OVERVIEW

This annual clinical update provides a review of the ongoing experience with the AFX2 Endovascular AAA System (AFX2 System) intended for the endovascular repair of abdominal aortic or aorto-iliac aneurysms. The data presented in this annual clinical update includes post-market clinical experience with the AFX2 System through February 28, 2023.

The US Food and Drug Administration (FDA) issued premarket approval of the first generation of the device, the Powerlink System, in 2004. The AFX System, the next generation of the Powerlink System, received FDA approval in 2011. Initially, the implantable components of the device were manufactured with what was known as Strata ePTFE, but this was subsequently changed to Duraply ePTFE due to an increase of Type III Endoleaks observed in Strata devices. This incidence of Type III Endoleaks also led to updates to the IFU and the removal of Strata devices from hospital inventory. (Please refer to the sections WORLDWIDE RECALLS, SAFETY COMMUNICATIONS & FIELD SAFETY NOTICES and TYPE III ENDOLEAKS below for additional information regarding Type III Endoleaks with the legacy AFX System devices.) In 2016, FDA approval was issued for delivery system modifications resulting in the AFX2 Bifurcated device. Prior to launch, Endologix implemented manufacturing changes to reduce the potential for damage to the graft during loading onto the delivery system and an increase in the average thickness of the Duraply graft material by tightening of the manufacturing specifications. After multiple product iterations involving updates to the manufacturing, labeling, and design, the resulting, currently marketed device is the AFX2 System. The currently marketed AFX2 System consists of the AFX2 Bifurcated device as well as proximal and limb extension devices, all of which are manufactured with Duraply ePTFE.

Links to Source Information	
PMA Approval Letter Order	https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040002A.pdf
SSED	https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040002B.pdf
Instructions for Use (IFU)	www.e-labeling.eu/ELX10022
2016 – 2019 AFX Clinical Update	https://endologix.com/wp-content/uploads/2022/09/MM2165-ALL-Rev-03.pdf

Note: Refer to the ***2016 – 2019 AFX Clinical Update*** for additional details and information from previous reporting periods for previous generations of the device.

CLINICAL EVALUATIONS

COMPLETED CLINICAL EVALUATIONS

Endologix has completed five US pivotal clinical studies of the Powerlink System, the predecessor of the AFX System, for endovascular abdominal aortic aneurysm (AAA) repair that were the basis for determination of reasonable assurances of safety and effectiveness by the US Food and Drug Administration. Additional details are provided in the ***2016 – 2019 AFX Clinical Update***.

Link to Summary Information for the Pivotal Studies	
Protocol TP00-005 (Infrarenal Bifurcated Study) (original)	https://endologix.com/wpcontent/uploads/2019/10/MM2165-Rev-01Endologix-2016-2019-AFX-Clinical-Update.pdf
Protocol TP00-006 (Suprarenal Bifurcated Study) (S018)	
Protocol CP03-023 (34mm Proximal Extension Study) (S019)	
Protocol CP04-022 (25/28mm Suprarenal Proximal Extension Study) (S022)	
Protocol CP-0001 (PEVAR Trial) (S039)	

The clinical data encompasses the legacy Powerlink System device; however, it remains relevant and can, in part, be extrapolated to the AFX2 System. Although the Powerlink System and the AFX2 System delivery systems have a number of differences, the only difference between the stent grafts is the ePTFE graft processing method: the Powerlink System grafts were tube extruded and the AFX2 System grafts are sheet extruded. This difference in processing method ultimately resulted in a different ePTFE graft wall thickness for the current ePTFE grafts, which allows the ePTFE graft to better respond to a pressure difference between the stent graft lumen and the aneurysm sac. Referred to as "ActiveSeal," this allows the AFX2 System ePTFE graft to readily conform to and press against the flow lumen of the aorta. Additionally, the current ePTFE has some different graft properties compared to Powerlink, including improved suture retention and tear resistance.

LEOPARD TRIAL

The LEOPARD (**L**ooking at **E**VAR **O**utcomes by **P**rimary **A**nalysis of **R**andomized **D**ata) Trial is an Endologix-initiated, multicenter, prospective, randomized trial of endovascular abdominal aortic aneurysm repair (EVAR) in the US. The trial was initiated to obtain Level I evidence for the purpose of comparing outcomes in a contemporary, real-world EVAR patient population. LEOPARD is the first trial designed to directly compare endograft outcomes using the methodology of a randomized controlled trial. LEOPARD utilized CoreLab findings in addition to site-reported findings and utilized CT imaging based on physician discretion as per the guidelines of the Society of Vascular Surgery (SVS). In addition, an independent physician adjudicator evaluated adverse events based upon all clinical information available. NOTE: The trial was not designed to fulfill any FDA post-market requirements and the protocol was not reviewed by the FDA prior to trial initiation.

The LEOPARD Trial compared the anatomically fixated AFX with Duraply/AFX2 System to a reference group of proximally fixated EVAR devices (Cook Zenith, Gore Excluder, and Medtronic Endurant). Subjects were randomized between these two groups at a ratio of 1:1. The comparator device was selected by each investigator prior to enrolling the first subject, and this device served as the comparator device for that investigator throughout the course of enrollment. Thus, randomization was between the AFX with Duraply/AFX2 System devices and one selected proximally fixated device, specific for each investigator. The protocol-specified primary endpoint in the LEOPARD Trial was one-year survival in the absence of Aneurysm-Related Complications (ARC), which was a composite of relevant EVAR-related outcomes, including perioperative death (≤ 30 days), aneurysm rupture, conversion to open surgical repair, post-operative endoleaks, endograft migration (≥ 10mm), aneurysm enlargement (≥ 5mm), endograft occlusion, and any reinterventions for device- or aneurysm-related complications. Using ARC, the trial was designed to sequentially evaluate non-inferiority and superiority hypotheses, with comparisons between the AFX System with Duraply/AFX2 System and the proximally fixated endografts. This Endologix-initiated trial started enrollment in 2015, with the intention to enroll up to 800 subjects. However, in August 2017, Endologix made a voluntary decision to halt further randomization into the study, capping the trial at 455 subjects.

Links to Source Information	
ClinicalTrials.gov	https://www.clinicaltrials.gov/ct2/show/NCT02407457?term=leopard&cond=AAA&draw=2&rank=1
Published LEOPARD Trial	https://pubmed.ncbi.nlm.nih.gov/37068528/

LEOPARD OUTCOME RESULTS

As of February 28, 2023, all subjects have completed the 5-year follow-up. As shown in **Figure 1,** freedom from ARC with the AFX System with Duraply/AFX2 System devices was similar to the three proximally fixated comparator devices at 1 year and trended similarly out to 5 years.

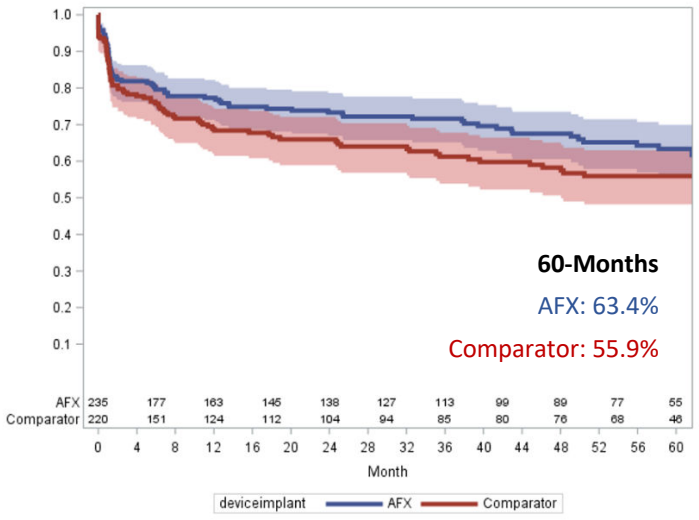

Figure 1. Freedom from Aneurysm-Related Complications (ARC), LEOPARD Trial

Table 1. LEOPARD Trial Summary of Results – March 30, 2022

Event Type	Freedom-from-Event Estimates at 5 years	
	AFX/AFX2 System with Duraply	Comparators
Aneurysm-Related Mortality (ARM)	97.0%	98.5%
Aneurysm Rupture	98.9%	99.3%
Conversion to Open Repair	100%	98.0%
Type I Endoleak	93.4%	95.7%
Type II Endoleak	78.8%	68%
Type III Endoleak	98.5%	100%
Migration ≥ 10mm	96%	96.8%*
Device Occlusion	97.2%	94.2%
Secondary Intervention	84.4%	85.5%

**There was one Type Ib event that was reported to be secondary to Migration in the comparator cohort; however, the associated Migration was not reported and, therefore, not included in this freedom-from-event estimate.*

Based on the outcomes outlined in **Table 1**, the LEOPARD Trial provides objective, directly comparative, clinical evidence that the AFX with Duraply/AFX2 System devices perform at or better than contemporary EVAR devices when assessed using a composite clinical outcome to 60 months (63.4 ± 3.60% for the anatomically fixated cohort compared to 55.9 ± 3.78% for comparators, expressed as KM estimate ± S.E.). Note that the protocol defined ARC definition was inclusive of Type II Endoleaks; excluding this event type from ARC results in freedom from ARC of 73.3 ± 3.5% for AFX/AFX2 compared to 72.9 ± 3.59% for comparators at 60 months.

Strengths of the LEOPARD Trial:

- The LEOPARD Trial was a prospective, randomized trial comparing AFX Duraply/AFX2 to other EVAR devices.
- The LEOPARD Trial utilized an independent core lab in addition to independent adjudication.
- There was a sample size of 235 AFX Duraply/AFX2 and 220 EVAR Comparator devices.

Limitations of the LEOPARD Trial:

- Imaging follow-up data ranged from 79-94% per imaging window, with 59-73% subjects with adequate imaging to assess endoleak.
- There was a limited number of subjects with 5-year follow-ups.
- The sample size planned at the beginning of the study was not enrolled. However, 455 patients provide sufficient numbers to evaluate the cohorts through 5 years and sufficient for formal non-inferiority testing of the primary endpoint.
- There is a degree of subjectivity when a non-inferiority margin is chosen.
- The trial was not designed to compare the Endologix devices to individual devices within the comparator cohort.

WORLDWIDE RECALLS, SAFETY COMMUNICATIONS & FIELD SAFETY NOTICES

Since the introduction of the original AFX System in 2011, the following worldwide recalls, safety communications, and field safety notices occurred:

December 2022: FDA Safety Communication

- On December 6, 2022, FDA published an update to the January 2022 field safety communication to inform health care providers that FDA approved new labeling for the currently available product, the AFX2 Endovascular AAA System (AFX2 System), that includes information to better inform patients and health care providers of the risk of Type III Endoleaks with previous iterations of the AFX System and acknowledges the limited clinical follow-up on the current AFX2 System. It was further discussed that Endologix will perform a post-market study to compare outcomes for patients implanted with the AFX2 System to patients with other commercially available AAA endovascular grafts, using real world data.
  Safety Communication Link: https://www.fda.gov/medical-devices/safety-communications/update-endologix-afx-endovascular-aaa-graft-systems-and-risk-type-iii-endoleak-fda-safety
  Post-Market Study Link: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=758886&c_id=7231
- Note: FDA published an update in May 2023 to add recent published research that compares safety outcomes for Endologix AFX endovascular grafts to other endovascular grafts. There were no changes to FDA's previous recommendations.

January 2022: FDA Safety Communication

- On January 13, 2022, FDA published a field safety communication to inform patients and health care providers that FDA recommends health care providers consider using available alternative treatment options for AAA patients rather than the AFX2 device. It was further communicated that FDA would taking additional steps to address Type III Endoleak risks associated with AFX endovascular grafts, including working with Endologix to identify patients who may benefit from treatment with the AFX2 device, update the device labeling, and collect and evaluate additional data to assess the long-term safety of AFX endovascular grafts. https://www.fda.gov/medical-devices/safety-communications/update-risk-type-iii-endoleaks-use-endologix-afx-endovascular-aaa-graft-systems-fda-safety-0

November 2021: FDA Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting

- On November 2, 2021, FDA convened an advisory committee meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee to further discuss the totality of data available regarding Type III Endoleak risk for the AFX/AFX2 System and how it relates to the overall safety profile of the currently marketed AFX2 System. Based on the analysis of the currently available data, FDA concluded there appears to be a higher-than-expected rate of Type III Endoleaks with the AFX System, regardless of the device iteration. Because of the limitations with data sources, there was uncertainty regarding whether the mitigation measures implemented by Endologix adequately addressed Type III Endoleak concerns for the currently marketed AFX2 device. https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-2-3-2021-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting
- Endologix believes it is important to distinguish the safety and effectiveness data on the currently marketed AFX2 from previous versions of the device. With respect to the AFX2 device, Endologix presented a compendium of clinical evidence at the Advisory Committee meeting supporting its safety and effectiveness. Additionally, the data presented by clinical research groups demonstrated comparable outcomes between AFX2 and an aggregate of all other EVAR grafts., as shown in **Figure 2**. A summary of the information presented by clinical research groups at the Advisory Committee meeting is included in Section 6 of the IFU and is also available on the FDA website linked above.

December 2020: FDA Safety Communication & Endologix Response

- On December 4, 2020, FDA published a field safety communication to inform patients and health care providers that FDA recommendations had not changed from the October 2019 Safety Communication, and that the FDA will convene an advisory committee meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee in 2021 to discuss the Type III Endoleak risk for the AFX/AFX2 System, the Type III Endoleak treatment options for patients who are implanted with the AFX/AFX2 devices, as well as future post-market surveillance strategies for all endovascular grafts used for the treatment of AAA. https://www.fda.gov/medical-devices/safety-communications/update-fda-reminds-patients-and-health-care-providers-importance-least-yearly-lifelong-follow-use

October 2019: FDA Safety Communication & Endologix Response

- On October 28, 2019, FDA published a safety communication to inform patients and health care providers that data published in a recent conference abstract (Rothenberg et al.) suggest there may be a higher than expected risk of Type III Endoleaks occurring with the use of AFX with Duraply and AFX2 endovascular grafts. https://www.fda.gov/medical-devices/safety-communications/update-risk-type-iii-endoleaks-use-endologix-afx-endovascular-aaa-graft-systems-fda-safety
- In response, Endologix issued a response on October 30, 2019 to provide clarification to health care providers as well as the company's perspective on the totality of data on the AFX/AFX2 System with respect to Type III Endoleaks. https://endologix.com/wpcontent/uploads/2019/10/Endologix-Response-to-FDA-Communication-AFX-Oct30_2019.pdf

October 2018: FDA Class I Recall of Endologix Safety Update (July 2018) & Endologix Response

- On October 15, 2018, FDA issued a Class I recall notifying patients and health care providers about the risk of Type III Endoleaks with use of the AFX System. Although the recall applied to all AFX devices, most reports of endoleaks have concerned the AFX System with Strata devices, which had been removed from the field. However, the AFX with Duraply graft material and AFX2 devices have been distributed for a shorter time. Therefore, Endologix continues to monitor the performance of these devices. https://www.fda.gov/medical-devices/letters-health-care-providers/update-type-iii-endoleaks-associated-endovascular-graft-systems-letter-health-care-providers#:~:text=October%2015%2C%202018%20%2D%20The%20FDA,Endologix%20AFX%20Endovascular%20AAA%20System.
- In response, Endologix issued a response on October 19, 2018 to provide clarification to health care providers and an update to the Type III Endoleak complaint trending previously provided in the July 2018 Endologix Safety Update. https://endologix.com/wpcontent/uploads/2018/10/Endologix_Comment_Oct-2018.pdf

July 2018: Endologix Safety Update

- On July 20, 2018, Endologix issued a field safety notice to provide physicians with updated information to the December 2016 update, as well as revisions to the IFU to enhance patient safety. The notification provided an update on Type III Endoleak rates, refined patient-tailored surveillance recommendations, sizing recommendations for the AFX System with Duraply (which aligned with the AFX2 IFU), and recommendations for intervening through an AFX device or re-intervening on an AFX device.
  - AFX Users: https://endologix.com/wp-content/uploads/2018/07/AFX-Safety-Update-AFX-Users_July2018.pdf
  - Non-AFX Users: https://endologix.com/wp-content/uploads/2018/07/AFX-Safety-Update-Non-AFX-Users_July2018.pdf

December 2016: Endologix Safety Update

- On December 30, 2016, Endologix issued a field safety notice to provide updated information on the rates of Type III Endoleaks, along with suggestions for patient surveillance and treatment as well as the voluntary recall of the small remaining quantity of the original AFX System with Strata due to elevated Type III Endoleak rates. This field safety notice also included the voluntary recall of the larger diameter sizes of AFX2 (28mm main body and 20mm iliac limbs), which was taken as a precautionary measure while additional investigation was ongoing. https://endologix.com/wp-content/uploads/2016/12/12-30-Physician-Letter-AFX-TIII-Endoleak-FINAL.pdf

WORLDWIDE COMMERCIAL EXPERIENCE

DEVICE DISTRIBUTION

Table 2 provides a summary of the AFX with Duraply System and the AFX2 System devices that were sold in the US, EU, and ROW through February 28, 2023, and **Table 3** provides a summary of the AFX with Duraply System and the AFX2 System devices that were sold in the US, EU, and ROW within the reporting period (March 1, 2022 – February 28, 2023). As noted above, Endologix released the AFX2 Bifurcated device in 2016. Since then, the AFX Bifurcated device was gradually phased out and remained on the market while global approvals were pending. Distribution of the AFX Bifurcated device ceased within the US in August 2018 and globally in July 2020.

Note: *The US data depicts the number of devices sold through direct sales. The OUS data depicts the number of devices sold through both direct sales and distributor sales. Therefore, the data presented provides the largest number of devices that may have been implanted in each region. ROW is defined as "Rest of World".*

Table 2. Devices Sold Worldwide - Lifetime

Product Type	AFX System with Duraply / AFX2 System			
	US	EU	ROW	Total
Bifurcated	34,031	11,599	26,245	71,875
AFX Bifurcated (01 JUL 2014 – 31 MAY 2020)	10,833	3,881	7,983	22,697
AFX2 Bifurcated (01 FEB 2016 – 28 FEB 2023)	23,198	7,718	18,262	49,178
Extensions	34,710	9,545	26,377	70,632
Proximal Extensions *(01 JUL 2014 – 28 FEB 2023)*	28,776	7,790	20,913	57,479
Infrarenal Extensions	6,079	3,301	5,994	15,374
Suprarenal Extensions	22,697	4,489	14,919	42,105
Limb Extensions *(01 JUL 2014 – 28 FEB 2023)*	5,934	1,755	5,464	13,153

Table 3. Devices Sold Worldwide – Reporting Period (APR 1, 2019 – FEB 28, 2023)

Product Type	AFX System with Duraply / AFX2 System			
	US	EU	ROW	Total
Bifurcated	9,518	5,071	12,276	26,865
AFX Bifurcated	0	0	*433*	*433*
AFX2 Bifurcated	9,518	5,071	11,843	26,432
Extensions	8,163	3,504	11,544	23,211
Proximal Extensions	7,424	2,865	10,027	20,316
Infrarenal Extensions	1,737	1,095	2,884	5,716
Suprarenal Extensions	5,687	1,770	7,143	14,600
Limb Extensions	739	639	1,517	2,895

REPORTED ADVERSE EVENTS

As of February 28, 2023, the current AFX2 System devices demonstrate low incident counts for adverse events when compared to 49,178 total AFX2 Bifurcated implants sold globally. The events and occurrence rate percentages (calculated using the number of lifetime total of events as the numerator and the total AFX2 Bifurcated implants sold as the denominator) are as follows: aneurysm-related mortality (59 lifetime events, 0.12%), aneurysm rupture (post-implant) (99 lifetime events, 0.20%), surgical conversion (80 lifetime events, 0.16%), device migration (48 lifetime events, 0.10%), and stent graft integrity events (152 lifetime events, 0.31%). The highest incident counts reported are Type III Endoleaks, but the occurrence rate remains acceptable (0.34% and 0.38% for Type IIIa and Type IIIb Endoleaks, respectively).

The total adverse events for the reporting period (April 1, 2019 – February 28, 2023) are as follows: aneurysm-related mortality (34 events), aneurysm rupture (post-implant) (70 events), surgical conversion (54 events), device migration (35 events), stent graft integrity events (88 events), Type IIIa Endoleaks (136 events), and Type IIIb Endoleaks (149 events).

NOTE: Sales data by year is not interpretable when evaluating adverse events. This is because most adverse event types for EVAR devices are delayed and occur years after implantation. As an example, a Type III Endoleak event reported during this reporting period could be the result

of a case whose sale and implantation was performed in a previous reporting period. For this reason, looking at lifetime total of events against total sales is the most clinically meaningful when evaluating adverse event occurrence rates.

Though a denominator of the total implanted devices would provide more comprehensive occurrence rate percentages, implant data outside of the US is unknown as there is no device tracking requirement in those regions. Additionally, the majority of Endologix's sales outside of the US and outside of the EU are through a third-party distributor, which handles sales with the hospitals directly. Therefore, total AFX2 Bifurcated implants sold is the best option.

EXPLANT ANALYSIS

Over the lifetime of the AFX2 System, there have been a total of twenty-two (22) devices returned to Endologix for explant evaluation (February 2016 – February 2023). Of the devices that were returned for explant evaluation, the leading reason for device explanation with AFX2 System grafts were attributed to acute factors such as implantation difficulties, infection, or intra-operative complications (totaling 10 events) with the second leading causative event for AFX2 System explants being a Type IIIb Endoleak (5 events). The results of the explant evaluation found that the majority of the device explant cases with the AFX2 System grafts were attributed to patient anatomy and involved patients whose devices were implanted outside of the IFU recommendations/requirements (17 events). It is important to highlight that 100% of all AFX/AFX2 System subjects in the LEOPARD Trial data are free from surgical conversion (and subsequently device explantation) at 5 years.

TYPE III ENDOLEAKS

Endologix has an active post-market surveillance program that has been monitoring and evaluating the performance of the AFX/AFX2 System since its introduction to the market. Through this monitoring, an increased rate of Type III Endoleaks with the first AFX iteration, the AFX System with Strata, was detected. In response, Endologix has made corrective actions to address Type III Endoleaks. Specifically, Endologix implemented various product changes including: commercialization of the Duraply graft material (2014), longer bifurcated lengths (January 2013 and November 2014), and the AFX2 Bifurcated device (2016). Additionally, several IFU updates were made between 2013 and 2018. These corrective actions were made to address Type III Endoleaks, however, it is still uncertain whether the increased risk of Type III Endoleaks and AAA-related adverse events have been addressed with the currently marketed AFX System as the risk of Type III Endoleaks and AAA-related adverse events at three (3) years and beyond is not yet established. There are limited datasets which evaluate Type III endoleaks for the currently marketed AFX2 System, which are included in Section 6.3 of the IFU. Additionally, Endologix monitors the overall device performance of the AFX2 System compared to other EVAR devices on the market, which are included in Section 6.4 of the IFU. As discussed above, Endologix has initiated a postmarket study to compare outcomes for patients implanted with the AFX2 System to patients with other commercially available AAA endovascular grafts, using real world data.

LITERATURE REVIEW

A literature review of the publications for the AFX/Powerlink Systems in the reporting period since the last PMA Annual Clinical Update (2016-2019) includes twelve (12) articles pertaining to the AFX/AFX2 System in elective endovascular aortic repair found through April 15, 2023. Brief summaries are provided below.

1. Akkaya et al.[i] retrospectively evaluated the postoperative performance of patients implanted with non-AFX endografts (n=66) compared to patients implanted with AFX endografts (n=64). The 5-year survival rate was similar between the two groups (84.8% for non-AFX and 78.4% for AFX, p = 0.703). In the early postoperative period, there were 7 Type II Endoleaks (10.6%) in the non-AFX group and 3 Type II Endoleaks (4.7%) in the AFX group. There were no Type III Endoleaks in the early postoperative period for both groups. The mean follow-up period was 35.6 months. At follow-up, there were 2 Type Ia Endoleaks, 2 Type Ib Endoleaks, and no Type III Endoleaks in the non-AFX group compared to no Type Ia or Ib Endoleaks and 4 Type III Endoleaks in the AFX group. Although there were no significant differences in overall rates of endoleaks for both groups, Type III Endoleak was more common in the AFX group (6.2% vs. 0%). However, this was attributed to the AFX Strata graft, and it was noted that Endologix had provided information regarding Type III Endoleaks with

AFX Strata in 2016-2017 and subsequently made improvements with the AFX Duraply. Overall, the authors concluded that the results demonstrate that both the non-AFX and AFX endografts used in the study are effective, reliable, and successful for endovascular AAA repair.

2. Vetsch et al.[ii] retrospectively analyzed outcomes for 405 patients implanted with AFX2 endografts at 5 US centers. This is the largest series of patients implanted with AFX2 for endovascular AAA repair to date. Perioperative mortality was 1.7%. Freedom from aneurysm-related mortality was 98.2% at 1, 2, 3, and 4 years postoperatively, there were no post-operative aortic ruptures, and 2 patients required open conversion. Freedom from Type Ia Endoleaks was 99.4% at 1, 2, 3, and 4 years. Freedom from Type IIIa and Type IIIb Endoleaks were 100% and 100% (year 1), 100% and 99.6% (year 2), 99.4% and 99.6% (year 3), 99.4% and 99.6% (year 4); therefore, Type Ia and Type III Endoleak rates at 4 years appear to be within acceptable limits. Freedom from all device-related reintervention (including Type II Endoleaks) at 4 years was 86.8%. Although further follow-up studies are warranted, the authors concluded AFX2 endograft appears to perform to a satisfactory standard in terms of patient-centric outcomes at mid-term follow-up.

3. Chang et al.[iii] retrospectively analyzed a prospectively gathered dataset of 605 patients treated within the Kaiser integrated health system using AFX with Strata (n=375), AFX with Duraply (n=197) and AFX2 (n=33). The median follow-up for the cohort was 3.9 years. The crude 2-year incidence of overall endoleak, any subsequent reintervention or conversion, and mortality was 8.8% (95% confidence interval [CI], 6.3-12.3), 12.0% (95% CI, 9.1-15.9), and 8.8% (95% CI, 6.3-12.2) for AFX-S. Respective estimates for AFX-D were 7.9% (95% CI, 4.8-13.0), 10.6% (95% CI, 6.9-16.1), and 9.7% (95% CI, 6.3-14.7); for AFX2, they were 14.1% (95% CI, 4.7-38.2), 16.2% (95% CI, 6.4-37.7), and 21.2% (95% CI, 10.7-39.4). The authors note the study does have several limitations including its descriptive nature, reporting the crude incidence of outcomes without a comparator group. The size of the AFX-2 cohort was limited to 33 subjects. Analysis was limited to the data captured by the registry, so details on IFU compliance and adjunctive procedures are lacking. There was no core lab imaging, and the authors were unable to accurately subcategorize Type I and Type III Endoleaks. Based on their analysis, the sponsors conclude a concerning rate of adverse postoperative events and that patients with these devices should receive close clinical surveillance to prevent device-related adverse events.

4. Martinelli et al.[iv] investigated an important clinical phenomenon seen across the EVAR landscape, post-implantation syndrome (PIS). While not specific to AFX, the AFX group had a lower incidence of PIS relative to the other EVAR devices (33.3% vs 46.6%, P=0.33), in addition, to a lower incidence of complications (8.9% vs. 16.4%, P=0.43). Both findings represent trends in the data as the sample size was insufficient to provide statistical significance.

5. Meshii et al.[v] retrospectively investigated a cohort of 375 patients with seven different EVAR devices to determine if hypogastric embolization was associated with Type II Endoleaks at 1-year follow-up. The study included 21 subjects with AFX Powerlink grafts. The main conclusion of the paper is that no significant association was seen between hypogastric embolization and the incidence of Type II Endoleaks.

6. Montross BC et al.[vi] retrospectively evaluated 272 elective EVAR cases and found that the AFX graft was associated with a lower likelihood of ambulatory surgery center eligibility. The authors note the need for additional aortic cuffs other than that customarily required was required more frequently with Endologix AFX than with other grafts. While this factor was associated with increased operative time, the need for an additional cuff did not directly translate to increased MAE for Endologix AFX. Amongst other grafts, MAEs significantly increased when additional cuffs were required. The authors were unable to identify concrete reasoning for decreased ASC eligibility with Endologix and therefore would not consider it an exclusion criterion.

7. Forsyth et al.[vii] retrospectively analyzed Endologix AFX endografts implanted from October 2011 to October 2016. This time period aligns with the AFX System with Strata and the AFX System with Duraply, which are previous iterations of the AFX2 System. The purpose of this study was to identify the incidence of Type III Endoleaks associated with these endografts over a long-term follow-up (>4 years) period and discuss current management strategies. The study concluded that early-generation Endologix AFX stent grafts have a high rate of Type III Endoleaks, with freedom from Type III Endoleak <50% at 8-year follow-up. Most of these are not detected until several years (>4.5 years) after initial implantation, beyond the range of the follow-up interval of most published reports. Long-term imaging

surveillance is critical, and a low threshold for complete relining should be considered with any sign of sac enlargement, even if endoleak is not clearly demonstrated in patients with early-generation Endologix AFX grafts.

8. Goodney et al.[viii] performed an observational surveillance study to evaluate long-term outcomes (reintervention and late rupture of abdominal aortic aneurysm) of aortic endografts in real-world practice using linked registry claims data. The analysis groups the Endologix devices into Early and Late AFX, based on the date before and after January 1, 2015. The Late AFX cohort (n=1,350) includes a 50:50 mix of AFX Duraply and AFX2, which is more representative of the currently marketed AFX2 System. The linked registry claims surveillance data identified the increased risk of reintervention with the early AFX device as early as mid-2013, well before the first regulatory warnings were issued in the US in 2017. No differences were observed between patients who received the late AFX and those who received comparator devices, although these results were limited to follow-up for three years.

9. Lescan et al.[ix] compared the outcomes of patients treated with tube grafts and AFX stent-graft in the narrow infrarenal aortic anatomy, including patients with penetrating aortic ulcers (PAUs) or sacciform aneurysms of the infrarenal aorta and an aortic bifurcation diameter ≤20 mm who underwent endovascular aneurysm repair (EVAR) with bifurcated AFX or tube stent-grafts (TUBE) between 2012 and 2020. It is unclear which iterations of the AFX System were used, however, the AFX System with Strata, AFX System with Duraply, and AFX2 System were available between 2012 and 2020. The study concluded using demographic data that AFX stent-grafts showed a lower rate of Type I Endoleaks and reinterventions in sacciform infrarenal aortic pathologies during the early and midterm follow-up, although these results were limited to follow-up for 10-months and the shorter distal landing zone in the AFX group may bias the technical success rate comparison.

10. Prentice et al.[x] conducted a matched cohort study to evaluate the risk for 90-day returns to care and long-term subsequent surgical interventions after primary endovascular aneurysm repair (EVAR) with an Endologix AFX Endovascular AAA System device compared with three other high-volume endograft devices. Of the Endologix devices (n=470), 60% of the Endologix devices were the AFX System with Strata, 34% were the AFX System with Duraply, and 8% were the AFX2 System. The study concluded patients who received an Endologix AFX System during their primary EVAR had a higher risk for several adverse longitudinal outcomes, as well as aneurysm-related mortality, when compared with patients who received other high-volume devices, however when stratifying by AFX iterations, higher risks for Type III Endoleaks were observed for the AFX System with Strata and AFX System with Duraply compared to the currently marketed AFX2 System. No differences were observed in overall mortality, conversions to open repair, or 90-day returns to care between device groups.

11. Secemsky et al.[xi] retrospectively evaluated whether unibody aortic stent grafts (i.e., Powerlink, AFX System with Strata, AFX System with Duraply, and AFX2 System) are non-inferior to non-unibody aortic stent grafts with respect to the composite primary outcome of aortic reintervention, rupture, and mortality. The study evaluated all procedures from August 1, 2011, to December 31, 2017, resulting in 87,163 patients who underwent aortic stent grafting, 11,903 of which received a unibody device, with a median follow-up of 3.5 years. The study concluded that unibody aortic stent grafts failed to meet noninferiority compared with non-unibody aortic stent grafts with respect to aortic reintervention, rupture, and mortality and supported the urgency of instituting a prospective longitudinal surveillance program for monitoring safety events related to aortic stent grafts.

12. Kwolek et al.[xii] conducted a prospective, randomized, multicenter trial to compare the anatomically fixated AFX/AFX2 Endovascular AAA System to endografts with proximal fixation in patients with infrarenal abdominal aortic aneurysms (AAA). The 5-year results from the LEOPARD study demonstrated that there was no clinically significant difference in overall aneurysm-related outcomes between patients randomized to the AFX/AFX2 Endovascular AAA System or commercially available endografts with proximal fixation.

13. Gennai et al.[xiii] conducted a retrospective, single-arm, single-center study to assess the real-world incidence, outcomes, and risk factors of Type III Endoleaks after endovascular aneurysm repair (EVAR). The study concluded Type III Endoleaks are a severe condition that is often fatal if left untreated. Old endografts, the implantation of non-proprietary extensions, large AAAs, and angulated and calcified necks are risk factors for Type III Endoleaks that require careful follow-up due to the high rate of recurrence. The AFX analysis presented in this article indicated a slightly higher cumulative incidence of Type III Endoleaks compared to proximally fixed bifurcated stent grafts, however, this was not determined to be statistically significant by Cox Regression (p=0.12).

14. Wang et al.[xiv] conducted a retrospective cohort study to assess the methodological requirements and feasibility of post-marketing device surveillance using endovascular aneurysm repair devices using clinical data from a large health care system. The study concluded it was feasible to perform post-marketing surveillance using large national healthcare datasets, and limitations of the data led the team to develop tools and custom classifiers for the analysis. The authors state that the risk difference of Type III Endoleaks by 5 years (estimated by doubly robust mean difference) was higher in the AFX2 device relative to other EVAR devices (+11.6%, 95%CI: 8.1%,15.1%). The Cox Model-derived hazard ratio Type III Endoleak estimate for AFX2 was numerically higher but not statistically significant at year 5 (1.19, 95%CI: 0.85,1.66), relative to non-AFX devices. In addition, all-cause mortality with AFX2 was not statistically or numerically higher at year 1 (0.88, 95%CI 0.57, 1.34) or year 5 (0.93, 95%CI: 0.73, 1.18) relative to non-AFX devices.

CONCLUSION

Based on available clinical study data and worldwide clinical experience to date, Endologix believes that endovascular therapy with the AFX2 Endovascular AAA System continues to be a valuable and effective treatment option for the treatment of abdominal aortic aneurysms in appropriately selected patients.

NOTES TO CLINICIANS

ADVERSE REPORTING

Any adverse event (i.e., clinical incidents) involving an Endologix device should be reported to Endologix LLC immediately or to the FDA (MedWatch Form 3500). To report an incident, call the Customer Service Department at 800-983-2284 (24-hour message service). Outside the US, contact your local Endologix representative.

PATIENT FOLLOW-UP AND SELECTION

Continued monitoring and follow-up of patients treated with the AFX2 System devices is essential. All patients should be advised that endovascular treatment requires life-long, regular follow-up to assess their health and the performance of their endovascular graft is a critical part of ensuring the ongoing safety and effectiveness of endovascular treatment of AAAs. Patients should be counseled on the importance of adhering to the follow-up schedule during the first year and at yearly intervals thereafter, and that subsequent reintervention including catheter based and open surgical conversion are possible following endograft placement.

Physicians should evaluate patients on an individual basis and prescribe their follow-up relative to the needs and circumstances of each individual patient. At a minimum, Endologix recommends that high resolution CT scan (contrast-enhanced and non-contrast) imaging follow-up to be performed at one month, six months, one year, and annually thereafter for examination of:

- Device integrity (e.g., absence of stent fracture or graft holes/tear);
- Maintained overlap between bifurcated and extension stent grafts;
- Absence of clinically relevant migration or lateral movement;
- Aneurysm enlargement, perigraft flow, loss of patency, increased tortuosity, or progressive disease.

Refer to the ***Instructions for Use*** for detailed patient selection and follow-up recommendations.

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