Type IIIa Endoleak Complaint Trends in 2016 Physician Letter

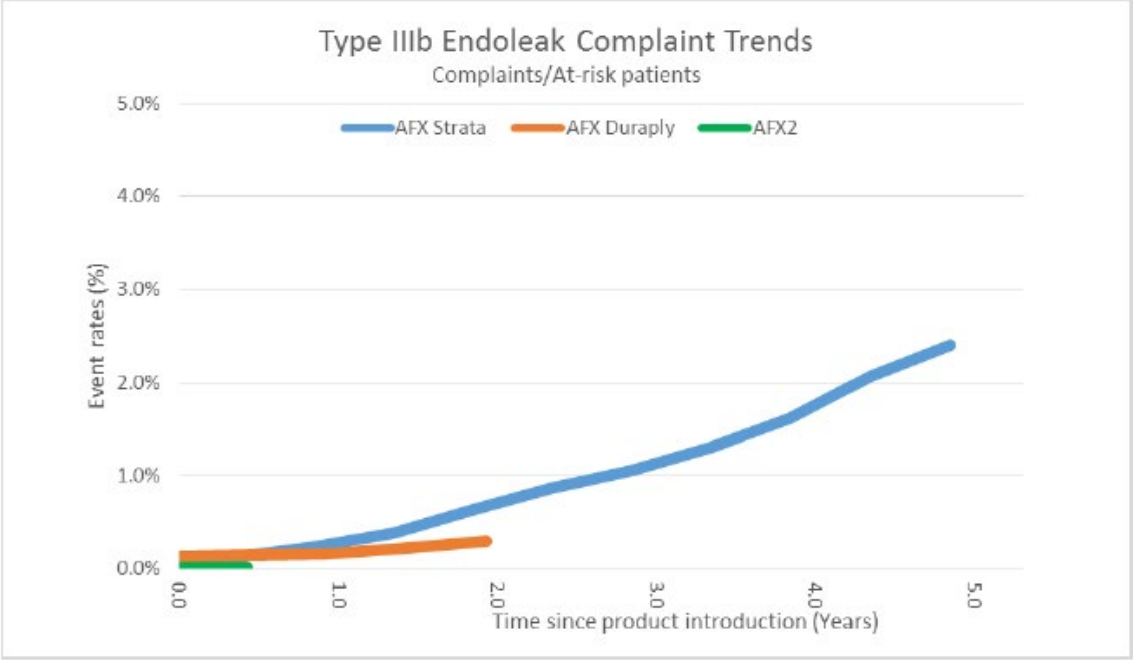


Figure 12: Type IIIb Endoleak Complaint Trends in 2016 Physician Letter

Endologix issued a Physician Letter in December 2016 that discussed the following potential factors contributing to Type IIIa and IIIb endoleaks:

- Type IIIa endoleaks
    - Inadequate component overlap at the index procedure

    - Lateral movement in large or tortuous aortas leading to reduction or loss of component overlap
    - Use of an excessively oversized proximal extension relative to the bifurcated main body device
- Type IIIb endoleaks
    - Procedural factors such as guidewire/catheter manipulation or aggressive balloon molding
    - Off-label device use in highly calcified lesions
    - Lateral movement and changes in implant stability
    - Implant of other manufacturer's devices as proximal extensions

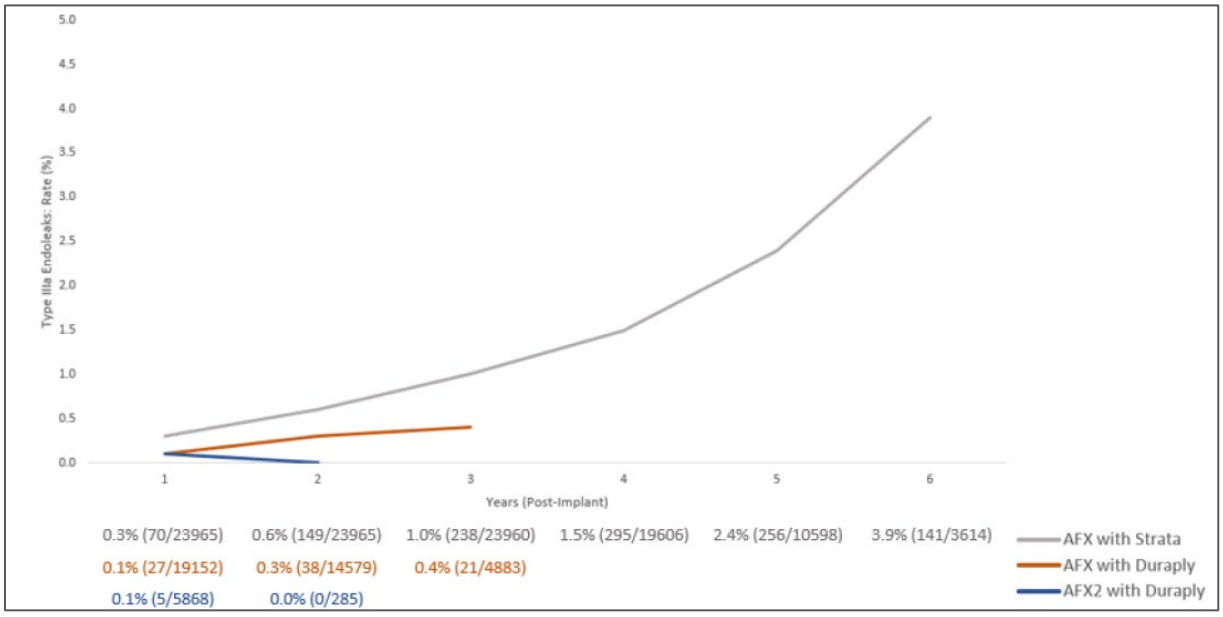
Additionally, the letter included mitigation strategies to address type III endoleaks including changes to the IFU, manufacturing changes, and device design changes. As reported by Endologix, the mitigation strategies covered activities that were implemented between 2013 – 2016. A summary of the mitigations is as follows:

- **Graft material change to Duraply:**
  In response to the high number of Type IIIb endoleak complaints, a CAPA investigation was opened in 2013. One corrective action was the change of Strata material to Duraply material. As noted in Section 2.4.3, this change resulted in a modified wrapping process during the manufacturing of the graft material.
- **IFU updates:**
    - To address the Type IIIa endoleaks, Endologix updated the IFU in 2013to reinforce the importance of device selection and emphasize maximizing the overlap region between bifurcated and extension components.
    - To further address the Type IIIa endoleaks, Endologix updated the IFU in 2015 to clarify information related to patient selection, procedure planning, and post-operative follow-up imaging. Endologix also provided a sizing algorithm to help ensure maximum overlap and determine the need for an additional infrarenal extension. The update clarified device sizing guidelines when using proximal extensions with bifurcated stent grafts.
    - To address the Type IIIb endoleaks, Endologix updated the IFU in 2014 to further clarify existing cautions and warnings related to over-inflation of balloons (if used) beyond the nominal diameter of the stent graft, guidewire manipulation, and vessel calcification.
- **AFX2 changes:**
    - Stent loading process change: A process change was developed for the AFX2 delivery system using a tension loading fixture that pulls the stent through a series of compression tubes and into the body cover, thus avoiding or reducing the risk of graft material damage.
    - Increased graft thickness: The specification for thickness was changed increasing the average thickness by 12.5%.
- **Selected product removal:**
  Endologix announced removal of the remaining Strata devices and the largest diameter sizes of the AFX2. The recall of the AFX2 devices was a corrective action after an investigation revealed that holes in the stent graft were observed during accelerated aging tests and that the larger diameter AFX2 devices were more susceptible compared to other sizes.

3.2.2 2018 Class I Recall (Recall ID: 80812)

In July 2018, following continued reports of Type III endoleaks across the AFX device family, Endologix submitted another recall to FDA. The firm received a total of 544 reports of Type III endoleaks with 535 serious/life-threatening injuries and 25 deaths related to the recall from the time period of November 2016 to August 2018. Endologix indicated the majority of event reports had been for the AFX with Strata (372 for AFX with Strata, 129 for AFX with Duraply, and 41 unidentified). Endologix reported a 2.4% rate of Type IIIa and a 2.0% rate of Type IIIb endoleaks at 5 years from their complaint data for the AFX with Strata.

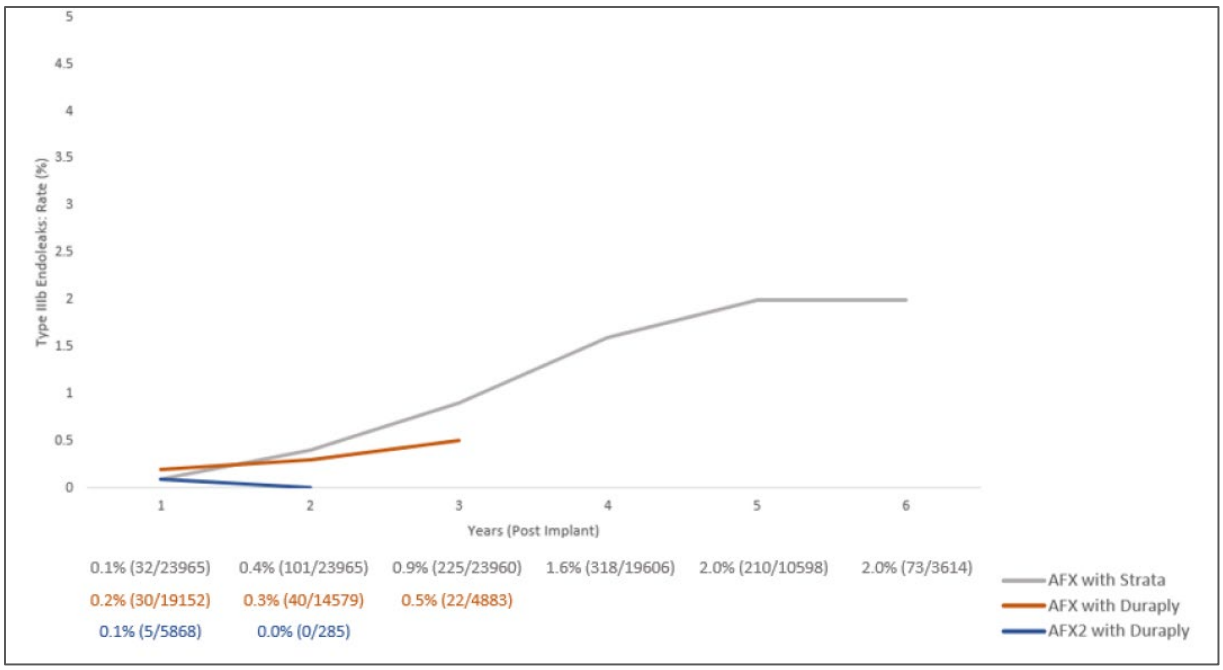
Endologix released follow-up letter to physicians in which they provided an update on the Type III endoleak rates. Figures 13 and 14 show the complaint rates at the time of the recall.



**NOTE: Complaint rates are calculated based on voluntary complaint reporting and units sold, which may underestimate the true event rate on a per patient basis. This underestimate may be greater for the more recent versions (i.e. AFX System with Duraply and AFX2 System with Duraply), which may have a larger hospital inventory as compared to the AFX System with Strata, which is no longer available.*

*** NOTE: Rates are generated by first summing all patients that have the minimum designated length of follow-up, based on the bifurcated implant sales. Then, all events that occur within the designated period among that same group of patients are summed together. The cumulative rate for each period is found by dividing the event sum by the number of at-risk patients. This approach provides cumulative complaint rates across a range of follow-up periods. Note that events known to have occurred within the designated length of follow-up, but occur in patients who have not yet reached the minimum required follow-up, are not included.*

Figure 13: Type IIIa Endoleak Complaint Trends by Product Type in 2018 Physician Letter



**NOTE: Complaint rates are calculated based on voluntary complaint reporting and units sold, which may underestimate the true event rate on a per patient basis. This underestimate may be greater for the more recent versions (i.e. AFX System with Duraply and AFX2 System with Duraply), which may have a larger hospital inventory as compared to the AFX System with Strata, which is no longer available.*

*** NOTE: Rates are generated by first summing all patients that have the minimum designated length of follow-up, based on the bifurcated implant sales. Then, all events that occur within the designated period among that same group of patients are summed together. The cumulative rate for each period is found by dividing the event sum by the number of at-risk patients. This approach provides cumulative complaint rates across a range of follow-up periods. Note that events known to have occurred within the designated length of follow-up, but occur in patients who have not yet reached the minimum required follow-up, are not included.*

Figure 14: Type IIIb Endoleak Complaint Trends by Product Type in 2018 Physician Letter

Endologix took corrective actions by updating the IFU focused on refining patient surveillance recommendations, sizing recommendations for AFX with Duraply, and recommendations for intervention/reintervention for patients with existing AFX devices when repair with AFX devices is not successful.

FDA Comment: AFX device recalls indicate a serious Type III endoleak concern. Although most data are from the AFX device versions that are no longer on the market, it is not clear if the mitigations implemented by Endologix have adequately addressed the issue for the current generation AFX2 device.

3.3 Summary of FDA Safety Communications

Part of FDA's public health mission is to help the public get the accurate, science-based information about medical products to maintain and improve patient health. At the time a medical device is approved, it has a benefit-risk profile that health care providers, patients, and consumers use to make patient management decisions. Once a medical device is on the market, new information, including unanticipated problems, may change a device's benefit-risk profile. Timely notification to relevant stakeholders about

emerging safety signals is intended to provide health care providers, patients, and consumers with access to the most current information concerning the performance and benefits and risks of marketed medical devices so that they can make informed patient management decisions about treatment and diagnostic options. Public notification at an early stage may reduce or limit the number of patients exposed to potential risk while the issue is being further evaluated and may promote enhanced vigilance on the part of clinicians, risk managers, patients and consumers.[29]

FDA continuously monitors reports of device-related adverse events related to endovascular grafts and publicly communicated concerns identified in alignment with the principals described above. As new information became available, updates were made to communicate in a timely fashion. Links are provided to the public notifications; they are also provided in Appendix 1 for ease of reference.

- September 2017: The FDA issued a Letter to Health Care Providers to communicate concerns related to an increase in the occurrence of Type III endoleaks with the use of endovascular graft systems.

- June 2018: In an updated Letter to Healthcare Providers, the FDA informed providers that the Endologix AFX with Strata device was at greater risk for a Type III endoleak compared to other endovascular AAA graft systems, and recommended providers closely monitor patients who have previously undergone implantation with the AFX with Strata device.

- October 2019: The FDA issued a Safety Communication to inform patients and health care providers about the potential higher than expected risk of Type III endoleaks occurring with the use of AFX with Duraply and AFX2 endovascular grafts.

- December 2020: The FDA updated the Safety Communication with new information which continued to suggest the risk of Type III endoleaks occurring with the use of AFX endovascular grafts with Duraply graft material (AFX with Duraply or AFX2) may be higher than expected. The new information cited included the following information (described in Section 3.1):
  - (Article) Chang, Robert W. et al. Mid-term outcomes for 605 patients receiving Endologix AFX or AFX2 Endovascular AAA Systems in an integrated healthcare system. Journal of Vascular Surgery 2020, Jul 3; S0741-5214(20)31470-1.[25]
  - (Abstract) Wanken, Zachary J; Anderson, Peter; Trooboff, Spencer; Columbo, Jesse; Goodney, Philip. Comparison of Endologix Endografts Made With Strata Fabric Versus IntuiTrak and Duraply Fabrics. Journal of Vascular Surgery 2019, Vol. 70(3), p. e44.[26]
  - (Abstract) Aranson, Nathan et al. Six-Year Outcomes of the Endologix AFX Endovascular AAA System: A Single-Center Experience. Journal of Vascular Surgery 2020, Vol. 72(1), p. e6[27]

  Because of the ongoing concerns regarding Type III endoleaks with AFX endovascular grafts, in this Safety Communication, FDA committed to obtaining additional postmarket data to better

[29] Center for Devices and Radiological Health. "Public Notification of Emerging Postmarket Medical Device Signals." U.S. Food and Drug Administration, FDA, www.fda.gov/regulatory-information/search-fda-guidance-documents/public-notification-emerging-postmarket-medical-device-signals-emerging-signals.

understand the risk and announced plans to convene an Advisory Committee meeting of the Circulatory System Devices Panel in 2021.

3.4 Additional Information Available since the 2020 FDA Safety Communication

3.4.1 Findings from MDR Analysis

Background Information Regarding MDR analyses

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and malfunctions. The database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters from health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
  - rare, serious, or unexpected adverse events;
  - adverse events that occur during long-term device use;
  - adverse events associated with vulnerable populations;
  - off-label use; and
  - use error.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. As a result, MDRs comprise only one of the FDA's several postmarket surveillance data sources. Other limitations of MDRs and the MDR database include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subject to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDR Review of Relevant AAA EVAR Devices

A review was performed of the MDRs reported to FDA relevant to the Endologix AFX Type III endoleak risk. The data were queried from the MAUDE database on August 27, 2021. The search included reports from all approved aortic endovascular grafts received by FDA between January 1, 2016 and July 31,

2021. Only MDRs for FDA approved and currently marketed AAA endovascular graft were included in the analyses (Table 1, Section 2.2.3).

There were 14,075 MDRs for the AAA device class. From there, each device was separated by manufacturer and device. Endologix reached its highest point of MDRs in 2018, which correlates with the 2018 Class I Recall discussed in Section 3.2.2 related to AFX Type III endoleak complaints. Note that in 2018, Endologix reported more MDRs than any other manufacturer (Endologix was responsible for 41% of AAA MDRs reported to FDA); note that this is not adjusted for sales or number of implants.

A MDR narrative search was performed to find MDR reports that mentioned specific keywords related to Type III endoleak: Type III, Type IIIa, Type IIIb, Type 3, 3A, 3B. These reports were again separated by manufacturer and device name**.**

In this analysis, FDA found that at least 45% of Endologix's total MDRs mentioned a Type III endoleak keyword, with a maximum reaching 55% in 2017. Endologix AFX (Strata and Duraply not differentiated) had 65% and AFX2 38% of the total MDRs mentioning Type III endoleak key words. Other marketed devices had between 0 and 30% of their MDRs mentioning Type III endoleak key words (See Figure 15 below). For the Endologix AFX (Strata and Duraply together) reports that mentioned Type III endoleak key words, 91% provided an implant date, with a mean implant date in 2014, median implant date in 2013, and mode implant date in 2014.

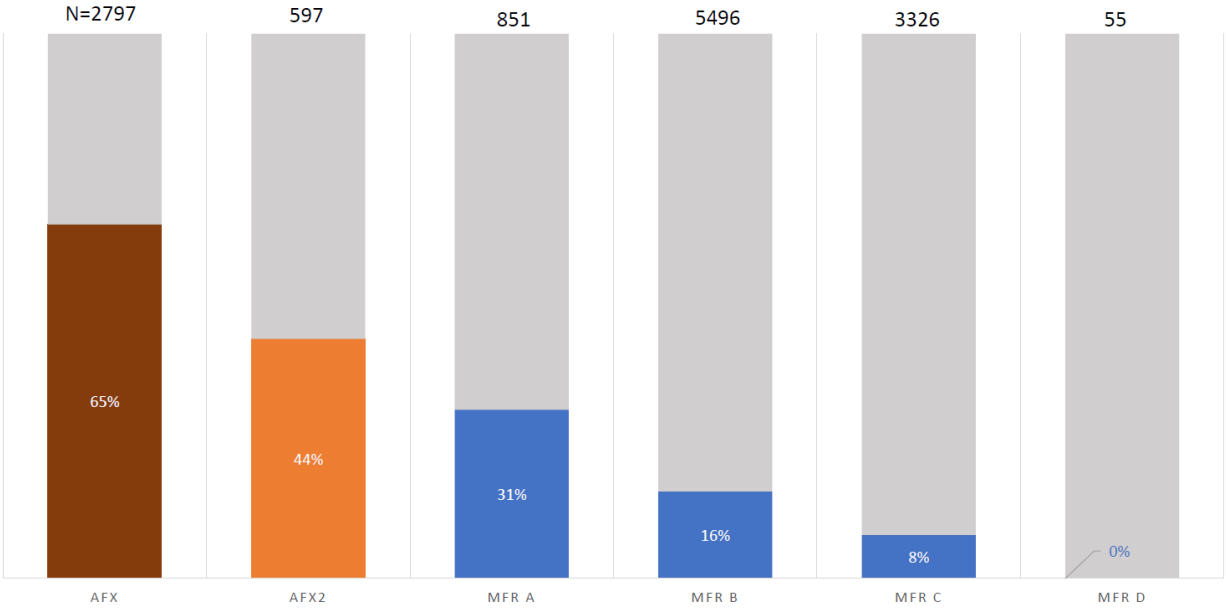


Figure 15: Percentage of Type III Endoleak Keyword by Device Brand Manufacturer

The majority of MDRs for the AAA device class were received 30-days post-implantation (n=4675), while the total number of MDRs for the AAA device class never exceeded n=1940 for 1 year, 3 years, 5 years, and 10+ years post-implantation. Endologix AFX had 46.4% of MDRs reported 5 years post-implantation and 41.3% of MDRs reported 10+ years post-implantation (see Figure 16).

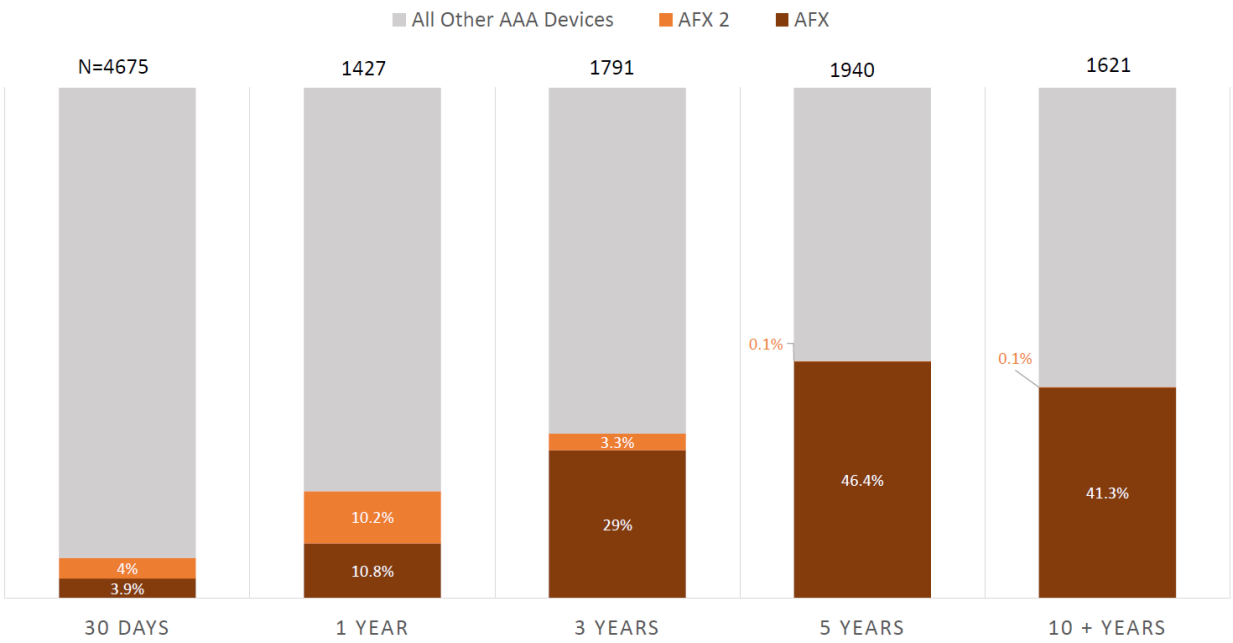


Figure 16: Percentage of AFX and AFX2 per Total MDRs by Time Post-Implantation

FDA Comment: Although there are limitations with MDR analyses, the data raise the possibility of a Type III Endoleak issue with all iterations of the AFX device platform that is not apparent with devices from other manufacturers. Additionally, Endologix tends to have a higher percentage of MDRs than other manufacturers after 3+ years, which is when Type III endoleaks start to become more apparent. These MDR trends are notable in view of the smaller Endologix market share compared to other AAA device manufacturers.

Of note, given the AFX analysis is inclusive of AFX with Strata and AFX with Duraply (and given limitations of the way the MDRs were reported), a particular device iteration (e.g., AFX with Strata) could be driving the MDR totals.

3.4.2 Information Provided by Endologix

To evaluate Type III endoleak risk, Endologix conducted independent post-market analyses. They believe that these post-market analyses provide support that mitigation efforts to date have lowered the rate of Type III Endoleak for AFX with Duraply and AFX2.

LEOPARD Trial

In 2015, the Endologix-sponsored LEOPARD (Looking at EVAR Outcomes by Primary Analysis of Randomized Data) Trial began enrollment. The study is a multicenter, prospective, US randomized trial designed to compare 5-year outcomes for the AFX System (AFX with DURAPLY and AFX2 Bifurcated Systems) to a reference group of EVAR devices (Cook Zenith, Gore Excluder and Medtronic Endurant devices). Annual CT imaging was not mandated, and enrollment was ended in 2017.

The LEOPARD trial includes 235 AFX subjects (124 subjects AFX with Duraply, 111 AFX2), of whom 75% were treated in close accordance to the labeled instructions for use. As of the February 28, 2021 data

cut, approximately half the original 235 subjects (52%) were eligible for 4-year follow-up. Although Endologix provided updated data on September 21, 2021, at the time of preparation of this Executive Summary, FDA has not fully reviewed these data. Of these subjects, about 28% of the AFX cohort had adequate imaging to evaluate for endoleak at 4 years (vs. 38% for the reference group). As of the February 28, 2021 data lock, one Type IIIa endoleak was reported in the AFX group, and two Type IIIb endoleaks were reported in the AFX group. The most recent results indicate a 1.3% cumulative probability of Type III endoleaks for AFX devices (see Table 7 below). No Type III endoleaks were identified in 220 patients treated with non-AFX endovascular grafts.

Table 7: Aneurysm-Related Complications

Aneurysm-Related Complications (ARC) Through February 28, 2021	**AFX/AFX2 with Duraply (n=235)**	**Comparators (n=220)**
Aneurysm Related Mortality (ARM)	5	3
Peri-Operative Mortality	3	0
ARM ≥ 30 Days	2	3
Aneurysm Rupture	2	1
Conversion to Open Surgical Repair	0	4
Device/AAA-Related Re-interventions	25	24
Endoleaks	3	0
Type Ia Endoleak	4	3
Type Ib Endoleak	5	4
Type II Endoleak*	34	43
Type IIIa Endoleak	1	0
Type IIIb Endoleak	2	0
Migration ≥10 mm	0	1
Aneurysm Enlargement ≥5 mm	7	6
Device Occlusion	4	8
Total Number of Subjects**	43	35

**These events are not device-related issues*

***Each reported adverse event is not mutually exclusive and a given subject may have had multiple adverse events*

Study strengths and limitations

Strengths

- Large multicenter, prospective randomized trial
- Imaging core lab review

Limitations

- Annual CT scans not required per protocol
- Substantial missing imaging data
- Limited longer-term follow-up for AFX2 subjects

VQI Registry

Endologix engaged M2S, Inc. to analyze previous iterations of AFX and the current AFX2 System compared to other EVAR devices utilizing information from the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI) database. VQI maintains an independent large data source that can compare peri-operative and 1-year follow-up outcomes amongst endografts in a contemporary, real-world EVAR patient population.

Follow-up data at 1 year for 1,011 patients treated with Endologix AFX (AFX with Duraply and AFX with Strata together) showed a 0.9% and 0.2% rate of Type IIIa and Type IIIb endoleaks, respectively compared to 0.2% and 0.1%, respectively, in 15,728 pooled patients treated with other devices ($p<0.0001$ and $p=0.161$, respectively). Follow-up data at 1 year for 343 patients treated with Endologix AFX2 showed a 0.9% and 0.0% incidence of Type IIIa and Type IIIb endoleaks, respectively, compared to 0.2% and 0.1%, respectively, in pooled 16,396 patients treated with other devices ($p=0.03$ and $p=1$, respectively).

Study strengths and limitations

Strengths

- VQI has 775 participating centers distributed across the US and Canada.
- VQI represents real-world practice and has obtained some one-year follow-up information in >70% of cases when patients return to the physician's office for follow-up.

Limitations

- The registry reports the Type III endoleak rate of AFX with Strata and AFX with Duraply together, so individual rates by device iteration are not available.
- VQI captures very limited outcome data past 1-year; no long-term data available.
- AFX with Strata and AFX with Duraply devices are included in the "All Other Devices" group when comparing results to the AFX2, which potentially increases the rate of Type III Endoleaks for the "All Other Devices" comparator group.

Endologix Complaints Database

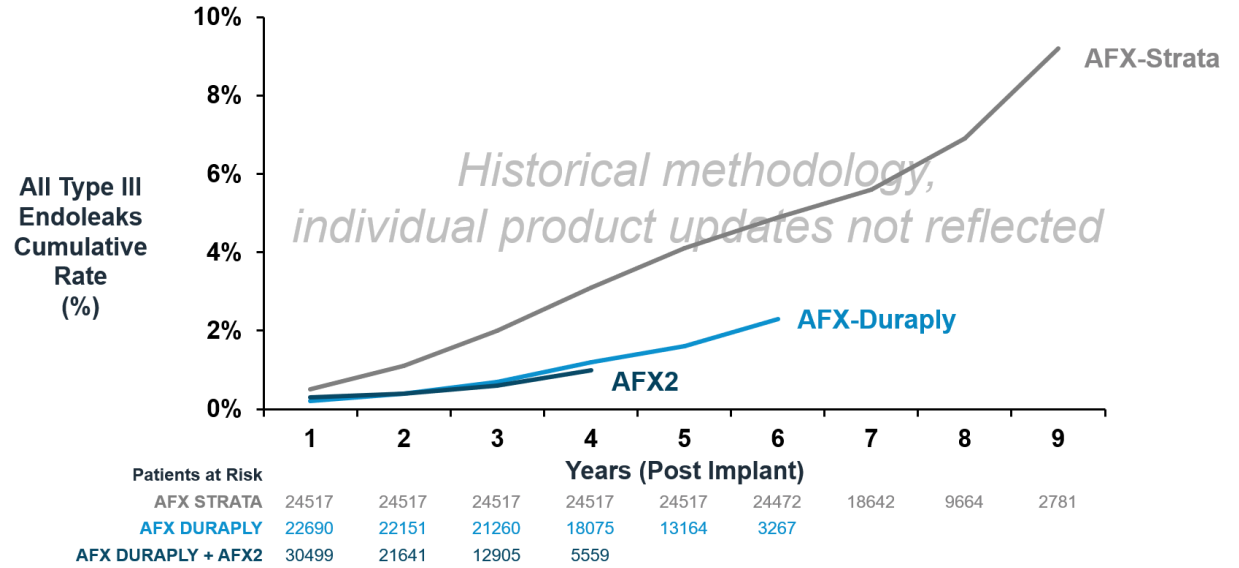
Endologix provided a summary of their complaint database (data cut through February 28, 2021) analysis for all iterations of the AFX System (see Figure 17 – 19 for complaint trends of the different AFX iterations for Type III, IIIa, and IIIb endoleaks, respectively). There are increases in the cumulative complaint rates reported for all AFX device iterations, with these cumulative rates being double to triple the previously publicly available cumulative rates from 2018 in many cases (Table 8).

Table 8: Comparison of Type III Endoleak Cumulative Rates between July 2018 Customer Letter and February 2021 data lock

July 2018 Endologix customer letter for class I labeling recall related to Type III endoleaks[30]	***Feb 28, 2021 Endologix data** (sent to FDA July 27, 2021)
Type III Endoleaks - Overall	
Strata – N/A	**Strata – 9.2% at 9 years (257/2781)**
Duraply – N/A	**Duraply – 2.3% at 6 years (76/3267)**
AFX2 – N/A	**AFX2 – 1.0% at 4 years (57/5559)**
Type IIIa	
Strata – 3.9% at 6 years (141/3614)	Strata – 6.2% at 9 years (173/2781)
Duraply – 0.4% at 3 years (21/4883)	Duraply – 1.1% at 6 years (35/3267)
AFX2 – 0.1% at 1 year (5/5868)	AFX2 – 0.6% at 4 years (33/5559)
Type III b	
Strata – 2.0% at 6 years (73/3614)	Strata – 4.2% at 9 years (117/2781)

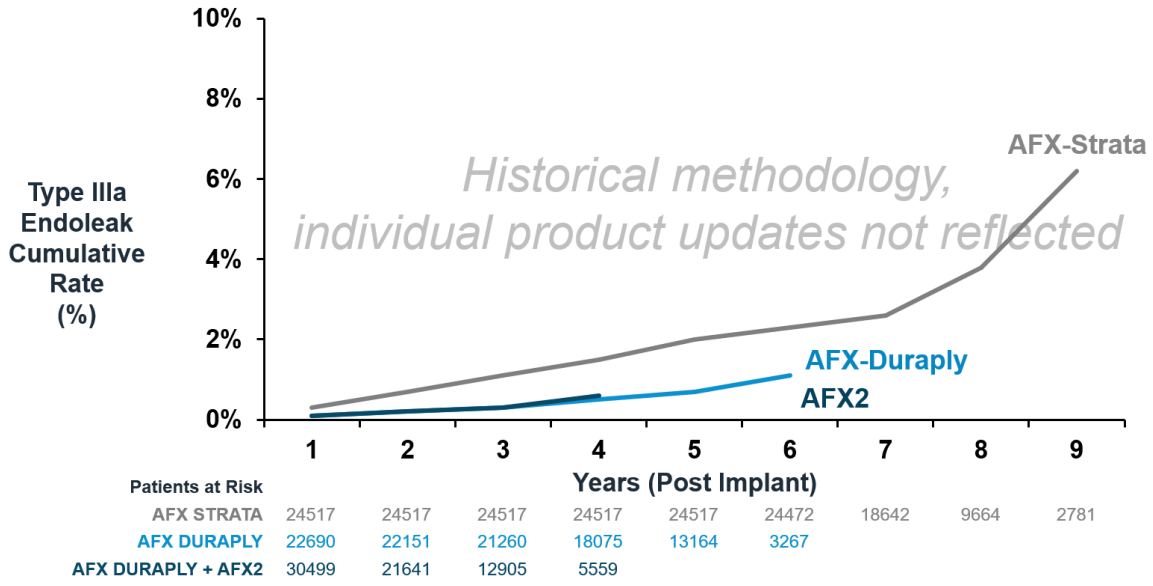
[30] Urgent: Important Safety Update Medical Device Correction for the AFX® Endovascular AAA System. Endologix, LLC., 20 July 2018, endologix.com/wp-content/uploads/2018/07/AFX-Safety-Update-AFX-Users_July2018.pdf

Duraply – 0.5% at 3 years (22/4883)	Duraply – 1.4% at 6 years (46/3267)
AFX2 – 0.1% at 1 year (5/5868)	AFX2 – 0.5% at 4 years (28/5559)



± For this graphic, Type III Endoleak events are depicted based on the bifurcated device used at time of implantation. Based on this approach, Type III Endoleak events reported on extensions for which the bifurcated device is unknown have been excluded. This includes fifteen (15) Duraply extensions. Furthermore, reported events which did not report sufficient or accurate information to depict time to event have been excluded. This includes: thirty-eight (38) events reported on the Strata Bifurcated device and five (5) events reported on the Duraply Bifurcated device. Additionally, there were fifty-two (52) events reported on devices with an unknown material type.
** Five-year data for grafts implanted with an AFX2 Bifurcated device have been excluded due to a low denominator at this time point (< 5 devices).*
NOTE: zero (0) events have been reported at this timepoint.

Figure 17: Type III Endoleak (Combined) Complaint Trends, Bifurcated Device Type (February 28, 2021)
[Note that Endologix included the statement "Historical methodology, individual product updates not reflected" in the graphic they provided FDA of their complaint data. This is not a statement from FDA.]

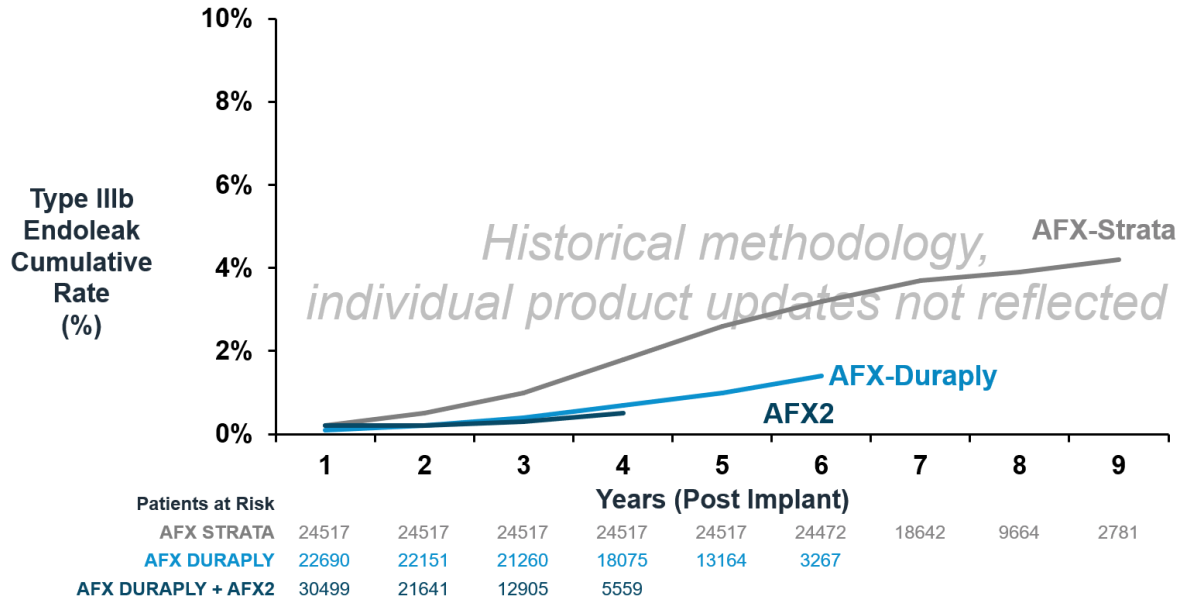


‡For this graphic, Type III Endoleak events are depicted based on the bifurcated device used at time of implantation. Based on this approach, Type III Endoleak events reported on extensions for which the bifurcated device is unknown have been excluded. This includes eleven (11) Duraply extensions. Furthermore, reported events which did not report sufficient or accurate information to depict time to event have been excluded. This includes: sixteen (16) events reported on the Strata Bifurcated device and two (2) events reported on the Duraply Bifurcated device. Additionally, there were twenty-five (25) events reported on devices with an unknown material type.

** Five-year data for grafts implanted with an AFX2 Bifurcated device have been excluded due to a low denominator at this time point (< 5 devices). NOTE: zero (0) events have been reported at this timepoint.*

Figure 18: Type IIIa Endoleak (Combined) Complaint Trends, Bifurcated Device Type (February 28, 2021)

[Note that Endologix included the statement "Historical methodology, individual product updates not reflected" in the graphic they provided FDA of their complaint data. This is not a statement from FDA.]



± For this graphic, Type III Endoleak events are depicted based on the bifurcated device used at time of implantation. Based on this approach, Type III Endoleak events reported on extensions for which the bifurcated device is unknown have been excluded. This includes four (4) Duraply extensions. Furthermore, reported events which did not report sufficient or accurate information to depict time to event have been excluded. This includes: twenty-three (23) events reported on the Strata Bifurcated device and three (3) events reported on the Duraply Bifurcated device. Additionally, there were thirty-two (32) events reported on devices with an unknown material type.
** Five-year data for grafts implanted with an AFX2 Bifurcated device have been excluded due to a low denominator at this time point (< 5 devices). NOTE: zero (0) events have been reported at this timepoint.*

Figure 19: Type IIIb Endoleak Complaint Trends, Bifurcated Device Type (February 28, 2021) ±
[Note that Endologix included the statement "Historical methodology, individual product updates not reflected" in the graphic they provided FDA of their complaint data. This is not a statement from FDA.]

Data strengths and limitations

Strengths

- Event comparison duration starting at time zero (implant) and presenting years post-implant that the event occurred

Limitations:

- Complaint data may underestimate the true event rate.
- Denominators represent all devices sold rather than devices implanted.
- Numerators likely underestimate Type III endoleak events since as they are not always reported to the manufacturer and therefore not reflected in the complaint data.

FDA Comment: FDA has the following comments on the additional data sources:

- *LEOPARD Trial* - This is randomized controlled clinical study which includes outcomes data on AFX with Duraply and AFX2 compared to a reference group of devices. There are few Type III endoleaks reported in the trial but all in the AFX with Duraply and AFX2 group (i.e., 1.3% cumulative probability of Type III endoleaks for AFX and no Type III endoleaks for the comparator group). Although the Type III endoleak rate is not as high as reported in some literature sources, it is not clear that these data definitively addresses the outstanding concerns regarding the Type III endoleak risk for the AFX platform given information from other published literature. Also, there is an important lack of imaging follow-up compliance at later timepoints, which may underestimate Type III endoleak rates. We are encouraged that Endologix is incorporating Core Lab review of imaging and that, along with additional longer term imaging follow-up data, will be important to critically consider when available.

- *VQI Registry* – The analysis provided is based upon available 1-year data. There is a significantly higher rate of Type IIIa endoleaks for AFX with Strata/AFX with Duraply and AFX2 as compared to the rate for other endovascular grafts at one year of follow-up. Type IIIb endoleaks generally tend to occur several years after device implantation and become more frequent over time. Therefore the follow-up duration limits the ability to adequately assess Type IIIb endoleaks. These data support early concerning Type III endoleak trends for all AFX device iterations.

- *Endologix Complaint Database* – The complaint data suggests that the mitigations Endologix implemented to reduce the Type III Endoleaks (i.e., labeling and design/manufacturing updates) may have reduced the reported complaint rates at earlier timepoints for AFX with Duraply and AFX2 compared to AFX with Strata. However, the rate of Type III endoleaks continues to increase over time even with the mitigation measures in place. In particular, the Type III endoleak cumulative rate for AFX with Duraply has exceeded 2.0% at 6 years, which was the threshold Endologix used internally to trigger the CAPA investigation for the AFX with Strata that eventually led to removal of AFX with Strata from the market.

  Given the similar trends observed for AFX with Duraply and AFX2, this complaint analysis suggest that long-term AFX2 performance may be similar to AFX with Duraply.

Based on the limitations of Endologix's data collection efforts and data available from other sources, it is unclear if mitigation strategies implemented by Endologix have solved the Type III endoleak issue with the currently marketed AFX2. As such, FDA has engaged in additional data collection efforts, which are described in Section 3.5.3.

3.4.3 FDA Data Collection Efforts in Collaboration with External Collaborators

FDA has been collaborating with external research groups on real-word data analyses to investigate safety concerns associated with EVAR. The analyses described below are ongoing FDA-funded safety studies. Preliminary results are expected to be available for Advisory Committee consideration.

Medicare Claims Data Analysis
This study is being conducted at Beth Israel Deaconess Medical Center/Harvard Medical School. The study is an observational retrospective cohort study of Medicare beneficiaries who underwent infrarenal EVAR with an Endologix AFX endograft or other commercially available FDA approved endovascular graft. The treatment observation period is from August 1, 2011 through December 31, 2017, with long-term outcomes ascertained through December 31, 2019. Approximately 30,000 patients are included in this study. The primary objective is to evaluate the composite outcome of late aneurysm rupture, endograft relining, graft extension, conversion to open repair, or all-cause mortality following infrarenal EVAR with an AFX unibody endovascular graft compared with other commercially available endovascular grafts. The secondary objectives are to: (1) evaluate late aneurysm rupture, endograft relining, graft extension, or conversion to open repair; (2) examine individual secondary outcomes of late aneurysm rupture, endograft relining, graft extension, conversion to open repair, perioperative outcomes, other reinterventions, morbidity and mortality associated with reintervention and aneurysm rupture, and long-term survival; and (3) perform sensitivity analyses to assess outcomes related to the availability of different AFX device iterations over the study period.

Electronic Health Records Analysis from Veterans Affairs Dataset
This study is being conducted at the Harvard-MIT Center for Regulatory Science (HMCRS). The analysis examines the use of medical devices in endovascular aneurysm repair in order to determine the effect of endovascular graft choice on perioperative and long-term outcomes, focusing on outcomes and adverse events associated with the Endologix AFX Endovascular AAA Systems. The study will use Electronic Health Records (EHR) data from a national cohort of Veteran's Affairs (VA) patients, identifying patients who underwent endovascular repair of an intact abdominal aneurysm between 2011 (first year of AFX device marketing) and 2020. Based on preliminary assessments of EVAR rates and availability of key data elements, the cohort with adequate follow up in the national VA dataset is approximately 25,000 patients with EVAR and available device name and model. The study will characterize EVAR procedure outcomes at various timepoints over a 5-year follow-up period, including perioperative surgical complications (e.g., Type III endoleaks, relining, conversion), medical complications (e.g., myocardial infarction, pneumonia), and all-cause mortality.

4 Regulatory Considerations

The Advisory Committee will be asked to provide recommendations on whether additional mitigation strategies should be implemented to address the Endologix AFX Type III endoleak risk. In this section, FDA offers some regulatory considerations regarding risk mitigation strategies. FDA also provides information on mandated post-market surveillance in response to a safety concern.

4.1 Risk Mitigation Strategies

Risk mitigation strategies may include device design modifications, additional recommendations for surgical technique, proper labeling, and training. All postmarket device and labeling changes must be reported to FDA, and significant changes that may affect safety or effectiveness of the device require approval by the FDA prior to implementation.

To mitigate the risk of Type III endoleaks:

- Device design considerations include whether there are design/performance features that could be modified
- Surgical technique considerations include graft placement methods
- Labeling and training considerations include instructions/directions for device use.

Another important aspect of proper labeling is informed decision-making. To make an informed decision about a medical device, a patient should understand the expectations associated with that device, including the potential risks and anticipated benefits. Patient labeling is designed to assist a patient's informed decision-making process. There may be ways that patients could benefit from a structured and standardized presentation of Type III endoleak risks, such as a boxed warning or a shared decision-making tool such as patient-directed decision checklist.

Additional examples of risk mitigation measures include voluntary product recall/removal and withdrawal of the PMA.

4.2 Mandated Post Market Surveillance

CDRH may identify device issues that are appropriate for evaluation in a postmarket surveillance study at any point during the device life cycle.[31] Relevant issues may be identified through an analysis of adverse event reports, a recall or corrective action, post-approval study data, premarket data, reports from other governmental authorities, or the scientific literature.

If a public health concern arises, postmarket surveillance under Section 522 of the Act is a mechanism by which the FDA can obtain additional safety and/or effectiveness data for a device after it has been cleared via a 510(k) or approved through a PMA.

Section 522 of the Act [21 U.S.C. 360l] authorizes the FDA to require postmarket surveillance in the following instances:

- a Class II or Class III device for which failure of the device would be reasonably likely to have a serious adverse health consequence (Section 522(a)(1)(A)(i) of the Act),
- a Class II or Class III device expected to have significant use in pediatric populations (Section 522(a)(1)(A)(ii) of the Act),
- a Class II or Class III device intended to be implanted in the human body for more than one year (Section 522(a)(1)(A)(iii)(I) of the Act), or
- a Class II or Class III device intended to be a life-sustaining or life-supporting device used outside of a user facility (Section 522(a)(1)(A)(iii)(II) of the Act).

One or more of the criteria above need to be met for Section 522 postmarket surveillance to be considered by the FDA.

In general, Section 522(b)(1) of the Act authorizes the FDA to order prospective postmarket surveillance for a duration of up to 36 months unless the manufacturer and the FDA agree to extend that timeframe. Alternative study designs (e.g., beyond prospective surveillance, or a broad approach such as an all-

[31] Center for Devices and Radiological Health. "Postmarket Surveillance (Section 522 of FDC Act) Guidance." *U.S. Food and Drug Administration*, FDA, www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act-0.

comers registry) may be recommended by the FDA or proposed by the sponsor. An interim and final reporting schedule is required as part of the study plan.

5 Treatment of Endologix AFX Devices That Have Experienced a Failure Mode

An important clinical consideration related to the Type III endoleak risk is the optimal management of this potentially fatal device failure mode. Some AFX device design features can present challenges to subsequent catheter-based procedures or reinterventions. As reported by Lemmon et al., the unique endoskeleton design feature can complicate guidewire and device entry on redo procedures due to the potential for device entrapment between the wireframe and fabric.[32] These authors caution that prior to intervention, it is essential that the operator avoid wireframe entrapment by using a preformed catheter to advance through the AFX endovascular graft and confirm passage of a partially inflated balloon through the entire endovascular graft while observing for wireframe movement or deformation.

When treating AFX failures related to fabric leaks (Type IIIb endoleaks), Lemmon et al. note the potential for additional component devices increase the metallic burden within the endograft, and caution is needed to completely reline type IIIb endoleak cases with a second complete endograft system. The authors state *"as there are no data to support any endograft type as superior, and endograft relining should be performed with the stent graft that vascular surgeons are most familiar with to provide the same principles of adequate proximal and distal seal zone with secure fixation and adequate component overlap as an original EVAR placement."*

In their 2018 presentation to the Western Vascular Society, Barleben and colleagues from University of California, San Diego reported on lessons learned in the management of 107 subjects with early generation AFX endografts.[24] Of 107 patients with AFX grafts (specific iteration not clarified), 26 developed Type III endoleaks (24.3%). Complete endograft relining was performed in 22 patients; indications were Type IIIa (n=4) and Type IIIb (n=18) endoleaks. Concomitant reasons for reintervention included Type Ia endoleak (n=1), type Ib endoleak (n=2), and device migration (n=1). Complete endograft relining was performed with 100% technical success. After relining with a variety of endografts (86% Ovation iX), all patients had resolution of Type III endoleak. The average follow-up period was 13 months (1.0-41.8 months).

Aside from these reports, there remains a paucity of clinical data to support the longer-term performance of any endovascular bailout measures to treat AFX-related Type III endoleaks.

An "AFX within AFX" results in the situation where the new fabric layer is sandwiched between the metal endoskeleton of the failed AFX device and that of the new AFX endograft. The durability of this overlapped device configuration remains uncertain. Clinicians facing the challenge of treating patients with Type IIIb endoleaks after AFX implants must rely primarily on their best clinical judgement. Open surgical conversion may be necessary when an endovascular bailout fails or is not a good option.

Endologix has not outlined a plan to prospectively gather data on patients with AFX device failures including Type III endoleaks that may help guide patient treatment. They have, however, interacted with

[32] Lemmon G, Barleben A, et al. Diagnosis and relining techniques for delayed type IIIB endoleaks with the second-generation AFX endograft. J Vasc Surg Cases and Innovative Techniques 2019;5:51-3.

the FDA on a proposal to retrospectively evaluate information available on AFX-in-AFX relinings based upon their complaint analysis. FDA has also held conversations with Endologix about a potential labeling update regarding AFX-in-AFX relining procedures.

6 Benefit/Risk Discussion

FDA considers both the benefits and risks of a device for regulatory decision-making, and factors include: the extent of the probable benefits and risks, including the type, magnitude/severity, probability, and duration; the uncertainty surrounding these factors; whether alternative treatment exist; the patient's perspective, and the public health need.

FDA's original approval of the Endologix AFX System was based on the available leveraged Endologix Powerlink clinical data, supportive engineering and biocompatibility testing, and the potential benefits of the unique device design. At the time of product approval, these data led FDA to determine that the probable benefits of the device outweighed the probable risks.

Numerous AFX System iterations have been implemented, as is common with approved devices. At the time of each iterative change (e.g., from Strata to Duraply graft material, delivery system updates, labeling updates, manufacturing updates), FDA reviewed the supportive information (e.g., engineering bench testing) provided by the sponsor and believed the benefit-risk assessment was favorable for the changes to be implemented (i.e., the information provided by the sponsor indicated that the safety and effectiveness profile of the device would remain consistent or improve due to the implemented changes). However, because of the ongoing concern of Type III endoleaks developing longer-term with the currently marketed device iteration (AFX2), it is important to re-evaluate the benefit-risk profile of the device.

Based upon the currently available information, FDA is seeking Advisory Committee input on the benefit-risk profile of the Endologix AFX device family with a focus on the currently marketed AFX2 device. FDA's rationale for this focus is that there is a known significant problem with the previous iteration of the device (the AFX with Strata that was recalled), and it is uncertain whether the device design/manufacturing changes and other mitigation measures have been adequate to address the Type III endoleak issue in the currently marketed AFX2 device.

7 Conclusion

FDA has provided information related to the Type III endoleak risk for the Endologix AFX System from several different data sources, including ongoing real-world studies, published abstracts and peer-reviewed literature, MDR and Endologix complaint data, the Endologix LEOPARD trial, and the Endologix VQI analysis. Based on an analysis of the currently available data, there appears to be a higher than expected rate of Type III endoleaks with the AFX System, regardless of the device iteration. However, because of the limitations with the data sources, there is residual uncertainty whether the mitigation measures implemented by Endologix have been adequate to address the Type III endoleak concerns for the currently marketed AFX2 device.

The Committee will be asked to provide input and recommendations regarding the totality data and the benefit-risk profile of the device, as well as recommend additional risk mitigation measures if deemed appropriate.

8 References

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Appendix 1: Trends in AAA Management Discussion

Over the past three decades, the refinement of EVAR technology and the availability of various commercial endograft systems, many now in their 3rd of 4th generations, have led to a shift in the elective management of AAAs. As show in Figure 20, By 2015, 83% of elective AAA repairs were performed with EVAR in the US, and EVAR continues to be the most common treatment for AAA repair in the US.[9]

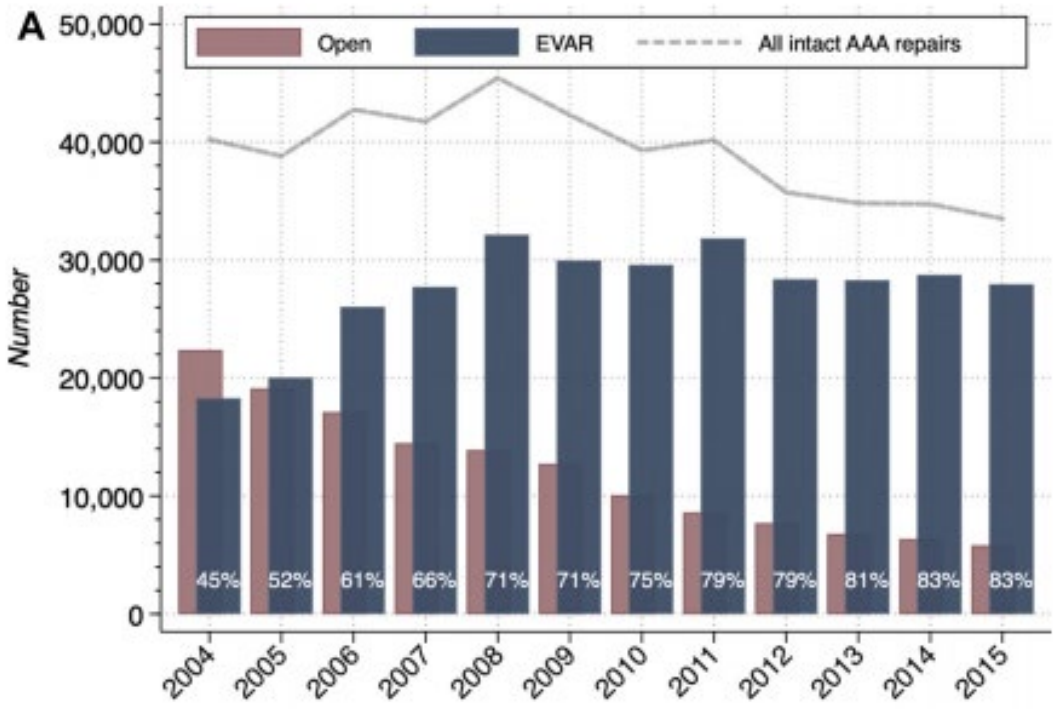

Figure 20: Comparison of Open Repair vs. EVAR by Year

Comparative Benefits of EVAR vs. Open Repair

During the early years of EVAR, randomized trials vs. open surgical repair were completed. A Cochrane meta-analysis of the pooled data from 2790 subjects enrolled in the four largest randomized trials demonstrated that the in-hospital or 30-day mortality rate with EVAR was 1.4% vs. 4.2% for open surgery (odds ratio 0.3, 95% confidence interval 0.22-0.50; P<0001).[33] While the short-term benefit provided by EVAR is clear, analysis of longer-term subject outcomes in the both the randomized trials and in the Medicare population shows that this mortality benefit over open surgery is not sustained beyond the intermediate term.[14] Figure 21 illustrates the Hazard Ratios for EVAR compared to open surgical repair for all-cause mortality, AAA-related mortality and secondary interventions over time.

[33] Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm.

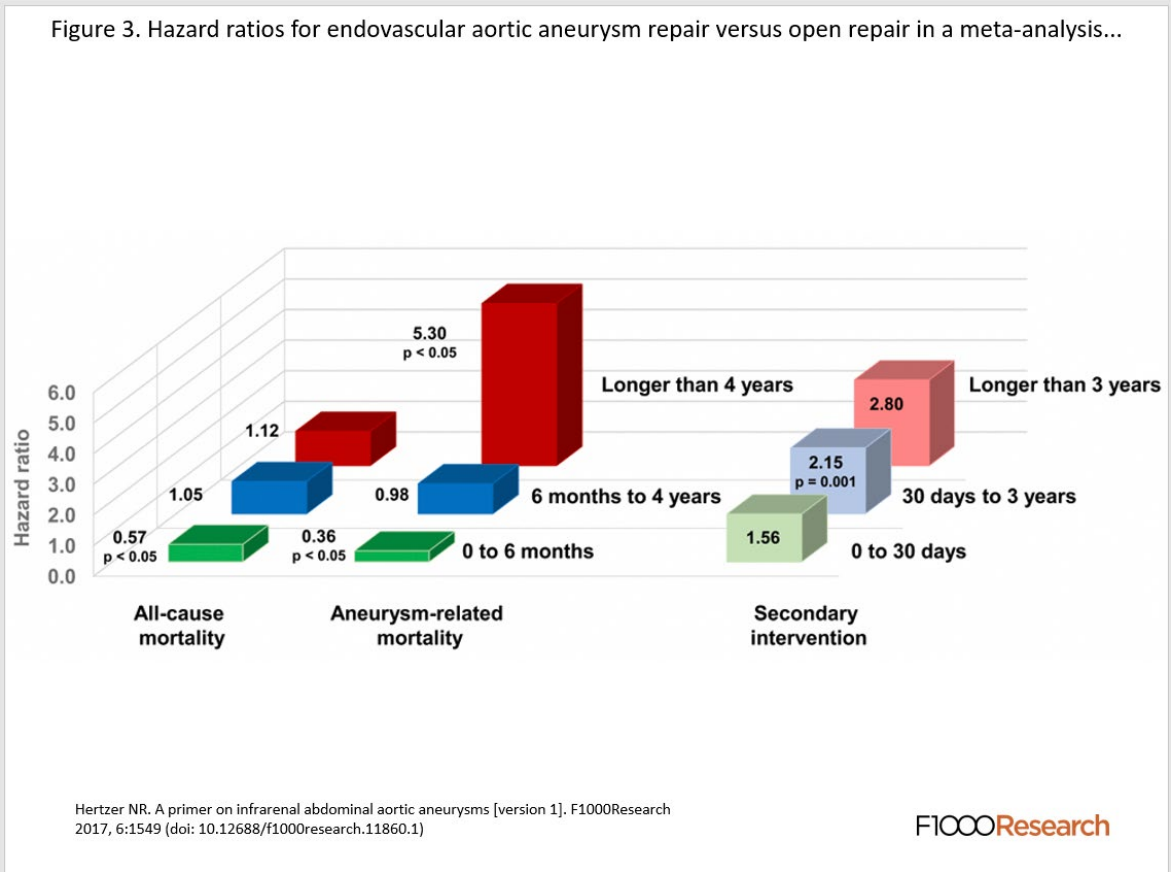

Figure 21: Hazard ratios for EVAR vs. Open Repair

The Kaplan-Meier (KM) mortality curves for the EVAR I trial are reproduced below. The survival curves for Aneurysm Related Mortality (ARM) cross after 6 years and further diverge after 8 years with the late increase in aneurysm-related mortality in the EVAR group being mainly attributable to aneurysm ruptures.

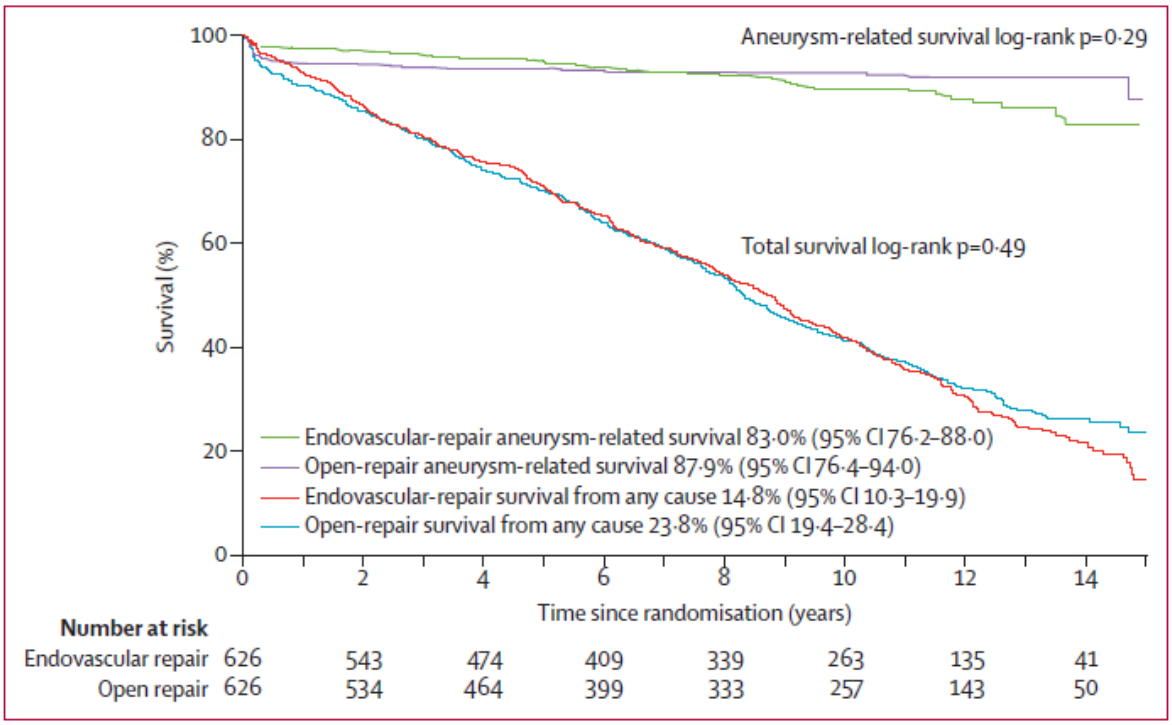

Figure 22: Kaplan-Meier estimates for total survival and aneurysm-related survival up to 15 years of follow-up

Based on the analysis of the outcomes of the open and endovascular approaches, EVAR has distinct short-term mortality benefits in anatomically eligible candidates. The early survival benefit favoring EVAR is lost over the intermediate term and beyond. As seen in the KM graph, EVAR related survival out to 15 years were estimated at 83.0% and 14.8% from ARM and all-cause mortality, respectively. These same rates for open-repair survival were estimated at 87.9% and 23.8%, respectively. The endovascular mode of treatment requires careful lifelong surveillance because of the greater potential for late AAA rupture and the need for secondary interventions required to maintain device benefit and to prevent AAA-related events.[15]

Appendix 2: Key Peer Reviewed Publications

The following publications were provided to the panelists (same references as provided in bibliography)

23. Lemmon GW, Motaganahalli RL, et al. Failure mode analysis of the Endologix endograft. J Vasc Surg. 2016 Sep; 64(3):571-6
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27. Ta TM, Aranson NJ, et al., J Vasc Surg , 2020, Six-Year Outcomes of the Endologix AFX1 Endovascular AAA System: A Single-Center Experience 72(3) pp.e291

Appendix 3: Previous Safety Communications

December 2020 - UPDATE: The FDA Reminds Patients and Health Care Providers of the Importance of At Least Yearly, Lifelong Follow-Up with Use of Endologix AFX Endovascular AAA Graft Systems: FDA Safety Communication

The U.S. Food and Drug Administration (FDA) is updating our October 28, 2019 safety communication on the use of AFX endovascular grafts with Duraply material (AFX with Duraply or AFX2) to provide new data, review current recommendations, and announce the FDA's intention to convene an Advisory Committee meeting in 2021.

The FDA recommendations from our October 2019 safety communication have not changed. The FDA is reminding patients and health care providers of the importance of at least yearly, lifelong follow-up for all patients who have any type of Endologix AFX endovascular graft (AFX with Strata, AFX with Duraply, or AFX2) in order to monitor for Type III endoleaks.

The FDA continues to evaluate new information which suggests the risk of Type III endoleaks occurring with the use of AFX endovascular grafts with Duraply graft material (AFX with Duraply or AFX2) may be higher than expected. Because of ongoing concerns regarding this issue, the FDA is committed to obtaining additional postmarket data to better understand the risk of Type III endoleaks for AFX endovascular grafts. In addition, the FDA will convene an Advisory Committee meeting of the Circulatory System Devices Panel in 2021 to discuss the Type III endoleak risk for AFX endovascular grafts, the Type III endoleak treatment options for patients who are implanted with AFX devices, and future postmarket surveillance strategies for all endovascular grafts used for the treatment of abdominal aortic aneurysms (AAA). Further details concerning the agenda, timing and location of the Advisory Committee meeting will be announced in the first quarter of 2021.

Important Recommendations for Patients Who Have or Are Considering an Endologix AFX Endovascular Graft System for Treatment of Abdominal Aortic Aneurysms (AAAs), including: AFX with Strata, AFX with Duraply, or AFX2.

The FDA is reminding patients of the following recommendations. The FDA recommendations from our October 2019 safety communication have not changed. Notably, FDA recommends at least yearly, lifelong follow-up for all patients who have had their AAA treated with any AFX endovascular graft system.

- Be aware that the FDA has approved endovascular grafts made by various manufacturers for the treatment of AAA, and each device has specific benefits and risks.
- Prior to surgery, discuss the benefits and risks of all available AAA treatment options with your health care provider.
- If you have already had treatment of your AAA with an endovascular graft system, review the implant card you received at the time your AAA was treated to determine if you have any type of Endologix AFX endovascular graft implanted. If you do not know if you have an AFX endovascular graft or if you do not have your implant card, contact the health care provider who treated your AAA or the hospital where you were treated to find out.

- If you have any type of Endologix AFX endovascular graft, contact the health care provider who treated your AAA or another vascular specialist about further care and to discuss continued follow-up.
- Be aware that data suggest there may be a higher than expected risk of blood continuing to leak into the AAA (Type III endoleak) which can result in serious injury, including death when any AFX endovascular graft is used for the treatment of AAA.
    - As a result the FDA recommends at least yearly, lifelong follow-up for all patients who have had their AAA treated with any AFX endovascular graft system.
    - If you have an AFX endovascular graft and are overdue for a follow-up, make an appointment with the health care provider who treated your AAA or another vascular specialist to get your device checked.

Important Recommendations for Health Care Providers who treat and follow patients with an Endologix AFX Endovascular Graft System for Treatment of Abdominal Aortic Aneurysm (AFX with Strata, AFX with Duraply, or AFX2)

The FDA is reminding health care providers of the following recommendations. The FDA recommendations from our October 2019 safety communication have not changed.

- Prior to surgery, discuss the benefits and risks of all available AAA treatment options with your patients.
    - The benefit-risk profile of AFX endovascular grafts compared to alternative treatment options should be considered for each individual patient.
    - When making AAA treatment recommendations, and as part of the informed consent process, consider that data suggest there may be a higher than expected risk of Type III endoleaks in patients treated with any Endologix AFX endovascular grafts.
- Read and carefully follow the Endologix AFX Endovascular AAA System Instructions for Use (IFU), which was revised in 2018 with updated information regarding Type III endoleaks.
    - The IFU includes component overlap recommendations, Type III endoleak risk factors and patient-tailored surveillance recommendations to assist health care providers in developing individualized patient follow-up plans.
- Closely monitor patients who have previously undergone implantation with any AFX endovascular graft and evaluate their risk profile for Type III endoleaks per the IFU.
    - Ensure yearly imaging follow-up at a minimum to monitor for the development of Type III endoleaks and aneurysm expansion for any patients under your care who have previously undergone implantation with any AFX endovascular graft (AFX with Strata, AFX with Duraply, or AFX2).
    - A benefit-risk determination for each individual patient should be considered to assess the need for additional procedures related to the risk of developing Type III endoleaks.

Reporting Problems with Your Device to the FDA

If you think you had a problem with your device or a device your patient uses, we encourage you to report the problem through the MedWatch Voluntary Reporting Form , including, but not limited to, the following:

- Early or late device-related adverse events, such as Type III endoleaks.
- Adverse events related to secondary interventions to treat Type III endoleaks.

Health care personnel employed by facilities that are subject to the FDA's user facility reporting requirements should follow the reporting procedures established by their facilities.

Device Description:

An endovascular graft can be used to treat an abdominal aortic aneurysm (AAA). Endovascular grafts are flexible fabric tubes supported by a metal framework either on the inside or outside of the fabric. The endovascular graft is permanently implanted inside the largest blood vessel (aorta) so that blood flows through the endovascular graft instead of to the aneurysm, reducing the risk of further aneurysm growth or rupture. These devices are made by various manufacturers, and each of the devices used to treat AAAs has specific benefits and associated risks.

The AFX Endovascular AAA System (AFX), manufactured by Endologix, Inc., is an endovascular graft system intended to treat patients with AAA. The AFX endovascular graft was approved by the FDA in 2011 and over time, the manufacturer has made changes to the device resulting in the following versions of the device being implanted in patients in the United States:

- **AFX with Strata graft material,** which was implanted in patients between 2011 and 2016 but is no longer available on the market, after Endologix requested that all AFX with Strata devices be removed from hospital inventory because of an increase in Type III endoleaks.
- **AFX with Duraply graft material,** which was implanted in patients between 2014 and 2018 but is no longer available on the market, with the change in graft material from Strata to Duraply intended to help prevent Type III endoleaks.
- **AFX2 (Duraply graft material),** which has been implanted in patients since 2016 with changes to the manufacturing of the Duraply graft material to increase the average thickness and intended to further help prevent Type III endoleaks.

In addition, the manufacturer over time has updated the instructions for use (IFU) for the device. The main change to address Type III endoleaks occurred in 2015, which included instructions regarding device sizing, as well as to increase the amount of overlap between graft segments that are joined together to treat the AAA.

Type III Endoleak
Various types of endoleaks can occur after repair with any endovascular graft and typically do not result in any symptoms.

Therefore, patients who have been treated with **any** endovascular graft require regular, lifelong follow-up imaging (for example, a CT scan with contrast) for the detection of endoleaks.

Type III endoleaks in particular consist of blood flowing or leaking into the AAA either between endovascular graft segments that were joined together to treat the AAA at the time of implantation but have now separated (Type IIIa) or through holes in the graft material (Type IIIb). Type III endoleaks may lead to expansion and rupture of the AAA which can result in serious patient injury, including death. Imaging should be performed as part of the regular, lifelong follow-up, to determine whether the device remains effective in excluding blood flow into the AAA (e.g., no Type III endoleak) and to be sure that the aneurysm is not enlarging over time.

Once diagnosed, Type III endoleaks require treatment because of their life-threatening nature. Type IIIa endoleaks can generally be treated by relining the endograft to bridge the separated device components. Type IIIb endoleaks may require either complete relining of the endograft, or open surgical conversion.

FDA Actions

AFX with Strata graft material

Patients previously treated for an AAA with the **AFX with Strata** endovascular graft are at greater risk for a Type III endoleak compared to other endovascular graft systems. As a result, Endologix has not manufactured the AFX with Strata graft material since July 2014 and health care providers were advised to remove any remaining inventory from shelves in December 2016. Given the greater risk for Type III endoleaks occurring with the AFX with Strata endovascular graft, we continue to work with Endologix to assess the Type III endoleak treatment options for patients who remain implanted with this specific device and will discuss this topic further at the Advisory Committee meeting in 2021 in order to provide further instructions on this concern. **At this time, the FDA does not have definitive recommendations for treatment of Type III endoleaks in patients with the AFX with Strata device**. In addition, a benefit-risk determination for each individual patient with the AFX with Strata device should be considered to assess the need for additional procedures related to the risk of developing Type III endoleaks.

AFX with Duraply graft material or AFX2

We continue to evaluate real world data which suggest a higher than expected risk of Type III endoleaks occurring in patients treated for a AAA with an AFX endovascular graft with Duraply graft material **(AFX with Duraply or AFX2).**

- A published article[1] of real-world data from a prospective registry of patients treated in a large U.S. integrated healthcare system reports the incidence of Type III endoleaks at 2 years of follow-up to be 4.0% (95% CI 2.4 to 6.7) for patients with the AFX with Strata device and 5.1% (95% CI 2.7 to 9.7) for patients with the AFX with Duraply device. The incidence of Type III endoleaks at 2 years of follow-up was 14.1% (95% CI 4.7 to 38.2) for patients with the AFX2; however, the number of patients with AFX2 was small (n=33, compared to n=375 patients with AFX with Strata and n=197 patients with AFX with Duraply). The FDA recognizes the limitations of these data, including, the results not being stratified by Type IIIa and Type IIIb endoleak, and no comparison of the results to other endovascular graft systems. However, the article provides published results from the largest cohort of patients receiving Endologix AFX endovascular grafts.
- We are also aware of results from two conference abstracts which each present retrospective single-center data that suggest the risk of AAA-related major complications was similar for AFX with Duraply devices and AFX with Strata devices. One abstract[2] reported that 25% of patients treated with an Endologix AFX device had major complications within 4 years, and there was no difference in this high risk of major complications for the group of patients with AFX with Strata devices compared to the group of patients with AFX with Duraply devices (p=0.76). The other abstract[3] reported a similar high risk of major complications within 3 years for patients with AFX with Strata devices (14%) and patients with AFX with Duraply devices (22%, p=0.26). The FDA recognizes the limitations of the real-word data presented in these abstracts, including the challenges of generalizing results from single-center experiences, the small number of patients with AFX with Duraply devices in each abstract (n=51 and n=44, respectively) and the lack of

comparison to the results for other endovascular graft systems. However, both abstracts concluded that patients with Endologix AFX devices should be closely monitored.

In addition to these real world data sources, the FDA continues to review data provided by Endologix from their ongoing clinical trial of AAA patients who randomly received either an AFX endovascular graft device with Duraply (AFX with Duraply or AFX2) or an FDA approved endovascular graft from other manufacturers, called the LEOPARD Trial (Looking at EVAR Outcomes by Primary Analysis of Randomized Data). The most recent results indicate that the cumulative probability of Type III endoleaks remains at 1.0% for AFX devices and 0% for other endovascular grafts. Follow-up data is not available on all patients out to 4 years and results from this trial may represent Type III endoleak rates under ideal circumstances, such as closer adherence to the labeling with regards to patient selection and treatment instructions.

There is a need for continued evaluation of real world data about the risk of Type III endoleaks for AFX endovascular grafts with Duraply graft material (AFX with Duraply and AFX2) as compared to AFX endovascular grafts with Strata and compared to other endovascular graft systems. The FDA intends to gather and analyze additional real-world postmarket data to better understand the longer-term outcomes of AFX endovascular grafts. The FDA will discuss this topic further at the Advisory Committee meeting in 2021 in order to obtain the panel's input on possible mitigation strategies or other actions, as needed. In addition, we encourage providers, medical centers, health care systems and professional societies to evaluate outcomes for endovascular grafts utilized in their setting, and participate in a discussion at the panel which will consider current and future postmarket surveillance strategies for all endovascular grafts.

Communications About AFX Endovascular AAA System (AFX):

From the FDA:

- On October 28, 2019, the FDA issued a safety communication to inform patients and health care providers about the potential higher than expected risk of Type III endoleaks occurring with the use of AFX with Duraply and AFX2 endovascular grafts.
- On October 15, 2018, the FDA issued a Class I recall to notify patients and health care providers about the risk of Type III endoleaks with use of the Endologix AFX Endovascular AAA System.
- On June 19, 2018, in an updated letter , the FDA informed providers that the Endologix AFX with Strata device is at greater risk for a Type III endoleak compared to other endovascular AAA graft systems.
- On September 28, 2017, the FDA issued a Letter to Health Care Providers about the risk for Type III endoleaks with endovascular graft systems.

From Endologix, Inc:

- Endologix 2016-2019 Clinical Update for AFX Endovascular AAA System
- Endologix Urgent: Important Safety Update - Medical Device Correction for the AFX® Endovascular AAA System (July 20, 2018)
- Endologix Important Safety Update: AFX™ Endovascular AAA System (December 30, 2016)

Publications:

1. (Article) Chang, Robert W. et al. Mid-term outcomes for 605 patients receiving Endologix AFX or AFX2 Endovascular AAA Systems in an integrated healthcare system. Journal of Vascular Surgery 2020, Jul 3; S0741-5214(20)31470-1.

2. (Abstract) Wanken, Zachary J; Anderson, Peter; Trooboff, Spencer; Columbo, Jesse; Goodney, Philip. Comparison of Endologix Endografts Made With Strata Fabric Versus IntuiTrak and Duraply Fabrics. Journal of Vascular Surgery 2019, Vol. 70(3), p. e44.
3. (Abstract) Aranson, Nathan et al. Six-Year Outcomes of the Endologix AFX Endovascular AAA System: A Single-Center Experience. Journal of Vascular Surgery 2020, Vol. 72(1), p. e65.

October 2019 - Update on Risk of Type III Endoleaks with Use of Endologix AFX Endovascular AAA Graft Systems: FDA Safety Communication

The FDA is evaluating new information about the risk of blood continuing to leak into the aneurysm (Type III endoleak) when Endologix AFX endovascular grafts (AFX with Strata, AFX with Duraply, or AFX2) are used for the treatment of abdominal aortic aneurysms (AAA). We've previously communicated about the greater risk of Type III endoleaks occurring with the Endologix AFX with Strata device compared to other endovascular graft systems, which can result in serious injury. It is important for patients and health care providers to be aware that data from an integrated healthcare system, published in a recent conference abstract, suggest there also may be a higher than expected risk of Type III endoleaks occurring with the use of AFX with Duraply and AFX2 endovascular grafts. We recommend lifelong follow-up for patients treated with any endovascular graft. However, while we continue our evaluation, we are emphasizing the importance of at least yearly, lifelong follow-up for all patients who have any type of Endologix AFX endovascular graft in order to monitor for Type III endoleaks.

Patients: Important Recommendations If You Have or Are Considering An Endologix AFX Endovascular Graft System for Treatment of Abdominal Aortic Aneurysm

- Be aware that the FDA has approved endovascular grafts made by various manufacturers for the treatment of AAA, and each device has specific benefits and risks.
- Prior to surgery, discuss the benefits and risks of all available AAA treatment options with your health care provider.
- If you have already had treatment of your AAA with an endovascular graft system, review the implant card that you received at the time your AAA was treated to determine if you have any type of Endologix AFX endovascular graft implanted. If you do not know if you have an AFX endovascular graft or if you do not have your implant card, please contact the health care provider who treated your AAA or the hospital where you were treated to find out.
- If you have any type of Endologix AFX endovascular graft, contact the health care provider who treated your AAA or another vascular specialist about further care and to discuss continued follow-up.
- Be aware that recent data suggest there may be a higher than expected risk of blood continuing to leak into the AAA (Type III endoleak) which can result in serious injury, including death when any AFX endovascular graft is used for the treatment of AAA.
    - As a result the FDA recommends at least yearly, lifelong follow-up for all patients who have had their AAA treated with any AFX endovascular graft system.
    - If you have an AFX endovascular graft and are overdue for a follow-up, make an appointment with the health care provider who treated your AAA or another vascular specialist to get your device checked.

Important Recommendations for Health Care Providers who treat and follow patients with an Endologix AFX Endovascular Graft System for Treatment of Abdominal Aortic Aneurysm:

- Prior to surgery, discuss the benefits and risks of all available AAA treatment options with your patients.

  - The benefit-risk profile of AFX endovascular grafts compared to alternative treatment options should be considered for each individual patient.
  - When making AAA treatment recommendations, and as part of the informed consent process, consider that recent data suggest there may be a higher than expected risk of Type III endoleaks in patients treated with any Endologix AFX endovascular grafts.
- Read and carefully follow the Endologix AFX Endovascular AAA System Instructions for Use (IFU), which was revised in 2018 with updated information regarding Type III endoleaks.
  - The IFU includes component overlap recommendations, Type III endoleak risk factors and patient-tailored surveillance recommendations to assist health care providers in developing individualized patient follow-up plans.
- Closely monitor patients who have previously undergone implantation with any AFX endovascular graft and evaluate their risk profile for Type III endoleaks per the IFU.
  - Ensure yearly imaging follow-up at a minimum to monitor for the development of Type III endoleaks and aneurysm expansion for any patients under your care who have previously undergone implantation with any AFX endovascular graft (AFX with Strata, AFX with Duraply, or AFX2)
  - A benefit-risk determination for each individual patient should be considered to assess the need for additional procedures related to the risk of developing Type III endoleaks.

Device Description:

An endovascular graft can be used to treat an abdominal aortic aneurysm (AAA). Endovascular grafts are flexible fabric tubes supported by a metal framework either on the inside or outside of the fabric. The endovascular graft is permanently implanted inside the largest blood vessel (aorta) so that blood flows through the endovascular graft instead of to the aneurysm, reducing the risk of further aneurysm growth or rupture. These devices are made by various manufacturers, and each of the devices used to treat AAAs has specific benefits and associated risks.

The AFX Endovascular AAA System (AFX), manufactured by Endologix, Inc., is an endovascular graft system intended to treat patients with AAA. The AFX endovascular graft was approved by the FDA in 2011 and over time, the manufacturer has made changes to the device resulting in the following versions of the device being implanted in patients:

- **AFX with Strata graft material,** which was implanted in patients between 2011 and 2016 but is no longer available on the market , after Endologix requested that all AFX with Strata devices be removed from hospital inventory because of an increase in Type III endoleaks.
- **AFX with Duraply graft material,** which has been implanted in patients since July 2014 with the change in graft material from Strata to Duraply, which was intended to help prevent Type III endoleaks.
- **AFX2 (Duraply graft material),** which has been implanted in patients since February 2016 with changes to the manufacturing of the Duraply graft material to increase the average thickness and further help prevent Type III endoleaks.

In addition, the manufacturer over time has updated the instructions for use (IFU) for the device. The main change to address Type III endoleaks occurred in 2015, which included instructions regarding device sizing, as well as to increase the amount of overlap between graft segments that are joined together to treat the AAA.

Type III Endoleak

Various types of endoleaks can occur after repair with any endovascular graft and typically do not result in any symptoms. Therefore, patients who have been treated with **any** endovascular graft require regular, lifelong follow-up imaging (for example, a CT scan) for the detection of endoleaks.

Type III endoleaks in particular consist of blood flowing or leaking into the AAA either between endovascular graft segments that were joined together to treat the AAA at the time of implantation but have now separated (Type IIIa) or through holes in the graft material (Type IIIb). If left undetected and without treatment, a Type III endoleak may lead to expansion and rupture of the AAA. This may result in serious patient injury, including death. Imaging should be performed as part of the regular, lifelong follow-up, to determine if blood is continuing to flow through the endovascular graft device and not leaking into the AAA.

FDA Actions

AFX with Strata graft material

Patients previously treated for an AAA with the **AFX with Strata** endovascular graft are at greater risk for a Type III endoleak compared to other endovascular graft systems. As a result, Endologix has not manufactured the AFX with Strata graft material since July 2014 and health care providers were advised to remove any remaining inventory from shelves in December 2016. Given the greater risk for Type III endoleaks occurring with the AFX with Strata endovascular graft, we continue to work collaboratively with Endologix to assess the Type III endoleak treatment options for patients who remain implanted with this specific device, and to provide further instructions in the labeling on this concern.

AFX with Duraply graft material or AFX2

We are evaluating recent real world data published in a recent conference abstract which suggest a higher than expected risk of Type III endoleaks occurring in patients treated for an AAA with an AFX endovascular graft with Duraply graft material **(AFX with Duraply or AFX2)**. The abstract presents prospective registry data from an integrated healthcare system that suggest an early Type III endoleak risk for all AFX endovascular grafts (AFX with Strata, AFX with Duraply and AFX2). According to the abstract, there was a 2.5% cumulative probability of additional procedures needed to treat Type III endoleaks at two years of follow-up for patients with AFX endovascular grafts (95% CI 1.5 to 4.2). The FDA recognizes the limitations of the data presented in the abstract, including the small number of patients with AFX2 (n=32 patients with AFX2; n=197 patients with AFX with Duraply; n=374 patients with AFX with Strata), the results not being stratified by Type IIIa and Type IIIb endoleak, and no comparison of the results to other endovascular graft systems. However, the abstract provides published results from the largest US cohort of patients receiving Endologix AFX endovascular grafts.
We are also evaluating early postmarket data which compares the risk of Type III endoleaks with AFX endovascular grafts to other endovascular graft systems.

- The FDA has reviewed real world data from a vascular registry which suggest a significantly higher rate of Type III endoleaks for AFX with Strata and AFX with Duraply endovascular grafts as compared to the combined Type III endoleak rate for other endovascular grafts at one year of follow-up. The registry reports the Type III endoleak rate of AFX with Strata and AFX with Duraply together, so individual rates by graft material are not available. At this time, specific to AFX2, the data only include a small number of patients with follow-up (i.e., approximately 12%

of AFX2 patients have follow-up data at one year) which does not allow for a meaningful interpretation.
- The FDA has reviewed data provided by Endologix from their ongoing clinical trial of AAA patients who randomly received either an AFX endovascular graft device with Duraply (AFX with Duraply or AFX2) or an FDA approved endovascular graft from other manufacturers. This study is called the LEOPARD Trial (Looking at EVAR Outcomes by Primary Analysis of Randomized Data). In contrast to the registry data, the most recent results indicate that the cumulative probability of Type III endoleaks is 1.0% for AFX devices and 0% for other endovascular grafts. The follow-up is limited (i.e., data is not available on all patients out to 3 years) and results from this trial may represent Type III endoleak rates under ideal circumstances, such as closer adherence to the labeling with regards to patient selection and treatment instructions.

Because the AFX endovascular graft devices with Duraply (AFX with Duraply and AFX2) have been distributed for a shorter time than the AFX with Strata endovascular graft, longer-term (i.e., out to five years and beyond) follow-up of patients receiving devices with Duraply is needed to fully define the risk of Type III endoleaks with these products. We will continue to evaluate information from several sources, including the manufacturer and real world data, about the risk of Type III endoleaks for AFX endovascular grafts with Duraply graft material (AFX with Duraply and AFX2) as compared to AFX endovascular grafts with Strata graft material, and compared to other endovascular graft systems.

As new information or recommendations become available, we will continue to share updates.

Communications About AFX Endovascular AAA System (AFX):

From the FDA:

- On October 15, 2018, the FDA issued a Class I recall notify patients and health care providers about the risk of Type III endoleaks with use of the Endologix AFX Endovascular AAA System.
- On June 19, 2018, in an updated letter , the FDA informed providers that the Endologix AFX with Strata device is at greater risk for a Type III endoleak compared to other endovascular AAA graft systems.
- On September 28, 2017, the FDA issued a Letter to Health Care Providers about the risk for Type III endoleaks with endovascular graft systems

From Endologix, Inc:

- Endologix 2016-2019 Clinical Update for AFX Endovascular AAA System
- Endologix Urgent: Important Safety Update - Medical Device Correction for the AFX® Endovascular AAA System (July 20,2018)
- Endologix Important Safety Update: AFX™ Endovascular AAA System (December 30, 2016)

Published Abstract from American College of Surgeons' Clinical Congress 2019:

- Rothenberg, Kara A. et al. Risk of Reintervention with Endologix AFX Endovascular Abdominal Aortic Aneurysm Systems in an Integrated Health Care System. Journal of the American College of Surgeons, Volume 229, Issue 4, S334.

Reporting Problems with Your Device to the FDA

If you think you had a problem with your device or a device your patient uses, we encourage you to report the problem through the MedWatch Voluntary Reporting Form , including, but not limited to, the following:

- Adverse events related to secondary interventions to treat Type III endoleaks.
- Health care personnel employed by facilities that are subject to the FDA's user facility reporting requirements should follow the reporting procedures established by their facilities.

June 2018 - UPDATE on Type III Endoleaks Associated with Endovascular Graft Systems – Letter to Health Care Providers

The FDA continues to evaluate information from several sources, including endovascular graft system manufacturers, regarding the risks associated with Type III endoleaks with various aortic endovascular graft systems indicated for the treatment of abdominal aortic aneurysms (AAA) and aorto-iliac aneurysms.

In our September 2017 letter to health care providers, FDA communicated about its concern related to an increase in the occurrence of Type III endoleaks with the use of endovascular graft systems indicated for a procedure known as endovascular aneurysm repair (EVAR). Since that communication, and based on new information, the increased risk for Type III endoleak appears to be specific to one device at this time. The Endologix AFX with Strata device is at greater risk for a Type III endoleak compared to other endovascular AAA graft systems.

Based on currently available data from the manufacturer, estimated Type IIIa endoleak rates for the AFX with Strata are 0.90 percent at 2 years and 5.0 percent at 5 years. Estimated Type IIIb endoleak rates are 0.66 percent at 2 years and 2.4 percent at 5 years. Because these estimates are calculated using voluntary reporting and units sold, the rate estimates may be low compared to the true endoleak event rates. Endologix has not manufactured the AFX with Strata graft material since July 2014, and in December 2016 requested that all AFX with Strata devices be removed from hospital inventory. However, there are patients that have previously been implanted with the device. Given the increased risk for Type III endoleaks with the AFX with Strata device, the FDA recommends health care providers to:

- Contact Endologix with questions as to whether your patient has been implanted with the AFX with Strata device. Physicians may send requests to device.tracking@endologix.com Physicians may also contact their Endologix representative to request the data, or contact Endologix's medical affairs office at medicalaffairs@endologix.com with questions.
- Closely monitor your patients who have previously undergone implantation with the AFX with Strata device. Ensure annual follow-up at a minimum to monitor for Type III endoleaks.
- Remain alert for further updates and recommendations from Endologix and FDA. The FDA continues to work collaboratively with Endologix to assess the treatment options for patients with the AFX with Strata device and Type III endoleaks, and to provide further instructions in the labeling on this concern.

FDA continues to recommend that health care providers who follow patients treated with any endovascular AAA graft system:

- Continue lifelong surveillance as recommended in the labeling for each endovascular graft system–which typically includes annual follow-up of patients.
- Consider Type III endoleaks in the differential diagnosis of patients presenting with symptoms of potential aneurysm expansion or rupture.
- Discuss all available treatment options to address Type III endoleaks with patients, including the risks and benefits of each, before deciding the best treatment approach.
- Review the annual clinical updates as posted on the manufacturer's web site for current information on the safety and effectiveness of each endovascular graft system.

- Report any of the following events to MedWatch's (FDA Safety Information and Adverse Event Reporting program) Online Voluntary Reporting Form :
    - Early or late device-related adverse events–including Type IIIa and IIIb endoleaks–associated with the use of endovascular graft systems in AAA repair
    - Device-related adverse events that occur as a result of a secondary intervention to treat Type III endoleaks
- Device manufacturers and user facilities must comply with applicable Medical Device Reporting (MDR) regulations. Health care personnel employed by facilities that are subject to FDA's user facility reporting requirements facilities. Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices.

The FDA will keep the public informed as any new information or recommendations become available.

September 2017 - Type III Endoleaks Associated with Endovascular Graft Systems - Letter to Health Care Providers

Dear Vascular and Cardiothoracic Surgeons, Radiologists, and Cardiologists:

The FDA is evaluating recent information regarding Type IIIa and IIIb endoleaks with the use of endovascular graft systems indicated for a procedure known as endovascular aneurysm repair (EVAR). EVAR treats abdominal aortic aneurysms (AAA) and aorto-iliac-aneurysms.

Recent information from several sources, including FDA's Medical Device Reporting (MDR) system and Annual Clinical Updates to Physicians by the manufacturers, suggests an increase in the occurrence of Type III endoleaks. This increase is compared to earlier clinical update reports in patients with various device models and implant duration lengths, including some patients who had previously stable repairs.

We are bringing this potential complication to your attention to remind and encourage you to report Type IIIa and IIIb endoleak events to the manufacturer and the FDA. This may include reporting individual events as well as rates you may have experienced in your practice.

BACKGROUND

EVAR is intended to exclude the AAA sac from the arterial circulation and prevent AAA rupture, which is a life-threatening event. In the presence of a Type III endoleak, AAA is not excluded from flow and systemic arterial pressurization of the aneurysm sac, resulting in an increased risk of rupture.

The FDA considers a Type III endoleak a device-related event which requires treatment with additional interventions such as relining, insertion of additional endograft components, or open surgical repair. The secondary interventions to address endoleaks carry added risks for impacted patients. Predictors of Type III endoleak may include treatment with early generation graft materials, the presence of calcified plaque, and inadequate overlap between components.

RECOMMENDATIONS

The FDA recommends that health care providers:

- Continue lifelong surveillance of patients who have been treated with endovascular grafts
- Consider Type III endoleaks in the differential diagnosis of patients presenting with symptoms of potential aneurysm expansion or rupture.
- Discuss with your patients all available treatment options to address Type III endoleaks, including the risks and benefits of each, before deciding the best treatment approach.
- Report any of the following to MedWatch's (FDA Safety Information and Adverse Event Reporting program) Online Voluntary Reporting Form :
    - early or late device-related adverse events–including Type IIIa and IIIb endoleaks–associated with the use of endovascular graft systems in EVAR;
    - device-related adverse events that occur as a result of a secondary intervention to treat Type III endoleaks.

- Device manufacturers and user facilities must comply with the applicable Medical Device Reporting (MDR) regulations. Health care personnel employed by facilities that are subject to FDA's user facility reporting requirements should follow the reporting procedures established by their facilities. Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices.

FDA ACTIONS

The FDA continues to work with all manufacturers of endovascular graft systems to better understand this issue, including the prevalence of Type III endoleaks, contributing factors, and the risks and benefits of secondary interventions to address these endoleaks.

The FDA will keep the public informed as significant new information becomes available.