AFX®2 Endovascular AAA System (AFX2 System) P040002

Sponsor Executive Summary

Circulatory System Devices Panel

Meeting Date:
November 2, 2021

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1. INTRODUCTION

1.0. RATIONALE FOR CIRCULATORY SYSTEM DEVICES PANEL (CSDP) MEETING

The Food and Drug Administration (FDA) has convened the Circulatory System Devices Panel to discuss the benefit-risk profile of the Endologix AFX Endovascular AAA System (AFX System) with regard to the risk of Type III Endoleaks. With respect to endograft performance, Endologix takes a patient centric view by looking at the totality of data, as endografts utilized for endovascular aneurysm repair (EVAR) are complex and have varied failure modes based on their different designs. Concentrating on one isolated failure mode to the exclusion of all others (e.g., Type Ia Endoleak, aneurysm expansion, limb occlusion), and the exclusion of patient centric outcomes (e.g., aortic rupture, reintervention, death) does not give a picture of overall device performance and the benefit-risk profile for patients. While single failure modes are important and should not be minimized, the evaluation of the benefit-risk profile requires a holistic approach and comparative analysis.

As detailed in this document, Endologix acknowledges that the early iteration of the AFX product line, AFX Strata, had a clinically relevant Type III Endoleak failure mode that was apparent in the mid- and long term. Endologix has undertaken a series of actions that provide clinical information to aid the management of these patients.

A compendium of clinical data will be presented which includes nearly 5,000 patients treated with AFX Duraply or AFX2. These data will include relevant comparative outcomes and complications after EVAR in addition to Type III Endoleak rates. These data demonstrate that the product design, manufacturing, and labeling changes made to the AFX product family since 2013, have been effective. The rate of Type III Endoleaks with AFX Duraply and AFX2 is clinically acceptable within an overall benefit-risk analysis that is both favorable and is similar to all other EVAR grafts in clinical practice.

AFX2 is an essential component in the armamentarium of medical devices used to treat patients with abdominal aortic aneurysms (AAA). The AFX product family and the AFX2 System, in particular, are well studied in a variety of settings and follow-up periods. The AFX2 System remains a safe and effective device for use in the treatment of AAA.

2. EXECUTIVE SUMMARY

The AFX product family encompasses several generations of endografts used for the endovascular repair of AAA. The initial AFX device, AFX Strata, was associated with a clinically relevant rate of Type III Endoleaks, that required reintervention and had the potential to cause adverse clinical outcomes. Since the identification of this failure mode, Endologix LLC has implemented a series of product design, manufacturing, and labeling updates that have been incorporated firstly into AFX Duraply and subsequently, into the only currently available endograft, AFX2. This document contains information on the design of the AFX product family, the mitigation of the Type III Endoleaks, a compendium of comparative clinical evidence, a synopsis of actions taken to provide information relating to the management of patient implanted with AFX Strata and a description of the unique clinical utility of AFX2 in contemporary practice. AFX2 is an essential component in the armamentarium of medical devices used to treat patients with AAA and has clinical outcomes that are comparable with or superior to all other contemporary EVAR devices. The AFX2 System remains a safe and effective device for use in the treatment of AAA.

The AFX2 Unibody Endograft – Differentiated Design

The AFX platform main body is a unibody endograft for the treatment of AAA which is anatomically fixated on the aortic bifurcation. Endovascular aneurysm repair using an AFX device, commences with insertion of the unibody graft, which is seated on the aortic bifurcation. A proximal aortic seal is then achieved with placement of a proximal aortic extension cuff, and iliac extensions may be used to extend the iliac seal zone (Figure 1). It is important to ensure that there is sufficient overlap between the unibody graft and the proximal aortic cuff to prevent modular disconnection and a Type IIIa endoleak.

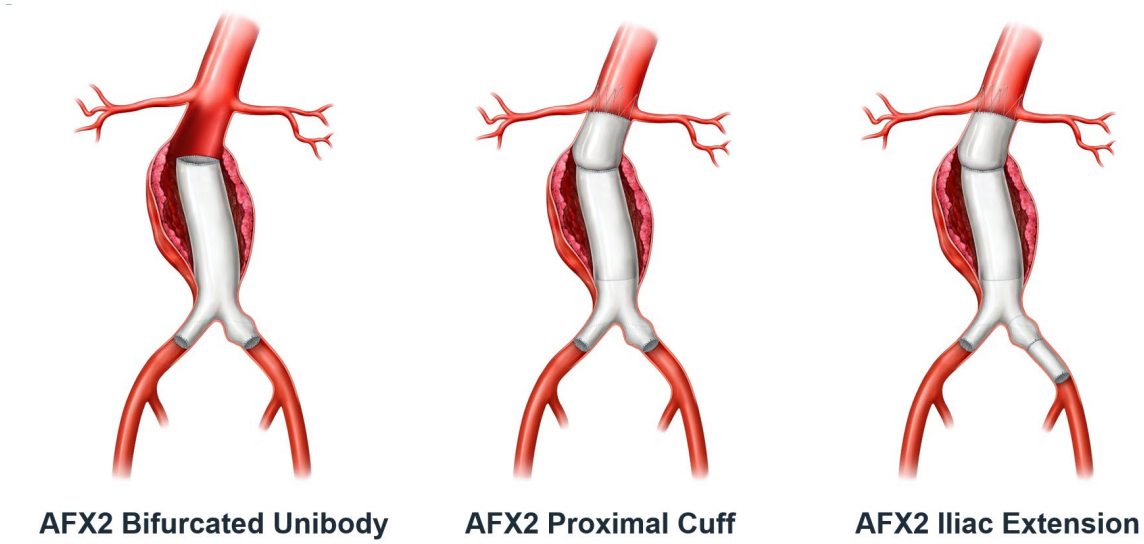


Figure 1: Components of the AFX2 System Used in EVAR

The AFX2 device has a unique design which is fundamentally different from proximally fixated endografts used in EVAR (the majority of these proximally fixated endografts in the United States (US) would be the Gore Excluder, the Medtronic Endurant and the Cook Zenith). Some of the key differentiated features of the AFX2 design include:

- A cobalt chromium endoskeleton stent, with a covering of ePTFE graft material free to move independently from the metal stent, which facilitates achievement of an acute seal
- Anatomical fixation on the aortic bifurcation which preserves the native aortic anatomy
- A unibody design which makes implantation technically straightforward

- The lowest profile contralateral access requirement (7F)

The differences in design between proximally and anatomically fixated endografts have implications for the preferential application of these different endograft designs in certain clinical situations.

Unmet Need and Clinical Utility of the AFX2 Endograft

There are fundamental differences between proximally fixated endografts and the anatomically fixated endografts, which translates to preferential use in certain clinical situations. Pragmatically, the key question is whether AFX2 offers advantages in certain patients, who may achieve better outcomes with an anatomically fixated endograft as opposed to a proximally fixated endograft. Clinical experience, physician opinion and clinical data suggest that AFX2 may have advantages in the following clinical situations:

- When the duration of the operative procedure, fluoroscopy or contrast volume needs to be minimized: both the LEOPARD Randomized Clinical Trial (RCT) (Section 5.1) and VQI data (Section 5.2.2) demonstrate that AFX2 has a significantly shorter operative procedure with a reduction in fluoroscopy use and contrast volume when compared to proximally fixated endografts.
- When it is imperative to achieve an immediate peri-operative aneurysm seal with prevention of Type Ia Endoleak: this may be particularly important in symptomatic (or ruptured) aneurysms. The VQI data (Section 5.2.2) demonstrate that AFX2 has a significantly lower peri-operative Type Ia Endoleak rate than comparator grafts (Type Ia rate 0.7%, other EVAR grafts 2.8%).
- When low-profile contralateral access is desired: this is relevant when treating patients with challenging contralateral access. This may be observed in women who have more challenging iliac access than men or in patients with significant peripheral vascular disease. The VQI (Section 5.2.2) and Medicare (Section 5.2.1) datasets demonstrate preferential use of AFX2 in female patients. The contralateral limb requirement for access for AFX2 is 7F, which is much lower than for any other EVAR graft.
- When preservation of the level of the native aortic bifurcation is key: in patients with downstream peripheral vascular disease in whom it may be desirable to preserve the option for retrograde "up and over" contralateral access. The preferential use of AFX2 in patients with peripheral vascular disease is observed in the Medicare (Section 5.2.1) data where the proportion of patients with peripheral vascular disease (PVD) was 44.9% as compared to 34.8% in the other EVAR group.
- In patients with a narrowed aortic bifurcation: 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. Clinical opinion supports this statement.

The clinical scenarios and robust clinical data above describe that a large number of patients and specific patient groups would be disadvantaged if physicians were restricted in therapeutic choice to proximally fixated endografts only, without recourse to anatomically fixated endografts. The AFX2 System offers physicians an important and relevant choice of graft options when determining personalized treatment of patients with AAA.

Brief Review of AFX Product Line and Nomenclature

The initial version of the AFX product line, AFX Strata, was launched in 2011 after approval of a PMA Supplement by the FDA (the original PMA related to the Powerlink Unibody endograft). During the first years of AFX Strata use, Endologix's post-market surveillance system (complaint reporting as part of the Quality System) identified atypical reports of Type III Endoleaks that prompted an internal investigation and a process of continuous improvement. This process involved a series of product design, manufacturing, and labeling updates that aimed to reduce the incidence of Type III Endoleaks.

During the process of continuous improvement, the nomenclature of the AFX product changed to reflect the product updates, such that there are three distinct versions of AFX – AFX Strata, AFX Duraply and AFX2. Five (5) significant groups of updates (some updates had more than one change) have occurred since the launch of AFX Strata in 2011 and are chronologically summarized below, along with the nomenclature of the associated product. One of the most significant updates was a change of ePTFE processing, which increased suture retention strength and tear propagation resistance in the transverse direction. This manufacturing change was reflected in a nomenclature change from Strata to Duraply. It should be noted that all updates have been incorporated in the currently available product, AFX2.

Table 1: Updates Made to the AFX Product Family

Date	AFX Nomenclature	Description of Update	Endoleak Addressed*
July 2011 (1)	AFX Strata	Baseline, prior to any updates	N/A
Jan 15, 2013 (2)	AFX Strata	Longer Bifurcated Lengths and IFU Overlap Recommendations to address inadequate overlap between main body and proximal cuff	Type IIIa
July 21, 2014 (3)	AFX Duraply	• Introduction of new ePTFE processing - Duraply – to improve suture retention strength and tear propagation resistance in transverse direction • Labelling update to warn of against excessive guidewire manipulation, ballooning, and vessel calcification	Type IIIb
Sept 9, 2015 (4)	AFX Duraply	Labelling update to address excessive oversizing of the proximal cuff in relation to the main body and patient selection recommendations (aortic tortuosity)	Type IIIa
Feb 22, 2016 (5)	AFX2	• Improved delivery system with cover to protect endograft bifurcation during deployment • Increased mean thickness of graft material • Introduced sizing algorithm	Type IIIa & IIIb

**Type IIIa Endoleaks can lead to a Type IIIb Endoleak. As lateral movement leads to a reduction/loss in component overlap, the angulation of the accessory component to the bifurcated component can increase and may result in the stent cage of the accessory or bifurcated component damaging the ePTFE of the neighboring stent graft. Therefore, by address Type IIIa Endoleak mechanisms, Type IIIb rates may also be positively impacted.*

The occurrence of Type III Endoleaks with AFX Strata was a mid- and long-term failure mode. It took approximately four (4) years of follow up with a large cohort of patients for the Type III Endoleak rate with AFX Strata to become clinically apparent. In 2016, with increasing length of follow-up after implantation, it became apparent that AFX Strata had a higher long-term Type III Endoleak rate than was observed with AFX Duraply. At that time AFX Strata was physically recalled. However, due to low rates of Type III Endoleaks with AFX Strata at earlier follow-up time periods, which did not breach trigger thresholds, commercial availability of AFX Strata and AFX Duraply overlapped (Figure 2). Similarly, AFX Duraply and AFX2 had a period where both devices were commercially available. During these periods, it was the newer version of AFX that was predominantly utilized. At present, the only available version of the AFX product family is AFX2.

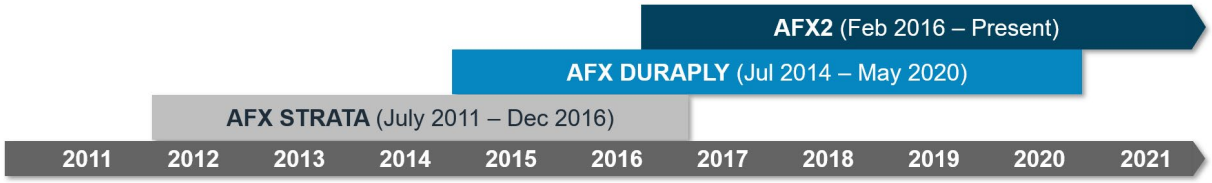


Figure 2: Timeline showing overlap of available AFX products
Note: At times of significant product overlap, the newer product was the predominant version

AFX Update, Reported Complaint Rates and Internal Signal Trending

Endologix uses reported complaints to generate internal signals to track the effect of continuous improvement programs on product performance. The effect of the product design, manufacturing, and labeling changes as described in Table 1 on the reported rates of Type III Endoleaks is illustrated in Figure 3.

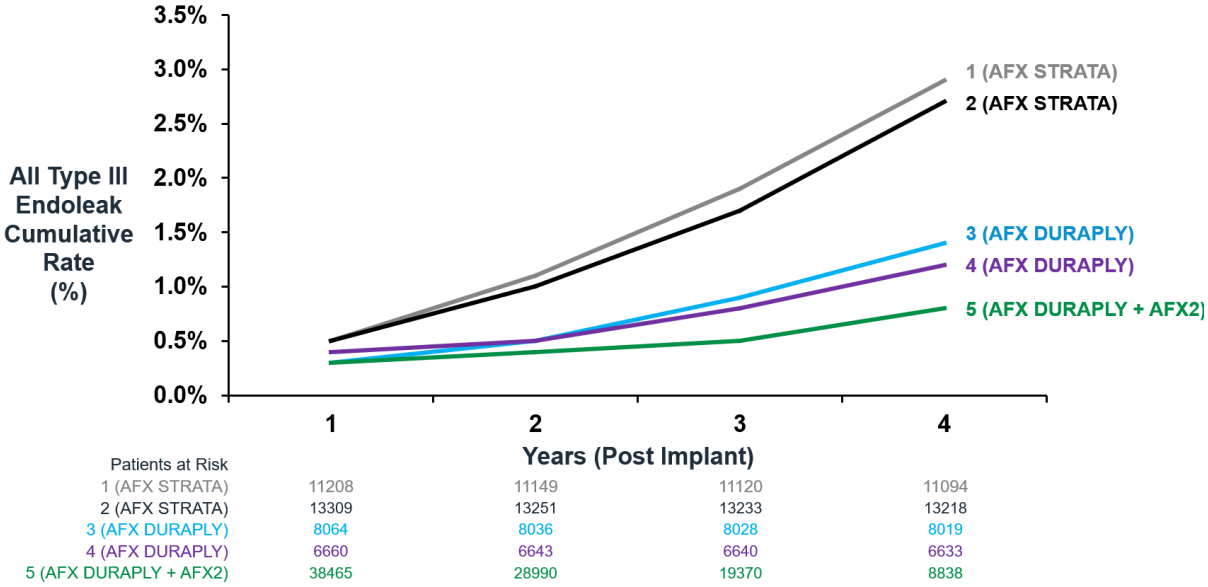


Figure 3: Time-to-Event Graph Demonstrating the Cumulative Type III Endoleak Rate for the AFX Product Family Stratified by the Chronological Product Updates
Note: The rates of Type III Endoleaks correspond to the time points of product update implementation

The complaint data suggest that each update to the AFX product line has serially and chronologically reduced the mid- and long-term Type III Endoleak rate. However, although this trend is encouraging, complaint data have significant limitations due to known under-reporting and should not be considered to be equivalent to complication rates observed in clinical practice.[1] The effect of the product updates and the comparative clinical performance of AFX2 should therefore be evaluated by a compendium of clinical evidence.

Management of Patients Implanted with AFX Strata

Endologix recognizes that patients implanted with the AFX Strata endograft will experience Type III Endoleaks at a higher incidence than patients treated with an updated version of the AFX product family, i.e., AFX Duraply or AFX2. In order to provide guidance on the management of these patients, Endologix has undertaken the following actions:

- **Investigated the clinical sequelae of Type III Endoleak**: While Type III Endoleaks are a serious clinical complication, they are usually amenable to endovascular treatment and are less complex to manage than Type Ia Endoleaks. The clinical sequelae of Type III Endoleaks affecting the AFX product family were investigated using complaint trending data. In the US there were 18,234 patients treated with AFX Strata, 1331 patients had a Type III endoleak (7.3%), 154 had a ruptured aneurysm secondary to a Type III Endoleak (0.84%) and there were 61 deaths secondary to a Type III Endoleak (0.33%). The analogous rates for patients treated with AFX2, were a Type III Endoleak prevalence of 0.8%, a rupture prevalence of 0.12% and death of 0.06%.
- **Convened three (3) Medical Advisory Boards (MAB):** MABs were convened to discuss the management of patients implanted with AFX Strata with particular attention on post-EVAR surveillance, indications for reintervention, and whether the product updates have been effective in mitigating Type III endoleaks (Section 4.4). Conclusions from the MAB were communicated to physicians through a letter from the Chief Medical Officer and subsequently were incorporated in the 2018 field communication related to patient tailored surveillance.
- **Issued a Field Safety Communication in 2018**: This communication provided guidance on navigating and reintervening through the unique endoskeleton of the AFX product family in order to minimize iatrogenic damage to the graft caused by endovascular manipulations. This communication also provided physicians with enhanced surveillance recommendations for patients with or at higher risk of graft related complications.
- **Investigated the feasibility of AFX-in-AFX relining as a solution for Type III Endoleaks**: Following advice from the MAB, a novel set of bench testing protocols were devised with FDA to investigate the feasibility and durability of AFX-in-AFX relining. The bench testing was completed and passed all pre-specified parameters.
- **Performed a clinical study to investigate outcomes after AFX-in-AFX relining**: A clinical protocol was devised to retrospectively collect data on patients who had been treated for a Type III Endoleak in an AFX graft, with AFX relining. A retrospective design was chosen as a prospective study would be logistically challenging and would not provide meaningful clinical data for many years. In the retrospective study, 76 patients were identified with AFX-in-AFX relining. The technical success of the procedure was 98.7%. Freedom from aneurysm related mortality, post-intervention aortic rupture, and Type III Endoleak at 3 years was 95.2%, 97.8% and 100%, respectively. These findings suggest that AFX-in-AFX relining is a viable and durable solution to treat patients with a Type III Endoleak related to an AFX graft[a]. Endologix proposes to make the bench and clinical data available to physicians in a labelling update which will be submitted to FDA for review.

The actions detailed above represent Endologix's actions to provide information that may help guide the management of patients implanted with AFX Strata.

Compendium of Clinical Data

Given the recent debate on the durability of EVAR as a therapy[2,3], the methodology for defining and reporting clinical outcomes is relevant. The outcomes of EVAR for any device should ideally be evaluated using multiple datasets, some of which would include an assessment of comparative graft performance and some of which should be independent of the manufacturer. The design and quality of each study should be carefully weighed, and the level of evidence assessed.

[a] As requested by FDA, these data were provide to FDA on September 22, 2021.

Different endografts have differing design intentions and consequently a spectrum of failure modes that are unique to that endograft. It is important that endograft outcomes are evaluated using a holistic assessment of graft function with single failure modes being weighed appropriately. Additionally, there has recently been an acknowledgement that a focus on specific technical failure modes, favored by medical device manufacturers and regulators, may not be reflective of patient centric issues.[4] From a patient's perspective it is suggested that the more injurious events of reintervention, aortic rupture and aortic related mortality are more relevant than a detailed description of Endoleaks without supporting clinical information. Endologix will present all relevant clinical outcomes that are pertinent to EVAR within each study.

Endologix takes a broad and patient centric approach to defining the clinical outcomes of AFX Duraply and AFX2. Data sources encompass a randomized clinical trial (LEOPARD – Level 1 evidence), two large contemporary independent datasets with comparative information (Medicare Fee-for-Service and VQI – Level 2 evidence) and a retrospective multicenter series of 405 patients (Level 3 evidence). Endologix believes that the highest quality and most robust clinical evidence comes from the LEOPARD RCT and the Medicare data.

Hypotheses Tested Throughout the Clinical Compendium

In analyzing the clinical data that Endologix has compiled, 2 hypotheses have been tested:

- That the product design, manufacturing, and labeling updates that have been made to the AFX product family since 2013 have been effective and that AFX2 (AFX Duraply additionally in some datasets) has a Type III endoleak rate that is clinically acceptable within an overall and holistic benefit-risk analysis of endograft performance
- That the current AFX product, AFX2 (and previously AFX Duraply), has a clinically favorable benefit-risk analysis that is similar to contemporary proximally fixated endografts used in EVAR

LEOPARD Randomized Clinical Trial

Looking at **E**VAR **O**utcomes by **P**rimary **A**nalysis of **R**andomized **D**ata) (LEOPARD), is the first contemporary, real-world, randomized clinical trial comparing the performance of commercially available EVAR devices and provides the highest level of evidence for the evaluation of long-term patient outcomes. LEOPARD used an "at or better statistical design" and after the trial ceased enrollment due to futility of reaching a superiority claim, was adequately powered to evaluate non-inferiority of the AFX platform.

Between 2015-2017, 105 investigators at 56 sites randomized 455 patients to AFX Duraply (124)/AFX2 (111) or a proximally fixated comparator endograft (from Medtronic, Gore Medical or Cook Medical). Patients will eventually be followed for 5 years[b]. The primary end point was freedom from aneurysm related complications (ARC) at 1 year.[5] The trial continues to accrue follow-up data, but there are sufficient patients at 4 years to evaluate both ARC and individual outcomes at this time-point. Among the 455 patients enrolled into LEOPARD, 422 (92.7%) had CT imaging performed, and 403 (88.6%) currently have CoreLab reviewed images.

At 1 year, the AFX Duraply/AFX2 group was statistically non-inferior to the comparator group and continued to have a higher freedom from ARC rate at all time points out to four years (Figure 4). Most of the difference between the two groups was driven by Type II Endoleaks. If these are removed from the ARC endpoint, then the curves are similar.

[b] Follow-up is ongoing with expected completion in 2022.

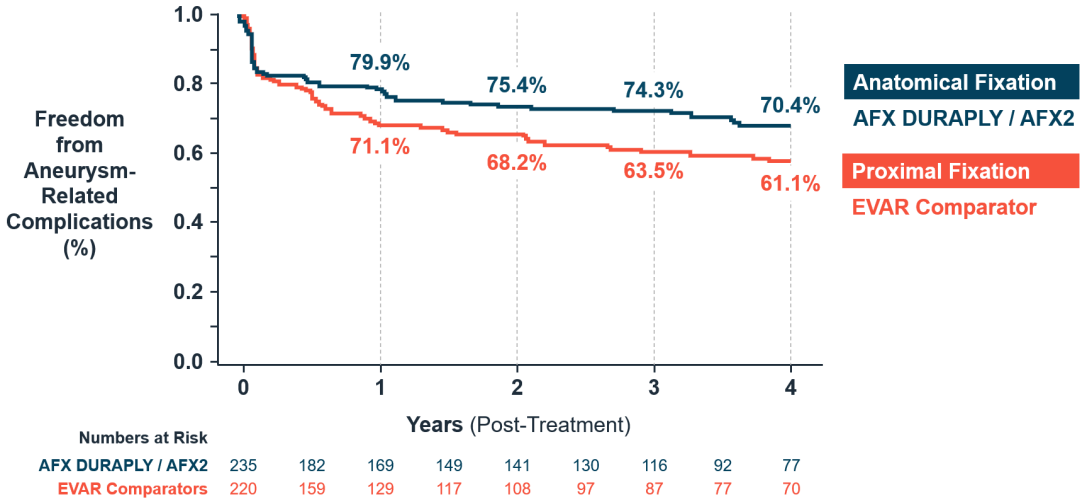


Figure 4: Aneurysm Related Complications (ARC) for the AFX Duraply/AFX2 group and the Proximally Fixated Comparator Group out to 4 Years of Follow-up

Note: At all time points the AFX Duraply/AFX2 group had fewer ARC than the comparator group. ARC is a composite of 30-day mortality, aneurysm related mortality, all Endoleaks, graft occlusions, graft migration, open conversion, aortic rupture, and device related reinterventions

At the 4-year time point, all secondary endpoints were similar between the randomized groups (Table 2). There were minor differences between some endpoints but nothing that would be regarded as demonstrating a meaningful clinical disparity. Given the previous issues with Type III Endoleaks with AFX Strata, its noteworthy that the 4-year freedom from Type IIIa Endoleaks was 100% and for Type IIIb, 98.7%.

Table 2: Four-year Freedom from Outcomes from the LEOPARD RCT for Relevant Secondary Endpoints

Outcome	AFX Duraply/ AFX2	Comparator
All-cause mortality (ACM)	77.5%	77.9%
Aneurysm related mortality (ARM)	97.1%	98.5%
Open conversion	100%	98.0%
Aortic rupture	98.9%	99.3%
Device related reinterventions	87.9%	88.2%
Type Ia Endoleak	99.2%	98.5%
Type Ib Endoleak	97.4%	98.5%
Type II Endoleak	83.2%	73.5%
Type IIIa Endoleak	100%	100%
Type IIIb Endoleak	98.7%	100%
Graft occlusion	97.8%	95.3%

Note: Values are freedom from rates of the relevant outcome measure. There were three peri-operative deaths in the AFX group which were included in the aneurysm related mortality outcome endpoint. Aneurysm related mortality after 30 days was the same in both groups.

The LEOPARD RCT provides the highest level of clinical data ever to directly evaluate the performance of contemporary endografts. In this randomized study, the AFX Duraply/AFX2 group was non-inferior to the comparator group in freedom from ARC at 1 year. The AFX Duraply/AFX2 group had better performance in freedom from ARC at all time points. This difference was principally related to a reduction in Type II Endoleaks. At 4 years, the incident rates of all significant endograft complications were similar between the two randomized groups. The Type III Endoleak rate for the AFX Duraply/AFX2 group was 1.3% at 4 years. Overall, the LEOPARD RCT provides robust, core lab evaluated, randomized evidence that AFX Duraply/AFX2 produces similar aortic-related outcomes to other contemporary endografts used in EVAR.

Medicare Fee-for-Service Database

Patients undergoing EVAR between 2012 and 2018 were identified from the Medicare Fee-for-Service (FFS) administrative claims database. Anatomically fixated grafts (AFX product family) were differentiated from single / double docking limb devices (essentially proximally fixated endografts) using CPT codes[c]. The study of the Medicare beneficiaries was performed for Endologix by an independent third party (Clarify Insights), advised by an independent surgeon scientist with specific expertise in analysis of outcome data in the Medicare population. The study population was divided into three-time cohorts to allow the effect of changes to the AFX product family to be evaluated. The cohorts were:

- Cohort 1 (96.2% AFX Strata, 3.8% Powerlink, January 1, 2012- July 20, 2014)
- Cohort 2 (91.04% AFX Duraply, 8.96% AFX Strata, July 21, 2014 - May 9, 2016)
- Cohort 3 (93.8% AFX2, 6.2% AFX Duraply, May 9, 2016 – December 31, 2017)

Outcomes of interest, all-cause mortality (ACM), post-EVAR aortic rupture and aortic related reintervention, were evaluated through September 30, 2020. The Medicare dataset does not have granular detail on the aortic related complications that led to the need for reintervention. Specifically, there are no details on the number and classification of Endoleaks, the incidence of migration or sac expansion. However, aortic rupture and aortic related reintervention give a broad perspective on endograft performance.

There were 32,031 patients who underwent EVAR during the study period: 4,729 received an anatomically fixated unibody endograft (AFX/AFX2) and 27,302 received a single and double docking limb endograft (proximally fixated endografts approved in USA – in a previous publication (6) 95% of proximally fixated grafts were those from Medtronic, Cook and Gore). There were a higher proportion of women and patients with peripheral vascular disease in the AFX group. Peri-operative mortality and peri-operative complications were similar between the two graft designs in all time cohorts.

The effect of the updates to the AFX product family was investigated by looking at the cumulative reintervention rate between the cohorts representing AFX Strata, AFX Duraply and AFX2 (Figure 5). Patients implanted with AFX Strata had a similar reintervention rate to those implanted with AFX Duraply and AFX2 up until year 3, but there is then a disparity with AFX Strata being associated with a higher reintervention rate than AFX Duraply or AFX2. This pattern may reflect a high rate of late Type III Endoleaks requiring interventions with AFX Strata, which was then mitigated by the cumulative product updates that were incorporated in AFX Duraply and AFX2. This pattern is similar to that observed in Endologix internal complaint trending.

[c] At the end of 2017, CPT codes changed; it is no longer possible to differentiate between unibody and single / double docking limb devices

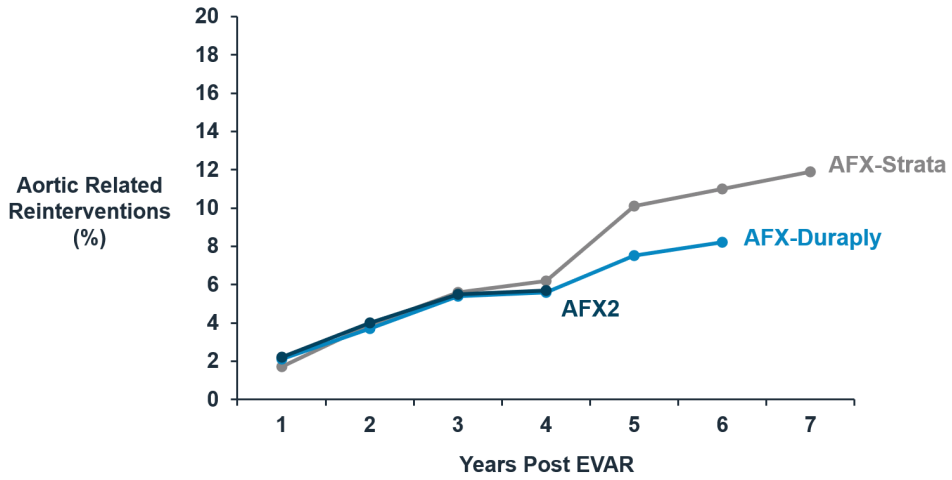
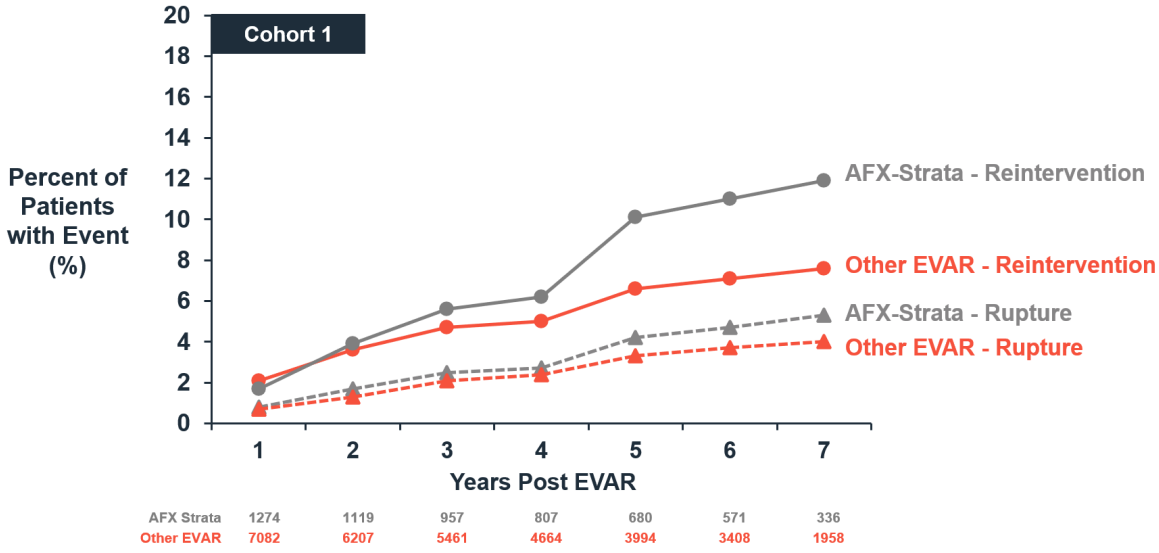


Figure 5: Device-Related Reinterventions in Medicare Beneficiaries Implanted with AFX Strata, AFX Duraply and AFX2

The comparative outcomes between the various iterations of the AFX product family and contemporaneous proximally fixated grafts were investigated by comparing both device related reinterventions and the rates of post-EVAR aortic rupture between the AFX and proximally fixated cohorts (Figure 6).



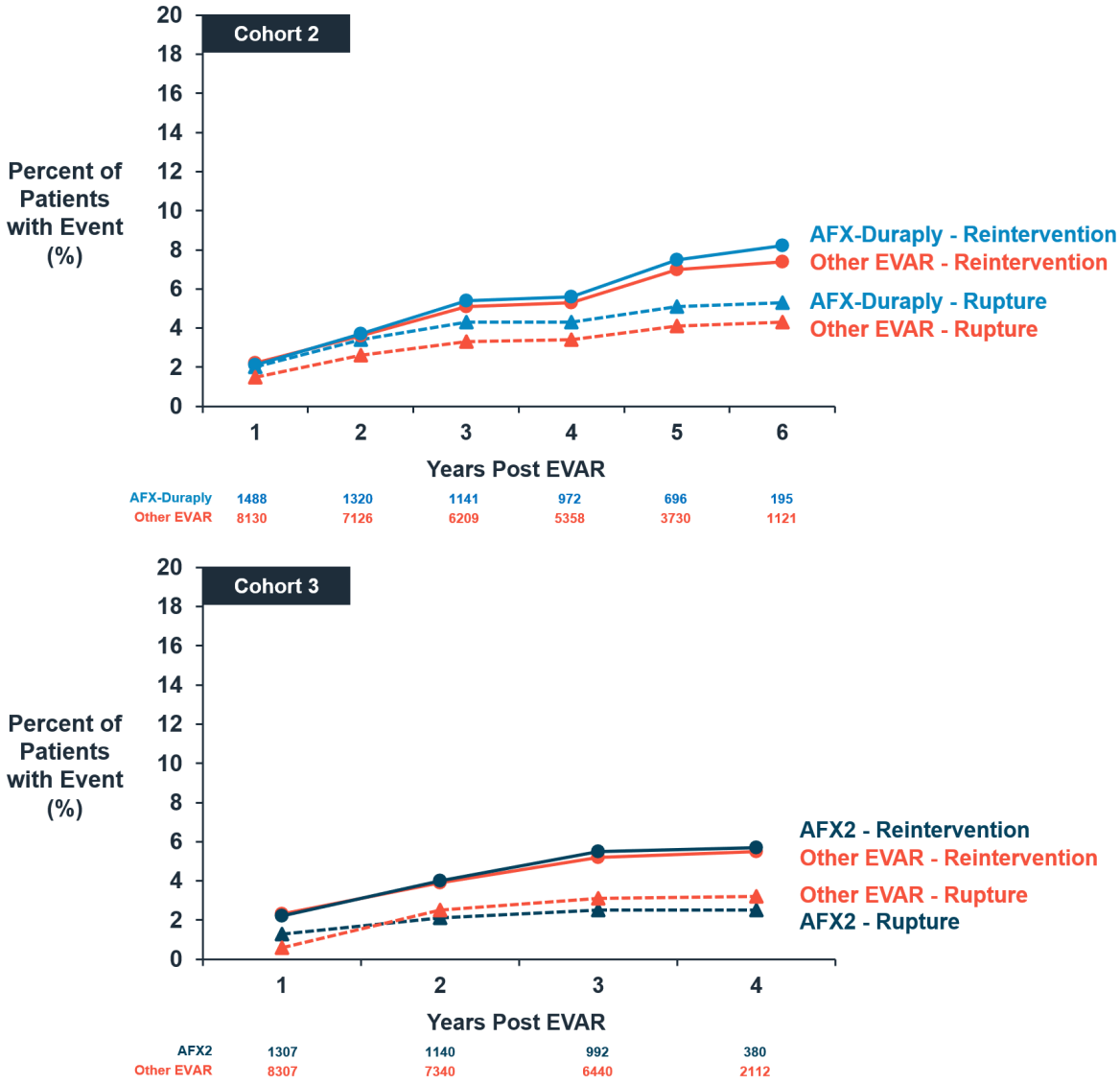


Figure 6: Cumulative Rates of Device Related Reintervention (DVR) and Post-EVAR Aortic Rupture (R) for the Three Time Cohorts Representing AFX Strata, AFX Duraply and AFX2

Note: Rates are given for the AFX family and for contemporary proximally fixated grafts per year of follow up. Note that the follow up periods for the three time cohorts are different.

AFX Strata had a higher rate of reintervention ($p<0.001$ at 7 years) and aortic rupture ($p<0.001$ at 7 years) than the comparator group. Reintervention between AFX Duraply and the comparator endografts were similar. The rate of aortic rupture trended higher in AFX Duraply after 6 years of follow up with an absolute magnitude of 1% after 6 years of follow up (or 0.17% per annum, $p=0.059$ at 6 years). AFX2 and comparator grafts had similar reintervention rates to 4 years of follow-up. The rate of aortic rupture trended lower in the AFX2 grafts with an absolute magnitude of 0.7% after 4 years of follow up (or 0.18%% per annum, $p=0.13$).

The Medicare FFS dataset provides a powerful set of independent data, with many patients and direct contemporaneous comparator groups for AFX Strata, AFX Duraply and AX2. AFX Strata had higher rates of both aortic rupture and reintervention when compared to proximally fixated grafts at long-term follow up. The updates made to the AFX product family reduced subsequent reintervention rates with AFX Duraply and AFX2. AFX Duraply and AFX2 had similar rates of both reintervention and post-EVAR aortic

rupture when compared to contemporaneous proximally fixated endografts. The results from Medicare beneficiaries undergoing EVAR provide robust data that AFX Duraply and AFX2 produce similar aortic-related outcomes to other contemporary endografts used in EVAR and that both AFX Duraply and AFX2 grafts have a favorable benefit-risk profile.

Vascular Quality Initiative (VQI)

The Vascular Quality Initiative (VQI) was established in 2011 by the Society for Vascular Surgery (SVS). It provides an unbiased assessment of EVAR device performance – with a focus on peri-operative and 1-year outcomes. As of March 31, 2021, VQI currently has 331 centers participating in the EVAR Registry. VQI data are able to differentiate AFX2 from all other EVAR devices. The peri-operative and 1-year data for AFX2 and the other comparator devices are tabulated below.

Table 3: 30-Day Outcomes Reported from the VQI Registry

30-Day Outcomes	**AFX2 N = 1,030**	**All Other EVAR Devices N = 35,226**
Procedure time (min), mean ± SD	108 ± 65	124 ± 66*
Contrast use (ml), mean ± SD	74 ± 53	92 ± 54*
Any Endoleak	8.3%	23.2%*
Type Ia	0.7%	2.8%*
Type Ib	0.6%	0.7%
Type II	4.7%	16.7%*
Type IIIa	0.2%	0.2%
Type IIIb	0%	0.1%
Peri-operative mortality	0.6%	0.7%

**p<0.01*
Note: AFX2 has a lower procedure time and contrast use than the comparator endografts. The reduced rate of all Endoleaks, Type II Endoleaks and all Endoleaks in the AFX2 group is clinically relevant.

Table 4: 1-Year Outcomes Reported from the VQI Registry

1-Year Outcomes	AFX2 N = 1,030	All Other EVAR Devices N = 35,226
Any Endoleak	9.0%	16.5%*
Type Ia	0.9%	0.8%
Type Ib	0.3%	0.7%
Type II	3.5%	12.1%*
Type IIIa	0.9%	0.2%
Type IIIb	0%	0.1%
Freedom from reintervention	97.9%	97.2%
Freedom from mortality	92.3%	92.6%

$p<0.01$

The VQI data provide another independent dataset that can evaluate the performance of AFX2 directly against other contemporary EVAR grafts. This dataset focusses primarily on peri-operative and short-term outcomes (i.e., through 1 year). In the peri-operative period, AFX2 has advantages in terms of procedural duration and the ability to achieve an acute seal with a clinically relevant, lower rate of Type Ia Endoleak as compared with other endografts.

405 Patient Retrospective Multi-Center Series Reporting Outcomes of AFX2

Endologix sponsored a retrospective, multi-center study of patients receiving an AFX2 device from January 2016 through December 2020. All patients receiving an AFX2 device within the study timeframe, at one of the five participating centers, were included. Standard data pertaining to aortic related outcomes were collected and analyzed. Overall, 460 patients were included in the study cohort, 405 patients underwent elective repair of an AAA, 50 patients were treated for a ruptured AAA, and five (5) were for aorto-iliac occlusive disease. In this summary, data on the elective cohort will be presented (mean age 73.7 years, 77% male, mean AAA diameter 5.4cm). The peri-operative mortality for elective EVAR was 1.7%.

The freedom from device related reinterventions is illustrated below (Figure 7).

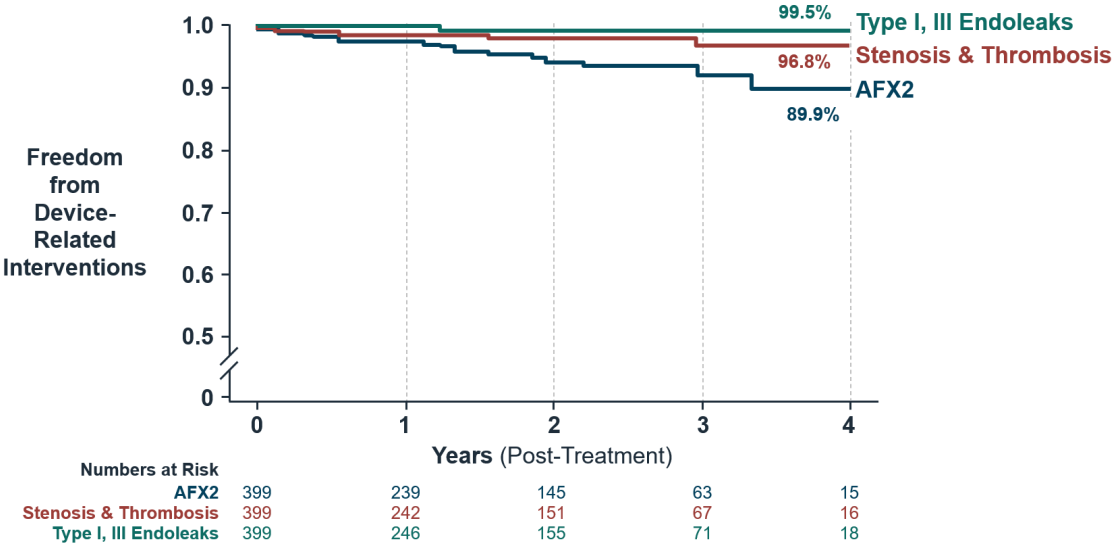


Figure 7: Device-Related Reinterventions for the Endologix-Sponsored Multi-Center Series

Note: Reinterventions are given as total reinterventions for stenosis/thrombosis and for treatment of Type I and III Endoleak.

As illustrated in Figure 7, there are sufficient patients with follow up to 3 years to make the cumulative rates evaluable at this follow-up. The relevant aortic related outcomes at 3 years from this study are tabulated below.

Table 5: Three-Year Freedom from Aortic-Related Outcomes in the Endologix-Sponsored Multi-Center Series

3-Year Freedom from Outcomes	**AFX2 N = 405**
All-cause mortality	81.3%
Aneurysm-related mortality	98.2%
Open conversion	98.8%
Aortic rupture	100%
Type Ia Endoleak	99.4%
Type III Endoleak	98.9%
Device-related reintervention	91.7%

In this Multi-Center Series, the AFX2 endograft performs to a satisfactory standard in terms of patient centric outcomes in mid-term follow up. The Type Ia and Type III Endoleaks rates at 3 years are within acceptable limits and consistent with other EVAR outcomes.

Concordance of Outcomes Across Compendium of Clinical Data

Endologix has presented a broad set of clinical data relating to the AFX product family. This compendium includes data on 4,901 patients implanted with AFX Duraply or AFX2. The data are derived from a variety of study designs, all of which have their own individual strengths and limitations. To assess whether there is a degree of consistency in the outcomes from these studies, the figures below plot the cumulative rates

of both device related reinterventions and Type III Endoleaks from the various data sources per year of follow-up reporting. For illustrative purposes, the data from AFX2 have been presented.

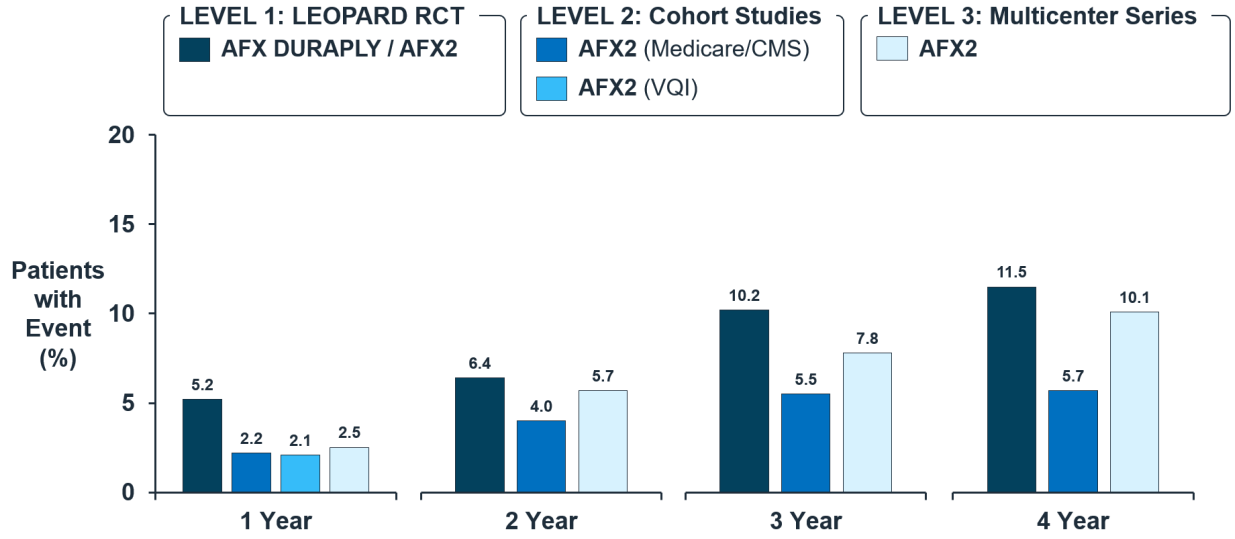


Figure 8: Device-Related Reinterventions for the 4 Studies in the Compendium of Clinical data, Presented per Study per Year

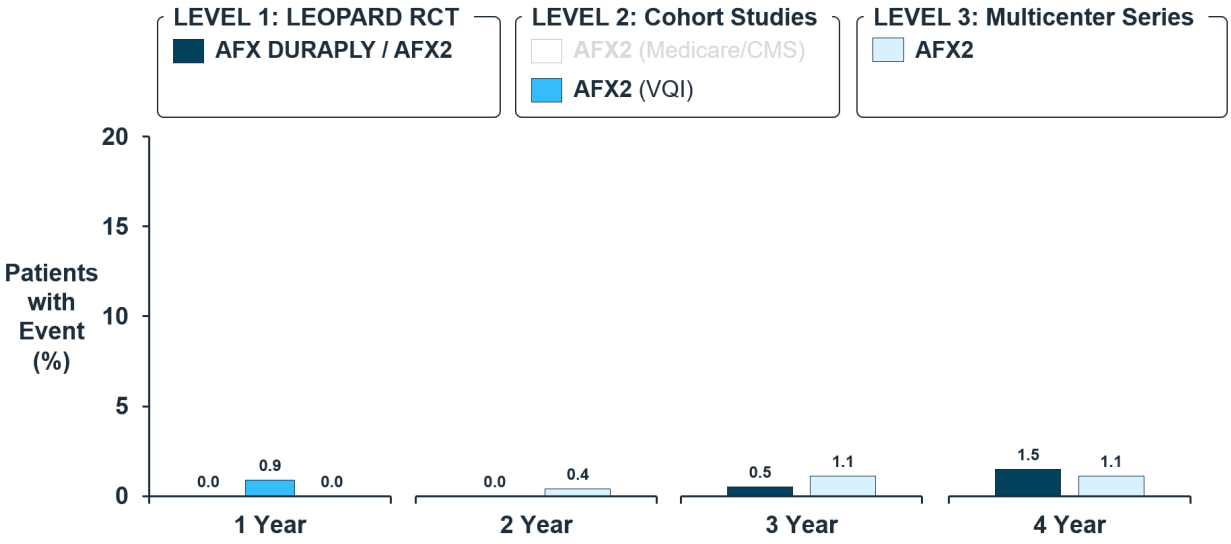


Figure 9: Rate of Type III Endoleak for the 4 Studies in the Compendium of Clinical Data, Presented per Study per Year

Note: The Medicare data set does not include Type III Endoleak as an outcome measure

Overall, there is a high degree of consistency across all four (4) studies. The rates of device related reintervention in the LEOPARD RCT appear higher than the others, which might be expected given the prospective nature of the study, the core laboratory assessment and the compliance with follow up. There are no studies in the Endologix compendium of clinical evidence that are outliers in terms of outcome incidence rates. The rates of device related reintervention and Type III Endoleak reported here, would therefore appear to be a good reflection of clinical outcomes achieved with the AFX2 graft in the US at mid-term follow-up.

Comparison of Endologix Compendium of Clinical Data and Outcomes Previously Reported

The data published by Chang et al.[6] was originally an oral communication at the American College of Surgeons Annual Meeting and reported mid-term outcomes of the AFX product family in a single hospital system. These data related to patients treated with AFX Strata (375 patients), AFX Duraply (197 patients) and AFX2 (33 patients). These data were given prominence in the 2020 FDA safety communication (https://www.fda.gov/medical-devices/safety-communications/update-risk-type-iii-Endoleaks-use-endologix-afx-endovascular-aaa-graft-systems-fda-safety) that suggested there may be a higher than expected rate of Type III Endoleak with AFX Duraply and AFX2. Given the conclusions that were drawn from the published data, and the limitations acknowledged by the authors, a comparison was made of the outcomes reported by Chang et al.[6] and the outcomes derived from the four (4) studies that comprised the compendium of clinical data collated by Endologix (Figure 10 and Figure 11). The graphs below compare the rates of device related reintervention and Type III Endoleak for both AFX Duraply and AFX2 as reported by Chang et al.[6] and the studies included in the clinical compendium.

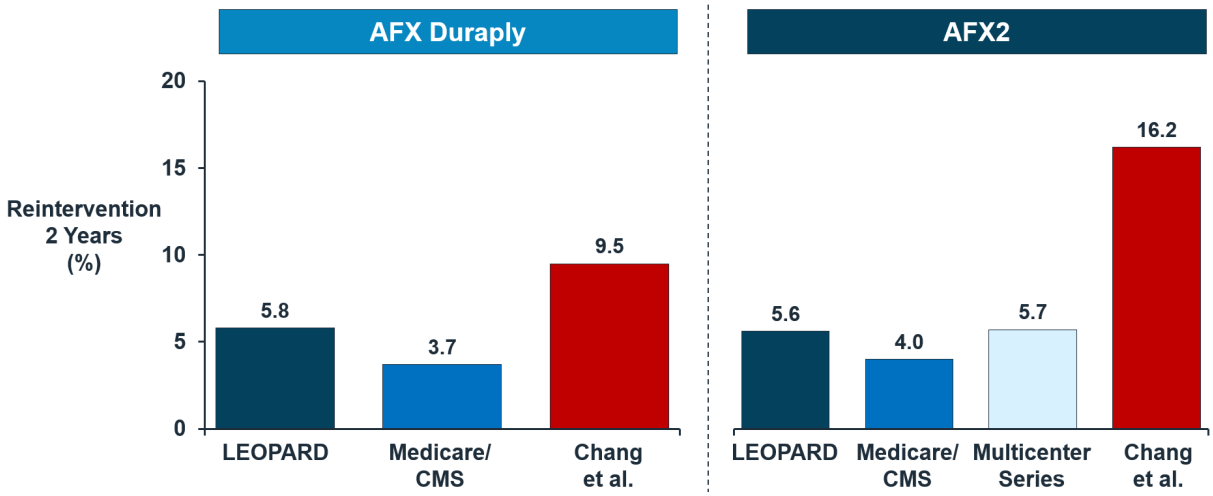


Figure 10: Rate of Device Related Reintervention at 2 Years Reported by Chang et al.[6] and Compared to the Studies in the Clinical Compendium that Reported that Outcome Measure
Note: The LEOPARD data have been dichotomized to report AFX Duraply and AFX2 separately

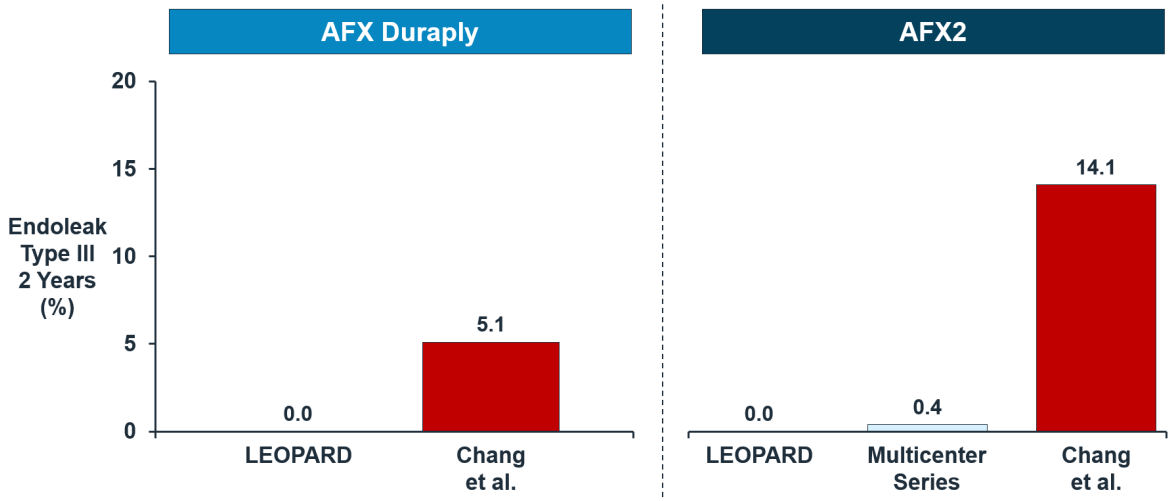


Figure 11: Rate of Type III Endoleak at 2 years Reported by Chang et al.[6] and Compared to the Studies in the Clinical Compendium that Reported that Outcome Measure
Note: The LEOPARD data have been dichotomized to report AFX Duraply and AFX2 separately

It is acknowledged that not all studies within the Endologix compendium of clinical data reported the same outcome parameters as the Chang manuscript and at the same time points. However, from the comparisons illustrated above, it is clear that the outcomes reported by Chang et al.[6]are worse than studies which would be considered broadly reflective of vascular practice in the US (given the number of centers and patients reported). In this regard, the outcomes achieved by Chang et al.[6] might be considered to be unrepresentative of the outcomes achieved by the AFX2 graft in other centers. It is clearly not within the purview of Endologix to comment on facets of clinical practice in specific hospital systems in isolation.

There have been several other studies that have reported on the AFX product family. Lemmon et al.[7] Barleben et al.[8] and Ta et al.[9] investigated the outcomes associated with AFX Strata and observed a high rate of Type III Endoleak in mid- and long-term follow-up. None of these studies reported on the AFX product family after the final product updates were incorporated.

Wanken et al.[10] performed a comparative analysis of patients treated with AFX Strata as compared to patients treated with a mix of AFX Duraply and IntuiTrak[d]. The proportion of grafts in the non-AFX Strata group are not given in the abstract. Rates of freedom from relining were plotted using Kaplan-Meier estimates and appear interpretable to 3 years. The freedom from relining at 3 years was 100% in the non-AFX Strata group and Major Adverse Event (MAE) rates appear similar between both groups. This abstract provides limited information relating to the AFX family after product updates.

Benefit-Risk of the AFX2 Device

AFX2 is completely differentiated from the prior member of the AFX product family, AFX Duraply since initial commercialization, by design, manufacturing and labelling updates. AFX2 has 1) an increased mean thickness of the ePTFE fabric[e], 2) a cover to protect the bifurcation during endograft deployment, and 3) a sizing algorithm to ensure adequate component overlap.

FDA's concerns over the benefit-risk of the AFX2 endograft appear to derive from historical extrapolation and a cohort of 33 patients described by Chang et al.[6], with 14 of these patients having follow up at 2 years.

In the clinical compendium, we present a comprehensive set of clinical outcomes for over 3000 patients implanted with AFX2 (LEOPARD:111, Medicare:1518, VQI:1030, Multi-Center Series:455). Not all outcomes are available at all time points, but there are robust data available to 4-year follow up.

The compendium of clinical data unequivocally demonstrates that AFX2 has clinical outcomes that are favorable from a benefit-risk profile. The rates of patient centric outcomes - all-cause mortality, aortic rupture, aneurysm related mortality and device related-reintervention are well within the rates that have been established for EVAR.

Notably, three of the datasets allow direct comparison between AFX2 and other contemporaneous EVAR grafts in clinical use. In all such comparisons, AFX2 has a performance profile that is similar to other EVAR grafts in all meaningful outcome measures.

To specifically address the question of Type III Endoleak rates, the clinical compendium suggests that the rate of Type III Endoleak with AFX2 is below 1.5% at 4-year follow-up. This compares favorably to the rate of 3%-4.5% quoted for Type III Endoleaks in the EVAR literature. Despite these positive findings, we reiterate that defining the performance of an endograft by reference to one single failure mode, to the exclusion of all others, is of limited value given the multiple failure modes that affects EVAR. Evaluation of benefit-risk profile requires a holistic approach and comparative analysis.

[d] IntuiTrak is a previous version of the device, which contained the Powerlink stent graft. It was in global distribution from 2008 – 2016 and in US distribution from 2008 – 2014.

[e] This change was implemented on AFX Duraply starting in May 2016; however, this implementation occurred after Endologix began transitioning customers to AFX2. Therefore, only a small percentage of AFX Duraply sold in the US incorporate this change.

AFX2 has clinical utility in clinical scenarios that are less well treated with proximally fixated endografts, as evidenced by the preferential use of AFX2 in women and patients with peripheral vascular disease.

Endologix remains committed to deriving a robust evidence base for the AFX2 endograft. Data collection for the LEOPARD RCT will continue to 5 years and we intend to perform a Medicare analysis annually to ensure we acquire data to long term follow up.

The AFX2 System is a safe and effective device for use in the treatment of AAA.

3. ENDOVASCULAR TREATMENT OF ANEURYSMS

Key Points

- Abdominal aortic aneurysms (AAAs) are treated to prevent aortic rupture and death.
- Death from aortic aneurysms and dissections equates to a rate of 3.0/100,000 population.
- Open surgical repair can be associated with major complications and may require a hospital stay of 7-10 days.
- There are known complications of EVAR, including Endoleaks, graft stenosis, occlusion, migration, infection, and sac enlargement.
- An Endoleak is persistent blood flow into the aneurysmal sac from within or around the graft and/or from patent collateral arteries.
    - Type III Endoleaks are due to modular disconnection or a hole in the fabric of an endograft and usually require treatment.
- Graft design intentions vary by manufacturer and consequently the range of failure modes are unique to each endograft design. It is important to note that the outcomes of EVAR for any particular device should be evaluated using multiple data sources.

An aneurysm is an excessive localized enlargement of an artery caused by a weakening of the artery wall. Abdominal aortic aneurysms (AAAs) develop in the part of the aorta that runs through the abdomen. Endovascular aneurysm repair (EVAR) is the most prevalent intervention for AAA repair in the US. A successful EVAR procedure is predicated on achieving proximal fixation and aortic seal to effectively exclude the aneurysm from the circulation. The majority of endografts used for EVAR have a design that includes an active mechanism for supra-renal or infra-renal fixation in the proximal aorta. In contrast to these proximally fixated grafts, the AFX product family (Endologix, Irvine, CA, US), uses anatomical fixation on the aortic bifurcation with a modular proximal cuff for aortic seal.[11]

3.1. ENDOGRAFT DESIGNS

3.1.1. PROXIMALLY FIXATED ENDOGRAFTS

Proximally fixated endografts (e.g., Cook Zenith, the Gore Excluder, and the Medtronic Endurant) are fixated using an active system of hooks and barbs in the proximal aorta and achieve seal by using an oversized self-expanding stent with high radial force to which fabric is closely attached. The proximally fixated endografts are modular with long iliac limbs.

3.1.2. ANATOMICALLY FIXATED ENDOGRAFTS

In contrast, the AFX product family is an anatomically fixated endograft. The design of the self-expanding stent and delivery system allows the endoluminal graft to fixate on the aortic bifurcation, thereby avoiding the need for active mechanical attachment (e.g., sutures, hooks, etc.) in the proximal aorta.

3.2. COMPLICATIONS OF ENDOVASCULAR ANEURYSM REPAIR

There are many therapy-specific complications which can impact both performance and durability of the EVAR procedure.

These include known peri-operative events as well as the specific complications that affect EVAR in the longer term, namely:

- Endoleaks
- Endograft stenosis

- Endograft occlusion
- Endograft migration
- Endograft infection
- Aneurysm sac enlargement

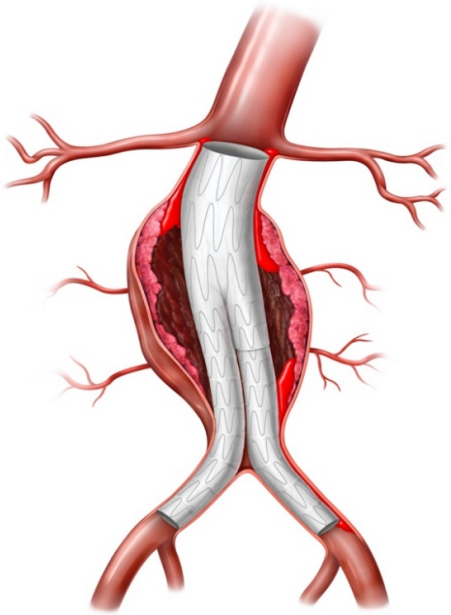
These complications may result in a reintervention to correct the complication, using endovascular or open surgery, or may result in aneurysm rupture and subsequent aortic related mortality.

3.2.1. ENDOLEAK TYPE OVERVIEW

Endoleaks are a complication specific to endovascular aortic repair. The definition of an Endoleak is persistent blood flow into the aneurysmal sac from within or around the graft and/or from patent collateral arteries. Endoleaks can be classified as primary or secondary depending on the time of occurrence (within 30 days of implantation or following apparent initial seal, respectively)[12] and are grouped into five separate categories:

1. **Type I Endoleaks:** These occur at the proximal (Type Ia) or distal (Type Ib) ends of the endograft and usually occur because of inadequate seal, migration, or aortic neck degeneration.
2. **Type II Endoleaks**: These are the most common type of Endoleak, which are caused by retrograde flow through collateral vessels into the aneurysm sac.
3. **Type III Endoleaks**: Type IIIa Endoleaks are caused by a separation of modular components, most often because of discrepancies in device sizing, inadequate overlap of the modular components during the procedure, or changes in aortic morphology. Type IIIb Endoleaks are caused by holes in the stent graft material.
4. **Type IV Endoleaks**: These are caused by porous graft material.
5. **Type V Endoleaks**: These occur from an unidentified source that results in aneurysm sac enlargement.

In terms of clinical sequelae, aortic rupture is most highly associated with Type I and Type III Endoleaks[13], with Type Ia being more common than Type Ib Endoleaks. Renderings of the most common Endoleak types (Type I, Type II, and Type III) are included in the figures that follow:



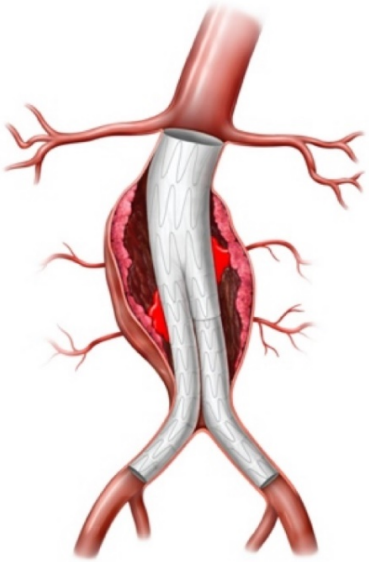
Type Ia Endoleaks

Endoleak between the proximal end of the endograft and the aneurysm sac. Type Ia Endoleaks usually require treatment as the aneurysm sac is highly pressurized. Treatment may involve placement of aortic extensions, the use of fixation screws, or open surgery.

Type Ib Endoleaks

Endoleak between the distal end of the endograft and the aneurysm sac. Type Ib Endoleaks usually require treatment as the aneurysm sac is highly pressurized. Treatment may involve placement of iliac extensions or open surgery.

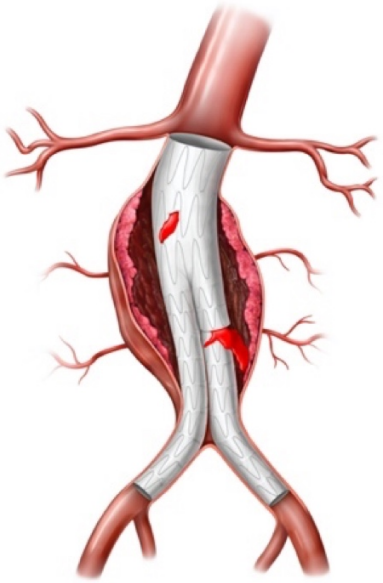
Figure 12. Rendering of Type I Endoleaks



Type II Endoleaks

Endoleak due to retrograde flow from branch vessels. The treatment of Type II Endoleaks remains controversial and the subject of debate. Many physicians will choose to treat Type II Endoleaks when associated with aneurysm sac expansion. Treatment may involve embolization of the branch vessel or aneurysm sac.

Figure 13. Rendering of Type II Endoleaks



Type III Endoleaks
Endoleak due to modular disconnection (Type IIIa) or hole in the fabric of an endograft (Type IIIb). Type III Endoleaks usually require treatment as the aneurysm sac is re-pressurized. Treatment may involve placement of aortic extensions, iliac limb extensions, complete graft relining, or open surgery[14].

Figure 14. Rendering of Type III Endoleaks

3.2.2. TREATMENT OPTIONS

Patient selection for EVAR depends on clinical and anatomical features identified after preoperative imaging studies have been obtained.[15] The risk of early and late failure of EVAR is associated with adverse anatomic findings including proximal neck morphology (e.g., length, diameter, angulation, and shape) and iliac artery morphology (e.g., lumen size, atherosclerosis, and tortuosity).

In general, an endovascular approach for AAA repair offers several benefits over open AAA repair including: the ability of EVAR to be performed under local anesthesia, shorter operative time, reduced blood loss, and reduction in peri-operative complication, which may translate into better 30-day post-operative results.[16] Randomized clinical studies consistently demonstrated the early benefit with EVAR over open surgery.[17,18] This benefit, at least from the currently completed randomized studies and population-based studies, does not persist through long-term follow-up (beyond 5 years).[19,20,21,22,23]

Recent research with longer term follow-up is showing that the early mortality and morbidity advantages associated with EVAR are lost[24,25,26], and the trials that directly (or indirectly) compared open with endovascular repair demonstrated that EVAR was associated with:

1. Higher all-cause mortality in the long-term
2. Higher aneurysm-related mortality in the long-term
3. Higher rates of aortic rupture in the long-term
4. Higher rates of reintervention in the long-term

The concerns surrounding the durability of EVAR have also been identified in other study designs. The recent publications on this topic are relevant as the randomized controlled trial (RCTs) that compared open against endovascular surgery commenced early in the evolution of endovascular therapy and may not reflect modern practice. As an example, Columbo et al.[2] reported on 12,911 patients treated between 2003–2015. The endografts were of the proximally fixated design in 94.7% of the population. This study observed that 15% of patients required reintervention at 3 years, a figure that rose to 33% at 10 years (Figure 15). Additionally, the authors reported that 1 in 5 patients undergoing a reintervention suffered a ruptured aneurysm within 10 years from their initial aneurysm repair. Overall, 5% of patients in the study had an

aortic rupture at 10 years. This rate will be an under-representation of the true incidence, as only patients presenting to hospital were included in the analysis, which therefore excluded patients dying of a post EVAR aortic rupture outside of a hospital setting.

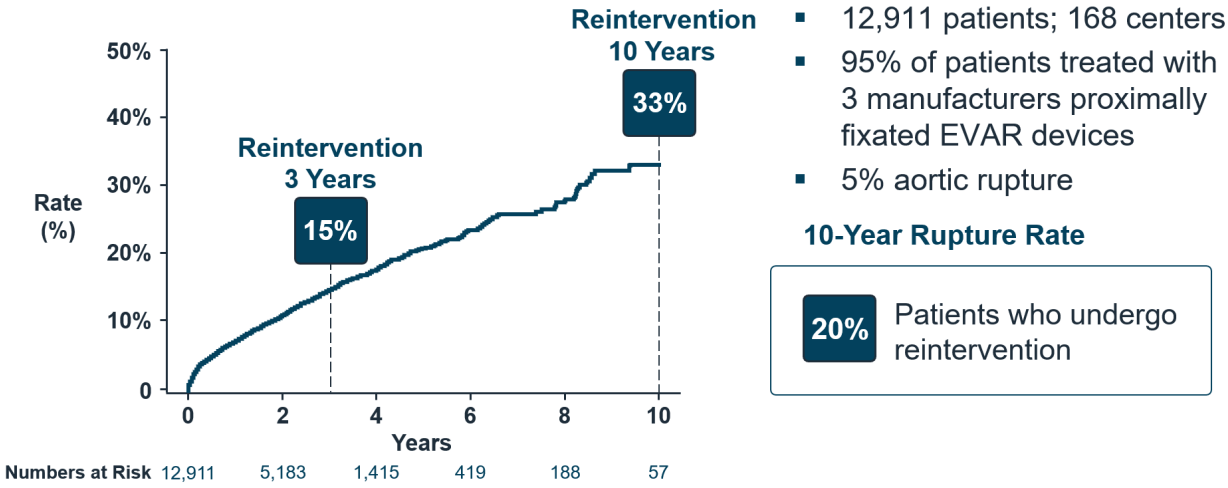


Figure 15. Rate of Reintervention with Proximally Fixated EVAR Devices
Source: Columbo et al.[2]

Such data sources, including the EVAR1 RCT from 2005[27], prompted the UK National Institute for Health and Care Excellence (NICE) to publish guidelines on the management of AAAs. NICE concluded that EVAR should be used as a second line therapy for AAAs, in patients where open surgery was contraindicated:

- *Recommendation 1.5.3: Offer open surgical repair for people with unruptured AAAs …, unless it is contraindicated because of their abdominal co-pathology, anesthetic risks, and/or medical comorbidities (NICE Guideline, 2020).*[28]

Despite EVAR-related endograft durability issues, aneurysm-related reinterventions and a low but clinically significant rate of post-repair aneurysm rupture, EVAR remains the dominant treatment modality for patients with infra-renal AAAs.[29] This preferred clinical practice stems from early benefits of less pain, earlier return of gastrointestinal function, shorter hospitalization, and more rapid return to normal activities.

While EVAR remains the preferred clinical modality, defining outcomes for individual EVAR endografts assumes greater importance with recent publications raising concerns about the durability of EVAR. Given the limitations of single center series and industry sponsored single device registries[4,30] it is important that the outcomes of EVAR for any particular device should be evaluated using multiple data sources, some of which would include an assessment of comparative graft performance and some of which would be independent from the device manufacturer.

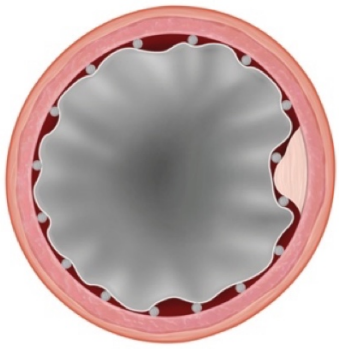
3.2.3. Failure Modes and Endograft Designs

Design intentions and tradeoffs vary by manufacturer and consequently the range of failure modes are unique to each endograft design. For this reason, endograft outcomes should be evaluated using a holistic assessment of overall graft function with single failure modes being weighed appropriately.

3.2.3.1. Proximally Fixated Endografts

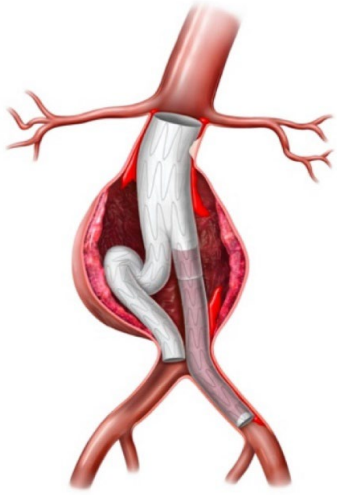
Proximally fixated endografts may be associated with Type Ia Endoleaks due to lack of conformance of the fabric to the irregular inner surface of the aorta in the proximal seal zone (Figure 16). This is demonstrated clinically in the VQI data in Section 5.2.1. The proximally fixated designs are also associated with iliac limb occlusions (Figure 17). This is demonstrated clinically in the LEOPARD RCT in Section 5.1 and van

Zeggeren et al.[31] However, these designs do have strong modular junctions between the aortic body and the iliac limbs and so have relatively low rates of Type III Endoleaks (as demonstrated in the VQI data in Section 5.2.1 and the LEOPARD RCT in Section 5.1).



Proximally fixated endografts rely on radial force of an oversized stent to seal in the proximal aorta. In some cases, aortic irregularities make this challenging, and Type Ia Endoleaks may result.

Figure 16. Proximally Fixated Endograft Complications: Type Ia Endoleaks

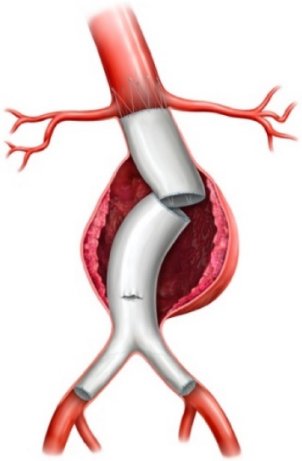


Iliac limb length and aorto-iliac tortuosity may predispose to limb occlusion in proximally fixated endografts.

Figure 17. Proximally Fixated Endograft Complications: Limb Occlusion

3.2.3.2. ANATOMICALLY FIXATED (UNIBODY) ENDOGRAFTS

In contrast, the design features of the AFX product family, an anatomically fixated endograft, result in a low rate of acute Type I Endoleaks (VQI data in Section 5.2.1). Additionally, the unibody design has short iliac limbs and is less constrained by the diameter of the aortic bifurcation which results in a low rate of iliac limb occlusion (LEOPARD data in Section 5.1). However, the need to be precise on achieving sufficient overlap between the modular components to accommodate morphological changes after EVAR and the fact that the graft rests on the aortic bifurcation, with an interaction between the aorta and graft fabric means that the unibody design may be associated with Type III Endoleaks (Figure 18).



With anatomically fixated endografts, inadequate overlap between the main bifurcated device and the proximal aortic cuff can predispose the graft to Type IIIa Endoleaks. Disruption of the graft fabric due to graft / aorta interaction may predispose the graft to a Type IIIb Endoleak.

Figure 18. Anatomically Fixated Endograft Complications: Type III Endoleaks

4. DEVICE INFORMATION

Summary

- The Endologix "AFX Product Family" denotes the last three commercialized systems: AFX System with Strata (2011), AFX System with Duraply (2014) and the current AFX2 System (2016).
- Endologix's unibody grafts allow the endoluminal graft to fixate against the aortic bifurcation, thereby avoiding the need for mechanical attachment in the proximal aorta.
- The AFX2 System consists of a bifurcated endograft and proximal and limb extension endografts.
- The AFX2 System is indicated for patients with suitable morphology for endovascular repair.
- The inclusion of anatomical limitations in labeling is consistent with other EVAR devices.
- The following design features differentiate the AFX Family from other EVAR systems:
  - Unibody design
  - Stabilization on the aortic bifurcation
  - Wide main body bifurcation

4.1. SYSTEM OVERVIEW

The currently marketed AFX2 System is intended for the endovascular repair of abdominal aortic or aorto-iliac aneurysms. The portfolio for the AFX2 System (the currently marketed system) is comprised of:

- Bifurcated Endografts and their respective delivery catheters
- Proximal (Aortic) Extension Endografts (Cuffs) and their respective delivery catheters
- Limb (Iliac) Extension Endografts and their respective delivery catheters

All AFX2 System endografts are pre-loaded onto a delivery catheter, which is compatible with the stand-alone AFX Introducer.

The AFX2 Bifurcated device is the primary device in the system. It is a unibody, infrarenal, bifurcated stent graft, which has a main body with two attached limbs. The accessory components, which are utilized to customize the AFX2 System to the patient anatomy, comprise infrarenal and suprarenal proximal extensions as well as limb extensions in straight, tapered, flared, and stepped configurations. These devices are used together to form a modular, customizable system (Figure 19).

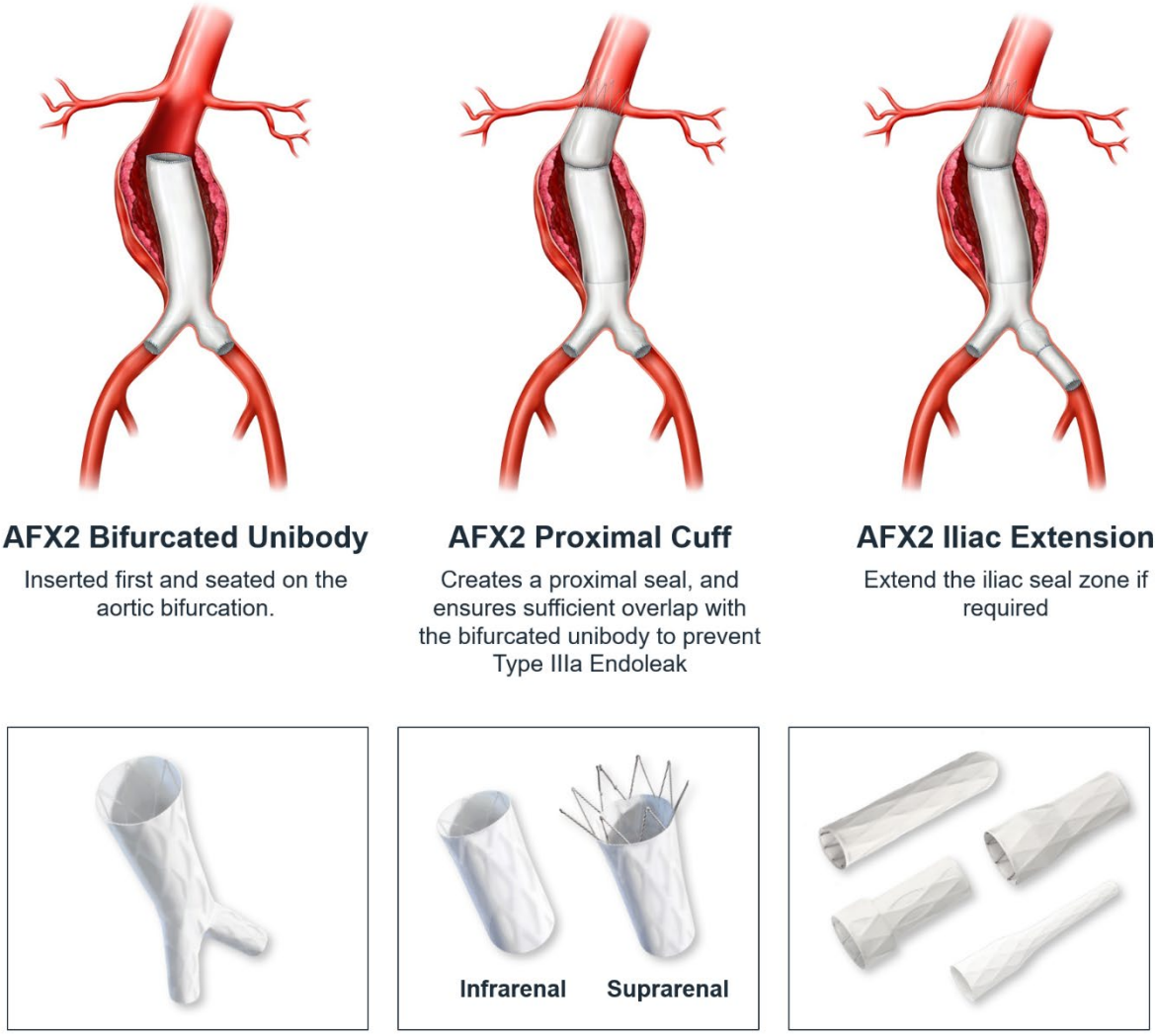


Figure 19. Endologix AFX2 Device Components

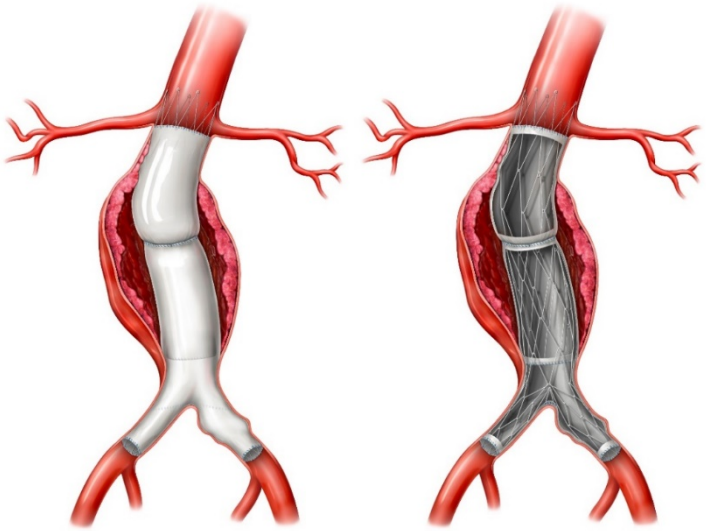


Figure 20. Rendering of the Implanted AFX2 System
Note: The graft is not attached to the stent cage throughout its entire length

4.1.1. AFX FAMILY OF DEVICES

There are three (3) iterations within the AFX Family of devices:

- AFX System with Strata: The initial version of the AFX product line, AFX Strata, was launched in 2011 after approval of a PMA Supplement by the FDA (the original PMA related to the Powerlink Unibody endograft). This system utilized an ePTFE graft material processing method referred to as Strata. In this method, the grafts material was sheet extruded and utilized a serial wrapping technique. Devices manufactured with the Strata ePTFE graft material process were recalled by Endologix in December 2016 and are no longer commercially available.
- AFX System with Duraply: Endologix received PMA approval for this system in 2014. This system utilized an ePTFE graft material processing method referred to as Duraply. In this method, the graft material was sheet extruded and utilized a combination of serial and helical wrapping. This new technique maximized the graft material suture retention and tear propagation resistance in the transverse direction, not just longitudinally. Duraply replaced Strata on all AFX System endografts starting in mid-2014, following necessary regulatory approvals. The AFX System with Duraply was subsequently discontinued in the US in August 2018 and globally in May 2020.
- AFX2 System: Endologix received PMA approval for this system in 2015 and first commercialized it in 2016. This system utilizes the Duraply ePTFE graft material processing method with additional changes made to the delivery system to improve usability and manufacturing methods to protect the ePTFE graft from damage during loading onto the delivery system. Additionally, during implementation of AFX2, Endologix implemented a sizing algorithm in the IFU as well as tighter manufacturing specifications on the ePTFE graft, which resulted in an increase in the average thickness of the Duraply graft material. AFX2 is the current and only commercialized system within the AFX family of devices.

4.2. DESCRIPTION OF CLAIMED USE

4.2.1. INTENDED MEDICAL PURPOSE

The AFX2 System is intended for single use in patients with abdominal aortic or aortoiliac aneurysms using either a surgical vascular access technique or a bilateral percutaneous technique. The AFX2 System is indicated for patients with suitable morphology for endovascular repair (as defined by the indications for

use, Appendix B: Indications and Contraindications). Additionally, the AFX Introducer is intended to facilitate the introduction of guidewires, catheters, and other medical devices into the vasculature and minimize blood loss associated with such introduction.

4.2.2. PRODUCT LABELING

Refer to Appendix B for the AFX2 Systems Indications for Use and Contraindications, as stated in the product's IFU. NOTE: The inclusion of anatomical limitations is consistent with other EVAR devices.

4.2.3. INTENDED CLINICAL BENEFITS / DESIGN INTENT

The AFX2 System is indicated for the endovascular treatment of AAAs using a surgical vascular access technique or a percutaneous technique in patients with suitable anatomy, including an adequate proximal aortic neck seal zone and common iliac artery seal zones. When deployed across the aortic aneurysm, the self-expanding stent graft implant provides a permanent conduit for blood flow and excludes the aneurysm sac from blood flow and pressurization.

The AFX2 System was designed to prevent or at least reduce the frequency of some of the complications of other devices. These enhancements can be briefly summarized as follows, which differentiates this design from endografts that use proximal fixation in the aortic neck:

Table 6: Features and Advantages of the AFX2 System

Figure 21 Reference	AFX2 Feature	Clinical Advantage
1	Stabilization on the Aortic Bifurcation	Designed to rest on the aortic bifurcation with intention to discourage endograft migration through two mechanisms: 1. Columnar support of the main body is buttressed against the aortic bifurcation with the potential to provide additional resistance against migration forces beyond that of proximal neck fixation alone ("anatomic fixation").[32,33] 2. The flow divider and the endograft bifurcation mimic that of the native aorta. In theory, this arrangement reduces caudally directed forces against the main body bifurcation, also potentially decreasing the long-term risk of endograft migration.[34]
2	Graft Material External to Stent and Attachment at Cranial and Caudal Aspects of the Stent	Allows the graft material to better adapt to irregular mural neck surfaces – surfaces that are not always perfectly circular.[35]
3	Wide Main Body Bifurcation	Endovascular procedures that require "up and over" access in patients with endografts are technically demanding with other devices. The wide angle of the AFX2 Bifurcated device, which is similar to that observed in the native aortoiliac bifurcation, facilitates this approach.[36] Theoretical hemodynamic benefits to an endograft bifurcation that mirrors that of a native aorta. Increased shear stress and associated turbulence in other configurations, where the path of blood flow continues from a large diameter main body into smaller diameter, abnormally angled limbs with the potential for narrowing at the gates, may potentiate endograft limb occlusion in other devices.[35]
4	Unibody Design	Prevents disunion at the junction of the main body and the endograft limbs, which is one mechanism for Type IIIa Endoleaks.[37,38,39,40,41] While disunion can still occur at the junction of the main body and the aortic extension, or between the limbs and the limb extenders in cases where either is employed, the unibody design limits one mechanism of Type IIIa Endoleak.

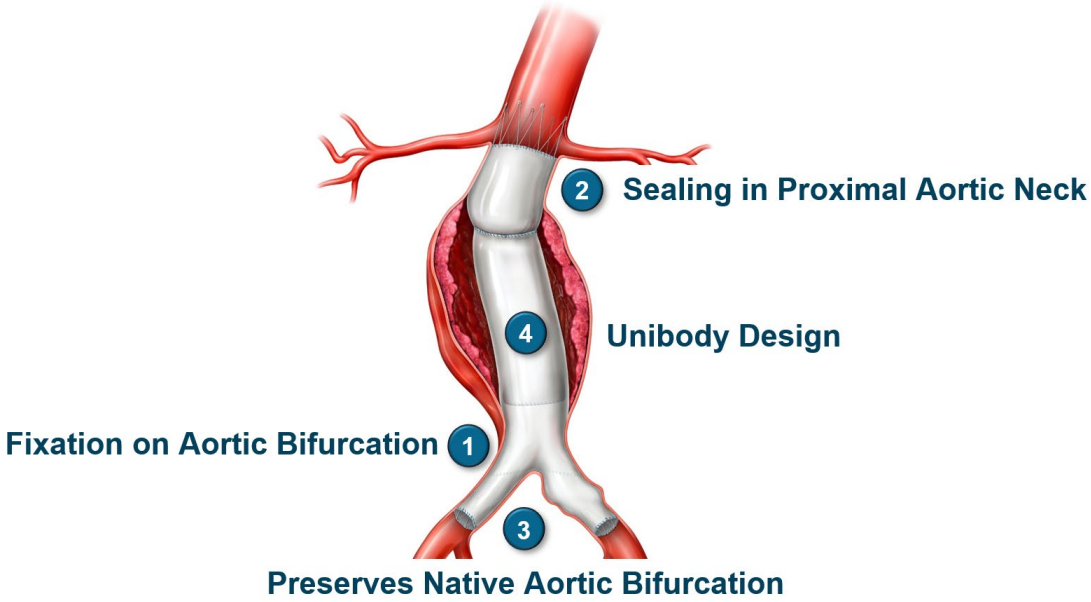


Figure 21. Endologix AFX2 System

Eighty-four (84) physicians with experience of AFX2 were asked when they would choose the AFX2 System over a proximally fixated endograft. The results are illustrated in Figure 22 and indicate that AFX2 has a clear clinical need in treating some specific aortic morphologies, such as a narrow distal aorta and challenging contralateral access (AFX2 has the lowest profile contralateral access at 7F) as well as having the ability to preserve the aortic bifurcation to facilitate treatment of co-existent peripheral vascular disease. AFX2 is the only available endograft with this ability.[f]

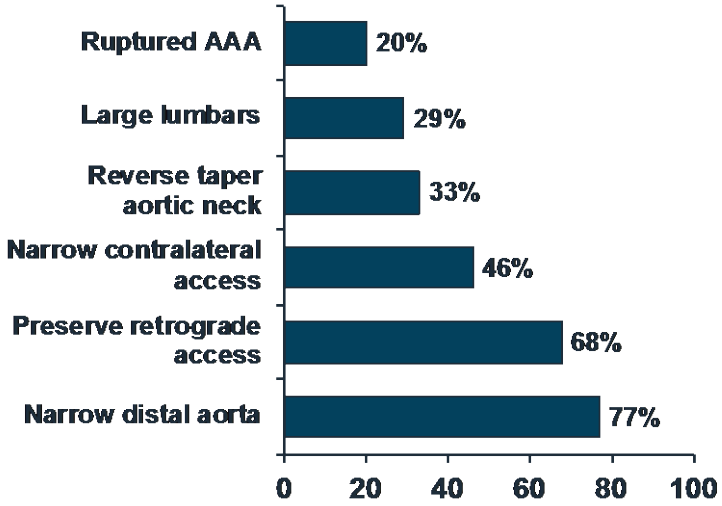


Figure 22. Features of AFX2 that Influence its Use in Preference to a Proximally Fixated Endograft by Physicians Who Use AFX2 Selectively in Practice

Pragmatically, the key question is whether AFX2 offers advantages in certain patients, who may achieve better outcomes with an anatomically fixated endograft as opposed to a proximally fixated endograft.

[f] AFX Survey by BIBA MedTech Insights. Data on File at Endologix.

Clinical experience, physician opinion, and clinical data suggest that AFX2 may have advantages in the following clinical situations:

- When the duration of the operative procedure, fluoroscopy or contrast volume needs to be minimized: both the LEOPARD RCT (Section 5.1) and VQI data (Section 5.2.2) demonstrate that AFX2 has a significantly shorter operative procedure with a reduction in fluoroscopy use and contrast volume when compared to proximally fixated endografts.
- When it is imperative is to achieve an immediate peri-operative aneurysm seal with prevention of Type Ia Endoleak: this may be particularly important in symptomatic (or ruptured) aneurysms. The VQI data (Section 5.2.2) demonstrate that AFX2 has a significantly lower peri-operative Type Ia Endoleak rate than comparator grafts (Type Ia rate 0.7%, other EVAR grafts 2.8%).
- When low-profile contralateral access is desired: this is relevant when treating patients with challenging contralateral access. This may be observed in women who have more challenging iliac access than men or in patients with significant peripheral vascular disease. The VQI (Section 5.2.2) and Medicare (Section 5.2.1) datasets demonstrate preferential use of AFX2 in female patients. The contralateral limb requirement for access for AFX2 is 7F – much lower than for any other EVAR graft.
- When preservation of the level of the native aortic bifurcation is key: in patients with downstream peripheral vascular disease in whom it may be desirable to preserve the option for retrograde "up and over" contralateral access. The preferential use of AFX2 in patients with peripheral vascular disease is observed in the Medicare (Section 5.2.1) data where the proportion of patients with PVD was 44.9% as compared to 34.8% in the other EVAR group.
- In patients with a narrowed aortic bifurcation: 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. Clinical opinion supports this statement.

The clinical scenarios and robust clinical data above describe that a large number of patients and specific patient groups would be disadvantaged if physicians were restricted in therapeutic choice to proximally fixated endografts only, without recourse to anatomically fixated endografts. The AFX2 System offers physicians an important and relevant choice of graft options when determining personalized treatment of patients with AAA.

4.3. TYPE III ENDOLEAK HISTORY

The initial version of the AFX product line, AFX Strata, was launched in 2011. During the first years of AFX Strata use, Endologix's post-market surveillance system (via complaint reporting) identified atypical reports of Type III endoleaks. Although the rate of reported complaints remained low and within acceptable internal trigger limits during this timeframe, Endologix proactively initiated an investigation and a process of continuous improvement activities. This process involved a series of product design, manufacturing, and labeling updates that aimed to reduce the incidence of Type III endoleaks.

Endologix uses reported complaints to generate internal signals to track the ongoing effect of continuous improvement programs on product performance.

4.3.1. INITIAL EXPERIENCE

4.3.1.1. TYPE IIIA ENDOLEAKS

The first two (2) Type IIIa Endoleaks were reported to Endologix in August 2011 (approximately 1 month after product launch). An additional 29 Type IIIa Endoleaks were reported by end-2012, bringing the lifetime complaint rate to 0.37%. While the event rates remained low and within acceptable limits per risk

documentation, as well as remaining within rates reported in the medical literature, an investigation was opened in January 2013 to investigate these 31 complaints, as this was an unanticipated failure mode for the product.

4.3.1.2. TYPE IIIB ENDOLEAKS

In December 2012, approximately 17 months after product launch, Endologix received the first complaint of a Type IIIb Endoleak. This had been the only Type IIIb Endoleak complaint received out of more than 7,700 devices sold (lifetime prevalence: 0.013%). By end-August 2013, a total of 14 Type IIIb Endoleak complaints had been received, which equated to a lifetime prevalence 0.099% complaint rate (14,200 bifurcated sales). Similar to Type IIIa Endoleaks, while the event rate remained low, Endologix proactively opened an investigation in mid-September 2013 to investigate these complaints. By the end of 2013 (~2.5 years after launch), an additional 10 complaints had been reported, bringing the total complaint rate to a lifetime prevalence of 0.138% (17,360 bifurcated sales). The rate at that time continued to remain within acceptable limits per Endologix's risk documentation and was also within the rates reported in the medical literature.

4.3.2. PRODUCT UPDATES

Following the initiation of these investigations, multiple product design, manufacturing, and labeling updates were implemented by Endologix in a process of continuous improvement. The chart below outlines the numerous changes that have taken place since 2013 (Figure 23). Endologix issued a customer communication in December 2016, which summarized the updates implemented to address Type III Endoleaks. This notification also requested the removal of any remaining AFX Strata devices from the field.

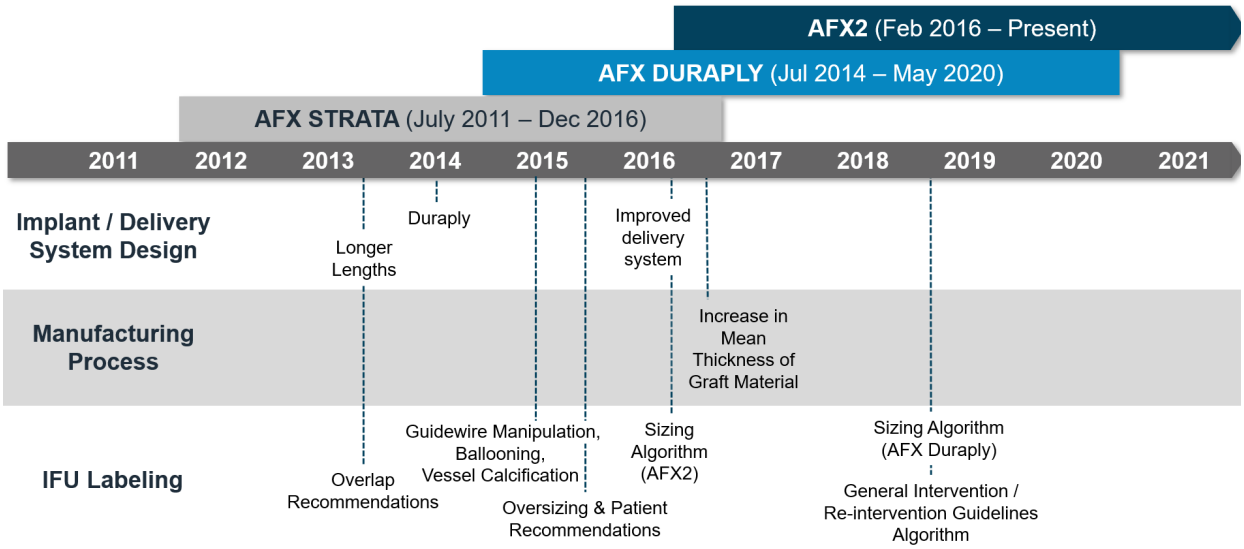


Figure 23. Timeline of Type III Endoleak Monitoring and Actions

4.3.2.1. TYPE IIIA ENDOLEAK INVESTIGATION AND PRODUCT UPDATES

The investigations into Type IIIa Endoleaks identified several contributing factors, including:

- 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

In January 2013 and November 2014, Endologix commercialized longer bifurcated lengths to provide more device options to maximize component overlap.[g] Additionally, the following IFU updates, made between 2013 and 2018, were identified to mitigate the identified contributing factors and help prevent the occurrence of Type IIIa Endoleaks:

- Reinforce the importance of device selection with an emphasis on maximizing overlap between the bifurcated and extension components.[h]
- Clarify important information related to anatomic considerations for patient selection, pre-procedure planning guidelines to maximize overlap with the primary bifurcated stent graft, and minimum post-operative follow-up imaging recommendations.[i]
- Provide further guidance in the form of a simple sizing algorithm that can be applied to ensure maximum overlap and determine the need for an additional infrarenal extension.[j]

4.3.2.2. TYPE IIIB ENDOLEAK INVESTIGATION AND PRODUCT UPDATES

The investigations into Type IIIb Endoleaks identified several contributing factors, including:

- Procedural factors such as guidewire/catheter manipulation or aggressive balloon molding.
- Off-label use (i.e., implantation in highly calcified anatomy/landing zone).
- Lateral movement and changes in implant stability.
- Implant of other manufacturer's devices as proximal extensions.

Endologix implemented additional IFU updates to clarify existing cautions and warning statements related to over-inflation of a balloon (if used) beyond the nominal diameter of the stent graft, guidewire manipulation, and vessel calcification. These IFU updates, which were made in 2014, were identified to mitigate the identified contributing factors and help prevent the occurrence of Type IIIb Endoleaks.

The investigations noted that although initial testing found that the Strata ePTFE graft met all the established mechanical and strength specifications, the Strata ePTFE graft remained susceptible to transverse propagation for a disruption in the graft material. In response to this, Endologix developed and commercialized a modified ePTFE graft material wrapping process in July 2014, known as Duraply. This modification increased the transverse graft material suture retention and tear propagation resistance compared to the Strata ePTFE graft while preserving biocompatibility, conformability, and other mechanical characteristics.

Most recently in February 2016, Endologix introduced the AFX2 Bifurcated device, the current and only commercialized system within the AFX product family. During the development of AFX2, Endologix implemented manufacturing changes to reduce the potential for damage to the graft during loading onto the delivery system and increased the average thickness of the Duraply ePTFE graft material by tightening manufacturing specifications. The tightening of specifications was subsequently applied to the remainder of the product family.

4.3.3. DECEMBER 2016 FIELD SAFETY NOTICE (FSN)

Endologix initiated multiple precautionary investigative efforts in 2013 based on unanticipated sporadic failure modes for the product. Although the complaint rates remained low, updates to the product line were

[g] Included in December 2016 recall notice.
[h] IFU Update implemented in May 2013. Included in the December 2016 recall notice.
[i] IFU Update implemented in September 2015. Included in the December 2016 recall notice.
[j] IFU Update implemented for AFX2 in February 2016 and for AFX Duraply in July 2018. Included in the December 2016 and July 2018 recall notices, respectively.

undertaken as a preventive measure to ensure continued device safety and to encompass a process of continuous improvement.

Even though preliminary data indicated that these actions had been effective, the Type III Endoleak incidence rates for AFX Strata continued to increase as a result of the devices which were implanted prior to the product updates. However, that the rates remained relatively low and within acceptable clinical limits through 2016 (compared to the Type III Endoleak rates for competitor EVAR grafts reported in the published literature and the MAUDE database). By late 2016, it became apparent that the AFX Strata and AFX Duraply populations had statistically significant different Type III Endoleak rates. Endologix issued a customer communication in December 2016 as a Field Safety Notice (FSN), which summarized the actions implemented to address Type III Endoleaks[k]. This notification also requested the removal of any remaining AFX Strata devices from the field[l].

4.3.4. EFFECTIVENESS OF PRODUCT UPDATES

In order to assess and monitor the effectiveness of the aforementioned updates, Endologix developed a cumulative rate approach for presenting Type III Endoleak trending data which is similar to how Kaplan Meier (KM) curves are constructed for clinical study data sets. Like KM curves, the Type III Endoleak trending graphs are representative of cumulative rates over time. Initially, Endologix trended these data by AFX product family iterations (i.e., AFX Strata, AFX Duraply, AFX2) and therefore, they had three lines representing each iteration. However, recognizing there have been more updates that just the introduction of Duraply and AFX2, the methodology of generating these graphs have evolved. This has resulted in the current trending graphs having two lines, one line that represents rates before the final product update to AFX2 and one line after the final product update (Figure 25, Figure 26, and Figure 27. For further details regarding the methodology used to generate these graphs as well as the history of evolution of these trending graphs, reference Appendix D: Complaint Data Trending.

4.3.4.1. IMPACT OF INDIVIDUAL PRODUCT UPDATES

As outlined in Table 7 the changes outlined in Section 4.4.1 can be grouped into 5 groups based on when they were introduced, as some were implemented concurrently.

[k] FDA Recall (Correction) Reference Numbers: Z-1035-2017, Z-1037-2017, Z-1038-2017, Z-1039-2017, Z-1047-2017, Z-1054-2017

[l] FDA Recall (Removal) Reference Number: Z-1048-2017

Table 7: Grouping of Type III Endoleak Product Updates

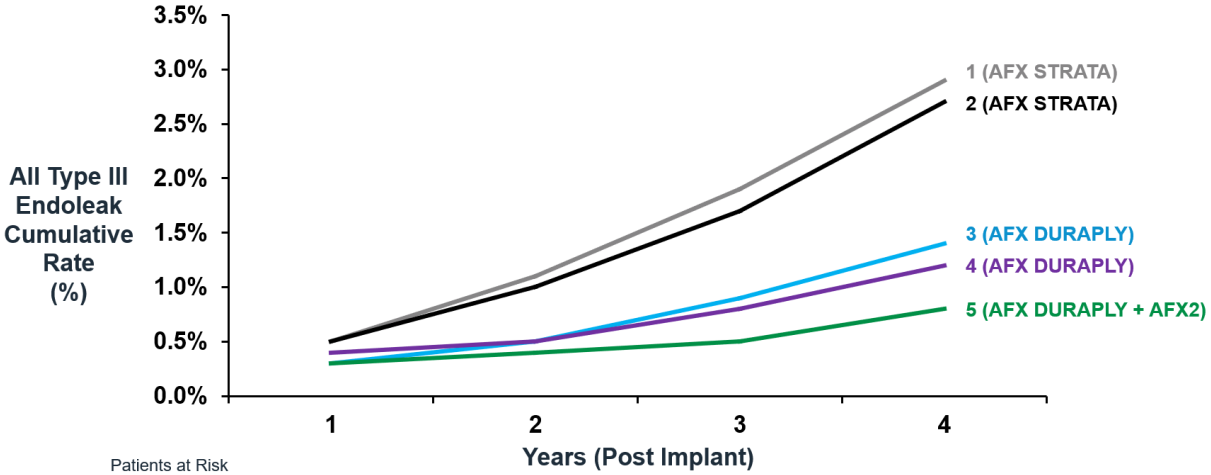
Date	AFX Nomenclature	Description of Update	Endoleak Addressed*
July 2011 (1)	AFX Strata	Baseline, prior to any action	N/A
Jan 15, 2013 (2)	AFX Strata	Longer Bifurcated Lengths and IFU Overlap Recommendations to address inadequate overlap between main body and proximal cuff	Type IIIa
July 21, 2014 (3)	AFX Duraply	• Introduction of new ePTFE processing - Duraply – to improve suture retention strength and tear propagation resistance in transverse direction • Labelling update to warn of against excessive guidewire manipulation, ballooning, and vessel calcification	Type IIIb
Sept 9, 2015 (4)	AFX Duraply	Labelling update to address excessive oversizing of the proximal cuff in relation to the main body and patient selection recommendations (aortic tortuosity)	Type IIIa
Feb 22, 2016 (5)	AFX2	• Improved delivery system with cover to protect endograft bifurcation during deployment • Increased mean thickness of graft material • Introduced sizing algorithm	Type IIIa & IIIb

**Type IIIa Endoleaks can lead to a Type IIIb Endoleak. As lateral movement leads to a reduction/loss in component overlap, the angulation of the accessory component to the bifurcated component can increase and may result in the stent cage of the accessory or bifurcated component damaging the ePTFE of the neighboring stent graft. Therefore, by addressing Type IIIa Endoleak mechanisms, Type IIIb rates may also be positively impacted.*

Using these 5 groups, Endologix has evaluated the impact each update has had on the occurrence of Type III Endoleaks. As can be seen in Figure 24, there has been a positive impact on the occurrence of Type III Endoleaks after each update, with a 2.1% absolute cumulative incidence decrease at 4 years between the baseline population and the current product offering (Figure 23). Specifically, the following updates are referenced in chronological order of implementation:

- The grey line represents the rate of Type III Endoleaks for AFX Strata devices prior to any action.
- The black line represents the rates of Type III Endoleaks for AFX Strata devices following the overlap recommendations that were implemented in 2013. As shown, this update resulted in a 0.2% absolute decrease in Type III Endoleaks at 4 years.
- The blue line represents the rate of Type III Endoleaks for the initial AFX Duraply grafts, including the Type IIIb IFU labeling updates implemented in 2014. As shown, these updates (Duraply ePTFE and labeling updates) resulted in an additional 1.3% absolute decrease in Type III Endoleaks at 4 years (total of 1.5% decrease from the baseline population).
- The purple line represents the rate of Type III Endoleaks for AFX Duraply following the oversizing and patient selection recommendations implemented in 2015 but before the changes made to AFX2. As shown, this update resulted in an additional 0.2% absolute decrease in Type III Endoleaks at 4 years (total of 1.7% decrease from the baseline population).
- The green line represents the rate of Type III Endoleaks for AFX2 and AFX Duraply following the sizing algorithm and ePTFE thickness changes in 2016. As shown, these updates resulted in an additional 0.4% absolute decrease in Type III Endoleaks at 4 years (total of 2.1% decrease from the baseline population).

*Note that each successive line includes the update(s) implemented prior (e.g., the green line includes all updates implemented and reflected in the black, blue, and purple lines).



Patients at Risk				
1 (AFX STRATA)	11208	11149	11120	11094
2 (AFX STRATA)	13309	13251	13233	13218
3 (AFX DURAPLY)	8064	8036	8028	8019
4 (AFX DURAPLY)	6660	6643	6640	6633
5 (AFX DURAPLY + AFX2)	38465	28990	19370	8838

Figure 24. Serial Chronological Product Updates on Type III Endoleak Rate

For this graphic, Type III Endoleak events are stratified by a product update implementation date. Based on the approach taken, reported events which did not report sufficient or accurate information to depict time to event have been excluded. This includes: sixty-seven (67) events reported "as the baseline population (AFX Strata)", fifteen (15) events reported "Overlap Recommendations (AFX Strata)", two (2) events reported "Duraply ePTFE + Type IIIb IFU Update (AFX Duraply)", two events reported "Oversizing & Patient Selection Recommendations (AFX Duraply)", and one (1) event reported "Sizing Algorithm + ePTFE Thickness (AFX Duraply + AFX2)". Additionally, there were eight (8) events reported with an unknown material type that could not be categorized.

4.3.4.2. ASSESSMENT OF CURRENT STATE

The total effectiveness of Endologix's Type III Endoleak product family updates must be reviewed holistically and as opposed to being viewed by just a single action (e.g., the implementation of the Duraply ePTFE graft). As such, using the same methodology to assess the effectiveness of each individual update, the data has been assessed based on the final product updates implemented prior to the Strata recall in December 2016.

More than 99% of patients treated after February 2016 are free from Type III Endoleaks at 4 years[m] (Figure 25). This population includes lifetime data for the currently marketed AFX2 System as well as data from the legacy AFX Duraply grafts, following implementation of these final product updates.

This trend also carries for Type IIIa and IIIb Endoleaks individually with 99.5% and 99.6% of patients treated with the current product offering as being free from Type IIIa (Figure 26) and Type IIIb (Figure 27) Endoleaks, respectively, at 4 years.

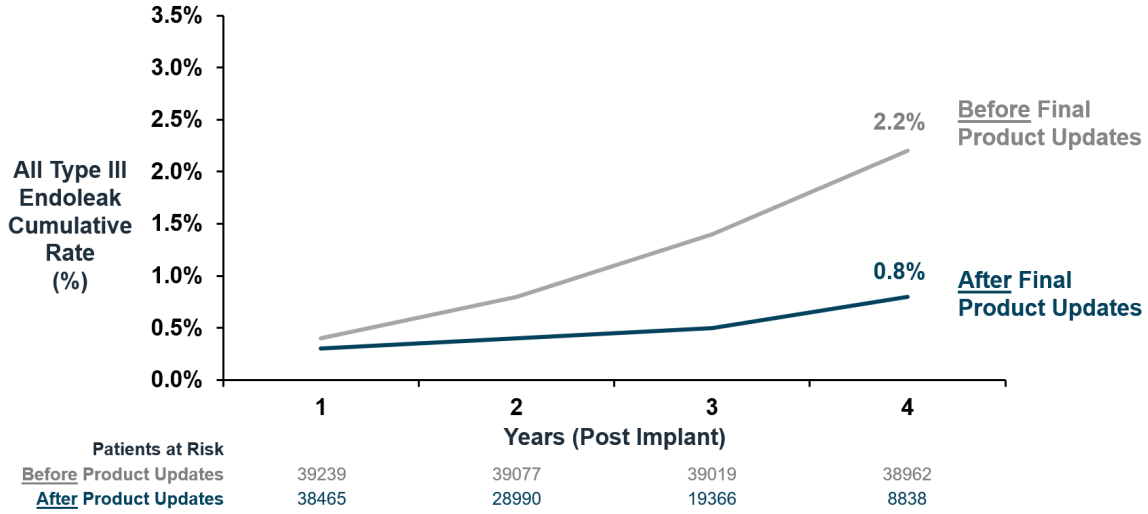


Figure 25. Impact of All Type III Endoleak Updates (February 28, 2021)

Note: For this graphic, Type III Endoleak events are stratified by product update implementation date(s). Based on the approach taken, reported events which did not report sufficient or accurate information to depict time to event have been excluded. This includes: 86 events reported "Pre-Final Product Update" and one event reported "Post-Final Product Update." Final product update represents Line 5 (green line) on Figure 24.

[m] These graphs have been truncated at 4 years to show comparative rates at comparative timepoints for the pre- and post-product update populations. Reference Appendix D: Complaint Data Trending for cumulative trending graphs pre- and post-product updates out to 9 years when available.

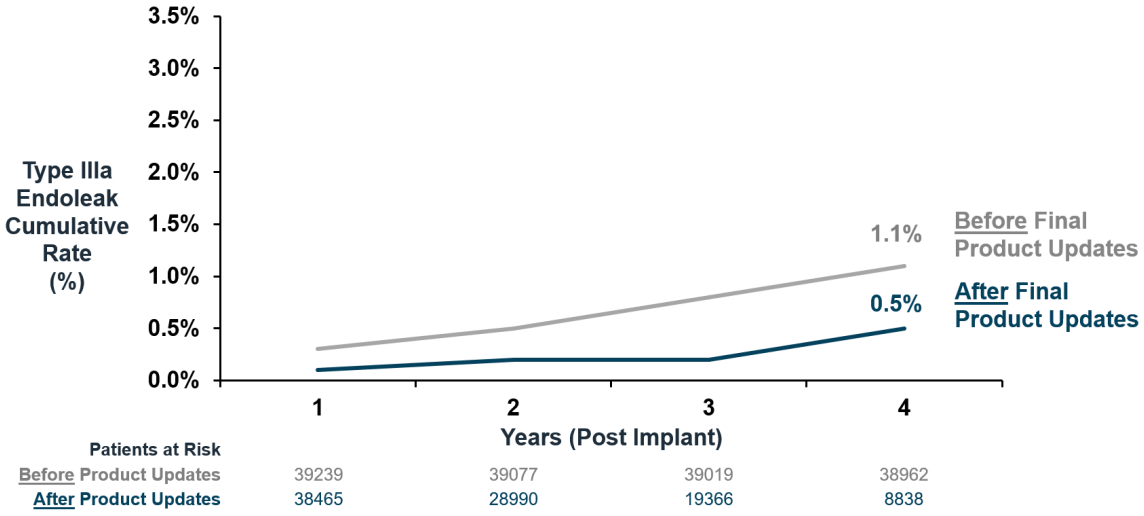


Figure 26. Impact of Final Product Updates on Type IIIa Endoleaks (February 28, 2021)

Note: For this graphic, Type III Endoleak events are stratified by product update implementation date(s). Based on the approach taken, reported events which did not report sufficient or accurate information to depict time to event have been excluded. This includes: 38 events reported "Pre-Final Product Update." Final product update represents Line 5 (green line) on Figure 24.

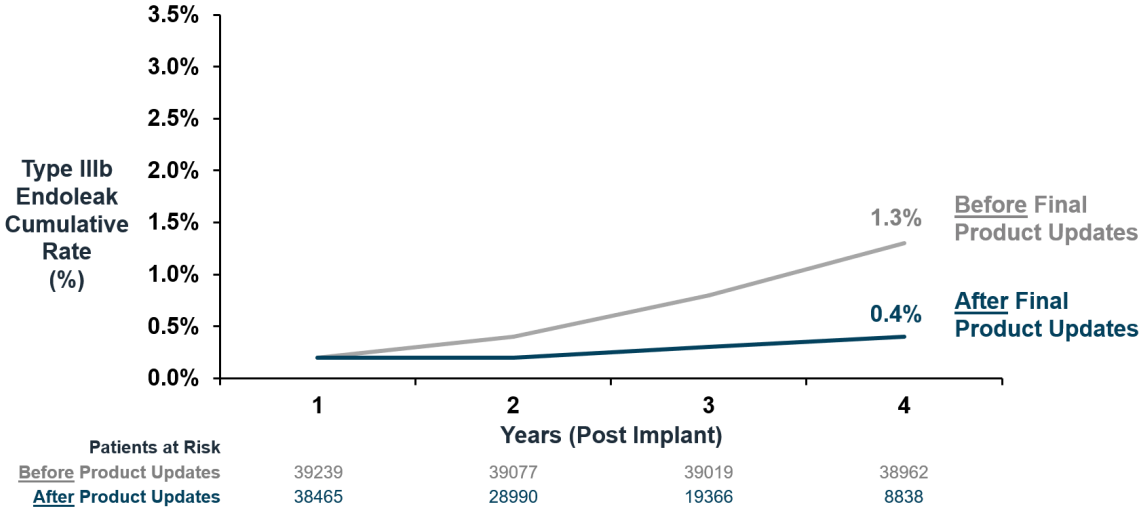


Figure 27. Impact of Final Product Updates on Type IIIb Endoleaks (February 28, 2021)

Note: For this graphic, Type III Endoleak events are stratified by product updates implementation date(s). Based on the approach taken, reported events which did not report sufficient or accurate information to depict time to event have been excluded. This includes: 54 events reported "Pre-Final Product Updates" and one event reported "Post-Final Product Updates". Final product update represents Line 5 (green line) on Figure 24.

4.3.5. SUMMARY

The complaint data suggest that each update to the AFX product line has serially and chronologically reduced the mid- and long-term Type III endoleak rate. However, although this trend is encouraging, complaint data have significant limitations due to under-reporting and should not be considered to be equivalent to complication rates observed in clinical practice. The effect of the product updates and the comparative clinical performance of AFX2 should be evaluated by a compendium of clinical evidence.

4.4. ADDITIONAL TYPE III ENDOLEAK ACTIONS FOR PATIENTS IMPLANTED PRIOR TO PRODUCT UPDATES

Since 2016, Endologix continue to work on a robust strategy for addressing patients previously implanted with an AFX Strata device that are at a higher risk of presenting with a Type III Endoleak. In order to provide guidance on the management of these patients Endologix has undertaken a number of actions, as discussed in the following sections.

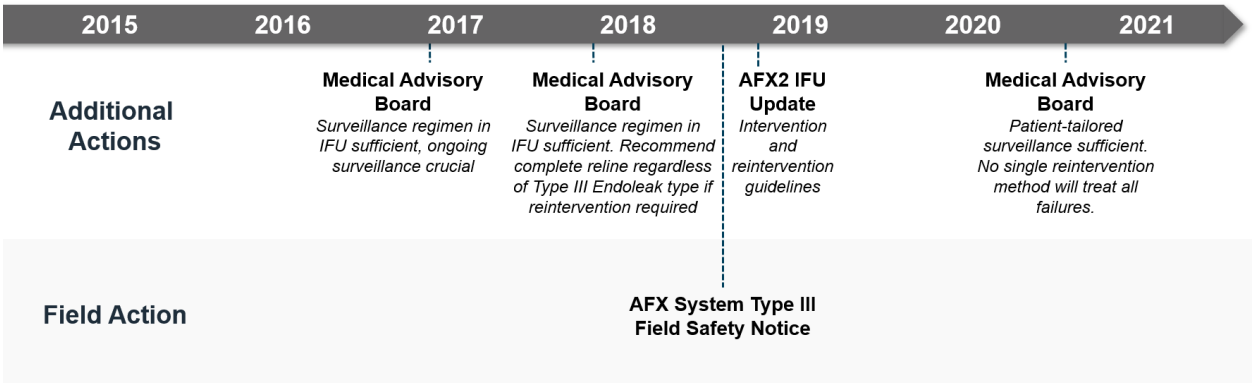


Figure 28. Timeline of Type III Endoleak Additional Actions

4.4.1. ASSESSMENT OF CLINICAL SEQUELAE OF TYPE III ENDOLEAK

In reviewing the reported Type III Endoleaks to Endologix, the resulting clinical complications can be described for AFX Strata and AFX Duraply/AFX2 devices. Of the 18, 234 AFX Strata implants in the US, there have been 1,331 (7.3%) reports of a Type III Endoleak. Table 8 summarizes the clinical sequelae reported as aneurysm enlargement (1.99%), rupture (0.84%), conversions (0.67%), death (0.33%) and secondary interventions (1.38%). The complications were reported at the time of the initial report of the Type III Endoleak.

Table 8: Clinical Sequelae of Type III Endoleaks for AFX Strata Patients

AFX Strata – Complications reported with Type III Endoleaks in the US[∞]	
Total	18,234
Type III (% of Total)	1,331 (7.3%)
Aneurysm Enlargement due to Type III Endoleak (% of Total)	363 (1.99%)
Rupture due to Type III Endoleak (% of Total)	154 (0.84%)
Conversions due to Type III Endoleak (% of Total)	123 (0.67%)
Death due to Type III Endoleak (% of Total)	61 (0.33%)
Secondary Interventions due to Type III Endoleak (% of Total)	251 (1.38%)

[∞] *Reference Appendix D: Complaint Data Trending for Worldwide rates*

In contrast, Type III Endoleaks reported to Endologix after the change to AFX Duraply/AFX2 and again, after all the product updates were implemented show a decrease in the complication rates. Table 9 summarizes the clinical sequelae reported as aneurysm enlargement (0.20%), rupture (0.12%), conversions (0.05%), death (0.06%) and secondary interventions (0.02%). While all these devices have not been in distribution for the same length of time and the general limitations with complaint reporting, the reduction in complications seen after implementation of all the product updates, is consistent with other AFX data

sources. These complications were reported at the time of the initial report of the Type III Endoleak, as well.

Table 9: Clinical Sequelae of Type III Endoleaks for AFX Duraply/AFX2 Patients

AFX Duraply and AFX2 – Complications reported with Type III Endoleaks in the US[∞]		
	Implants BEFORE final product updates	Implants AFTER final product updates
Total	10,278	19,731
Type III (% of Total)	253 (2.46%)	157 (0.80%)
Aneurysm Enlargement due to Type III Endoleak (% of Total)	91 (0.89%)	40 (0.20%)
Rupture due to Type III Endoleak (% of Total)	43 (0.42%)	23 (0.12%)
Conversions due to Type III Endoleak (% of Total)	22 (0.21%)	10 (0.05%)
Death due to Type III Endoleak (% of Total)	17 (0.17%)	12 (0.06%)
Secondary Interventions due to Type III Endoleak (% of Total)	38 (0.37%)	3 (0.02%)

[∞] *Reference Appendix D: Complaint Data Trending for Worldwide rates*

For patients implanted with AFX Strata, Endologix continues to recommend surveillance as provided in the product labeling and the Field Safety Notices in December 2016 and July 2018.

4.4.2. JANUARY 2017 MEDICAL ADVISORY BOARD

In conjunction with the December 2016 FSN with the AFX System, Endologix received requests from physicians on how to manage patients with Strata ePTFE grafts. In response, Endologix convened a panel of six experienced AFX users on January 28, 2017 in order to review evidence and to provide a consensus on recommendations. The physicians had a broad range of experience with the AFX System from users who primarily select competitive devices to the users who select AFX as their primary device of choice. The physicians came from a variety of hospital backgrounds, both community-based and some part of a University system. Some of the physicians had published their experience with Type III Endoleaks with the AFX device. One of the key topics of the physician advisory panel meeting was to evaluate surveillance of patients who have been implanted with AFX Strata to determine if any additional recommendations should be communicated. The physician panel was specifically asked to consider whether the current surveillance regimen in the IFU was sufficient in terms of surveillance type and intervals given the increased rates of reported Type IIIb Endoleaks in patients with the Strata ePTFE graft. The physician panel reached the consensus that annual CT imaging (the current surveillance recommendation) was sufficient, and that the increased radiation dosage and potential renal impairment from contrast associated with more frequent surveillance, was not warranted. The panel did recommend, however, that ultrasound be utilized if a physician deemed enhanced follow-up was necessary (as determined on a patient-by-patient basis), as the data did not outweigh the risks associated with increased radiation or contrast exposure.

Based on the outcome of this panel meeting, Endologix summarized the physician's recommendations and included these recommendations in the 2017 first quarter Chief Medical Officer Update. These recommendations, which are summarized in the bullets below, were also released and posted on Endologix's website in March 2017 and again in October 2019 as part of the 2016–2019 US Annual Clinical Update.

- Raise continued awareness of the possibility of Type IIIb Endoleaks in patients implanted with the AFX System with Strata, as well as the importance of ongoing surveillance.

- Some patients may be at increased risk of Type IIIb Endoleaks, especially if they have undergone endovascular procedures that involved wires and sheaths being passed through the existing endograft.
- The current surveillance regimen of an annual CT after one-year follow-up, as detailed in the IFU, is adequate.
- Physicians should consider a secondary intervention involving placement of an additional device component for patients with Type IIIb Endoleaks.

4.4.3. DECEMBER 2017 MEDICAL ADVISORY BOARD

Endologix convened a second consensus panel to revisit the recommendations regarding surveillance and reintervention options on December 12, 2017. This panel consisted primarily of the same physicians present at the January 2017 Medical Advisory Board, with some new panelists who also had a similar background and experience-level with the AFX System. The meeting involved a round table discussion with eight physicians on patient management, surveillance, and relining considerations for Type IIIb Endoleaks with the AFX System. The physician panel reached the consensus that there was still no need for increased surveillance for patients implanted with the Strata ePTFE graft at this time given the current rates and the fact that there are often no predictive signs of Type IIIb Endoleaks.

In addition to confirmation on the sufficiency of the surveillance regimen described in the IFU, the physician panel was specifically asked to discuss their experiences with re-intervening on AFX patients for Type IIIa and Type IIIb Endoleaks. It was discussed by some physicians that a complete reline is the preferred reintervention option regardless of the Type III Endoleak classification so as to prevent the need to re-intervene in the future.

4.4.4. JULY 2018 FIELD SAFETY NOTICE (FSN)

Endologix began working interactively with the FDA in 2016 on developing updated IFU to provide physicians with instructions to safely address Type III Endoleaks given the AFX System's unique endoskeleton design. Through these discussions, Endologix gained agreement with FDA on two sets of guidelines:

- **Intervention & Reintervention Guidelines:** This additional IFU language embodies basic guidelines that a physician should consider when performing a catheter-based procedure or secondary intervention on a patient implanted with the AFX System.

These guidelines were deemed particularly important for those patients implanted with a Strata device as any damage to the ePTFE may have a propensity to propagate, thus resulting in a Type IIIb Endoleak. In addition to these general intervention/reintervention guidelines, Endologix also supplemented the 2018 customer communicationn with patient-tailored surveillance recommendations, which were aligned with the clinical practice guidelines published by the SVS and the ESVS recommending personalized surveillance regimens[42,43].

4.4.5. JUNE 2020 MEDICAL ADVISORY BOARD

A third Medical Advisory Board (MAB) was convened in June 2020. The meeting involved a round table discussion with 4 physicians on patient management, surveillance, Type III Endoleak communication, and how physicians handle endograft revisions. A summary of the outcomes of this panel meeting are included in the bullets below:

- Based on available data, the product updates for Type III Endoleaks have been effective and the data shows significant progress in reducing the occurrence rate.

[n] FDA Recall (Correction) Reference Numbers: Z-0006-2019, Z-0007-2019, Z-0008-2019, and Z-0009-2019.

- The current warnings, cautions, and instructions in the IFU are sufficient to inform the off-label use that may lead to Type III Endoleaks.
- The current surveillance regimen of an annual CT after one-year follow-up or more frequent surveillance for patients with specific clinical findings, as detailed in the IFU, is adequate.
- Formal instructions / an indication in the IFU for secondary interventions is not feasible nor would it add useful therapeutic options for treating physicians.
    - There is no single reintervention method that will treat all failures for all patients; there are many factors including device availability (for emergent cases) as well as unique patient anatomy that must be considered.
    - The patient population (those requiring reintervention) is not capable of being evaluated in a formal study as patients often do not return to the implanting physician but, instead, seek help elsewhere requesting a different device.

4.4.6. AFX-IN-AFX RELINING

Concurrent with the efforts to develop intervention and reintervention guidelines, (which were communicated to the physician community in July 2018), Endologix has been working to evaluate the AFX-in-AFX Relining options as suggested by the physician participants during the December 2017 MAB meeting. This solution involves the placement of an AFX2 device within a previously placed AFX Strata device. This evaluation required the completion of extensive novel bench testing as well as the collection of clinical data from Endologix's complaint reporting.

The completed bench testing and complaint data review support that AFX-in-AFX may be a viable and durable treatment for patients experiencing a Type III Endoleak. Clinical interpretation of the bench results should be done cautiously, as this testing required novel test method development.

4.4.6.1. BENCH TESTING

As part of the project effort, Endologix executed three novel design verification/ validation testing protocols, all of which successfully met the pre-defined acceptance criteria that were agreed-to with FDA prior to execution.

1. ***Benchtop Leakage Testing:*** The purpose of this testing was to evaluate the acute performance results of the AFX-in-AFX relining configuration in mitigating leakage. All testing passed the acceptance criteria that were defined in the protocol.

   Notably, the results confirmed that the water leakage rate after relining is less than the water leakage rate through simulated Type IIIb Endoleaks without relining.

2. ***Stent Graft Pulsatile Fatigue Testing:*** The purpose of this testing was to evaluate the durability performance results of the AFX-in-AFX relining configuration out to 380 million cycles (10-year equivalent). This involved a novel test methodology that had been developed specifically for this evaluation (AFX-in-AFX) and therefore had limitations compared to standard fatigue test methodology utilized for general EVAR index procedure. All testing passed the acceptance criteria that were defined in the protocol.

3. ***Simulated Use Testing:*** The purpose of this testing was to support the usability of the specific procedural steps proposed in the relining IFU. All testing passed the acceptance criteria that were defined in the protocol.

4.4.6.2. CLINICAL STUDY USING COMPLAINT DATA

As part of the project, Endologix reviewed the existing complaint database for reports of AFX-in-AFX reline procedures. A protocol was developed to extend the available follow-up of the complaints received

over the past 6+ years (2014-2020). This allowed a method to obtain additional clinical data on AFX-in-AFX procedures given the significant limitations of a prospective clinical trial. In the retrospective study, 76 patients were identified with AFX-in-AFX relining. The technical success of the procedure was 98.7%. Freedom from aneurysm related mortality, post-intervention aortic rupture, and Type III Endoleak at 3 years was 95.2%, 97.8% and 100%, respectively. These findings suggest that AFX-in-AFX relining is a viable and durable solution to treat patients with a Type III Endoleak related to an AFX graft. Reference Appendix F: AFX-in-AFX Relining Extended Complaints Clinical Study Design and Results for further details. As requested by FDA, these data were provided to FDA on September 22, 2021.

4.4.6.3. PROPOSED IFU UPDATES

Based on the available bench and clinical data, Endologix has proposed updates to the AFX2 IFU. The proposed updates will provide physicians with an overview of the outcomes of these tests and clinical evaluation so that they may make an informed decision about treatment of their patients presenting with a Type III Endoleak. The proposed IFU updates will be submitted to FDA.

5. CURRENT AFX PERFORMANCE PROFILE

Summary

- Outcomes of EVAR for any device should be evaluated using multiple data sources.
- It is important to assess the quality and level of evidence when defining outcomes.
- LEOPARD (Level 1) is the only RCT designed to directly compare endograft outcomes.
  - The AFX System with Duraply/AFX2 System devices met the primary noninferiority endpoint; they are comparable in overall performance to the comparator devices at the 1-year absence of aneurysm related complications (ARC).
  - Freedom from ARC with the AFX System devices were clinically comparable to the comparator devices at 1 year and continue to trend similarly out to 4 years.
  - At 4 years, freedom from aneurysm-related mortality was 97.1% in the AFX family group and 98.5% in the comparator.
  - The Type III endoleak rate for the AFX arm in the LEOPARD RCT was 1.3% at 4 years
- Data from CMS (Level 2) shows:
  - More frequent use of AFX in females and patients with peripheral vascular disease
  - No difference in peri-operative outcomes between AFX and other devices.
  - The rates of aortic related reintervention have improved with the newer iterations of the AFX product line, and the product updates have reduced reintervention rates
  - AFX Duraply and AFX2 have similar rates of aortic -related reintervention and aortic rupture to contemporary comparator endografts
- Data from the VQI Registry (Level 2) shows:
  - The AFX2 Bifurcated device had equivalent or better outcomes in the perioperative period as compared with the other EVAR devices.
  - There was a significant difference in peri-operative Type Ia endoleak rates, operative duration and contrast use, in favor of AFX2
  - 405 Patient Multi-Center Series (Level 3) shows:
    - Type Ia and Type III Endoleaks rates at 4 years appear to be within acceptable limits.
    - Overall, the data demonstrate an ACM that is reflective of the typical rate observed in real-world series of patients with AAAs.
- The Endologix compendium of clinical data encompasses nearly 5,000 patients treated with AFX Duraply and AFX2. Overall, there is a high degree of consistency across all 4 studies. There are no studies in the Endologix compendium of clinical evidence that are outliers in terms of outcome incidence rates.
- The totality of the data demonstrates that the AFX2 System is an effective, durable, and necessary treatment option for patients with AAAs.

The data to support the AFX Duraply and AFX2 performance profile come from multiple data sources that, in totality, provide a robust assessment of device performance.

Data regarding adverse clinical events and device performance are derived from clinical studies. In this section, Endologix will not present data generated from the complaint system as these data do not typically

represent true clinical event rates, due to systemic under-reporting.[1] Endologix uses data derived from reported complaints for the generation of internal signals relating to device performance. Data from clinical studies are used to define clinical event rates in real-world practice.

This section focuses primarily on the outcomes generated by the currently available AFX2 device, although some data sets contain information on earlier versions. Data are presented in order of the level of evidence the data represent, with randomized clinical trials presenting the highest level of evidence.

The randomized controlled trial, LEOPARD (Section 5.1), provides Level 1 evidence to confirm that the currently available AFX2 (and AFX Duraply) performs similarly to contemporary comparator endografts both in terms of patient centric outcomes and with respect to Endoleak rates.

Data from CMS and VQI provide Level 2 evidence to demonstrate that the performance profile of AFX2 is comparable or better to that of other EVAR devices and support the findings from LEOPARD (Section 5.2).

A 405 patient Endologix sponsored multicenter center study provides Level 3 evidence on AFX devices (Section 5.3) and indicates that all outcomes and Type III Endoleaks rates at 3 years are within acceptable limits.

In addition to these studies, comment will also be made on several other data sources with a focus on a retrospective series published by Chang et al.[6] given the prominence given to these data by the FDA (https://www.fda.gov/medical-devices/safety-communications/update-risk-type-iii-endoleaks-use-endologix-afx-endovascular-aaa-graft-systems-fda-safety).

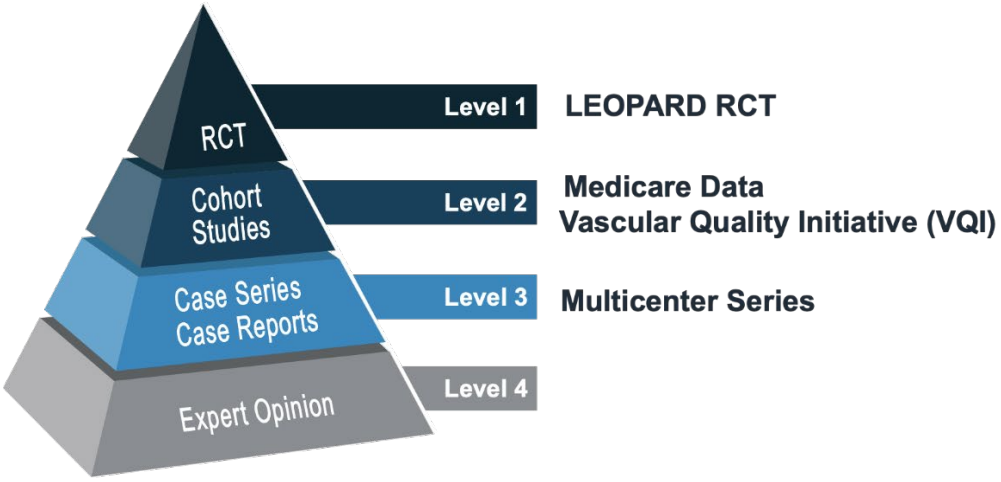


Figure 29. Summary of Evidence to Evaluate the Outcomes of the AFX2 Device

5.1. LEVEL 1 EVIDENCE: LEOPARD RANDOMIZED CLINICAL TRIAL

The LEOPARD (**L**ooking at **E**VAR **O**utcomes by **P**rimary **A**nalysis of **R**andomized **D**ata) RCT is an Endologix-initiated, multicenter, prospective, randomized trial of endovascular AAA repair in the US. LEOPARD is the only trial designed to directly compare endograft outcomes using the methodology of a randomized controlled trial and is therefore the highest level of evidence available. The trial was initiated to obtain Level 1 evidence for the purpose of comparing outcomes in a contemporary, real-world EVAR patient population.

The LEOPARD RCT compares the anatomically fixated AFX Duraply /AFX2 devices, to a reference group of proximally fixated EVAR devices: The Cook Zenith, the Gore Excluder and the Medtronic Endurant devices. Subjects were randomized between these two groups at a ratio of 1:1. At a site level, 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.

The protocol-specified primary endpoint in the LEOPARD RCT was 1-year survival in the absence of aneurysm related complications (ARC), which was a composite of relevant EVAR-related outcomes. While these would be analyzed together for the primary endpoint, they would also be evaluated separately to provide clarity and transparency to the trends seen within each cohort. This Endologix-initiated trial started enrollment in 2015, with the intention to enroll up to 804 subjects.

Based on the reporting of these data during periodic updates on the recall, Endologix began to receive additional queries regarding the complete safety profile of the AFX System with Duraply/AFX2 System devices. Based on these requests, Endologix made a decision on August 2, 2017 to complete a descriptive analysis using the site-reported data available in LEOPARD. This descriptive analysis showed that freedom from ARC with the AFX System with Duraply/AFX2 System were similar to the three proximally fixated comparator devices at 1 year, among the 246 subjects who had reached their first year of follow-up.

Since the trend at that time suggested continued enrollment for superiority was futile, Endologix made a voluntary decision to stop further randomization into the study in August 2017, capping the trial at 455 subjects.

All site-reported adverse events were independently adjudicated, and imaging was reviewed/measured by an independent core laboratory (Cleveland Clinic Foundation, Cleveland, OH. USA) to ensure uniform and unbiased image assessment. Among the 455 patients enrolled into LEOPARD, 422 (92.7%) had CT imaging performed at least 1 follow-up visit, and 403 (88.6%) currently have CoreLab reviewed images.

5.1.1. TRIAL DESIGN

5.1.1.1. STATISTICAL DESIGN

The LEOPARD RCT uses an "at-or-better" design which sequentially evaluates non-inferiority and superiority hypotheses, through comparison between the anatomically fixated AFX System with Duraply/AFX2 System, and the proximally fixated endografts. Several assumptions were required to determine the proper sample size for both hypotheses. These included the non-inferiority margin, expected relative performance of the two groups, and absolute performance of the two cohorts. This study design was discussed with the clinical steering committee on November 8, 2014, which included the following physicians: B. Starnes, D. Clair, F. Veith, C. Kwolek, K. Ouriel, T. Maldonado, T. Sullivan, J. Lee. It was at the recommendation of this clinical steering committee that an 8% non-inferiority margin represented a clinically meaningful difference. The design to evaluate the superiority hypothesis required up to 804 patients to be randomized at a 1:1 ratio to provide at least 80% power, after a predicted drop-out rate of 10% at 1 year. Given the larger sample size required for the superiority test, the final sample size of LEOPARD was driven by the superiority test. As non-inferiority would be tested with a sample size much larger than it required, the power of the non-inferiority test approached 99% with 804 patients. After the decision to cap enrollment was made, it follows that there is insufficient power to evaluate superiority under the original assumptions. However, with 455 patients, the trial remains adequately powered to evaluate non-inferiority under the original assumptions. While the formal hypothesis testing of these endpoints is at one year per the protocol, the design of the study also calls for evaluation of the ARC composite and its components across the duration of follow-up. These analyses provide the most comprehensive view of the results from LEOPARD and are provided in the review below.

5.1.1.1.1. PRIMARY ENDPOINTS

The primary trial endpoint is 1-year survival in the absence of ARC. ARC is a composite of the most relevant EVAR related outcomes and includes:

- Peri-operative death (< 30-days)
- Aneurysm rupture
- Conversion to Open Surgical Repair (OSR)

- Endoleaks; post-operative
- Endograft migration (≥ 10mm)
- Aneurysm enlargement (≥ 5mm compared to 1-month computed tomography [CT])
- Endograft occlusion
- Reinterventions for device- or ARC

Any imaging driven observations were included in the reported outcomes.

5.1.1.1.2. SECONDARY ENDPOINTS

Secondary endpoints to be assessed include:

- Major Adverse Events (MAEs) at 30-Days, 12-Months and Annually thereafter, up to 5 years:
  - Mortality (all-cause)
  - Bowel ischemia
  - Myocardial infarction
  - Paraplegia
  - Renal failure
  - Respiratory failure
  - Stroke
  - Procedural blood loss ≥1,000 mL
- ARC post 12 months, up to 5years
- Individual components of ARC post 12 months and up to 5years
- Aneurysm related mortality
- Endoleaks classified by type
- AAA-related secondary procedures up to 5 years
- Device integrity
- Any adjunctive procedures necessitated during the implant procedure

5.1.2. DISPOSITION AND DEMOGRAPHICS

5.1.2.1. PATIENT DISPOSITION

A total of 455 patients were enrolled in the LEOPARD RCT with 235 randomized to the AFX/AFX2 treatment arm and 220 to the comparator arm (Figure 30). Of the 220 enrolled in the comparator arm, 57 received a Cook Zenith, 72 received a Gore Excluder, and 91 received a Medtronic Endurant device. The trial continues to accrue follow-up data, but there are sufficient patients at 4 years to evaluate both ARC and individual outcomes at this time-point.

Figure 30. LEOPARD RCT: Patient Disposition

**One comparator device selected prospectively by each Investigator*

5.1.2.2. BASELINE DEMOGRAPHICS AND VASCULAR CHARACTERISTICS

Baseline demographics and anatomical characteristics were balanced across treatment groups (Table 10) and are typical of patients with AAAs. The mean age was 72 years old, and the majority of patients were white males. Most patients had severe systemic disease, classified as an American Society of Anesthesiologists physical status classification of ≥ 3. The majority of patients had hypertension and a history of smoking, and 40% had coronary artery disease.

Table 10. LEOPARD RCT Baseline Demographics

	Anatomical Fixation AFX Duraply/AFX2 (n=235)	**Proximal Fixation EVAR Comparator† (n=220)**
Age (years), mean ± sd	72 ± 8	72 ± 8
Male	90%	87%
Female	10%	13%
White	96%	90%
Severe Systemic Disease (ASA ≥ 3)	70%	72%
Hypertension	83%	83%
History of Smoking	52%	65%
Coronary Artery Disease	41%	40%

† Proximal Fixation EVAR devices included Cook Zenith, Gore Excluder, Medtronic Endurant.

Vascular characteristics were also similar across both treatment groups (Table 11). While the intent was to treat patients who were deemed suitable for implantation by a device in either group, LEOPARD was an investigator-driven trial, and approximately 35% of patients across the trial were treated outside the anatomical indications for use.

Table 11. LEOPARD RCT Vascular Characteristics

	Anatomical Fixation AFX Duraply /AFX2 (n=235)	**Proximal Fixation EVAR Comparator† (n=220)**
Max aneurysm diameter, mean (mm)	56.1	55.8
Max neck diameter (lowest renal), mean (mm)	24.6	24.8
Max iliac artery diameter, mean (mm)	18.5	18.3
External iliac minimum diameter, mean (mm)	7.3	7.2
Aortic neck angulation (mean, º)	15.1º	14.8º
Off anatomic IFU, mean (%) using neck criteria	25	24
Off anatomic IFU, using neck and iliac criteria (%)	34	35

† Proximal Fixation EVAR devices included Cook Zenith, Gore Excluder, Medtronic Endurant.

5.1.3. PROCEDURAL CHARACTERISTICS

Anatomical fixation devices (AFX Duraply/AFX2) had a shorter operating time, less contrast use, and a reduced radiation exposure than proximal fixation devices (Table 12).

Table 12. LEOPARD RCT Procedural Characteristics

	Anatomical Fixation AFX Duraply/AFX2 (n=235)	Proximal Fixation EVAR Comparator† (n=220)	p-value*
Total Procedure Time (Min), mean (range)	79.5 (30, 374)	90.5 (34, 303)	0.0001
Fluoroscopy Time (Min), mean (range)	16.0 (3, 116)	18.5 (5, 84)	0.0335
Total Anesthesia Time (Min), mean (range)	152.5 (57, 490)	166 (65, 390)	0.0152
Contrast Volume (mL), mean (range)	68 (15, 220)	84 (15, 345)	<0.0001
Bilateral Percutaneous Access, %	69.4%	66.4%	0.5467
General Anesthesia, %	82.1%	85.0%	0.4492
Requiring Blood Transfusion	0.4%	0.9%	0.6122
Time in Intensive Care Unit (Days)	0 (0, 7.3)	0 (0, 11.2)	0.6297
Time to Hospital Discharge (Days)	1.3 (0.7, 16)	1.3 (0.7, 31)	0.2162

**A p-value ≤0.05 is considered statistically significant. Continuous variables tested via two-sided Wilcoxon two-sample test; dichotomous variables evaluated by Fisher's exact test.*
† Proximal Fixation EVAR devices included Cook Zenith, Gore Excluder, Medtronic Endurant.

5.1.4. TRIAL RESULTS

5.1.4.1. SUMMARY

Per formal evaluation using site-reported data, the anatomically fixated AFX System with Duraply/AFX2 System devices were demonstrated to be noninferior and therefore comparable in overall performance to the proximally fixated comparator devices at the 1-year ARC endpoint. The one-year endpoint may be less relevant given the longer-term data now available, which shows the freedom-from-ARC rates for the AFX System with Duraply/AFX2 System devices trending higher out to beyond 4 years. While a post-hoc log rank test of the two Kaplan-Meier curves is not feasible due to early crossing of the curves, the standard errors of the estimates at year 4 are currently small enough to compare the two curves with reasonable accuracy [AFX freedom from ARC 70.4% (SE: 3.3%). Comparator freedom from ARC 61.1% (SE: 3.7%)] to infer that the AFX results would not likely drop below the Comparator performance through final, 5-year follow-up. The current lower limit of the 95% confidence band of freedom-from ARC in AFX appears to trend above the mean KM estimate for the Comparator between 8 months and through 4 years. The KM estimates of freedom-from-ARC and corresponding 95% confidence intervals for the AFX/AFX2 cohort are 79.9% (95%CI:74.7, 85.1) at 1 year, 75.4% (69.7, 81.1) at year 2, 74.3% (68.5, 80.1) at year 3, and 70.4% (63.9, 76.9) at year 4. For the comparator cohort, these are 71.1% (95%CI:64.8, 77.4) at 1 year, 68.2% (61.7, 74.7) at year 2, 63.5% (56.6, 70.4) at year 3, and 61.1% (53.8, 68.4) at year 4.

The subsequent sections contain a side-by-side comparison of those ARC reported in the LEOPARD RCT through August 31, 2021, followed by KM estimates for the most relevant EVAR-related outcomes.

5.1.4.2. SUBJECT STATUS AND DISPOSITION

Patients that were enrolled in the LEOPARD RCT between March 2015 and August 2017 have either completed or are currently completing the 5-year follow-up commitment. The available patient status and accountability for the 2 cohorts since initial enrollment through August 31, 2021 is presented in Table 13.

Table 13: Patient Disposition

	Anatomical Fixation AFX DURAPLY / AFX2 N = 235		**Proximal Fixation EVAR Comparator N = 220**	
	Eligible	Follow-up	Eligible	Follow-up
1 Month	231	229 (99.1%)	219	213 (97.3%)
6 Months	227	211 (93.0%)	208	194 (93.3%)
1 Year	218	194 (89.0%)	194	180 (92.8%)
2 Years	198	184 (92.9%)	175	159 (90.91%)
3 Years	181	156 (86.2%)	155	138 (89.0%)
4 Years	145	117 (80.7%)	129	107 (82.9%)
5 Years	80	61 (76.3%)	84	74 (88.1%)

5.1.4.3. ANEURYSM-RELATED COMPLICATIONS (ARC)

Aneurysm-Related Complication (ARC) events for the LEOPARD RCT reported from the time of enrollment through the primary endpoint (0 Days – 1 Year), and after 30-Days through 5-year follow-up are being collected under the study protocol. Available site- and CoreLab-reported follow-up data through August 31, 2021 are presented in Figure 31. As shown in the figure, the incidence of ARC events across the two cohorts remains similar, thus providing objective clinical evidence that the performance of the anatomically fixated AFX System with Duraply/AFX2 System devices have an overall performance profile equivalent to contemporary EVAR devices.

With regard to the primary endpoint, 79.9% of patients with AFX Duraply/AFX2 were free from ARC at 1 year, compared to 71.1% of patients treated with comparator endografts (per the Kaplan-Meier estimate and inclusive of Type II Endoleaks) (Figure 31 and Figure 32). Reviewing the data in the absence of Type II Endoleaks, 88.6% of patients with AFX Duraply/AFX2 were free from ARC at 1 year, compared to 87.1% of patients treated with comparator endografts

Further, the long-term performance of the AFX System with Duraply/AFX2 System is supported with 70.4% of subjects being free from ARC at 4 years (inclusive of Type II Endoleaks) and 80.0% of subjects being free from ARC at 4 years (exclusive of Type II Endoleaks). This is compared to the comparator group results of 61.1% and 80.9%, respectively.

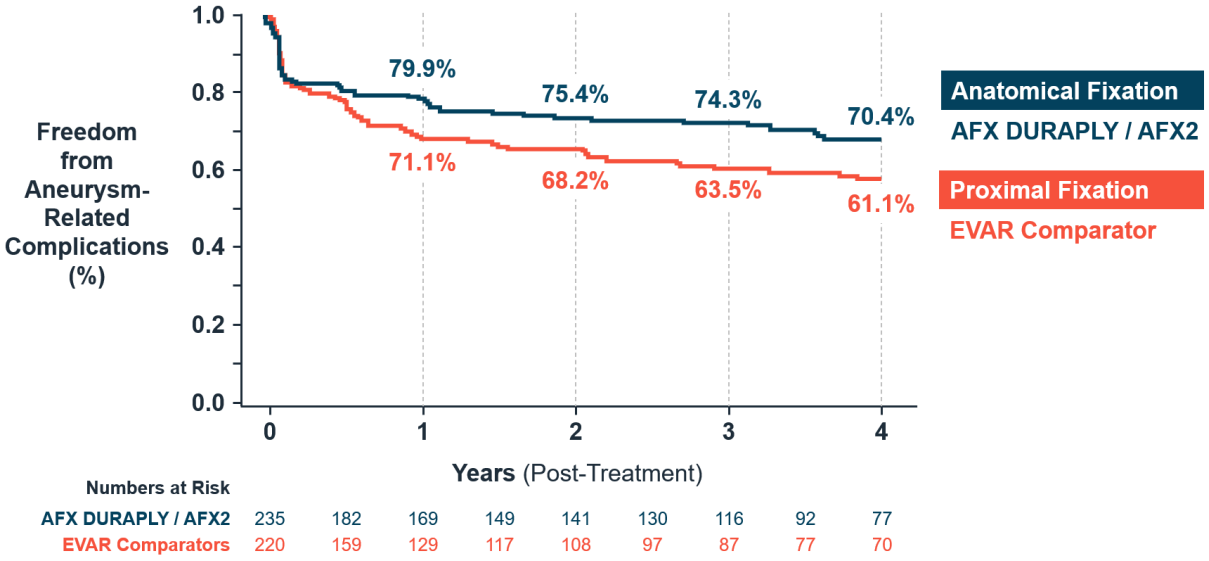


Figure 31. Freedom from Aneurysm-Related Complications (ARC), Including Type II Endoleaks, LEOPARD RCT

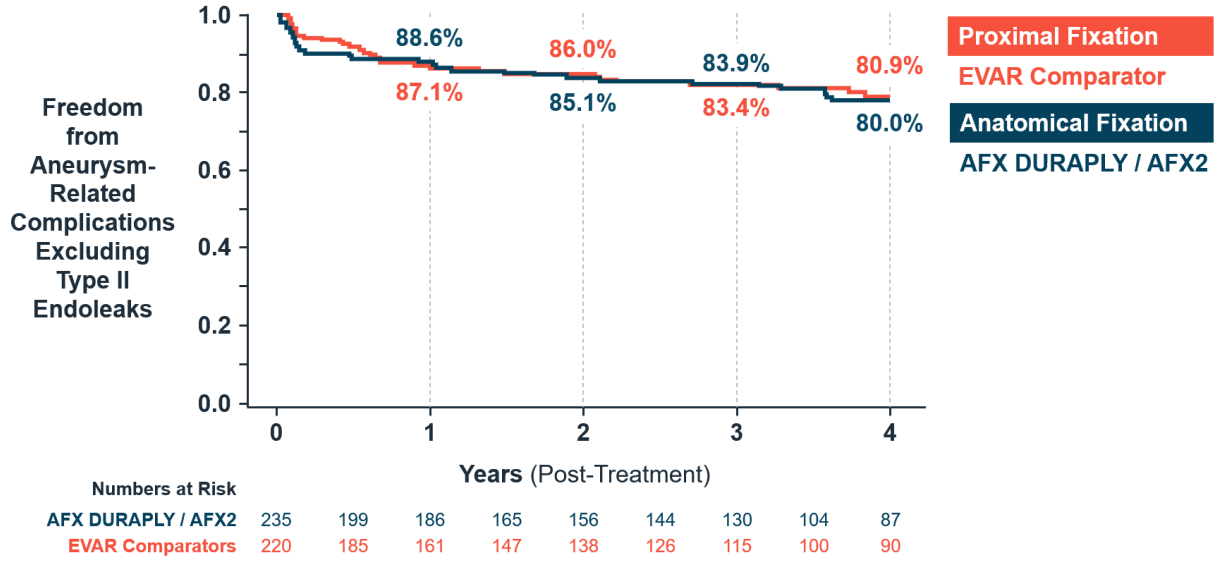


Figure 32. Freedom from Aneurysm-Related Complications (ARC), Excluding Type II Endoleaks, LEOPARD RCT

5.1.4.4. ALL-CAUSE MORTALITY

The long-term performance of the AFX System with Duraply/AFX2 System is supported with 77.5% of subjects being free from ACM at 4 years (Figure 33). This is compared to the comparator group results of 77.9%.

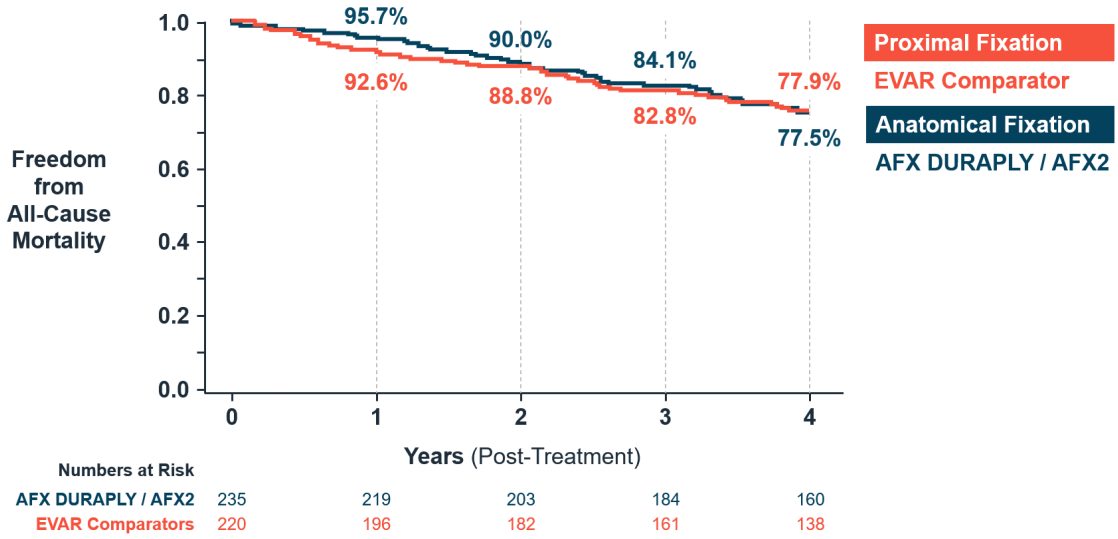


Figure 33. Freedom from All-Cause Mortality (ACM), LEOPARD RCT

5.1.4.5. SECONDARY INTERVENTIONS

There were 87.9% of patients free from secondary interventions at 4 years in the AFX System with Duraply/AFX2 System group (Figure 34) compared to the comparator group results of 88.2%.

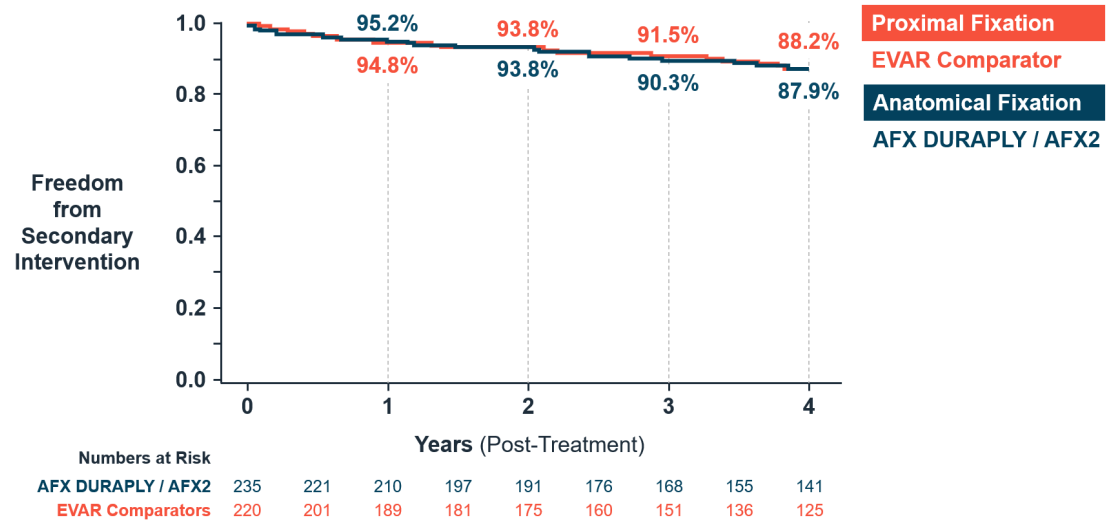


Figure 34. Freedom from Secondary Interventions, LEOPARD RCT

5.1.4.6. SECONDARY OUTCOMES

At the 4-year time point, all secondary endpoints were similar between the randomized groups (Table 14). There were minor differences between some end points but no differences that would be regarded as demonstrating a meaningful clinical disparity. Given the previous issues with Type III endoleaks with AFX Strata, its noteworthy that the 4-year freedom from Type IIIa endoleaks in the LEOPARD RCT (AFX Duraply/AFX2) was 100% and for Type IIIb, 98.7%.

Table 14: 4-Year Outcome for Relevant Secondary Endpoints

Outcome	AFX Duraply/ AFX2	Comparator
Aneurysm related mortality	97.1%	98.5%
Open conversion	100%	98.0%
Aortic rupture	98.9%	99.3%
Device related reinterventions	87.9%	88.2%
Type Ia endoleak	99.2%	98.5%
Type Ib endoleak	97.4%	98.5%
Type II endoleak	83.2%	73.5%
Type IIIa endoleak	100%	100%
Type IIIb endoleak	98.7%	100%
Graft occlusion	97.8%	95.3%

5.1.5. LIMITATIONS

The following are the recognized limitations of the LEOAPRD trial:

- There are several limitations inherent to the "at-or-better design" that utilizes a composite endpoint (i.e., freedom from "ARC"). While including multiple outcomes in a composite endpoint provides higher power with smaller sample sizes, it weighs different adverse event types equally even though there may be clinical differences in severity. To address this, individual components of ARC are presented. Additionally, ARC is presented as a composite endpoint without Type II Endoleaks.
- The sample size planned at the beginning of study was not enrolled. However, 455 patients will provide sufficient numbers to evaluate the cohorts through 5 years and sufficient for formal non-inferiority testing of the primary end-point.
- The primary endpoint at one year fails to capture adverse events that have higher incidence rates in the late post-op period. To address this, ARC and its components are analyzed through the entirety of follow-up.
- There is a degree of subjectivity when a non-inferiority margin is chosen. However, the non-inferiority margin for LEOPARD was chosen after careful consideration of the components of the composite endpoint and by a group of physicians with expertise in this area.

5.1.6. SUMMARY AND CONCLUSIONS

The LEOPARD RCT data provide objective, directly comparative, randomized clinical evidence that the performance of the AFX System with Duraply/AFX2 System devices is comparable to contemporary EVAR devices regarding overall outcomes at all representative time points. This Level 1 data shows that 70.4% of the AFX System with Duraply/AFX2 System patients are free from ARC at 4 years (inclusive of Type II Endoleaks) and 80.0% are free from ARC at 4 years (exclusive of Type II Endoleaks). This is compared to the comparator group results of 61.1% and 80.9%, respectively.

While the study was designed to evaluate non-inferiority and superiority at 1 year, the longer-term data clearly shows that the AFX System with Duraply/AFX2 System endografts are largely comparable yet

clearly trending above the comparator devices through 4 years in terms of freedom-from ARC. The ARC trendline of proximally fixated devices consistently remains above the comparator group from 3 months past 4 years. The trend towards fewer ARC events in the anatomically fixated AFX System with Duraply/AFX2 System device arm is primarily driven by fewer Type II Endoleaks. When the ARC endpoint is evaluated without consideration for Type II Endoleaks, the AFX System with Duraply/ AFX2 System device has an equivalent overall performance trend relative to other contemporary EVAR devices. This is also clearly shown via the Kaplan-Meier curves for ARC without Type II Endoleaks, as both groups overlap substantially across long term follow-up. The data suggest that, while each device may have unique strengths and weaknesses across different metrics, the overall clinical performance is comparable. These findings represent the only Level 1 direct comparison of endograft performance.

5.2. LEVEL 2 EVIDENCE: CONTROLLED LONGITUDINAL STUDIES

To ensure that all available independent data were reviewed, Endologix engaged the Center for Medicare and Medicaid Services (CMS) (via an independent third party and with an independent consultant) to compare the peri-procedural and longer-term outcomes achieved by anatomically fixated unibody endografts (i.e., AFX family) and contemporary single and double docking limb device (proximally fixated endografts) in Medicare beneficiaries, at three consecutive time periods. The study also investigated whether patients undergoing EVAR in recent years, have changed outcomes compared to earlier time periods. Details on this study and its results are included in Section 5.2.1.

Endologix also engaged M2S, Inc. to perform an analysis on the AFX2 System compared to comparator EVAR devices, utilizing data from the Vascular Quality Initiative (VQI) database. Background on the registry and a discussion of its limitations are included in Section5.2.2.

5.2.1. CENTER FOR MEDICARE AND MEDICAID SERVICES (CMS)

5.2.1.1. STUDY DESIGN

The study was a retrospective, observational study of EVAR patients using the Medicare Fee-for-Service (FFS) administrative claims database from the CMS Virtual Research Data Center. This dataset contained patients implanted with an EVAR device that had continuous enrollment in Medicare Parts A and B for a minimum of 1 year prior to EVAR and were implanted between January 1, 2012 to December 31, 2017. The index date was the first EVAR documented in each patient's claim record. Patients were followed until death, end of enrollment or end of study period, whichever occurred first. Patients with ruptured AAAs, thoracic aneurysms, thoracoabdominal aortic aneurysms, and aortic dissections were excluded.

It is not possible in this dataset to distinguish data by model number or finished good product number. Stent graft type could only be identified by CPT (current procedural terminology) codes. Due to FFS coding changes, the last index date for a patient receiving EVAR that could be distinguished by unibody (Endologix) versus other devices was December 31, 2017. Beginning in 2018, coding did not allow for separate identification.

As a proxy for model number, patients were segmented into 3 cohorts based on the date of EVAR, as described below. Segmentation into these cohorts allowed investigation of the various iterations of the anatomically fixed unibody grafts available during the study period.

- ***Cohort 1 (before any updates to the product family):*** This included patients implanted with EVAR between January 1, 2012 and July 21, 2014. For Endologix devices, the unibody sub-cohort would predominantly contain AFX System with Strata devices (96.2% AFX Strata, 3.8% Powerlink, since the Duraply ePTFE graft was first commercialized on July 21, 2014).
- ***Cohort 2:*** This included patients implanted with EVAR between July 22, 2014 and May 9, 2016. The Endologix unibody sub-cohort would predominantly contain AFX System with Duraply devices (91.04% AFX Duraply, 8.96% AFX Strata) and would reflect some – but not all – of the

updates implemented to address Type III Endoleaks. Namely, this would largely reflect the impact of the first five updates: Longer Bifurcated Lengths, IFU Overlap Recommendations, Duraply ePTFE Graft, Updated Warnings/Cautions regarding guidewire manipulation, ballooning and vessel calcification, and Oversizing/Patient Selection Recommendations. While this population would still contain some product manufactured with the Strata ePTFE graft, this remains the best division given the limitation of being unable to segregate data by model number or finished good product number.

- ***Cohort 3 (Current State):*** This included patients implanted with EVAR after May 9, 2016 and before December 31, 2017. This population would reflect the current state of Endologix's latest product update (93.8% AFX2, 6.2% AFX Duraply). December 31, 2017 reflects the last date in the analysis as the CPT codes changed in early-2018, preventing Endologix from being able to glean any meaningful results from Medicare given the overlap with general EVAR.

The primary outcomes of interest were reintervention and post-EVAR aortic rupture. Reintervention was defined as any repeat procedure related to the aneurysm or an aneurysm repair related complication after discharge from the initial EVAR admission. Perioperative outcomes were captured within 30 days of index EVAR. Long-term outcomes were captured for the duration of follow-up available for each patient.

As requested by FDA, these data were provided to FDA on September 22, 2021.

5.2.1.2. PATIENT DEMOGRAPHICS AND CHARACTERISTICS

There were 32,031 patients who underwent EVAR during the study period: 4,729 received an anatomically fixated unibody endograft and 27,302 a contemporaneous single and double docking limb devices endograft. Most of the docking limb endografts would have had a proximally fixated design based on approved devices in the US during the study dates.

The study population reflects a typical population of patients undergoing elective abdominal aneurysm repair. The demographics of the entire study population are detailed in Table 15, dichotomized in the three study periods.

The patients who received an anatomically fixated endograft had differing characteristics to the comparator group (Table 15). This trend was seen across the study irrespective of the individual cohorts. Specifically, there was a significantly higher proportion of females in the anatomically fixated group. Additionally, when evaluating co-morbidities, the anatomically fixated endografts generally had a slightly higher prevalence of many co-morbidities, but few reached a level of statistical significance. The exception to this was the presence of PVD which was elevated in the patients who received a unibody endograft.

5.2.1.3. STUDY RESULTS

5.2.1.3.1. PERI-OPERATIVE OUTCOMES

Peri-operative outcomes across the proximally fixated and anatomically fixated (unibody) endografts were similar for all three time periods studied (Table 16). There were no differences in peri-operative mortality, acute renal failure, myocardial infarction, mesenteric ischemia, pneumonia, or deep vein thrombosis between the unibody grafts and the contemporaneous comparator endografts. Readmission rates were also similar. In all three time periods studied, there was a higher rate of embolectomy in the anatomically fixed group. This difference reached statistical significance in Cohort 3 and approached significance in Cohort 1.

Table 15. Demographics, CMS Study

	Cohort 1 *Patients Undergoing EVAR before July 21, 2014*			**Cohort 2** *Patients Undergoing EVAR after July 21, 2014 and before May 9, 2016*			**Cohort 3** *Patients Undergoing EVAR after May 9, 2016*		
	AFX (1498)	Other (8256)	p-value	AFX (1713)	Other (9390)	p-value	AFX (1518)	Other (9656)	p-value
Length of follow up (years, mean SD	2.59 (2.35)	2.64(2.38)	-	2.20 (1.84)	2.21 (1.80)	-	1.66 (1.31)	1.65 (1.28)	-
Age (Mean, SD)	76.3 (7.5)	76.3 (7.4)	0.48[β]	75.7 (7.8)	76.0 (7.4)	0.0301[β]	75.2 (7.7)	75.7 (7.5)	0.0031 [β]
Male (%)	1155 (77.1%)	6707 (81.2%)	<0.0001	1322 (77.2%)	7670 (81.7%)	<0.0001	1169 (77.0%)	7899 (81.8%)	<0.0001
Female (%)	343 (22.9%)	1549 (18.8%)	<0.0001	391 (22.8%)	1720 (18.3%)	<0.0001	349 (23.0%)	1757 (18.2%)	<0.0001
White (%)	1393 (93.0%)	7719 (93.5%)	0.52	1582 (92.4%)	8627 (91.9%)	0.44	1390 (91.6%)	8882 (92.0%)	0.58
Black (%)	62 (4.1%)	300 (3.6%)	0.34	69 (4.0%)	415 (4.4%)	0.46	65 (4.3%)	418 (4.3%)	0.93
Myocardial Infarction (%)	442 (29.5%)	2301 (27.9%)	0.19	481 (28.1%)	2401 (25.6%)	0.03	388 (25.6%)	2348 (24.3%)	0.3
Valvular disease (%)	431 (28.8%)	2202 (26.7%)	0.09	487 (28.4%)	2520 (26.8%)	0.17	424 (27.9%)	2467 (25.5%)	0.049
CHF (%)	367 (24.5%)	1755 (21.3%)	0.005	372 (21.7%)	1955 (20.8%)	0.4	340 (22.4%)	2020 (20.9%)	0.19
Peripheral vascular disease (%)	682 (45.5%)	3042 (36.8%)	0.00001	758 (44.2%)	3520 (37.5%)	<0.0001	681 (44.9%)	3358 (34.8%)	<0.0001
Neurovascular disease (%)	579 (38.7%)	3033 (36.7%)	0.16	655 (38.2%)	3326 (35.4%)	0.025	507 (33.4%)	3038 (31.5%)	0.13
Hypertension (%)	1383 (92.3%)	7565 (91.6%)	0.37	1568 (91.5%)	8517 (90.7%)	0.27	1406 (92.6%)	8663 (89.7%)	0.0004
Diabetes (%)	523 (34.9%)	2629 (31.8%)	0.19	545 (31.8%)	2764 (29.4%)	0.05	215 (14.2%)	1229 (12.7%)	0.12
COPD (%)	798 (53.3%)	4145 (50.2%)	0.29	846 (49.4%)	4480 (47.7%)	0.2	707 (46.6%)	4132 (42.8%)	0.006
Renal Failure (%)	185 (12.3%)	1088 (13.2%)	0.38	212 (12.4%)	1213 (12.9%)	0.53	202 (13.3%)	1267 (13.1%)	0.84
ESRD (%)	22 (1.5%)	176 (2.1%)	0.09	26 (1.5%)	205 (2.2%)	0.03	39 (2.6%)	168 (1.7%)	0.26
History of Cancer (%)	402 (26.8%)	2176 (26.4%)	0.7	450 (26.3%)	2634 (28.1%)	0.13	430 (28.3%)	2770 (28.7%)	0.77
Obesity (%)	265 (17.7%)	1263 (15.3%)	0.019	300 (17.5%)	1573 (16.8%)	0.4	310 (20.4%)	2061 (21.3%)	0.41

[β]p-value calculated using a two-sample t-test statistic, value approximated with z-table

Table 16. Peri-Operative Outcomes, CMS Study

	Cohort 1 *Patients Undergoing EVAR before July 21, 2014*			**Cohort 2** *Patients Undergoing EVAR after July 21, 2014 and before May 9, 2016*			**Cohort 3** *Patients Undergoing EVAR after May 9, 2016*		
	AFX (1498)	Other (8256)	p-value	AFX (1713)	Other (9390)	p-value	AFX (1518)	Other (9656)	p-value
All-Cause Mortality	27 (1.8%)	157 (1.9%)	0.79	25 (1.5%)	147 (1.6%)	0.73	27 (1.8%)	154 (1.6%)	0.63
Acute Renal Failure	94 (6.3%)	542 (6.6%)	0.67	107 (6.2%)	709 (7.6%)	0.057	111 (7.3%)	738 (7.6%)	0.58
Hemodialysis	17 (1.1%)	114 (1.4%)	0.45	13 (0.8%)	136 (1.4%)	0.022	25 (1.6%)	125 (1.3%)	0.29
Mesenteric Ischemia	13 (0.9%)	65 (0.8%)	0.75	<11	49 (0.5%)	-	<11	29 (0.3%)	-
Embolectomy	21 (1.4%)	66 (0.8%)	0.022	15 (0.9%)	60 (0.6%)	0.27	17 (1.1%)	49 (0.5%)	0.004
Myocardial Infarction	43 (2.9%)	169 (2.0%)	0.044	33 (1.9%)	221 (2.4%)	0.28	26 (1.7%)	217 (2.2%)	0.17
Pneumonia	15 (1.0%)	97 (1.2%)	0.56	34 (2.0%)	186 (2.0%)	0.99	58 (3.8%)	389 (4.0%)	0.65
Conversion to Open Repair	<11	<11	-	<11	<11	-	<11	<11	-
Small Bowel Resection	0 (0.0%)	<11	-	<11	<11	-	<11	<11	-
Large Bowel Resection	<11	26 (0.3%)	-	<11	25 (0.3%)	-	<11	32 (0.3%)	-
Ileus or Bowel Obstruction without resection	30 (2.0%)	136 (1.6%)	0.32	20 (1.2%)	106 (1.1%)	0.89	<11	57 (0.6%)	-
DVT	27 (1.8%)	129 (1.6%)	0.50	26 (1.5%)	156 (1.7%)	0.67	26 (1.7%)	138 (1.4%)	0.42
Re-Operation for Bleeding	<11	28 (0.3%)	-	12 (0.7%)	34 (0.4%)	0.049	<11	25 (0.3%)	-
Tracheostomy	<11	11 (0.1%)	-	<11	<11	-	<11	<11	-
Readmission within 30 days of discharge	159 (10.6%)	874 (10.6%)	0.97	175 (10.2%)	996 (10.6%)	0.63	141 (9.3%)	944 (9.8%)	0.48

5.2.1.3.2. REINTERVENTION RATES BY GRAFT TYPE

All three cohorts demonstrated an increase in reintervention rate with time (Figure 35). The earliest time cohort (Cohort 1, which predominantly consists of AFX Strata) has a similar reintervention rate to the two more recent time cohorts up until year 3 (Cohort 2, which predominantly consists of AFX Duraply and Cohort 3, which predominantly consists of the AFX2 System). Starting at Year 3, there is a disparity with AFX Strata being associated with a higher reintervention rate than the AFX Duraply or the AFX2 System. This may reflect the known Type III Endoleak rate with AFX Strata. The unibody grafts for the latest two time-periods appear similar.

There is no obvious difference in reintervention rates with patients undergoing EVAR in the most recent time cohort (after May 9, 2016) when compared to the earlier cohorts (Figure 35). The proximally fixated grafts show a similar pattern and incidence of reintervention in the three time periods (i.e., cohort) studied.

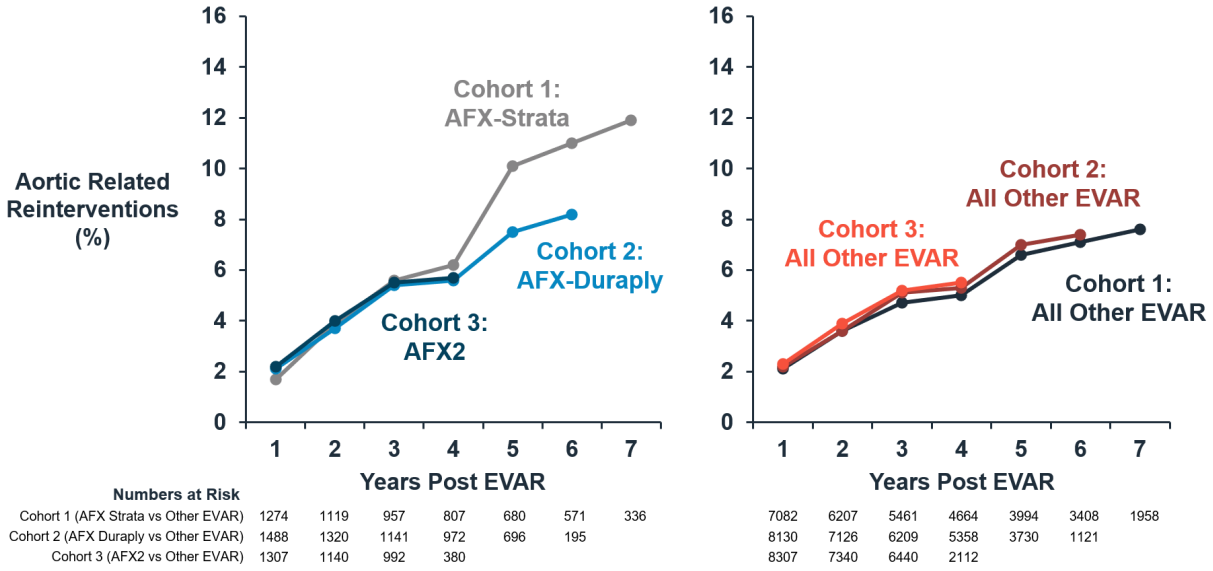


Figure 35. Aortic-Related Reintervention Rates for Anatomically-Fixated and Proximally-Fixated Stent Grafts, CMS Study

5.2.1.3.3. REINTERVENTION RATES BY COHORT

In the earliest cohort (Cohort 1, EVAR before July 21, 2014), the anatomically fixated grafts (which predominantly consists of the AFX Strata) had a higher rate of reintervention compared to the proximally -fixated (PF) comparator grafts. This became more apparent after 3 years of follow up ($p<0.001$ at 7 y – Chi-square). Similarly, the unibody group had a higher rate of post-EVAR aortic rupture, with an absolute magnitude of 1.3% after 7 years follow up (0.19% per year, $p=0.019$ at 7 year – Chi square).

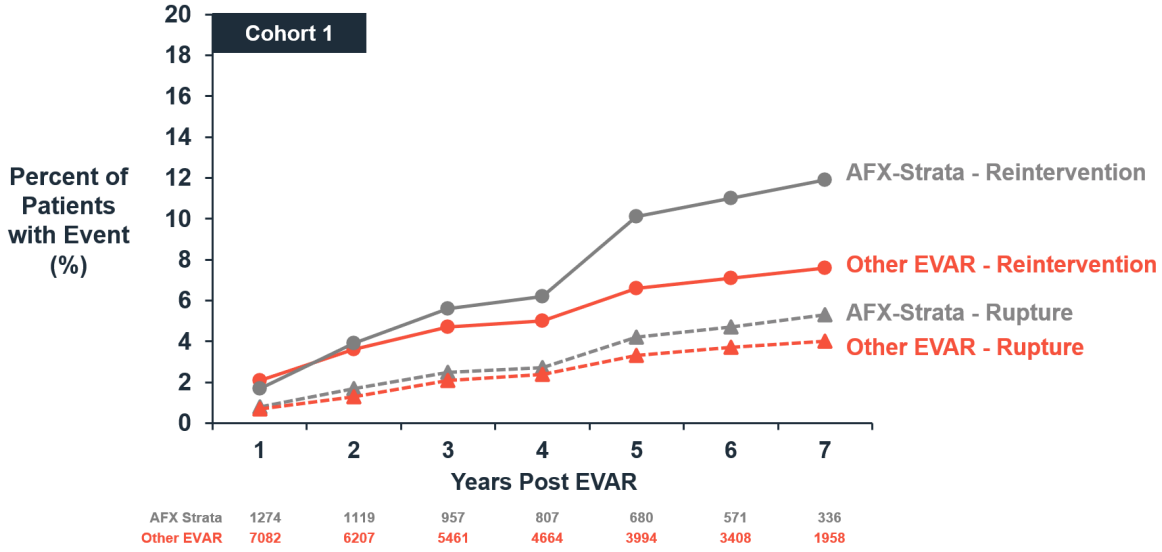


Figure 36. Aortic-Related Reintervention and Rupture Rates for Cohort 1 (Patients Implanted January 1, 2012 – July 21, 2014), CMS Study

In the second cohort (Cohort 2, EVAR after July 21, 2014 and before May 9, 2016), reintervention between the unibody grafts (which predominantly consists of AFX Duraply) and the proximally fixated (PF) endografts were similar. The rate of aortic rupture trended higher in the unibody grafts during 6 years of follow up with an absolute magnitude of 1% after six years of follow up (or 0.17% per annum, p=0.059 at 6y – Chi square). The difference in aortic rupture rates appeared to be partly driven by a higher rupture rate in the first year of follow-up, with relatively little degradation of comparative rates after this time.

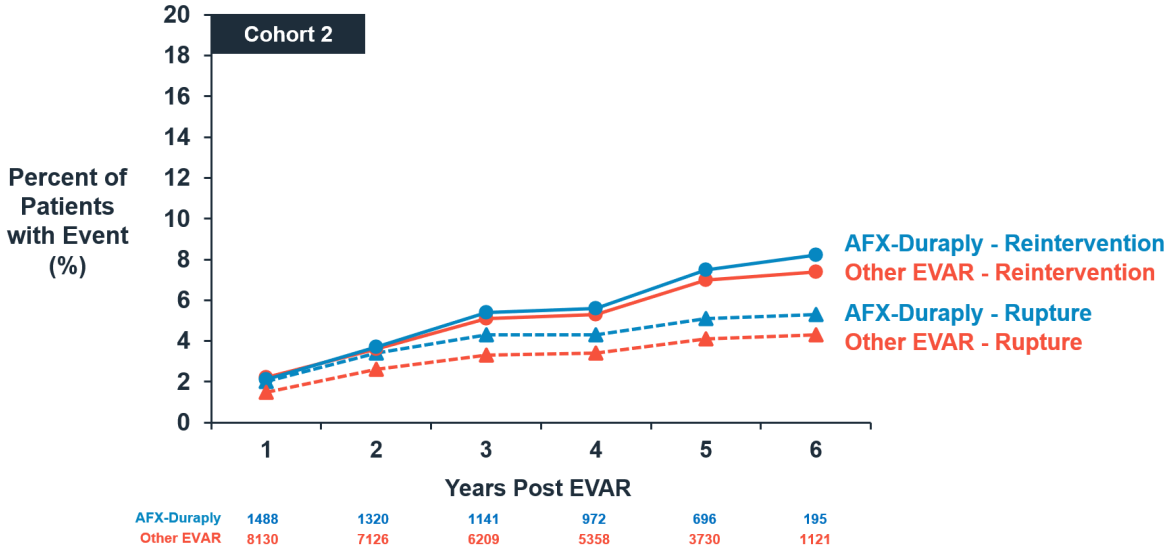


Figure 37. Aortic-Related Reintervention and Rupture Rates for Cohort 2 (Patients Implanted July 22, 2014 – May 9, 2016, CMS Study

In the latest cohort (Cohort 3, EVAR after May 9, 2016), reintervention between the unibody grafts (which predominantly consists of the AFX2 System) and the comparator endografts were similar to 4 years of follow-up. The rate of aortic rupture trended lower in the AFX2 grafts with an absolute magnitude of 0.7% after years of follow-up (or 0.18% per annum, p=0.13 – Chi square). Unlike the pattern observed in the second time cohort studied, the lower rate of post-EVAR aortic rupture was not driven by an early difference in rupture rates and became more apparent at mid-term follow up.

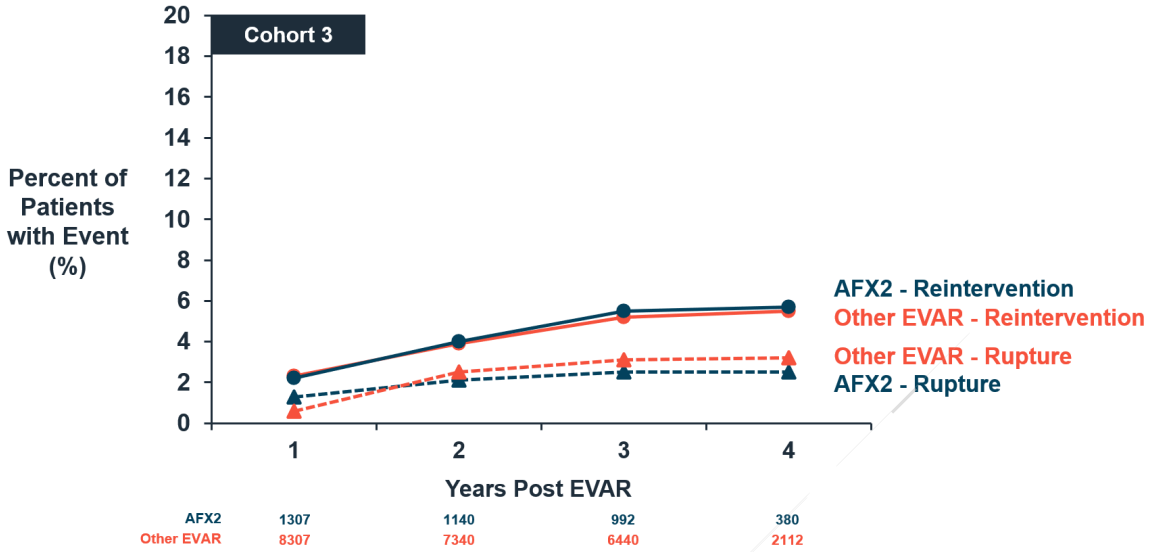


Figure 38. Aortic-Related Reintervention and Rupture Rates for Cohort 3 (Patients Implanted May 9, 2016 – December 31, 2017), CMS Study

5.2.1.3.4. FOUR-YEAR OUTCOMES

The 4-year outcomes for the patient cohorts at the three time periods studied is tabulated in Table 17. In all three cohorts the ACM was slightly higher in the patients treated with the anatomically fixated unibody stent grafts, and this difference reached statistical significance in Cohort 1. In terms of reinterventions, there were too many categories with less than 11 counts in the major reintervention category to allow meaningful analysis, but there did not appear to be any overall differences in major intervention rates between to the two graft types. In the endovascular reinterventions, the unibody grafts had higher rates of reintervention involving the placement of an aortic cuff. The proximally fixated grafts had higher rates of embolization.

Table 17. 4-Year Outcomes, CMS Study

	Cohort 1 *Patients Undergoing EVAR before July 21, 2014*			**Cohort 2** *Patients Undergoing EVAR after July 21, 2014 and before May 9, 2016*			**Cohort 3** *Patients Undergoing EVAR after May 9, 2016*		
	AFX (1498)	Other (8256)	p-value	AFX (1713)	Other (9390)	p-value	AFX (1518)	Other (9656)	p-value
All-Cause Mortality	517 (34.5%)	2633 (31.9%)	0.045	571 (33.3%)	2921 (31.1%)	0.068	455 (30.0%)	2673 (27.7%)	0.065
AAA Related Reinterventions	93 (6.2%)	415 (5.0%)	0.058	96 (5.6%)	498 (5.3%)	0.61	87 (5.7%)	528 (5.5%)	0.67
Post-EVAR Rupture	41 (2.7%)	198 (2.4%)	0.43	74 (4.3%)	316 (3.4%)	0.048	38 (2.5%)	313 (3.2%)	0.13
Major reintervention	15 (1.0%)	84 (1.0%)	0.95	21 (1.3%)	94 (1.0%)	0.40	15 (0.99%)	68 (0.7%)	0.23
Minor reintervention	121 (8.0%)	388 (4.7%)	<0.001	101 (5.9%)	505 (5.4%)	0.38	95 (6.3%)	568 (5.9%)	0.57
Conversion to Open Repair	<11	<11	-	<11	11 (0.1%)	-	0 (0.0%)	<11	-
Ax-Fem Bypass	<11	17 (0.2%)	-	<11	21 (0.2%)	-	<11	<11	-
Graft Repair	0 (0.0%)	<11	-	0 (0.0%)	<11	-	<11	<11	-
Fem-Fem Bypass	<11	53 (0.6%)	-	11 (0.6%)	62 (0.7%)	0.93	<11	42 (0.4%)	-
Endo-AAA Repair	37 (2.5%)	20 (0.2%)	<0.001	22 (1.3%)	56 (0.6%)	0.002	28 (1.8%)	128 (1.3%)	0.11
Embolization	18 (1.2%)	195 (2.4%)	0.005	31 (1.8%)	263 (2.8%)	0.19	32 (2.1%)	295 (3.1%)	0.04
Aortic Angioplasty	<11	<11	-	0 (0.0%)	<11	-	0 (0.0%)	0 (0.0%)	-
Extension Cuff	54 (3.6%)	94 (1.1%)	<0.001	37 (2.2%)	102 (1.1%)	<0.001	20 (1.3%)	127 (1.3%)	0.99
Thrombectomy	11 (0.7%)	77 (0.9%)	0.46	11 (0.6%)	79 (0.8%)	0.4	15 (1.0%)	72 (0.7%)	0.31

5.2.1.4. SUMMARY AND CONCLUSIONS

The present study describes the comparative performance of anatomically fixated (unibody) endografts to contemporary single and double docking limb devices (proximally fixated endografts) that were implanted from 2012 until 2018. The initial AFX System with Strata had a long-term failure mode of Type III Endoleaks and was recalled in 2016. Endologix has implemented various design, manufacturing and labeling changes to address the Type III Endoleak failure mode. Data from the present study, demonstrate that the rates of aortic related reintervention have improved with the newer iterations of the unibody family that have implemented some (Cohort 2) or all (Cohort 3) of the updates applied to the AFX product family.

The updates made to the AFX product family reduced subsequent reintervention rates with AFX Duraply and AFX2. AFX Duraply and AFX2 had similar rates of both reintervention and post-EVAR aortic rupture when compared to contemporaneous proximally fixated endografts. When comparing the peri-operative outcomes between unibody and the anatomically fixated proximally fixated grafts, there is no difference in peri-operative mortality for most acute complications. The one exception is a higher rate of embolectomy in the unibody group, which might be related to the higher incidence of PVD in these patients.

When comparing longer term outcomes, the unibody grafts in the earliest time cohort have a higher rate of both reintervention and aortic rupture when compared to the proximally fixated endografts. The timing of these outcomes is informative with rates in the unibody graft group increasing after the 3-year time point. This finding reinforces the need for long term surveillance of EVAR, as many complications requiring reintervention occur after 5 years. This increased reintervention and rupture in the unibody group is most likely related to the Strata ePTFE manufacturing process, which was associated with late Type III Endoleaks and have been reported to be responsible for more than 50% of reinterventions. This fact is reflected in the type of reinterventions in the unibody group, with a higher rate of both repeat EVAR and placement of aortic extension cuffs. In the proximally fixated group, there was a higher incidence of embolization as a secondary intervention.

All-Cause Mortality in the three cohorts was typical of patients undergoing aortic repair, with survival being marginally worse in the patients who received unibody grafts. This difference might reflect the increased incidence of co-morbidities and the increased proportion of women, in patients who had anatomically fixed grafts.

Despite the large sample size, there are limitations to the use of Medicare data for this type of comparative analysis. The current data set does not have details of aortic anatomy and whether the grafts were used in accordance with the anatomical indications for use. There is a broad consensus that aortic outcomes become worse with off-label use and the data set does not allow comment on this confounding factor. Similarly, the Medicare data set does not have granular detail on the aortic related complications that led to the need for reintervention. Specifically, there are no details on the number and classification of Endoleaks nor the incidence of migration or sac expansion. Whilst many studies that report the outcomes of EVAR concentrate on these technical complications, there has recently been an acknowledgement that a focus on these details may not be reflective of patient centric issue. From a patient's perspective it is suggested that the more injurious events of reintervention, aortic rupture and aortic related mortality are more relevant than a detailed description of Endoleaks.

The endografts used in EVAR have differing design intentions and consequently a spectrum of both clinical use and failure modes that are unique to that endograft. For this reason, it is important that endograft outcomes are evaluated using a holistic assessment of graft function. The outcomes reported from the Medicare data set give a broad picture of graft performance through the incidence of late aortic rupture and device related reinterventions. Reintervention and aortic rupture rates that complicated both types of endograft designs, increased with follow up across all time periods. This reinforces the need to ensure patients are enrolled in surveillance programs for the long-term. Finally, the lack of improvement in reintervention rates for the majority of patients undergoing EVAR in the last decade suggests that further efforts are warranted to improve outcomes.

A further limitation of the study was the inability to identify the different versions of AFX directly from the Medicare FFS administrative claims database. This was not possible using CPT codes and so time cohorts were used, based on dates of product updates for the unibody grafts.

Despite these limitations the results from Medicare beneficiaries undergoing EVAR, provide robust data that AFX Duraply and AFX2 produce similar aortic-related outcomes to other contemporary endografts used in EVAR.

5.2.2. VASCULAR QUALITY INITIATIVE (VQI)

5.2.2.1. BACKGROUND

In 2011, the Society of Vascular Surgery (SVS) and M2S Inc., a provider of clinical outcomes data, launched the VQI to improve the quality, safety, effectiveness, and cost of vascular healthcare through the collection and exchange of information. The VQI Registry is an independent data source that can be used to compare peri-operative and 1-year follow-up outcomes amongst endografts in a contemporary, real-world EVAR patient population. VQI, which is a registry-based collaboration of North American physicians and hospitals as a Patient Safety Organization, which allows collection of health care data for the purpose of quality improvement. Through periodic reporting, datasets from the VQI Registry can be used to help monitor the performance of a specific medical device to the aggregate data of all other similar devices.

In the VQI registry, EVAR device safety and performance data are obtained through the collection of peri-operative and 1-year follow-up data outcomes. This relevant, de-identified, and aggregate data is then made available to device manufacturers upon request to help monitor and improve the quality of their devices.

As of March 31, 2021, VQI currently has 775 participating centers, 331 of which are included in the EVAR Registry (Figure 39). These hospitals are equally apportioned as academic, teaching-affiliated, and community centers and encompass a wide range of institution sizes.

Further, the physicians participating in VQI represent the spectrum of specialties performing vascular procedures (e.g., vascular surgery, cardiology, radiology, general surgery, cardiac surgery, etc.). For these reasons, VQI represents real-world practice, and has now collected granular data for over 790,759 vascular procedures (66,279 of which are infrarenal AAA EVAR procedures) and has obtained 1-year follow-up in over 70% of cases when patients return to the physician's office for follow-up.

Figure 39. Geographical Distribution of 775 VQI Centers (March 2021)

5.2.2.2. DATA RESULTS: AFX2 SYSTEM

To evaluate the AFX2 Bifurcated device for non-ruptured AAA repair, we analyzed data from by 3,703 unique surgeons at 775 centers participating in the VQI EVAR Registry. All consecutive EVAR procedures for treatment for non-ruptured AAAs between January 1, 2015 and March 31, 2021 were selected (n = 36,256 patients and procedures). The AFX2 Bifurcated device (n = 1,030) was then compared with "All Other" EVAR devices (n = 35,226) used to treat non-ruptured AAAs in the VQI Registry "All Other" EVAR devices includes Bolton Treovance, Cook Zenith, Gore CTAG, Gore Excluder C3, Endologix AFXo, Endologix Ovation, Endologix Nellix, Lombard Aorfix, Medtronic Endurant, Medtronic Endurant II, Medtronic Talent and Medtronic Valiant Captiva.

5.2.2.2.1. BASELINE DEMOGRAPHICS AND VASCULAR CHARACTERISTICS

As shown in Table 18 and Table 19, the AFX2 Bifurcated devices reported in the VQI Registry have similar baseline demographics and vascular characteristics to the "All Other Devices" comparator. However, it should be noted that there is a nearly 5% higher proportion of females in the AFX2 cohort, which reaches statistical significance. This supports the preferential use of AFX2 in females which is seen in other datasets.

Table 18. Baseline Demographics, VQI Registry

Jan. 1, 2015 – Mar. 31, 2021[±]	AFX2 Bifurcated (n=1,030)	All Other Devices[†] (n=35,226)	p-value
Age, mean ± sd	73.15 ± 8.7	73.37 ± 8.58	0.422
Male	76.7% (790/1030)	81.3% (28622/35221)	< 0.001
Female	23.3% (240/1030)	18.7% (6599/35221)	
White	86.8% (894/1030)	86.6% (30494/35214)	0.889
Coronary Artery Disease (CAD)	30.5% (314/1030)	29.3% (10328/35208)	0.425
Congestive Heart Failure (CHF)	14.8% (152/1030)	12.7% (4479/35215)	0.058
Dysrhythmia	18.5% (190/1029)	19.7% (6943/35182)	0.321
Chronic Obstructive Pulmonary Disease (COPD)	33.4% (344/1029)	34.2% (12042/35218)	0.641

[±] *AFX2 Bifurcated was first commercialized in February 2016.*
† "All Other" EVAR devices includes Bolton Treovance, Cook Zenith, Gore CTAG, Gore Excluder C3, Endologix AFX, Endologix Ovation, Endologix Nellix, Lombard Aorfix, Medtronic Endurant, Medtronic Endurant II, Medtronic Talent and Medtronic Valiant Captiva.

Table 19. Vascular Characteristics, VQI Registry

Jan. 1, 2015 – Mar. 31, 2021[±]	AFX2 Bifurcated (n=1,030)	All Other Devices[†] (n=35,226)	p-value
Maximum AAA Diameter (mm)	51.87 ± 11.07	56.25 ± 11.15	< 0.001
Aortic Neck Length (mm)	29.5 ± 12.57	26.02 ± 11.78	< 0.001
Aortic Neck Diameter (mm)	23.69 ± 4.56	23.77 ± 4.19	0.694
AAA Aortic Neck Angulation			
< 45°	85.7% (431/503)	81.2% (15940/19635)	0.011
45-60°	10.3% (52/503)	12.4% (2426/19635)	0.191
61-75°	2.0% (10/503)	3.1% (602/19635)	0.188
76-90°	1.2% (6/503)	2.0% (400/19635)	0.257
> 90°	0.8% (4/503)	1.4% (267/19635)	0.428
Iliac Aneurysm			
None	81.5% (829/1017)	74.0% (25370/34290)	< 0.001

[º] M2S data output from the VQI Registry is setup in such a way that a given device can only be compared to All Other Devices, and not a subset of devices. As such, AFX Bifurcated device data exist in the presented analyses (Table 20 – Table 21). However, the included data points are low and would not impact the overall trend of the data presented**.**

Table 19. Vascular Characteristics, VQI Registry

Jan. 1, 2015 – Mar. 31, 2021[±]	AFX2 Bifurcated (n=1,030)	All Other Devices[†] (n=35,226)	p-value
Unilateral	11.2% (114/1017)	14.1% (4833/34290)	0.009
Bilateral	7.3% (74/1017)	11.9% (4087/34290)	< 0.001

[±] *AFX2 Bifurcated was first commercialized in February 2016*
† "All Other" EVAR devices includes Bolton Treovance, Cook Zenith, Gore CTAG, Gore Excludeer C3, Endologix AFX, Endologix Ovation, Endologix Nellix, Lombard Aorfix, Medtronic Endurant, Medtronic Endurant II, Medtronic Talent and Medtronic Valiant Captiva.

5.2.2.2.2. PERI-OPERATIVE OUTCOMES

The AFX2 Bifurcated device is shown to have equivalent or better outcomes in the perioperative period compared to the other EVAR devices (Table 20). The AFX2 Bifurcated device has statistically significantly better outcomes than comparators for any Endoleak at index completion, Type Ia Endoleak, Type II Endoleak and Type IV Endoleak. Additionally, as of March 31, 2021, there have been no observed Type IIIb Endoleaks, or conversions to open repair. Further, all observed acute rates for the AFX2 Bifurcated device remain low and are therefore not considered to be rates of clinical concern.

Table 20. AFX2 Bifurcated Peri-Operative Complications, VQI Registry

Jan. 1, 2015 – Mar. 31, 2021[±]	AFX2 Bifurcated (n=1,030)	All Other Devices[†] (n=35,226)	p-value
Endoleak at Index Completion			
None	91.7% (941/1026)	76.8% (26849/34976)	< 0.001
Type Ia Endoleak	0.7% (7/1026)	2.8% (989/34976)	< 0.001
Type Ib Endoleak	0.6% (6/1026)	0.7% (259/34976)	0.711
Type II Endoleak	4.1% (42/1026)	13.8% (4810/34976)	< 0.001
Type IIIa Endoleak	0.2% (2/1026)	0.2% (62/34976)	0.705
Type IIIb Endoleak	0% (0/1026)	0.1% (29/34976)	1
Type IV Endoleak	0% (0/1026)	0.7% (228/34976)	0.002
Indeterminate	2.3 % (24/1026)	3.2% (1117/34976)	0.147
Other Peri-Operative Outcomes			
Conversion to Open Repair	0% (0/1029)	0.1% (41/35186)	0.632
Peri-Operative Mortality	0.6% (6/1029)	0.7% (231/35219)	1
Major Adverse Event	3.0% (31/1030)	3.5% (1225/35224)	0.489

[±] *AFX2 Bifurcated was first commercialized in February 2016.*
† "All Other" EVAR devices includes Bolton Treovance, Cook Zenith, Gore CTAG, Gore Excluder C3, Endologix AFX, Endologix Ovation, Endologix Nellix, Lombard Aorfix, Medtronic Endurant, Medtronic Endurant II, Medtronic Talent and Medtronic Valiant Captiva.

5.2.2.2.3. ONE-YEAR OUTCOMES

In addition to the encouraging acute graft performance of the AFX2 Bifurcated device outlined above, the VQI Registry also supports equivalent or better performance results within the first year of follow-up compared to other EVAR devices. As shown in Table 21 below, the AFX2 Bifurcated device has a 7.5% higher freedom-from-Endoleak than all other devices, and this is highly statistically significant. This appears to be driven by an 8.6% lower rate of Type II Endoleaks, which is also highly statistically significant. The data shows no clinical or statistical difference in performance related to Type I Endoleaks, Type IIIb Endoleaks, ACM, or reintervention rates through one year of follow-up. The single exception to this trend is the reported Type IIIa Endoleak performance, with three Type IIIa endoleaks being recorded.

Table 21. AFX2 Bifurcated Long-Term (1-Year) Outcomes, VQI Registry

Jan. 1, 2015 – Jan. 31, 2021[±]	AFX2 Bifurcated (n=1,030)	All Other Devices[†] (n=35,226)	p-value
Endoleak, Cumulative Since Index			
None	91.0 % (312/343)	83.5 % (13686/16396)	< 0.001
Type Ia Endoleak	0.9 % (3/343)	0.8 % (133/16396)	0.759
Type Ib Endoleak	0.3 % (1/343)	0.7 % (108/16396)	0.73
Type II Endoleak	3.5 % (12/343)	12.1 % (1991/16396)	< 0.001
Type IIIa Endoleak	0.9 % (3/343)	0.2 % (32/16396)	0.034
Type IIIb Endoleak	0% (0/343)	0.1 % (12/16396)	1
Indeterminate	4.1 % (14/343)	3.0 % (491/16396)	0.26
Other Outcomes			
Freedom from Mortality (1-year KM)	92.3% ± 1.2%	92.6% ± 0.2%	0.226
Freedom from Reintervention (1-year KM)	97.9% ± 0.7%	97.2% ± 0.1%	0.217

[±] *AFX2 Bifurcated was first commercialized in February 2016.*
† "All Other" EVAR devices includes Bolton Treovance, Cook Zenith, Gore CTAG, Gore Excluder C3, Endologix AFX, Endologix Ovation, Endologix Nellix, Lombard Aorfix, Medtronic Endurant, Medtronic Endurant II, Medtronic Talent and Medtronic Valiant Captiva.

5.2.2.3. LIMITATIONS

Due to the number of statistical tests performed, it is possible that some variables are found to have a statistically significant difference. However, this does not necessarily mean these differences are of clinical significance. Reference Appendix E: VQI Limitations, for further discussion.

5.2.2.4. SUMMARY AND CONCLUSIONS

Overall, the VQI data demonstrate that AFX2 has some clinically meaningful advantages in peri-operative outcomes – a finding that may be relevant for some patient groups. At approximately 12 months follow-up, the performance profile for the AFX2 System is similar to all other EVAR Devices. AFX2 does have a significantly lower rate of all Endoleaks, a finding largely driven by a reduced incidence of Type II Endoleaks. While it is acknowledged that long-term follow-up is critical for the evaluation of EVAR devices, the VQI dataset provides a robust, unbiased assessment of device performance through 12 months. Importantly, the VQI results are concordant with the 1-year outcomes observed in the LEOPARD RCT.

5.3. LEVEL 3 EVIDENCE

5.3.1. 405 PATIENT RETROSPECTIVE MULTI-CENTER SERIES REPORTING OUTCOMES OF AFX2

The aggregated series is an Endologix sponsored, retrospective, multi-center study of patients receiving an AFX2 endograft from January 2016 through December 2020. Due to the commercial profile, the vast majority of patients receiving an AFX endograft after January 2016 would have received the AFX2 endograft as opposed to a previous iteration of the AFX family of devices.

5.3.1.1. STUDY DESIGN

The study was a retrospective, multicenter study of patients receiving an AFX2 endograft from January 2016 until Dec 2020. The study was performed in 5 US centers: Freeman Heart and Vascular Institute (Joplin, MI), Cooper University Healthcare (Camden, NJ), Baptist Memorial Hospital (Memphis, TN), Mercy Hospital (Springfield, MO), and Advent Health (Orlando, FL).

The study population included patients implanted with an AFX2 endograft within the study dates for the treatment of an AAA at the participating centers. Patients with an elective procedure for an unruptured AAA were reported and analyzed separately from those patients with a ruptured AAA. Patients who had a revisional procedure or had an AFX endograft as part of a procedure for aorto-iliac occlusive disease were

excluded. Patients were identified and cross referenced from institutional databases and commercial sales data. Treatment algorithms, including device sizing, technical implantation procedure, follow-up imaging and clinical follow-up protocol were at the discretion of the implanting site and were reflective of individual institutional protocols. All outcome measures were site reported, collected retrospectively, and entered into an electronic data management system for analysis.

Relevant outcomes analyzed included ACM, ARM, post-EVAR aortic rupture, open conversion, device-related reinterventions, graft occlusion, sac enlargement and Endoleaks as per established reporting standards[44]. Type I and Type III Endoleaks were classified into their "a" and "b" sub-classifications as per the same reporting standards.

Freedom from adverse events (ACM, ARM, open conversion, device-related reinterventions, graft occlusion, sac enlargement and Endoleak) are reported using Kaplan-Meier survival analysis, with numbers of patients at risk at each follow-up period presented.

As requested by FDA, these data were provided to FDA on September 22, 2021.

5.3.1.2. PATIENT DEMOGRAPHICS AND CHARACTERISTICS

The data set contains 405 patients electively treated for an intact AAA. The mean diameter of AAAs was 5.4 cm, and the mean follow-up was 1.7 years. Three hundred and fifty-two (86.9%) patients had recorded clinical or imaging follow-up after the peri-operative period. The mean sac diameter size was 54mm +/- 10mm (median 52 mm, max 100 mm, min 26 mm).

5.3.1.3. STUDY RESULTS

5.3.1.3.1. ALL-CAUSE MORTALITY

As shown in the data below, 71.4% of patients were free from ACM at 4 years (Figure 40).

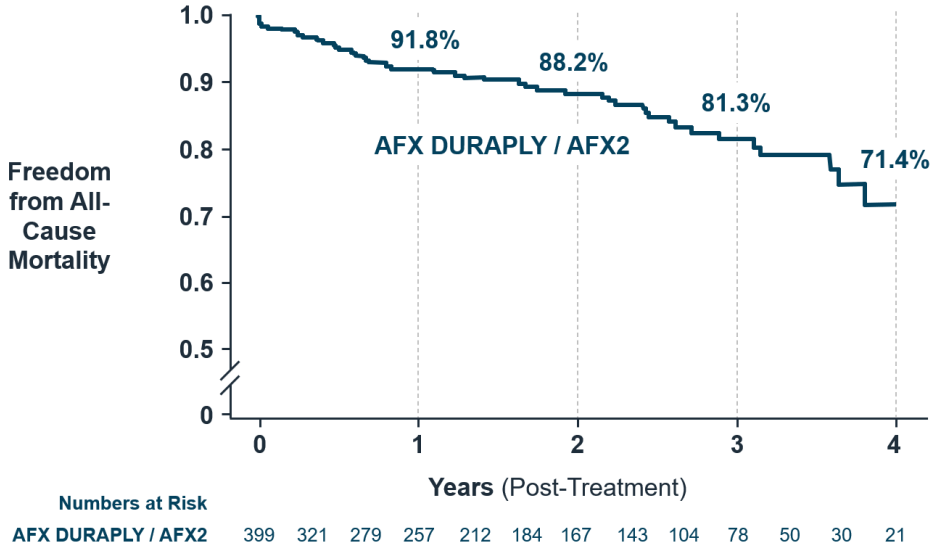


Figure 40. Freedom from ACM, Multi-Center Series

Regarding Aortic specific outcomes, At the 3-year time point AFX2 is performing at an acceptable level with low rates of aortic related death and aortic rupture (Table 22).

Table 22: 3-Year Freedom from Outcomes

3-Year Freedom from Outcomes	AFX2 N = 405
Aneurysm-related mortality	98.2%
Open conversion	98.8%
Aortic rupture	100%
Type Ia Endoleak	99.4%
Type III Endoleak	98.9%
Device-related reintervention	91.7%

5.3.1.4. SUMMARY AND CONCLUSIONS

There are a number of limitations to this study. The results may be considered not completely independent as Endologix sponsored the study. As is true with many retrospective studies, the patient demographics and the aortic anatomy were not well characterized. There was a lack of risk factor classification, which does not allow for the patient population to be clearly defined in terms of comorbidities. However, the ACM observed in the present study is similar to that reported in populations of patients with abdominal aneurysms[45] and so it seems likely that the present study involved a patient cohort with typical risk factors.

Given the study design and the retrospective nature of data acquisition, all outcomes were site reported and were not independently adjudicated. Similarly, a core laboratory was not used to verify imaging findings. As is typical with real-world practice there will be a loss to follow-up with patients generally having poor compliance with surveillance regimes[46,47]. It remains possible that some of the non-compliant patients may have presented to hospitals outside of the study centers and that their complications remain unidentified in the present study.

In the present study, the AFX2 endograft appears to perform to a satisfactory standard in terms of patient centric outcomes in mid-term follow-up. The Type Ia and Type III Endoleaks rates at 3 years appear to be within acceptable limits.

6. CONCORDANCE OF OUTCOMES ACROSS COMPENDIUM OF CLINICAL DATA

Endologix has presented a broad set of clinical data relating to the AFX product family. This compendium includes data on 4,901 patients implanted with AFX Duraply or AFX2. The data are derived from a variety of study designs, all of which have their own individual strengths and limitations. To assess whether there is a degree of consistency in the outcomes from these studies, the figures below plot the cumulative rates of both device related reinterventions and Type III endoleak from the various data sources per year of follow-up reporting. For illustrative purposes, the data from AFX2 have been presented.

Not all outcomes are represented in all data sets at all time points so there are some missing data in the analysis. However, there are sufficient data points to draw some broad conclusions.

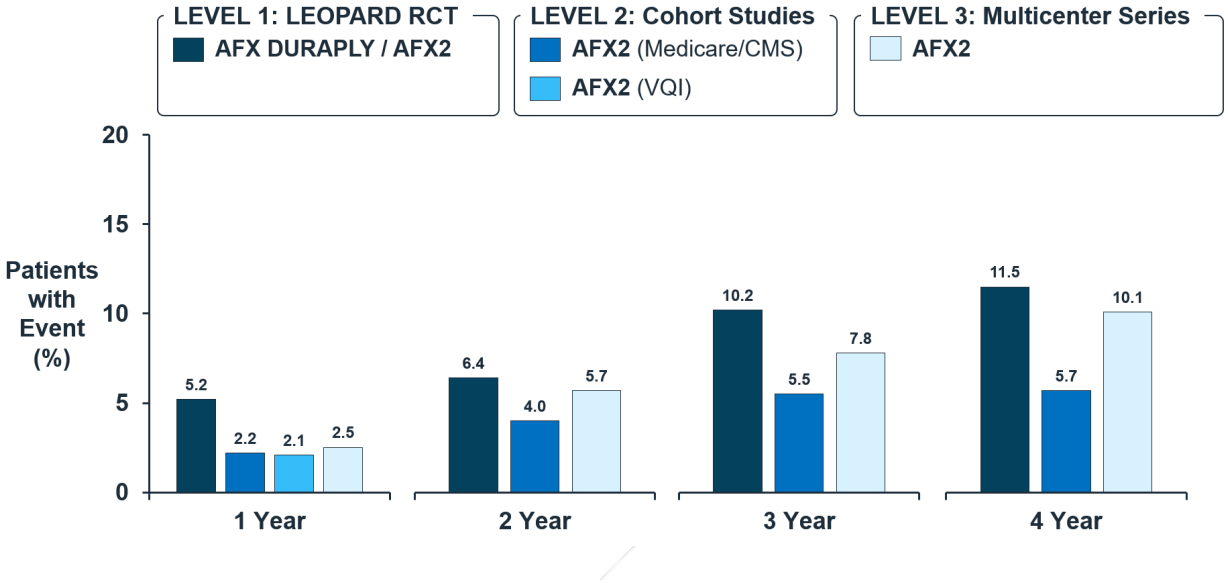


Figure 41: Device-Related Reinterventions for the 4 Studies in the Compendium of Clinical Data, Presented per Study per Year

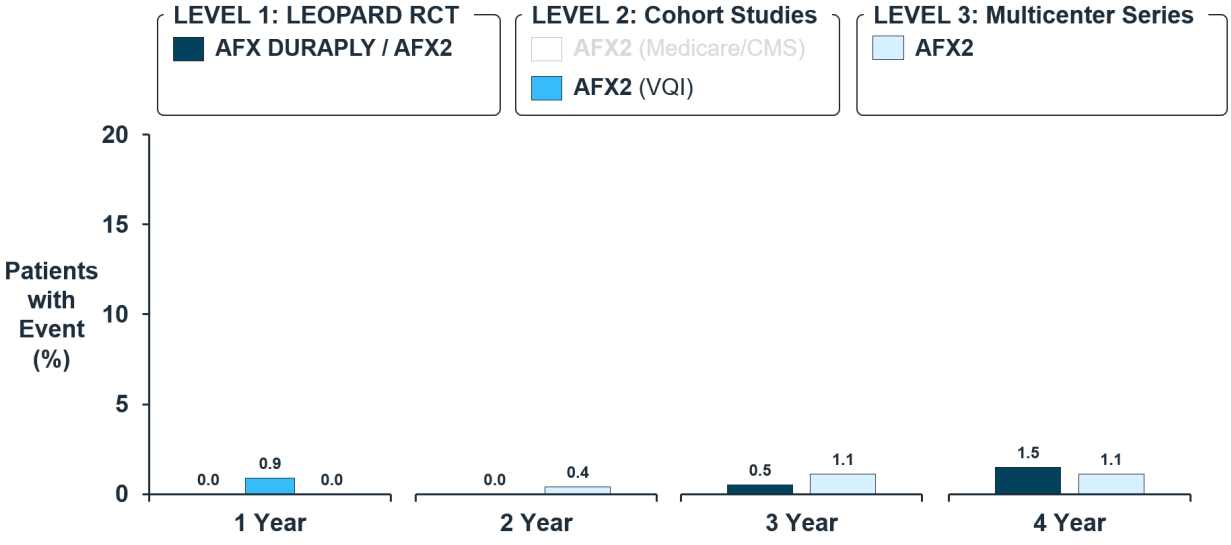


Figure 42: Rate of Type III Endoleak for the 4 Studies in the Compendium of Clinical Data, Presented per Study per Year

Note: The Medicare data set does not include Type III endoleak as an outcome measure

Overall, there is a high degree of consistency across all 4 studies. The rates of device related reintervention in the LEOPARD RCT appear higher than the others, which might be expected given the prospective nature of the study, the core laboratory assessment and the compliance with follow up. There are no studies in the Endologix compendium of clinical evidence that are outliers in terms of outcome incidence rates, and generally the event rates are within a few percentage points of each other. The rates of device related reintervention and Type III Endoleak reported here, would therefore appear to be a good reflection of clinical outcomes achieved with the AFX2 graft in the US at mid-term follow up.

6.1. COMPARISON OF ENDOLOGIX COMPENDIUM OF CLINICAL DATA AND OUTCOMES PREVIOUSLY REPORTED

The data published by Chang et al.[6] was originally an oral communication at the American College of Surgeons Annual Meeting and reported mid-term outcomes of the AFX product family in a single hospital system. These data were given prominence in the 2020 FDA safety communication (https://www.fda.gov/medical-devices/safety-communications/update-risk-type-iii-endoleaks-use-endologix-afx-endovascular-aaa-graft-systems-fda-safety) that suggested there may be a higher than expected rate of Type III Endoleaks with AFX Duraply and AFX2.

6.1.1. STUDY DESIGN

Chang, et al.[6]conducted a retrospective review of data on 605 patients who underwent EVAR by 60 surgeons at 23 sites within the Kaiser Health System between 2011 and 2017. In this dataset, 375 patients received an AFX device with Strata, 197 received an AFX device with Duraply, and 33 received an AFX2 device. Median follow-up for all groups was 3.9 years, and 2.0 years in patients treated with the AFX2 device. The authors did not provide information regarding patients' IFU status (e.g., adherence to the indications for use or procedural requirements), and an imaging CoreLab was not used.

6.1.2. STUDY RESULTS

The authors of this study suggest that all AFX devices were associated with a high complication rate and that the AFX2 device was associated with the highest rate of Type III Endoleaks, reintervention, and mortality at 2 years (Table 23). In addition, the authors reported rates of Type III Endoleaks ranging from 4% to 5% for AFX Strata and A Duraply.

However, the AFX2 observations are difficult to interpret given the limited sample size (14 patients with AFX2 devices at 2 years). Additionally, given that the study did not stratify between Type IIIa and Type IIIb Endoleaks, and the authors did not provide information regarding the index procedure, it is impossible to assess potential causation for these events.

Table 23. Chang et al.[6]: Freedom from Endpoints at 2 Years

2-Year Outcomes (95% CI)	Chang et al.[6]		
	AFX Strata	AFX Duraply	AFX2 Duraply
Type I Endoleak	4.9% (3.1, 7.7)	1.7% (0.6, 5.1)	0%
Type III Endoleak	4.0% (2.4, 6.7)	5.1% (2.7, 9.7)	14.1% (4.7, 38.2)
Reintervention	12.3% (9.3, 16.2)	9.5% (6.0, 14.8)	16.2% (6.4, 37.7)
AAA-Related Mortality	1.6% (0.7, 3.6)	2.6% (1.1, 6.0)	6.1% (1.6, 22.1)
All-Cause Mortality	8.8% (6.3, 12.2)	9.7% (6.3, 14.7)	21.2% (10.7, 39.4)

Source: Chang 2020

The authors acknowledge in their publication that there were many limitations to their findings:

- Inferences cannot be made due to the lack of a comparison group.
- Conclusions were based on a small sample of only 33 patients in the AFX2 group.
- The data were limited, with no information on surgeon decision making, no additional detail for the adjunct procedures performed, no information on IFU, and no imaging confirmation through a core imaging lab.
- There was a potential for misclassification error because they were unable to accurately subcategorize Type I or Type III Endoleaks, which would have provided more information on device design and potential failure mode. Type II Endoleaks may appear similar on CT to Type III Endoleaks and the lack of adjudication or centralized CoreLab potentially compounded misclassification.

6.1.3. COMPARISON WITH ENDOLOGIX COMPENDIUM OF CLINICAL DATA

Given the conclusions that were drawn from the published data, and the limitations acknowledged by the authors, a comparison was made of the outcomes reported by Chang et al.[6] and the outcomes derived from the 4 studies that comprised the compendium of clinical data collated by Endologix. The graphs below compare the rates of device related reintervention and Type III Endoleak for AFX Duraply and AFX2 as reported by Chang et al.[6] and the studies included in the clinical compendium.

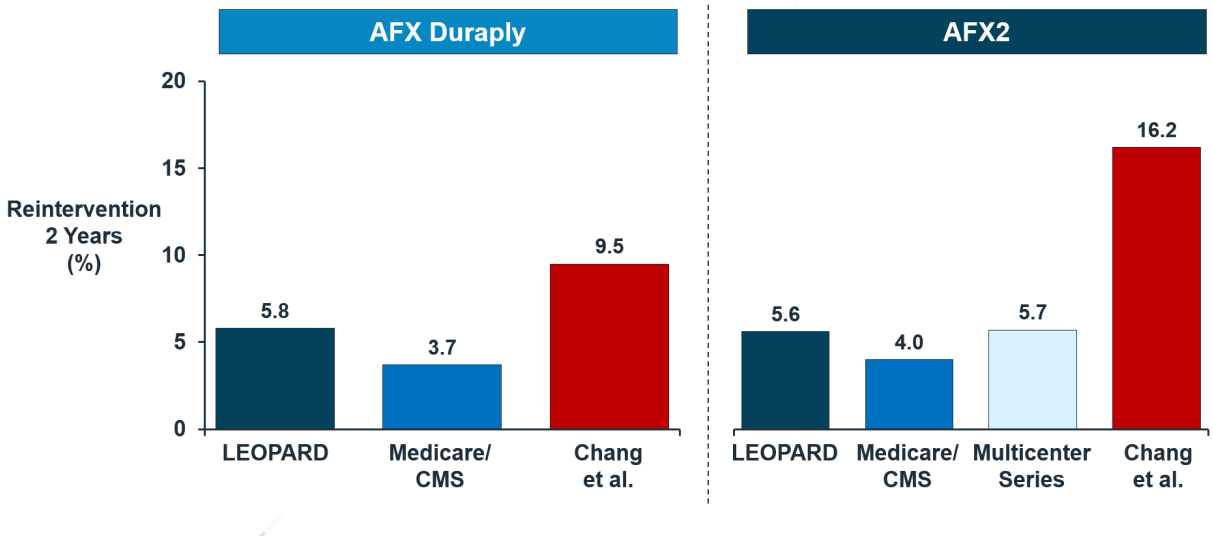


Figure 43: Rate of Device Related Reintervention at 2 Years Reported by Chang et al.[6] and Compared to the Studies in the Clinical Compendium that Reported that Outcome Measure
Note: The LEOPARD data have been dichotomized to report AFX Duraply and AFX2 separately.

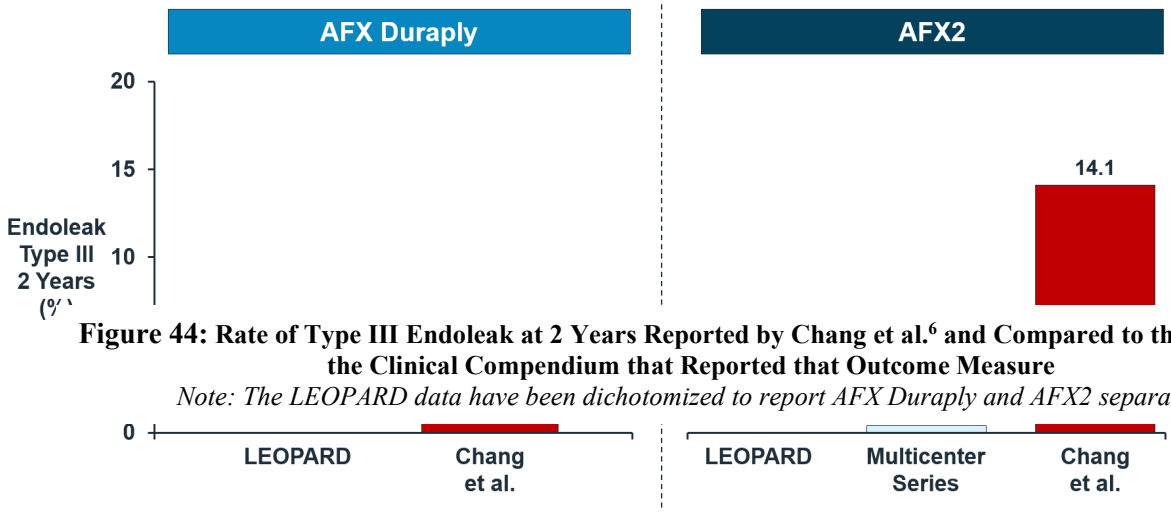


Figure 44: Rate of Type III Endoleak at 2 Years Reported by Chang et al.[6] and Compared to the Studies in the Clinical Compendium that Reported that Outcome Measure

Note: The LEOPARD data have been dichotomized to report AFX Duraply and AFX2 separately

6.2. LITERATURE REPORTING OUTCOMES OF AFX PRODUCT FAMILY

There have been several other studies that have reported on the AFX product family. Lemmon et al.[7] Barleben et al.[8] and Ta et al.[9] investigated the outcomes associated with AFX Strata and observed a high rate of Type III endoleak in mid- and long-term follow-up. None of these studies reported on the AFX product family after the product updates that were incorporated in AFX Duraply.

Wanken et al.[10] performed a comparative analysis of patients treated with AFX Strata as compared to patients treated with a mix of AFX Duraply and IntuiTrak. The proportion of grafts in the non-AFX Strata group are not given in the abstract. Rates of freedom from relining were plotted using Kaplan-Meier estimates and appear interpretable to 3 years. The freedom from relining at 3 years was 100% in the non AFX Strata group and MAE rates appear similar between both groups. This abstract provides limited information relating to the AFX family after product updates were made.

6.3. CONCLUSION

It is acknowledged that not all studies within the Endologix compendium of clinical data reported the same outcome parameters as the Chang manuscript and at the same time points. However, from the comparisons illustrated above, it is clear that the outcomes reported by Chang et al.[6] are worse than studies which would be considered broadly reflective of vascular practice in the US (given the number of centers and patients reported). In this regard, the outcomes achieved by Chang et al.[6] might be considered to be unrepresentative of the outcomes achieved by the AFX2 graft in other centers. It is clearly not within the purview of Endologix to comment on facets of clinical practice in specific hospital systems in isolation.

7. CONCLUSIONS

Current endografts offer diverse designs and therefore have both varying advantages and failure modes. Patient outcomes should be assessed using multiple indicators and the totality of relevant clinical information, with patient centric outcomes being prominent. Single failure modes should be weighted accordingly and considered as part of a holistic evaluation of endograft performance.

AFX2 is completely differentiated from the prior member of the AFX product family, AFX Duraply since initial commercialization, by design, manufacturing and labelling updates. AFX2 has 1) an increased mean thickness of the ePTFE fabric[e], 2) a cover to protect the bifurcation during endograft deployment, and 3) a sizing algorithm to ensure adequate component overlap.

FDA concerns over the benefit-risk profile of the AFX2 endograft appear to derive from historical extrapolation and a cohort of 33 patients described by Chang et al.[6], with 14 of these patients having follow up at 2 years.

The breadth of evidence reviewed demonstrates that the overall performance of the AFX2 device, the only commercial device within the AFX family, is comparable with other EVAR devices. High-quality, Level 1 evidence from the LEOPARD RCT confirms that the currently available AFX2 and the previous graft AFX Duraply device has an equivalent level of graft performance to proximally fixated comparator grafts. LEOPARD is the first contemporary, real-world, randomized controlled trial comparing the performance of commercially available EVAR devices and provides the highest level of evidence for the evaluation of long-term patient outcomes. When considered as a whole, AFX Duraply/AFX2 performed at a comparable level to the comparator endografts with no difference in ARCs or secondary endpoints out to 4 years. When performing an ad hoc analysis of secondary end points, it is apparent that there are minor differences between the evaluated endografts in terms of specific failure modes, but that overall performance is comparable.

The Medicare FFS dataset provides a powerful set of independent data, with many patients and direct contemporaneous comparator groups for AFX Strata, AFX Duraply and AX2. AFX Strata had higher rates of both aortic rupture and reintervention when compared to proximally fixated grafts at long-term follow up. The updates made to the AFX product family reduced subsequent reintervention rates with AFX Duraply and AFX2. AFX Duraply and AFX2 had similar rates of both reintervention and post-EVAR aortic rupture when compared to contemporaneous proximally fixated endografts

The VQI data demonstrate that AFX2 has some significant advantages in peri-operative outcomes, which may be relevant for some patient groups. At 12 months, the performance profile for the AFX2 device was similar to all other EVAR Devices. AFX2 has a significantly lower rate of all Endoleaks, which was largely driven by a reduced incidence of Type II Endoleaks. While long-term follow-up is critical for the evaluation of EVAR devices, the VQI dataset provides a robust, unbiased assessment of device performance through 12 months. Importantly, the VQI results are concordant with the 1year outcomes observed in the LEOPARD RCT.

In the clinical compendium, we present a comprehensive set of clinical outcomes for over 3000 patients implanted with AFX2 (LEOPARD-111, Medicare-1518, VQI-1030, multicenter series-455). Not all outcomes are available at all time points, but there are robust data available to 4-year follow up.

The compendium of clinical data unequivocally demonstrates that AFX2 has clinical outcomes that are favorable from a benefit-risk profile. The rates of patient centric outcomes - all-cause mortality, aortic rupture, aneurysm related mortality and device related-reintervention are well within the rates that have been established for EVAR.

AFX2 has clinical utility in clinical scenarios that are less well treated with proximally fixated endografts, as evidenced by the preferential use of AFX2 in women and patients with peripheral vascular disease.

Endologix remains committed to deriving a robust evidence base for the AFX2 endograft. Data collection for the LEOPARD RCT will continue to 5 years, and we intend to perform a Medicare analysis annually to ensure we acquire data to long term follow up.

The AFX2 System is a safe and effective device for use in the treatment of AAA.

8. APPENDIX A: DEFINITIONS OF TERMS/ACRONYMS

Family

AFX Family	The various systems commercialized under the AFX name. This includes the developmental progression from the AFX System with Strata to the AFX System with Duraply and, finally, to the current AFX2 System.

Systems

AFX2 Endovascular AAA System (AFX2 System)	A number of abdominal aneurysm endoluminal prostheses and delivery catheters intended for the endovascular repair of abdominal aortic or aortoiliac aneurysms. The portfolio for the AFX2 System comprises of bifurcated endografts, proximal aortic extension endografts, limb (iliac) extensions endografts, and delivery catheters.
AFX Endovascular AAA System (AFX System)	The predecessor to the AFX2 System. Like with the AFX2 System, the originally-branded AFX System was comprised of bifurcated endografts, proximal aortic extension endografts, limb (iliac) extensions endografts, and delivery catheters. The AFX System devices are further delineated based on the type of expanded polytetrafluoroethylene (ePTFE) graft and are subsequently referred to as the AFX System with Strata (See definition 'Strata' below) or the AFX System with Duraply (See definition 'Duraply' below).
AFX Introducer	Consisting of a single lumen dilator, an introducer sheath, and a wire straightener, the AFX Introducer facilitates the introduction of the AFX Bifurcated, AFX2 Bifurcated, AFX Accessory, and AFX Vela Endograft Systems into the vasculature while minimizing blood loss.

Endografts (i.e., Stent Grafts)

Bifurcated Endograft	The anatomically fixated unibody, infrarenal bifurcated endograft is the primary device of the AFX2 System and consists of a main body with two attached limbs.
Extension Endograft (Extension or Accessory)	The extension or accessory endografts, which are utilized to customize the AFX2 System to patient anatomy, are comprised of infrarenal and suprarenal proximal extensions as well as limb extensions in straight, tapered, flared, and stepped configurations.

Endograft Systems

AFX Strata/Duraply Endograft with the AFX Bifurcated (AFX) Delivery System	The first generation AFX bifurcated endograft system. AFX Bifurcated is further delineated based on the ePTFE graft processing method and is subsequently referred to as AFX Bifurcated with Strata (See definition 'Strata' below) or AFX Bifurcated with Duraply (See definition 'Duraply' below).
AFX Duraply Endograft with the AFX2 Bifurcated (AFX2) Delivery System	The second generation AFX bifurcated endograft system. This endograft system was first manufactured with the Duraply ePTFE graft and commercialized in 2016. It is the only bifurcated delivery system currently available. Subsequently, this bifurcated device will be referred to as AFX2.

ePTFE Graft Material Process

Strata	The original ePTFE graft material processing method utilized for the AFX System. In this method, the grafts were sheet extruded and utilized a serial wrapping technique. Devices with the Strata ePTFE graft material process were recalled by Endologix in December 2016 and are no longer commercially available.
Duraply	The current ePTFE graft material processing method utilized for the AFX2 System. In this method, the grafts are sheet extruded and utilize a mixture of serial and helical wrapping techniques. Duraply replaced Strata on all AFX System endografts starting in mid-2014, following necessary regulatory approvals.

Miscellaneous References

ActiveSeal	The ability of the AFX/AFX2 System ePTFE graft to readily conform and press against the flow lumen of the aorta in response to a pressure difference between the stent graft lumen and the aneurysm sac. This feature, which is predicated on a select number of attachment points of the ePTFE to the stent cage, allows the stent graft to rapidly achieve an effective seal to the aortic wall, and helps reduce Type Ia and Type Ib Endoleaks, which are known failure modes of existing EVAR grafts.

Additional Abbreviations

AAA	Abdominal Aortic Aneurysm
ACM	All-Cause Mortality
ARC	Aneurysm-Related Complication
ARM	Aneurysm-Related Mortality
ARR	Absolute Risk Reduction
CMS	Center for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CT	Computed Tomography
ePTFE	Expanded Polytetrafluoroethylene
ESVS	European Society for Vascular Surgery
EVAR	Endovascular Aneurysm Repair
FDA	Food and Drug Administration
FFS	Fee-for-Service
FSN	Field Safety Notice
ICU	Intensive Care Unit
IFU	Instructions for Use
KM	Kaplan Meier
MAB	Medical Advisory Board
LEOPARD	Looking at EVAR Outcomes by Primary Analysis of Randomized Data
NICE	National Institute of Health and Clinical Excellence
NNT	Number Needed to Treat
PVD	Peripheral Vascular Disease
RCT	Randomized Controlled Trial
RRR	Relative Risk Reduction
SVS	Society of Vascular Surgery
US	United States
VQI	Vascular Quality Initiative

9. APPENDIX B: INDICATIONS AND CONTRAINDICATIONS

9.1. INDICATIONS FOR USE

The AFX2 Endovascular AAA System is indicated for endovascular treatment in patients with AAAs using either a surgical vascular access technique or a bilateral percutaneous technique. The AFX Introducer facilitates the introduction of guidewires, catheters, and other medical devices into the vasculature and minimizes blood loss associated with such introduction. The devices are indicated for patients with suitable aneurysm morphology for endovascular repair, including:

- Adequate iliac/femoral access compatible with the required delivery systems (diameter ≥ 6.5 mm).
- Non-aneurysmal aortic neck between the renal arteries and the aneurysm:
  - with a length of ≥15 mm;
  - with a diameter of ≥18 mm and ≤32 mm;
  - with a neck angle of ≤60° to the body of the aneurysm.
- Aortic length ≥1.0 cm longer than the body portion of the chosen bifurcated model.
- Common iliac artery distal fixation site:
  - with a distal fixation length of ≥15 mm;
  - with ability to preserve at least one hypogastric artery;
  - with a diameter of ≥10 mm and ≤23 mm;
  - with an iliac angle of ≤90° to the aortic bifurcation.
- Extension stent grafts must overlap the bifurcated stent graft by at least by at least 30 to 40 mm proximally and at least 15 to 20 mm distally.

9.2. CONTRAINDICATIONS

The AFX2 Endovascular AAA System is contraindicated in:

- Patients who have a condition that threatens to infect the stent graft, and
- Patients with sensitivities or allergies to the device materials.

10. APPENDIX C: LITERATURE SEARCH

The publications identified in the alternative (non-AFX Family) endograft literature search are included below in Table 24.

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Ash J, Chandra V, Rzucidlo E, et al. LUCY results show females have equivalent outcomes to males following endovascular abdominal aortic aneurysm repair despite more complex aortic morphology. J Vasc Surg. 2020.[48]	225	P1MN	Ovation	2015-2017
Barleben A, Mathlouthi A, Mehta M, et al. Long-term outcomes of the Ovation Stent Graft System investigational device exemption trial for endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2020.[49]	161	P1MN	Ovation	2009-2011
Becquemin JP, Haupert S, Issam F, et al. Five-Year Patient Outcomes of Endovascular Abdominal Aortic Aneurysm Repair in the ENDURANT France Registry. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2020.[50]	180	R1MN	Endurant	2012-2017
Benveniste GL, Tjahjono R, Chen O, et al. Long-Term Results of 180 Consecutive Patients with Abdominal Aortic Aneurysm Treated with the Endurant Stent Graft System. Ann Vasc Surg. 2020.[51]	180	P1SN	Endurant	2008-2019
Bergonti M, Teruzzi G, Santagostino G, et al. Third- versus second-generation stent graft for endovascular aneurysm repair: A device-specific analysis. Ann Vasc Surg. 2017;44:67-76.[52]	64	R2SN	Excluder (SP and C3)	2008-2015
Beropoulis E, Fazzini S, Austermann M, Torsello GB, Damerau S, Torsello GF. Long-term Results of Thoracic Endovascular Aortic Repair Using a Low-Profile Stent-Graft. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2020:1526602820952416.[53]	44	R1SN	Zenith	2010-2014
Bisdas T, Weiss K, Eisenack M, et al. Durability of the Endurant stent graft in patients undergoing endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2014;60(5):1125-1131.[54]	273	P1MN	Endurant	2007-2011
Briggs C, Babrowski T, Skelly C, et al. Anatomic and clinical characterization of the narrow distal aorta and implications after endovascular aneurysm repair. J Vasc Surg. 2018;68(4):1030-1038.e1031.[55]	1,328	R1MN	Excluder	2010-2015
Buck DB, Soden PA, Deery SE, et al. Comparison of Endovascular stent grafts for abdominal aortic aneurysm repair in Medicare beneficiaries. Ann Vasc Surg. 2018;47:31-42.[56]	46,171 (43,911 with	R3MN	AneuRx, Excluder, Zenith, Powerlink	2005-2008

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
	Excluder or Zenith)			
Chen PL, Hsu HL, Chen IM, et al. The impact of aortic tortuosity on delayed Type I or III Endoleak after endovascular aortic repair. Ann Vasc Surg. 2017;41:110-117.[57]	118	R1SN	Zenith	2005-2013
de Donato G, Pasqui E, Mele M, et al. The use of a low-profile stent graft with a polymer ring sealing technology combined with bare renal stent (vent technique) in patients with juxtarenal aneurysm not eligible for open surgery and fenestrated endograft. J Vasc Surg. 2019.[58]	38	R1SN	Ovation	2015-2018
De Donato G, Setacci F, Bresadola L, et al. Aortic neck evolution after endovascular repair with TriVascular Ovation stent graft. J Vasc Surg. 2016;63(1):8-15.[59]	161	R1MN	Ovation	2010-2012
de Donato G, Pasqui E, Mele M, et al. The use of a low-profile stent graft with a polymer ring sealing technology combined with bare renal stent (vent technique) in patients with juxtarenal aneurysm not eligible for open surgery and fenestrated endograft. Journal of vascular surgery. 2020;71(6):1843-1850.[60]	38	R1SN	Ovation	2015-2018
Deery SE, Shean KE, Pothof AB, et al. Three-year results of the Endurant stent graft system post approval study. Ann Vasc Surg. 2018;50:202-208.[61]	178	P1SN	Endurant	2011-2012
Dijkstra ML, van Sterkenburg SM, Lardenoye JW, et al. One-year outcomes of endovascular aneurysm repair in high-risk patients using the Endurant stent-graft: comparison of the ASA classification and SVS/AAVS Medical Comorbidity Grading System for the prediction of mortality and adverse events. J Endovasc Ther: an official journal of the International Society of Endovascular Specialists. 2016;23(4):574-582.[62]	1,263	P1MN	Endurant	2009-2011
Donas KP, Torsello G, Weiss K, et al. Performance of the Endurant stent graft in patients with abdominal aortic aneurysms independent of their morphologic suitability for endovascular aneurysm repair based on instructions for use. J Vasc Surg. 2015;62(4):848-854.[63]	712	P1SN	Endurant	2007-2013
D'Oria M, Tenorio ER, Oderich GS, et al. Outcomes after Standalone Use of Gore Excluder Iliac Branch Endoprosthesis for Endovascular Repair of Isolated Iliac Artery Aneurysms. Annals of vascular surgery. 2020;67:158-170.[64]	11	P1SN	Excluder	2014-2018
Farber, M. A., G. S. Oderich, C. Timaran, L. A. Sanchez and Z. Dawson. "Results from a	30	P1MN	Zenith	2013-2015

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
prospective multicenter feasibility study of Zenith p-Branch stent graft." J Vasc Surg. 2019[65]				
Fujimura N, Obara H, Matsubara K, et al. Comparison of early sac shrinkage with third-generation stent grafts for endovascular aneurysm repair. J Vasc Interv Radiol: JVIR. 2016;27(10):1604-1612.e1602.[66]	162	R3MN	Endurant Excluder Zenith	2009-2013
Fujimura, N., S. Ichihashi, K. Matsubara, S. Shibutani, H. Harada, H. Obara, K. Kichikawa and Y. Kitagawa. "Type IIIb Endoleak Is Not Extremely Rare and May Be Underdiagnosed after Endovascular Aneurysm Repair." J Vasc Interv Radiol 2019, 30: 1393-1399.e1391[67]	433	R1MN	Zenith	2007-2016
Fujimura N, Imazuru T, Matsumura H, et al. Two-Year Results of a Multicenter Prospective Observational Study of the Zenith Spiral-Z Limb Deployed in the External Iliac Artery During Endovascular Aneurysm Repair. Circulation journal : official journal of the Japanese Circulation Society. 2020;84(10):1764-1770.[68]	65	P1MN	Zenith	2017-2017
Gallitto E, Faggioli G, Pini R, et al. Endovascular repair of thoraco-abdominal aortic aneurysms by fenestrated and branched endograftsdagger. Eur J Cardiothorac Surg. 2019;56.[69]	88	R1SN	Zenith	2010-2018
Gallitto E, Gargiulo M, Freyrie A, et al. Results of standard suprarenal fixation endografts for abdominal aortic aneurysms with neck length </=10 mm in high-risk patients unfit for open repair and fenestrated endograft. J Vasc Surg. 2016;64(3):563-570.e561.[70]	60	P1SN	Endurant Zenith Flex	2005-2010
Gentsu T, Okada T, Yamaguchi M, et al. Type II Endoleak after endovascular aortic aneurysm repair using the Endurant stent graft system for abdominal aortic aneurysm with occluded inferior mesenteric artery. Cardiovasc Interv Radiol. 2019;42(4):505-512.[71]	103	R1SN	Endurant	2012-2017
Georgiadis GS, Antoniou GA, Argyriou C, et al. Correlation of Baseline Plasma and Inguinal Connective Tissue Metalloproteinases and Their Inhibitors with Late High-Pressure Endoleak After Endovascular Aneurysm Repair: Long-term Results. J Endovasc Ther. 2019;26.[72]	72	P1SN	Endurant	2010-2013
Georgiadis GS, Chatzigakis PK, Kouvelos G, et al. Multicenter Mid-term Results After Endovascular Aortic Aneurysm Repair with the Incraft® Device. Annals of vascular surgery. 2020.[73]	77	P1MN	Incraft	2015-2018

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Greaves NS, Moore A, Seriki D, et al. Outcomes of endovascular aneurysm repair using the Ovation stent graft system in adverse anatomy. Eur J Vasc Endovasc Surg: the official journal of the European Society for Vascular Surgery. 2018;55(4):512-517.[74]	52	R1SN	Ovation	2012-2017
Gupta N, Hynes KL, Mahrouyan O, et al. Polymer leak with the Ovation Abdominal Stent Graft System: Early recognition and treatment. Vascular. 2020;28.[75]	26	R1MN	Ovation	2009-2016
Hammond CJ, Shah AH, Snoddon A, et al. Mortality and rates of secondary intervention after EVAR in an unselected population: influence of simple clinical categories and implications for surveillance. Cardiovasc Interv Radiol. 2016;39(6):815-823.[76]	234	R1SN	Aorfix Anaconda Endurant Excluder Talent Zenith	2007-2013
Han SM, Tenorio ER, Mirza AK, et al. Low-profile Zenith Alpha Thoracic Stent Graft Modification Using Preloaded Wires for Urgent Repair of Thoracoabdominal and Pararenal Abdominal Aortic Aneurysms. Ann Vasc Surg. 2020.[77]	20	R1MN	Zenith	2016-2019
Hernandez Mateo MM, Martinez Lopez I, Revuelta Suero S, et al. Impact of the repositionable C3 Excluder system on the endovascular treatment of abdominal aortic aneurysms with unfavorable neck anatomy. J Endovasc Ther: an official journal of the International Society of Endovascular Specialists. 2016;23(4):593-598.[78]	249	R2SN	Excluder C3	2000-2014
Ierardi AM, Tsetis D, Ioannou C, et al. Ultra-low-profile polymer-filled stent graft for abdominal aortic aneurysm treatment: a two-year follow-up. La Radiologia medica. 2015;120(6):542-548.[79]	36	R1MN	Ovation	2009-2011
Ioannou CV, Kontopodis N, Georgakarakos E, et al. Routine use of an aortic balloon to resolve possible inflow stenosis induced by the inflatable ring fixation mechanism of the Ovation endograft. La Radiologia medica. 2016;121(11):882-889.[80]	83	R1SN	Ovation	2011-2015
Ioannou CV, Kontopodis N, Kehagias E, et al. Endovascular aneurysm repair with the Ovation TriVascular stent graft system utilizing a predominantly percutaneous approach under local anaesthesia. Br J Radiol. 2015;88(1051):20140735.[81]	66	R1SN	Ovation	2011-2014
Irace L, Venosi S, Gattuso R, et al. Initial single-site experience with the Ovation abdominal stent-graft system in patients with challenging aortoiliac anatomy. J Cardiovasc Surg. 2016;57(6):846-852.[82]	14	P1SN	Ovation	2010-2012
Iwakoshi S, Nakai T, Ichihashi S, et al. Conformability and efficacy of the Zenith Spiral Z leg compared with the Zenith Flex leg in	56	R2SN	Zenith	2009-2017

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
endovascular aortic aneurysm repair. Ann Vasc Surg. 2019.[83]				
Jetty, P., D. Husereau, V. Kansal, T. Zhang and S. Nagpal. "Variability in aneurysm sac regression after endovascular aneurysm repair based on a comprehensive registry of patients in Eastern Ontario." J Vasc Surg(2019)[84]	1,060	R1SN	Zenith, Endurant, Talent, Zenith LP, Terumo Anaconda	1999-2015
Kapetanios D, Karkos CD, Pliatsios I, et al. Association between perioperative fibrinogen levels and the midterm outcome in patients undergoing elective endovascular repair of abdominal aortic aneurysms. Ann Vasc Surg. 2019;56:202-208.[85]	94	P1SN	Endurant	2012-2016
Katsargyris A, Mufty H, Wojs R, at al. Single-centre experience with the Gore C3 Excluder stent-graft in 200 consecutive patients. J Cardiovasc Surg. 2016;57(4):485-490.[86]	200	P1SN	Excluder C3	2010-2015
Kawamata H, Tajima H, Ueda T, et al. Long-term outcomes of endovascular aortic aneurysm repair with the Zenith AAA endovascular graft: a single-center study. Jpn J Radiol. 2020;38.[87]	95	R1SN	Zenith	2007-2013
Krajcer Z, Ramaiah VG, Henao EA, et al. Perioperative outcomes from the prospective multicenter least invasive fast-track EVAR (LIFE) registry. J Endovasc Ther: an official journal of the International Society of Endovascular Specialists. 2018;25(1):6-13.[88]	250	P1MN	Ovation	2014-2016
Le TB, Moon MH, Jeon YS, et al. Evaluation of aneurysm neck angle change after endovascular aneurysm repair clinical investigations. Cardiovasc Int Radiol. 2016;39(5):668-675.[89]	72	R1SN	Endurant Excluder Seal Zenith	2005-2014
Liao JL, Wang SK, Maijub JG, et al. Perioperative and Long-term Results of Zenith Fenestrated Aortic Repair in Women. Annals of vascular surgery. 2020;68:44-49.[90]	136	R1SN	Zenith	2012-2019
Malas MB, Hicks CW, Jordan WD, Jr., et al. Five-year outcomes of the PYTHAGORAS U.S. clinical trial of the Aorfix endograft for endovascular aneurysm repair in patients with highly angulated aortic necks. J Vasc Surg. 2017;65(6):1598-1607.[91]	218	P1SN	Aorfix	2006-2011
Matsagkas M, Kouvelos G, Peroulis M, et al. Standard endovascular treatment of abdominal aortic aneurysms in patients with very short proximal necks using the Endurant stent graft. J Vasc Surg. 2015;61(1):9-15.[92]	57	R1SN	Endurant	2008-2012

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Maudet A, Daoudal A, Cardon A, et al. Endovascular treatment of infrarenal aneurysms: comparison of the results of second- and third-generation stent grafts. Ann Vasc Surg. 2016;34:95-105.[93]	334	R2SN	Anaconda Excluder (low porosity) Talent Zenith Flex	2005-2013
Mazzaccaro D, Malacrida G, Amato B, et al. Preliminary experience with the use of ultra-low profile endografts. Diagn Interv Radiol (Ankara, Turkey). 2017;23(6):448-453.[94]	67	R2SN	Incraft Ovation	2011-2016
Mazzaccaro D, Occhiuto MT, Stegher S, et al. Tips about the Cordis INCRAFT endograft. Ann Vasc Surg. 2016;30:205-210.[95]	10	R1SN	Incraft	2014-2015
Melissano G, Rinaldi E, Mascia D, et al. Single-center mid-term results with the low-profile Zenith Alpha Thoracic Endovascular stent-graft. Journal of vascular surgery. 2020.[96]	262	R1SN	Zenith	2013-2019
Mirza AK, Sullivan TM, Skeik N, Manunga J. Superior mesenteric artery outcomes after large fenestration strut relocation with the Zenith Fenestrated endoprosthesis. CVIR endovascular. 2020;3(1):54.[97]	121	R1SN	Zenith	2013-2019
Morgan-Bates K, Chaudhuri A. Use of the Ovation Endograft System to Treat Abdominal Aortic Aneurysms With Hostile Anatomy. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2020;60(5):786-787.[98]	49	R1SN	Ovation	2014-2018
Mufty, H., S. Houthoofd, K. Daenens, I. Fourneau and G. Maleux. "Mid-to long-term outcome results of the Ovation stent-graft." Ann Vasc Surg. 2019[99]	74	R1SN	Ovation	2012-2019
Mwipatayi BP, Anwari T, Wong J, et al. Sex-related outcomes after endovascular aneurysm repair within the Global Registry for Endovascular Aortic Treatment (GREAT). Ann Vasc Surg. 2020.[100]	3,758	R1MN	Excluder	2010-2016
Nishibe T, Iwahashi T, Kamiya K, et al. Clinical and morphological outcomes in endovascular aortic repair of abdominal aortic aneurysm using GORE C3 EXCLUDER: comparison between patients treated within and outside instructions for use. Ann Vasc Surg. 2019.[101]	109	R1SN	Excluder C3	2013-2016
Nishibe T, Dardik A, Koizumi J, et al. Simple renal cyst and its association with sac shrinkage after endovascular aneurysm repair for abdominal aortic aneurysms. Journal of vascular surgery. 2020;71(6):1890-1898.e1891.[102]	155	R2SN	Excluder	2013-2017
Oderich GS, Farber MA, Schneider D, et al. Final 5-year results of the United States Zenith	67	R1MN	Zenith	2005-2012

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Fenestrated prospective multicenter study for juxtarenal abdominal aortic aneurysms. Journal of vascular surgery. 2020.[103]				
O'Donnell TFX, Verhagen HJ, Pratesi G, et al. Female sex is associated with comparable 5-year outcomes after contemporary endovascular aneurysm repair despite more challenging anatomy. J Vasc Surg. 2020;71.[104]	399	R1MN	Endurant	NR
Oliveira NFG, Bastos Goncalves FM, Van Rijn MJ, et al. Standard endovascular aneurysm repair in patients with wide infrarenal aneurysm necks is associated with increased risk of adverse events. Journal of vascular surgery. 2017;65(6):1608-1616.[105]	427	R1MN	Endurant	2008-2012
Oliveira-Pinto J, Oliveira NFG, Bastos-Goncalves FM, et al. Long-term results after standard endovascular aneurysm repair with the Endurant and Excluder stent grafts. J Vasc Surg. 2020;71.[106]	277	R1SN	Endurant Excluder	2004-2011
Orrico M, Ronchey S, Alberti V, et al. Outcomes of endovascular repair of abdominal aortic aneurysms in narrow aortic bifurcations using the ultra-low profile "INCRAFT" device: A retrospective multicenter study. J Vasc Surg. 2019.[107]	127	R1MN	Incraft	2014-2018
Pagliariccio G, Gatta E, Schiavon S, et al. Bell-bottom technique in iliac branch era: mid-term single stent graft performance. CVIR endovascular. 2020;3(1):57.[108]	71	R1SN	Endurant	2009-2012
Pecoraro F, Corte G, Dinoto E, et al. Clinical outcomes of Endurant II stent-graft for infrarenal aortic aneurysm repair: comparison of on-label versus off-label use. Diagn Interv Radiol (Ankara, Turkey). 2016;22(5):450-454.[109]	64	R1SN	Endurant II	2012-2015
Peters AS, Hatzl J, Bischoff MS, et al. Comparison of endovascular aneurysm sealing and repair with respect to contrast use and radiation in comparable patient cohorts. J Cardiovasc Surg (Torino). 2020;61.[110]	40	R2SN	Endurant Excluder	2012-2016
Pippin K, Hill J, He J, et al. Outcomes of Type II Endoleaks after endovascular abdominal aortic aneurysm (AAA) repair: a single-center, retrospective study. Clin Imaging. 2016;40(5):875-879.[111]	163	R1SN	Excluder	2005-2013
Pitoulias GA, Valdivia AR, Hahtapornsawan S, et al. Conical neck is strongly associated with proximal failure in standard endovascular aneurysm repair. J Vasc Surg. 2017;66(6):1686-1695.[112]	156	R1MN	Endurant	2007-2015

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Pitoulias GA, Torsello G, Austermann M, et al. Outcomes of elective use of the chimney endovascular technique in pararenal aortic pathologic processes. Journal of vascular surgery. 2020.[113]	165	R1SN	Endurant	2009-2018
Poublon CG, Holewijn S, van Sterkenburg SMM, et al. Long-term outcome of the GORE EXCLUDER AAA endoprosthesis for treatment of infrarenal aortic aneurysms. Journal of vascular and interventional radiology: JVIR. 2017;28(5):637-644.e631.[114]	248	R1MN	Excluder	2000-2015
Pratesi G, Pratesi C, Chiesa R, et al. The INNOVATION Trial: four-year safety and effectiveness of the INCRAFT(R) AAA stent-graft system for endovascular repair. J Cardiovasc Surg. 2017;58(5):650-657.[115]	60	P1MN	Incraft	NR
Ramirez JL, Schaller MS, Wu B, et al. Late graft failure is rare after endovascular aneurysm repair using the Zenith stent graft in a cohort of high-risk patients. J Vasc Surg. 2019;70.[116]	325	R1SN	Zenith	1998-2005
Reyes Valdivia A, Pitoulias G, Criado FJ, et al. Multicenter European registry for patients with AAA undergoing EVAR evaluating the performance of the 36-mm-diameter Endurant stent-graft. Cardiovasc Int Radiol. 2017;40(10):1514-1521.[117]	73	R1MN	Endurant	2007-2015
Rosenfeld ES, Macsata RA, Lala S, et al. Open Surgical Repair of Juxtarenal Abdominal Aortic Aneurysms in the Elderly is Not Associated with Increased Thirty-Day Mortality Compared to Fenestrated Endovascular Grafting. Journal of vascular surgery. 2020.[118]	136	R2SN	Zenith	2012-2018
Saha P, Hughes J, Patel AS, et al. Medium-term outcomes following endovascular repair of infrarenal abdominal aortic aneurysms with an unfavourable proximal neck. Cardiovasc Int Radiol. 2015;38(4):840-845.[119]	27	R1SN	Zenith	2006-2008
Sayed T, El Basty A, Hildebrand D, Bachoo P. Mid-term outcomes of endovascular aneurysm repair in challenging aortic neck anatomy based on experience from the GREAT C3 registry. The Journal of cardiovascular surgery. 2020;61(5):610-616.[120]	399	R1MN	C3	2010-2012
Senemaud JN, Ben Abdallah I, de Boissieu P, et al. Intraoperative adverse events and early outcomes of custom-made fenestrated stent grafts and physician-modified stent grafts for complex aortic aneurysms. J Vasc Surg. 2019.[121]	97	R2SN	Zenith	2012-2017
Singh MJ, Fairman R, Anain P, et al. Final results of the Endurant stent graft system in the United	150	P1MN	Endurant	2008-2009

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
States regulatory trial. J Vasc Surg. 2016;64(1):55-62.[122]				
Sirignano P, Capoccia L, Menna D, et al. Pushing forward the limits of EVAR: new therapeutic solutions for extremely challenging AAAs using the Ovation(R) stent-graft. J Cardiovasc Surg. 2016;57(6):839-845.[123]	21	R1SN	Ovation	2012-2014
Sirignano P, Mansour W, Capoccia L, et al. Immediate results of the expanding indications for treatment with standard EVAR in patients with challenging anatomies, a multi-centric prospective evaluation - EXTREME Study. EuroIntervention. 2019.[124]	122	P1MN	Ovation	2017-2018
Sirignano P, Mansour W, Pranteda C, et al. Real-life experience with Ovation stent graft: lesson learned from the first one hundred fifty treated patients. Ann Vasc Surg. 2017;45:253-261.[125]	156	R1MN	Ovation	2012-2015
Sirignano P, Capoccia L, Mansour W, et al. Type II Endoleak incidence and fate after endovascular aneurysms repair in a multicentric series: different results with different devices? Ann Vasc Surg. 2019;56:224-232.[126]	203	R1MN	Excluder	2012-2016
Sobocinski J, Briffa F, Holt PJ, et al. Evaluation of the Zenith low-profile abdominal aortic aneurysm stent graft. J Vasc Surg. 2015;62(4):841-847.[127]	208	R2SN	Zenith Flex Zenith LP	2010-2013
Starnes BW, Dwivedi A, Giglia J, Woo K, Yeh C. Updated outcomes from the TRANSFIX study to evaluate endovascular repair of blunt thoracic aortic injuries with the Zenith Alpha thoracic device. Journal of vascular surgery. 2020;71(6):1851-1857.[128]	50	P1SN	Zenith	2013-2014
Storck M, Nolte T, Tenholt M, et al. Women and men derive comparable benefits from an ultra-low-profile endograft: 1-year results of the European OVATION registry. J Cardiovasc Surg. 2017;58(5):658-664.[129]	501	R1MN	Ovation	2011-2013
Swerdlow, N. J., S. P. Lyden, H. J. M. Verhagen and M. L. Schermerhorn. "Five-year results of endovascular abdominal aortic aneurysm repair with the Ovation abdominal stent graft." J Vasc Surg. 2019[130]	1,137	R1MN	Ovation, Ovation Prime, Ovation iX	2009-2017
T Mannetje YW, Broos PP, van Poppel RF, et al. Late single-center outcome of the Talent Abdominal stent graft after a decade of follow-up. J Vasc Surg. 2016;64(3):557-562. [131]	149	R1SN	Talent	1999-2005
T Mannetje YW, Cuypers PWM, Saleem BR, et al. Comparison of midterm results for the Talent and Endurant stent graft. J Vasc Surg. 2017;66(3):735-742.[132]	221	R2SN	Endurant Talent	2005-2010

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Tadros RO, Sher A, Kang M, et al. Outcomes of using endovascular aneurysm repair with active fixation in complex aneurysm morphology. J Vasc Surg. 2018;68(3):683-692.[133]	340	R2SN	Endurant Excluder Zenith	2000-2015
Teijink, J. A. W., A. H. Power, D. Bockler, P. Peeters, S. van Sterkenburg, L. H. Bouwman, H. J. Verhagen, M. Bosiers, V. Riambau, J. P. Becquemin, P. Cuypers and M. van Sambeek. "Editor's Choice - Five Year Outcomes of the Endurant Stent Graft for Endovascular Abdominal Aortic Aneurysm Repair in the ENGAGE Registry." Eur J Vasc Endovasc Surg 2019, 58: 175-181[134]	1,263	P1MN	Endurant	2009-2011
Trellopoulos G, Georgakarakos E, Pelekas D, et al. Initial single-center experience with the Ovation stent-graft system in the treatment of abdominal aortic aneurysms: application to challenging iliac access anatomies. Ann Vasc Surg. 2015;29(5):913-919.[135]	42	P1SN	Ovation	2012-2014
Troisi, N., G. Pitoulias, S. Michelagnoli, G. Torsello, A. Stachmann, T. Bisdas, Y. Li and K. P. Donas. "Preliminary experience with the Endurant II short form stent-graft system." J Cardiovasc Surg (Torino) 2019, 60: 364-368†[136]	79	P1MN	Endurant II	2014-2015
Troisi N, Torsello G, Weiss K, et al. Midterm results of endovascular aneurysm repair using the Endurant stent-graft according to the instructions for use vs. off-label conditions. J Endovasc Ther: an official journal of the International Society of Endovascular Specialists. 2014;21(6):841-847. [137]	177	P1MN	Endurant	2007-2010
Tsolakis IA, Kakkos SK, Papageorgopoulou CP, et al. Improved effectiveness of the repositionable GORE EXCLUDER AAA endoprosthesis featuring the C3 delivery system compared with the original GORE EXCLUDER AAA endoprosthesis for within the instructions for use treatment of aortoiliac aneurysms. J Vasc Surg. 2019;69(2):394-404. [138]	313	R2SN	Excluder Excluder C3	2004-2017
Unsgard, R. G., M. Altreuther, C. Lange, T. Hammer and E. Mattsson. "Five-year results of endovascular aortic repair used according to instructions for use give a good general outcome for abdominal aortic aneurysm." SAGE Open Med 2019, 7: 20503121198534344[139]	123	R1SN	Zenith	2002-2006
Vaaramaki, S., J. P. Salenius, G. Pimenoff, I. Uurto and V. Suominen. "Systematic Long-term Follow Up After Endovascular Abdominal Aortic Aneurysm Repair with the Zenith Stent Graft." Eur J Vasc Endovasc Surg. 2019, 58: 182-188[140]	282	R1SN	Zenith	2000-2010

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Varkevisser RRB, Swerdlow NJ, Verhagen HJM, et al. Similar 5-year outcomes between female and male patients undergoing elective endovascular abdominal aortic aneurysm repair with the Ovation stent graft. J Vasc Surg. 2019. [141]	1,296	RM	Ovation	2009-2016
Veraldi GF, Mezzetto L, Vaccher F, et al. Technical success and long-term results with Excluder/C3 endoprosthesis in narrow aortic bifurcations: first Italian multicentre experience. Ann Vasc Surg. 2018;52:57-66.[142]	195	R1MN	Excluder C3	2005-2017
Verhoeven EL, Katsargyris A, Bachoo P, et al. Real-world performance of the new C3 Gore Excluder stent-graft: 1-year results from the European C3 module of the Global Registry for Endovascular Aortic Treatment (GREAT). Eur J Vasc Endovasc Surg: the official journal of the European Society for Vascular Surgery. 2014;48(2):131-137.[143]	400	R1MN	Excluder C3	2010-2012
Verzini F, Romano L, Parlani G, et al. Fourteen-year outcomes of abdominal aortic endovascular repair with the Zenith stent graft. J Vasc Surg. 2017;65(2):318-329.[144]	610	R1SN	Zenith	2000-2011
Volpe P, Massara M, Alberti A, et al. Preliminary results of Aorfix stent graft to treat infrarenal abdominal aortic aneurysms with severe proximal aortic neck angulation. Ann Vasc Surg. 2017;45:193-198.[145]	26	R1MN	Aorfix	2012-2014
Yang G, Zhang M, Muzepper M, et al. Comparison of Physician-Modified Fenestrated/Branched Stent-Grafts and Hybrid Visceral Debranching Plus Stent-Graft Placement for Complex Thoracoabdominal Aortic Aneurysm Repair. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2020;27(5):749-756.[146]	88	R2MN	Zenith Ankura Viabahn Omnilink	2016-2019
Yao C, Ning J, Li Z, et al. Parallel Covered Stents Technique in the Treatment of Abdominal Aortic Diseases. Journal of vascular and interventional radiology : JVIR. 2020;31(5):771-777.[147]	16	R1SN	Excluder Endurant	2016-2018
Zavatta M, Squizzato F, Balestriero G, et al. EARLY AND MID-TERM OUTCOMES OF EVAR WITH AN ULTRA LOW-PROFILE ENDOGRAFT FROM THE TRIVENETO INCRAFT REGISTRY. Journal of vascular surgery. 2020.[148]	209	R1MN	Incraft	2014-2019

Table 24. Publications Identified in the Alternative Endograft Literature Search

Publication	Patients	Study Design*	Device	Treatment Period
Zettervall SL, Deery SE, Soden PA, et al. Editor's Choice - Renal complications after EVAR with suprarenal versus infrarenal fixation among all users and routine users. Eur J Vasc Endovasc Surg: the official journal of the European Society for Vascular Surgery. 2017;54(3):287-293.[149]	2,574	R2MN	AneuRx Endurant Excluder Talent Zenith	2003-2014
Total patient population	**74,455 (Treated with Alternate Endografts)**			

**Study design:*
1st character — P, Prospective; R, Retrospective
2nd character — 1, One-arm study; 2, Two-arm study; 3, Three-arm study
3rd character — S, Single-center; M, Multicenter
4th character — R, Randomized; N, Non-Randomized
† An earlier publication, Troisi et al. 2017, on the same study was evaluated to obtain some of the safety and performance endpoints extracted.[136]

11. APPENDIX D: COMPLAINT DATA TRENDING

11.1. GRAPHICAL DATA FORMAT

In December 2016, in preparation for the 2016 FSN on Type III Endoleaks, Endologix developed a cumulative rate approach for presenting Type III Endoleak trending data, similar to how Kaplan Meier (KM) curves are constructed for clinical study data sets, which revolve around the concept of censoring. Like KM curves, the Type III Endoleak trending graphs are representative of cumulative rates over time. Just as KM curves will always decrease over time (showing fewer patients being free from a certain adverse event type), Endologix's Type III Endoleak trending graphs will always increase over time (which also shows fewer patients being free from this adverse event type). The trending lines will be completely flat if there are zero events from one year to the next. Even so, the trending line can never return to baseline as the data are cumulative. This presentation is clinically relevant, as one can establish what the expected Type III Endoleak risk is for a given patient upon implant through "x" years of follow-up. Further, one can understand the year-to-year adverse event rate by reviewing the delta in between the timepoints.

11.2. 3-LINE GRAPHS (AFX STRATA, AFX DURAPLY, AND AFX2) VS. 2-LINE GRAPHS (PRE- AND POST-FINAL PRODUCT UPDATES)

As part of continuous improvement efforts, Endologix continued to evaluate options to improve upon data analysis methodology and its representation to ensure that regulatory agencies and physicians would be able to evaluate the effectiveness of the product updates, as well as evaluate the performance of the currently available AFX2 System. In early 2019, it was recognized that viewing the data by material type only did not provide the full picture of all the product updates. When separating the data by each product update, there has been a positive impact on the occurrence of Type III Endoleaks after each product update – not just the change to Duraply and AFX2. Additionally, stent grafts manufactured with the Strata and Duraply ePTFE material overlapped on the market for a significant period of time. Due to this overlap, there were instances where a Duraply bifurcated device was implanted with a Strata extension and vice versa. Utilizing the original 3-line format as shown in the figures below, the AFX Duraply data was being artificially influenced by the existence of Strata extension grafts and other pre-product update Duraply product. Similarly, the AFX2 data line was being artificially influenced by the existence of data from pre-product update Duraply extensions.

Therefore, to provide meaningful trending data as it relates to the effectiveness of the product updates, Endologix developed a 2-line graphic that could appropriately assess the impact of all product updates on the product family.

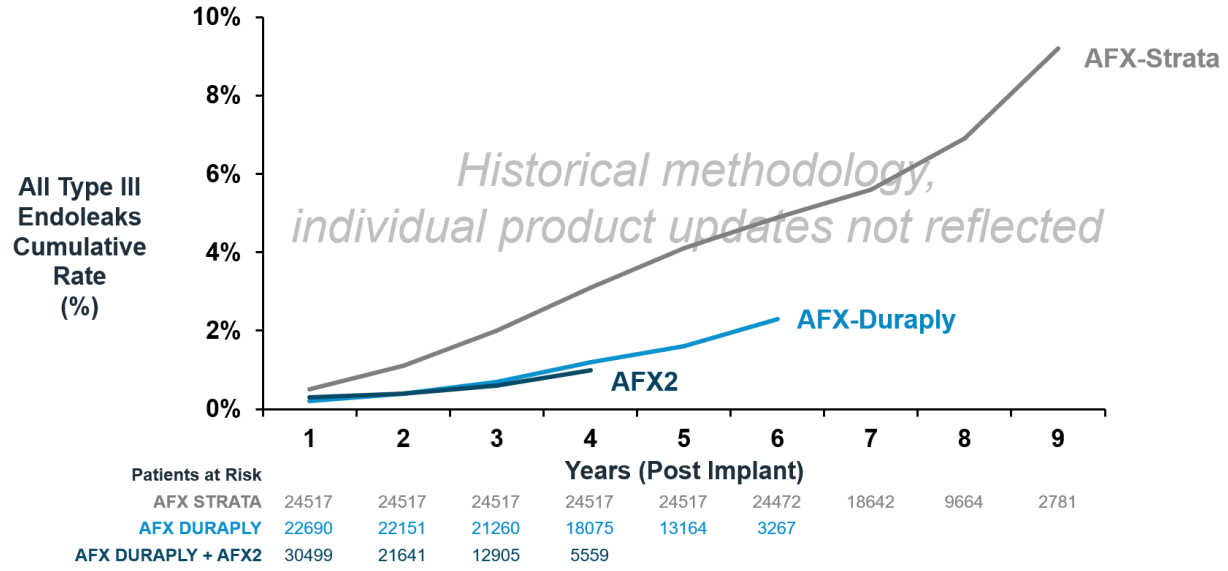


Figure 45. Type III Endoleak (Combined) Complaint Trends, Bifurcated Device Type (February 28, 2021) ±

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

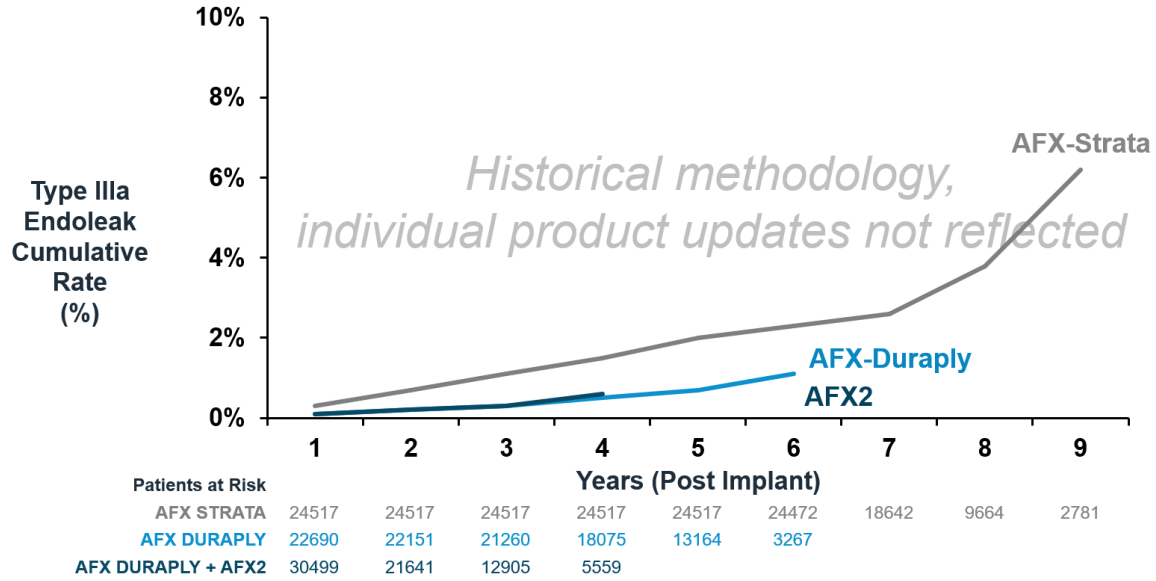


Figure 46. Type IIIa Endoleak Complaint Trends, Bifurcated Device Type (February 28, 2021) ±

± 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 events reported on the Duraply Bifurcated device. Additionally, there were twenty-five (25) events reported on devices with an unknown material type.
** 5-year data for grafts implanted with an AFX2 Bifurcated device have been excluded due to a low denominator at this time point (< five (5) devices). Note: Zero (0) events have been reported at this timepoint.*

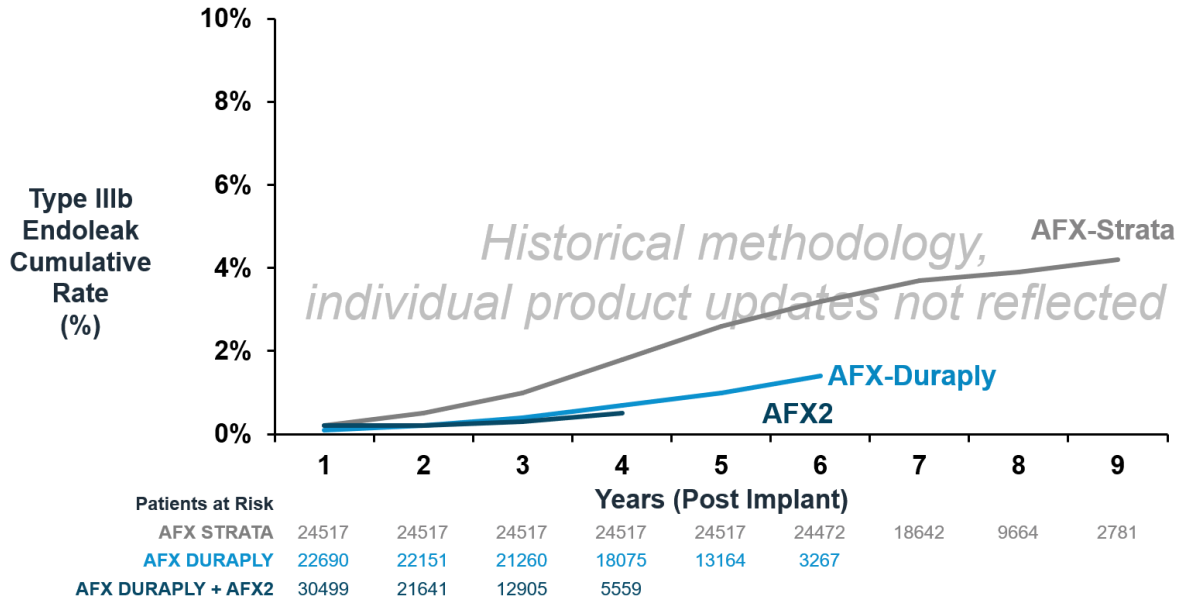


Figure 47. Type IIIb Endoleak Complaint Trends, Bifurcated Device Type (February 28, 2021) [±]

[±] 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 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.
** 5-year data for grafts implanted with an AFX2 Bifurcated device have been excluded due to a low denominator at this time point (< five (5) devices). Note: Zero (0) events have been reported at this timepoint.*

11.3. CLINICAL SEQUELAE OF TYPE III ENDOLEAKS: WORLDWIDE RATES

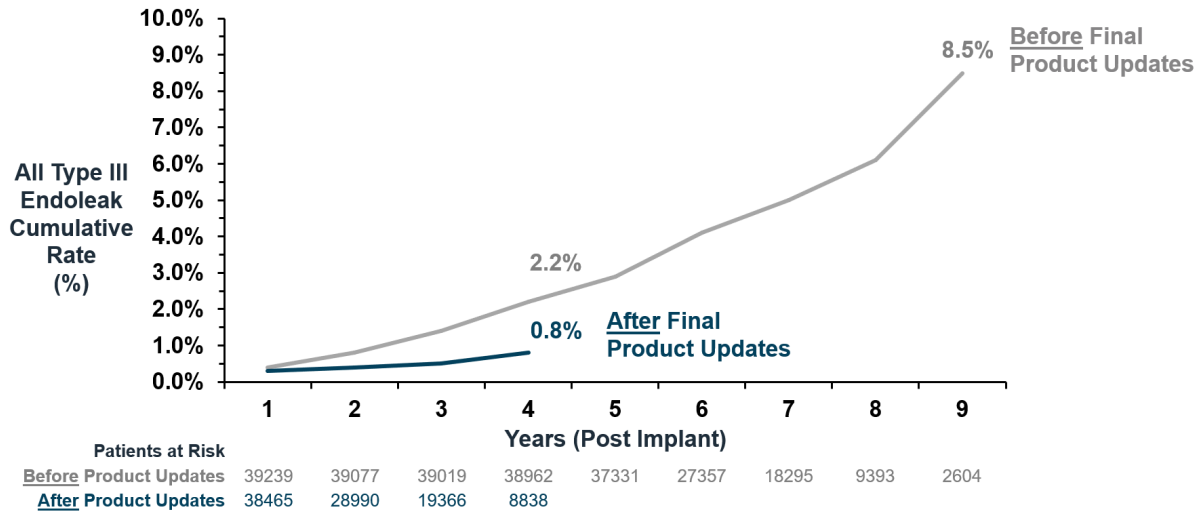
Table 25: Clinical Sequelae of Type III Endoleaks for AFX Strata Patients

AFX Strata – Complications reported with Type III Endoleaks Worldwide	
Total	24511
Type III (% of Total)	1,404 (5.73%)
Aneurysm Enlargement (% of Total)	380 (1.55%)
Rupture (% of Total)	161 (0.66%)
Conversions (% of Total)	140 (0.57%)
Death (% of Total)	66 (0.27%)
Secondary Interventions (% of Total)	260 (1.06%)

Table 26: Clinical Sequelae of Type III Endoleaks for AFX Duraply/AFX2 Patients

AFX Duraply and AFX2 – Complications reported with Type III Endoleaks Worldwide		
	Implants BEFORE final product updates	Implants AFTER final product updates
Total	14,724	45,105
Type III (% of Total)	272 (1.85%)	228 (0.51%)
Aneurysm Enlargement (% of Total)	94 (0.64%)	50 (0.11%)
Rupture (% of Total)	45 (0.31%)	29 (0.06%)
Conversions (% of Total)	26 (0.18%)	18 (0.04%)
Death (% of Total)	17 (0.21%)	16 (0.04%)
Secondary Interventions (% of Total)	38 (0.26%)	3 (0.01%)

11.4. TYPE III CUMULATIVE RATES PRE- AND POST-PRODUCT UPDATES OUT TO 9 YEARS



11.5. BENCHMARKED COMPLAINT RATE

Endologix is aware that complaints are under reported and therefore cannot equate to clinical event rates. To put this complaint data set into context, Endologix has explored a means of benchmarking the Type III Endoleak complaint rate against clinical events to determine the level of reliability in the complaint rate for the post-product update population. Specifically, this analysis included a comparison of clinical events (via the LEOPARD RCT with a data cut of February 28, 2021) to reported events (via the complaint database with a data cut of February 28, 2021). The analysis shown in Table 27 found that the clinical event rate to reported event rate ratio for the Duraply ePTFE graft (which makes up both the pre- and post-product update population) was 1.73, indicating a minimal degree of under-reporting in the complaint system (< 2x) and a high degree of reliability in the aforementioned complaint rate for Endologix's current ePTFE graft.

Table 27. Type III Endoleak Clinical Event to Reported Event Ratio

	Reported Events* ***(Point Prevalence)***	**Clinical Events** ***(LEOPARD Prevalence)***	**Clinical Event to Reported Event Ratio**
Type III Endoleak	0.74% (413/56,060)	1.28% (3/235)	1.73

**Events are for AFX/AFX2 Duraply devices. Complaint data rate based on sales and complaint data for the Duraply bifurcated grafts from March 23, 2015 (first implant in LEOPARD RCT) through February 28, 2021. Point prevalence data presented are reported Type III Endoleak complaints divided by sales (bifurcated units sold) during the reporting period. Endoleak Type III numerator derived by adding Type IIIa and Type IIIb values and subtracting duplicates.*

11.6. COMPARISON TO OTHER EVAR DEVICES

As depicted in Figure 25 above, the annual Type III Endoleak rate averages to 0.2% between 2- and 4-years post-implantation for the currently available product (AFX2). This rate is trending below the rate for the devices implanted before the final product update in 2016. The data depicted in Figure 25 continues to support the effectiveness of the updates as the current rates are also trending below those rates reported in the literature for non-AFX devices where comparison is available (reference Table 28 for a summary of the literature review) although it is acknowledged that complaint rates are not equivalent to complication rates in clinical practice or clinical trials. The Endoleak rates listed represent a point in time, not cumulative rates. As peri-operative rates are typically analyzed separately than other follow-up timepoints, this means that the cumulative Type III Endoleak rate for non-AFX devices is approximately 1.2% at 24-months (0.6% at 1 year + 0.6% at 2 years), and 1.6% at 48 months (0.6% at 1 year + 0.6% at 2 years + 0.0% at 3 years and 0.4% at 4 years).

The current post-product update population (which includes lifetime data for the AFX2 System), has a reported event rate of 0.8% at 4 years, which is half the rate reported in the literature for non-AFX devices. This conclusion serves as an internal guide for trending, and it not meant as a robust clinical comparison of endoleak rates.

Table 28. Published Clinical Outcomes for Type III Endoleaks*

Endpoint	**Published Type III Endoleak Rates Non-AFX Devices± (Non-Cumulative)**	**Estimated Cumulative Rates**
Type III Endoleak (30 d)	1.1% (0.7%-1.6%) N=4,137	1.1%
Type III Endoleak (12 m)	0.6% (0.4%-0.9%) N=4,548	0.6%
Type III Endoleak (24 m)	0.6% (0.3%-1.05%) N=2,217	1.2%
Type III Endoleak (36 m)	0.0% (0.0% - 0.9%) N=344	1.2%
Type III Endoleak (48 m)	0.4% (0.0%-2.0%) N=234	1.6%
Type III Endoleak (60 m)	1.1% (0.1%-8.8%) N=322	2.7%

**Literature Search conducted through February 28, 2021 (Appendix C: Literature Search) and includes 108 peer-reviewed publications that reported out on performance outcomes for non-AFX/Powerlink endografts at and beyond 30-days that were published within the last five years.*

±The Type III Endoleak rates reported are representative of a point in time and do not represent cumulative rates.

12. APPENDIX E: VQI LIMITATIONS

12.1. INTERPRETATION OF VQI REGISTRY DATA

The VQI Registry is an independent data source which can compare peri-operative and 1-year follow-up outcomes amongst endografts in a contemporary, real-world EVAR patient population. Through periodic reporting, datasets from the VQI Registry can be used to help monitor the performance of a specific medical device to the aggregate data of all other similar devices. In Endologix's case, for instance, the VQI Registry allows a relative risk comparison between the AFX2 Bifurcated device compared to "All Other" EVAR devices. While these data are beneficial, it is important to understand the limitations of this dataset and how the data can be best utilized and interpreted despite these limitations.

12.1.1. LIMITATION #1: STATISTICAL VS. CLINICAL SIGNIFICANCE

It is important to understand the limitations of this dataset and how the data can be best utilized and interpreted despite these limitations. One limitation to consider when viewing the VQI Registry data is that the data presented only depicts the statistical significance of relative risk and not the clinical significance of an outcome. To detail this further, an example has been provided in Table 29 below which analyzes a singular procedural complication for EVAR.

Table 29. Risk Analysis for Type Ia Endoleaks, VQI Registry

Risk of Type Ia Endoleak at Index Completion			Absolute Risk Reduction (ARR) |All Other Devices – AFX2|	Relative Risk Reduction (RRR) |ARR/All Other Devices|	Number Needed to Treat (NNT) |1/ARR|
All Other Devices	AFX2 Bifurcated	p-value*			
2.8 % (989/34976)	0.7 % (7/1026)	< 0.001	2.1%	75.0%	47.6

**A p-value is ≤0.05 is considered statistically significant, aligning with a 95% confidence level.*

The risk of a patient having a Type Ia Endoleak at index completion is 0.7% for AFX2 and 2.8% for All Other Devices ($p < 0.001$). Based on the data presented, the following can be concluded by comparing the AFX2 results to the All Other Devices "control":

- The Absolute Risk Reduction (ARR), also referred to as the risk difference, is 2.1%. This means that, if 100 patients were treated with AFX2 rather than other EVAR devices, 2 patients would be prevented from developing a Type Ia Endoleak at index completion.
- The Relative Risk Reduction (RRR) is 75.0%. This means that implanting a patient with AFX2 would reduce the risk of developing a Type Ia Endoleak at index completion by 75.0% compared to All Other Devices.

Although the data presented above depicts a statistically significant improvement in Type Ia Endoleak complications at index for AFX2 compared to All Other Devices, this statistical significance is limited to the relative risk of this outcome. As with any study results, it is also essential to understand whether the observed performance of a device is clinically significant. For instance, there may be a failure mode in which there exists statistical significance; however, both rates remain below 1%. This might imply that there may be little clinical significance to any observed statistical difference. The opposite can also be true. Using the dataset presented above, one can see that there is not only an observed statistical difference, but there is likely a clinically significant difference in outcomes. Specifically, the VQI Registry reports 0.7% of AFX2 cases resulted in a Type Ia Endoleak at index completion. A rate of <1% is likely to be considered an acceptable rate to physicians for this complication when weighing the overall benefit-risk determination of utilizing this stent graft. In contrast, the VQI Registry reports 2.8% of All Other Device cases resulted in a Type Ia Endoleak at index completion. Not only is this result statistically significant, but a nearly 3% rate for this complication may be considered clinically significant by most physicians as it would lead to reintervention or explantation in order to correct.

When interpreting VQI data, both the clinical and statistical significance must be considered. In general, Endologix considers that a difference between graft performance below 2% is unlikely to be clinically significant in this data set given number of parameters assessed.

Note: M2S performed multiple statistical tests across the numerous baseline and outcome variables available. Because of this, it is possible some tests reached the statistically significant threshold of 0.05 simply due to chance. This creates the possibility of false positive results, so any statistical differences must be interpreted with caution.

12.1.2. LIMITATION #2: LACK OF LONG-TERM FOLLOW-UP

The second limitation to consider when viewing the VQI Registry data is that the data presented is limited to peri-operative and 1-year follow-up outcomes. While VQI does not uniformly currently collect data past 1-year of follow-up, it is important to realize that this does not negate the applicability and usefulness of this dataset.

13. APPENDIX F: AFX-IN-AFX RELINING EXTENDED COMPLAINTS CLINICAL STUDY DESIGN AND RESULTS

13.1. STUDY DESIGN

This was an observational, multicenter study of patients initially receiving an AFX endograft, who underwent relining for a Type III Endoleak using an AFX Duraply or an AFX2 stent graft and were reported to Endologix as a complaint. The study was retrospective and assessed the clinical results for AFX-in-AFX procedures that initially presented with a Type III Endoleak. The protocol defined the methods used to open previously closed complaint investigations to request updated clinical outcomes for the reported AFX-in-AFX procedures. The patient population was derived from the Endologix Complaint System and consists of patients with identified Type III Endoleaks who underwent a relining procedure using the AFX with Duraply or the AFX2 stent graft. Given the source of the initial dataset (the Endologix complaints database), and the practical aspect of obtaining follow-up information, this study was conducted as a separate investigation to augment Endologix's initial complaint investigations.

The institutions considered for this study were identified directly from the complaint database. For the study population, 221 institutions were identified with 360 patients that underwent a relining procedure when reviewing the complaint system through December 2020. Thirty-two (32) institutions had two or more cases of relining; the remainder had one patient per site. To maximize data collection, the sites with two or more patients were included. As a result, a total number of 139 patients were identified at the beginning of this study, with a range of dates from August 23, 2011 through October 1, 2019.

The implanting physicians identified were contacted via email or via telephone to collect the data required. Twenty (20) sites responded and provided the data for a total of 80 patients. Of these, three patients were removed from scope as they only had a partial reline procedure. This totals 77 subjects.

As requested by FDA, these data were provided to FDA on September 22, 2021.

13.2. STUDY RESULTS

13.2.1. SUBJECT FOLLOW-UP

Of the 77 subjects included in the analysis, the median follow-up from the index procedure was 5.9 years with a maximum of 9.5 years, while the median follow-up from the relining procedure was 1.7 years with a maximum of 6.6 years.

13.2.2. BASELINE CHARACTERISTICS

13.2.2.1. REASONS FOR AND TYPE OF RELINING

Table 30 below shows the reasons for relining, where Type IIIb Endoleak is prevalent. Not all patients underwent a complete relining, as shown in Table 31. Seventy-six (76) patients were treated with a complete stent relining, three patients were treated with only extensions, either aortic or iliac, and one (1) patient was converted to open repair as a consequence of a failed relining. The three patients that were treated with only extensions have not been included in the analysis of the endpoints.

Table 30. Reasons for Relining, Extended Complaints Investigation

Reason for relining	Count
Type Ia Endoleak	0
Type II Endoleak	1
Type IIIa Endoleak	13
Type IIIb Endoleak	62
Type Unknown Endoleak	1
Arterial Thrombus distal to stent	1

Table 31. Intervention Type, Extended Complaints Investigation

Intervention Type	Count
Complete stent relining	76
Conversion to Open Repair*	1
Iliac Extension	1 (excluded)
Aortic Extension	2 (excluded)

**This is a failed endograft relining procedure that transitioned to open repair.*

13.2.2.2. BASELINE VASCULAR CHARACTERISTICS

Figure 48 below shows the distribution of sac diameter sizes in the index procedure: the patients had a mean aneurysm diameter of 59mm with a median of 56mm (maximum 91mm and minimum 40mm).

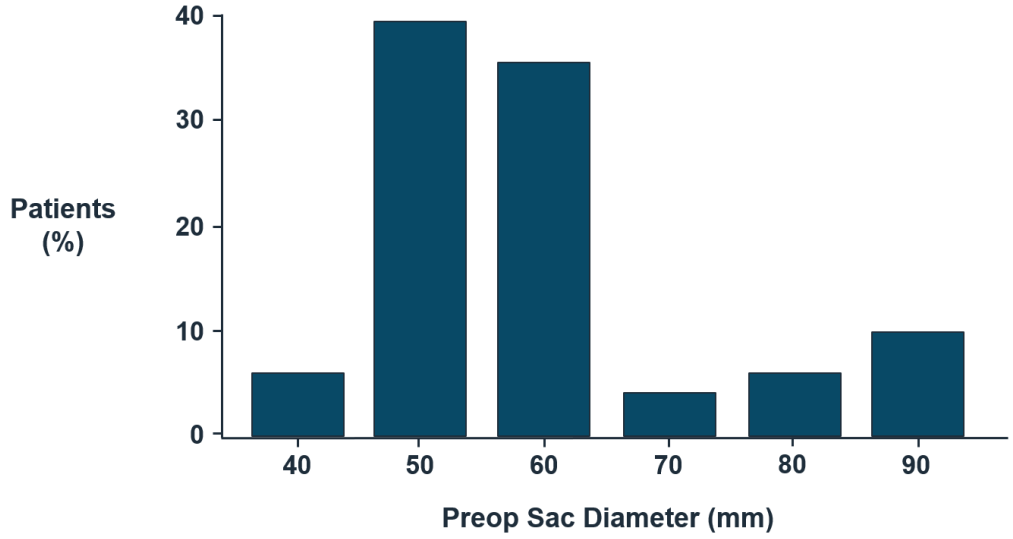


Figure 48. Distribution Aneurysm Sac Diameter, Extended Complaints Investigation

13.2.3. SAFETY OUTCOMES

The peri-operative death rate following the relining procedure was 3.9%.

13.2.4. PERFORMANCE OUTCOMES

13.2.4.1. TECHNICAL SUCCESS

Technical success was defined as the ability of the secondary AFX device to be implanted without any major procedural issue resulting in patient harm. This would include peri-operative mortality, conversion

to open repair, conversion to an aorto-uni-iliac endograft or failure to resolve the Type III Endoleak within the first 30 days of relining.

Among the perioperative deaths it is currently unknown how many were within the hospital, therefore at this point we cannot confirm that these are additional technical failures. Given that, the technical success rate is estimated to be 98.7% as a consequence of the only conversion that has been reported.

13.2.4.2. ALL-CAUSE MORTALITY

Figure 49 details the Kaplan-Meier estimates of freedom from ACM for subjects in the Extended Complaints Investigation. As shown in the data below, the performance of the AFX-in-AFX relining procedure is supported with 70.7% of subjects being free from ACM at 3-years. Note: After three years, there are insufficient data to give accurate rates.

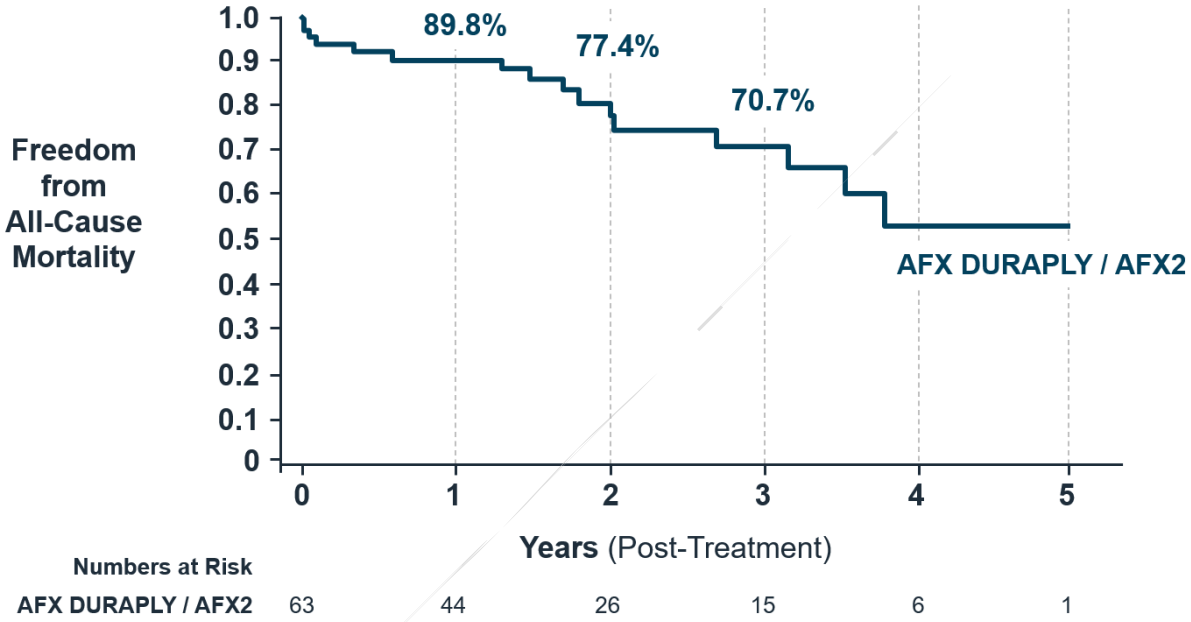


Figure 49. Freedom from All-Cause Mortality, Extended Complaints Investigation

13.2.4.3. ANEURYSM-RELATED MORTALITY (ARM)

Figure 50 details the Kaplan-Meier estimates of freedom from aneurysm-related mortality (ARM) for subjects in the Extended Complaints Investigation. As shown in the data below, the performance of the AFX-in-AFX relining procedure is supported with 95.2% of subjects being free from ARM at 3-years. Note: After three years, there are insufficient data to give accurate rates.

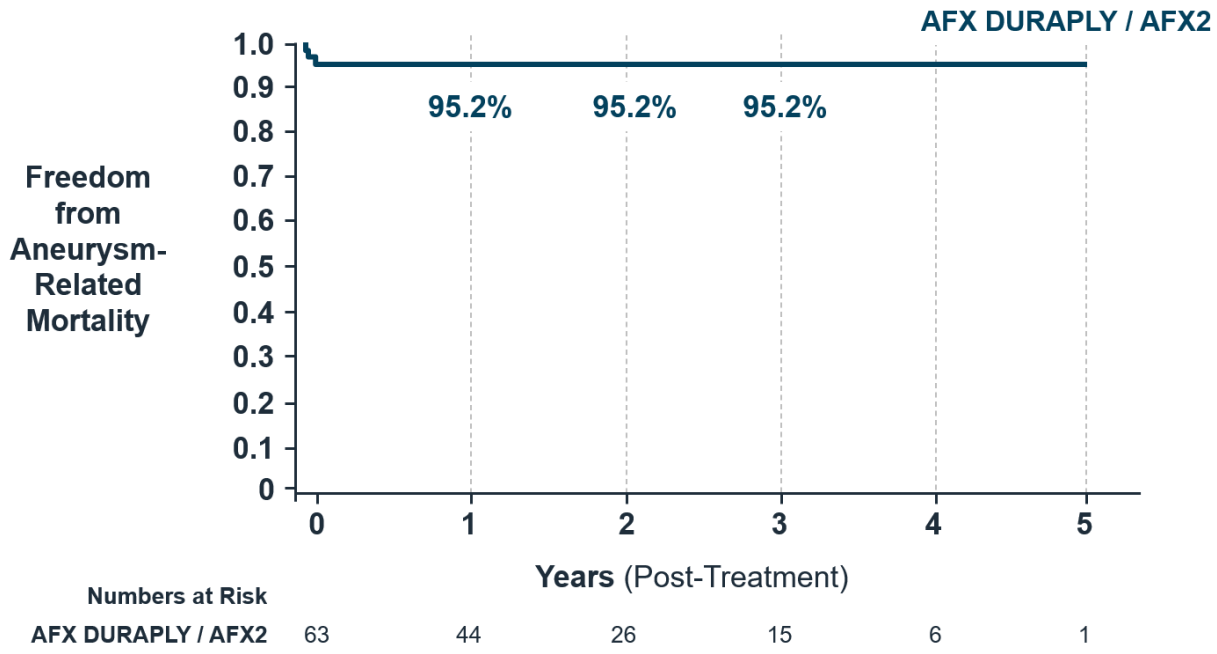


Figure 50. Freedom from Aneurysm-Related Mortality (ARM), Extended Complaints Investigation

13.2.4.4. CONVERSION TO OPEN SURGICAL REPAIR

Figure 51 details the Kaplan-Meier estimates of freedom from conversion for subjects in the Extended Complaints Investigation. As shown in the data below, the performance of the AFX-in-AFX relining procedure is supported with 98.4% of subjects being free from conversion at two-years. Note: After two years, there are insufficient data to give accurate rates.

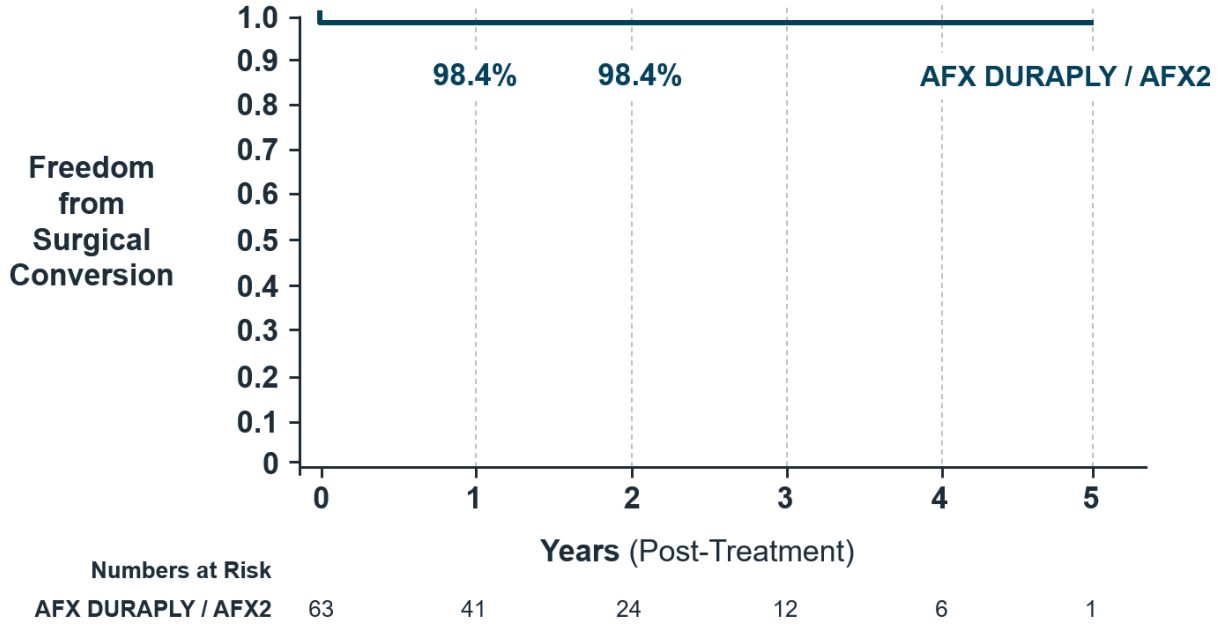


Figure 51. Freedom from Surgical Conversion, Extended Complaints Investigation

13.2.4.5. ANEURYSM RUPTURE

Figure 52 details the Kaplan-Meier estimates of freedom from aneurysm rupture for subjects in the Extended Complaints Investigation. As shown in the data below, the performance of the AFX-in-AFX relining procedure is supported with 97.8% of subjects being free from aneurysm rupture at three-years. Note: After three years, there are insufficient data to give accurate rates.

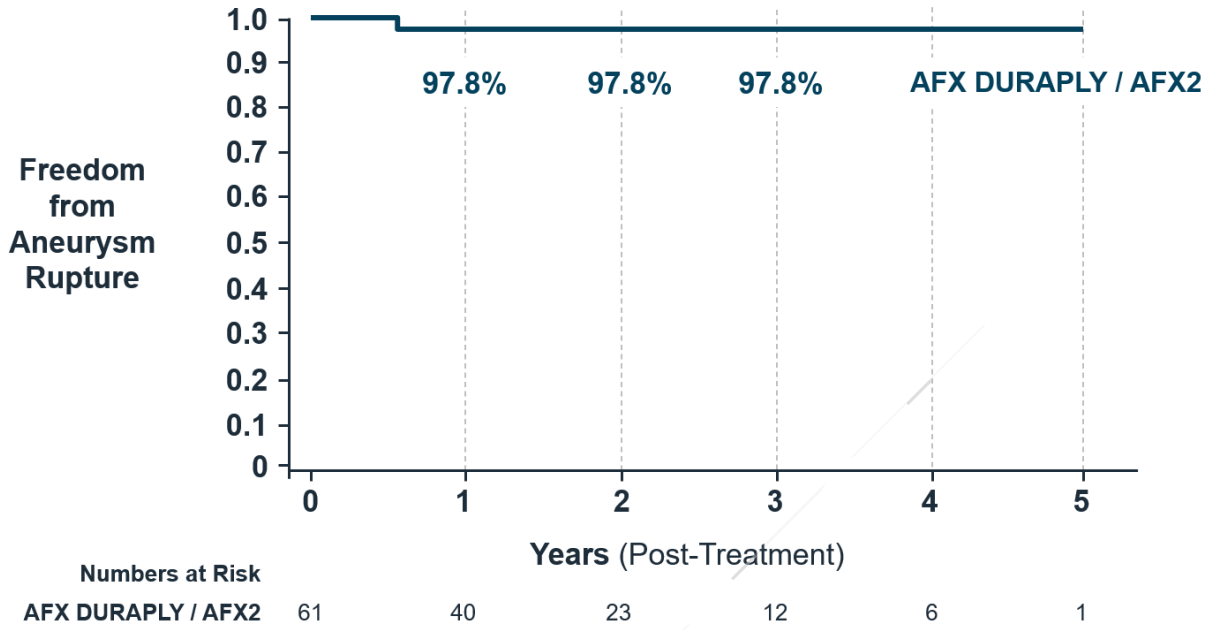


Figure 52. Freedom from Aneurysm Rupture, Extended Complaints Investigation

13.2.4.6. TYPE I ENDOLEAK

Figure 53 details the Kaplan-Meier estimates of freedom from Type I Endoleak for subjects in the Extended Complaints Investigation. As shown in the data below, the performance of the AFX-in-AFX relining procedure is supported with 100% of subjects being free from Type I Endoleak at three-years. Note: After three years, there are insufficient data to give accurate rates.

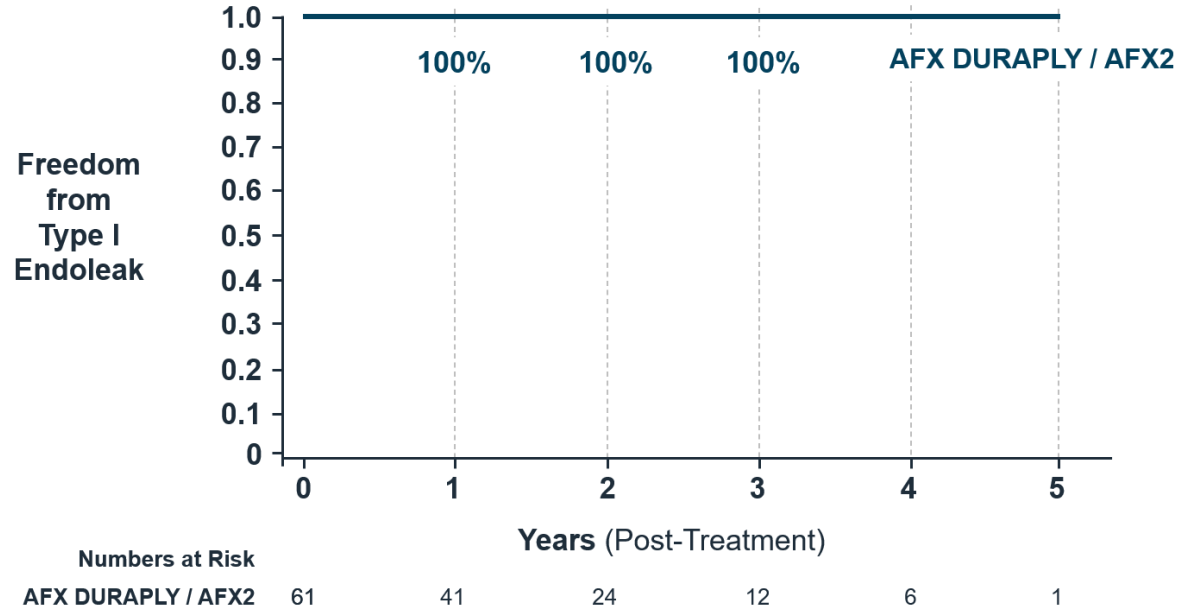


Figure 53. Freedom from Type I Endoleak, Extended Complaints Investigation

13.2.4.7. TYPE III ENDOLEAK

Figure 54 details the Kaplan-Meier estimates of freedom from Type III Endoleak for subjects in the Extended Complaints Investigation. As shown in the data below, the performance of the AFX-in-AFX relining procedure is supported with 100% of subjects being free from Type III Endoleak at three-years. Note: After three years, there are insufficient data to give accurate rates.

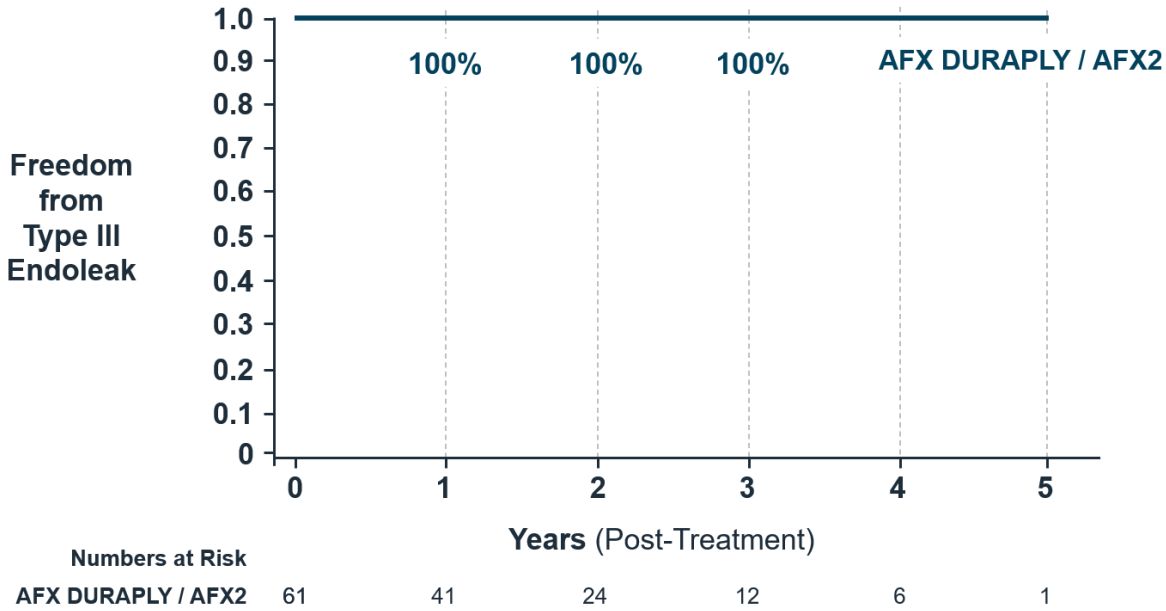


Figure 54. Freedom from Type III Endoleak, Extended Complaints Investigation

13.2.4.8. DEVICE-RELATED SECONDARY INTERVENTIONS

Table 32 shows freedom from device-related secondary interventions for subjects in the Extended Complaints Investigation. As shown in the data below, the performance of the AFX-in-AFX relining procedure is supported with 100% of subjects being free from device-related secondary interventions at two-years. Note: After two years, there are insufficient data to give accurate rates.

Table 32: Freedom from Device-Related Secondary Interventions for Subjects in the Extended Complaints Investigation

	12 months	24 months	36 months
All	100%	100%	(insufficient n)
Stenosis & Thrombosis	100%	100%	
Type I, III Endoleak	100%	100%	

13.3. DISCUSSIONS AND CONCLUSIONS

This is an observational, multicenter, retrospective study of patients with an initial AFX device who underwent relining using an AFX with Duraply or an AFX2 stent graft and reported to Endologix through the complaint system. The main objective was to assess the clinical results for relining following a Type III Endoleak and to determine if more information on clinical outcomes was available. The study identified and contacted sites that reported an AFX-in-AFX relining case (via Endologix's complaint database) and collect available data, including procedural/ long-term follow-up details, whenever available, and reported descriptively.

The analysis was based on the clinical data collected for patients that were treated with a relining with AFX Duraply or AFX2 between 2014 and 2020 from complaint reports between 2011 and 2019.

While this study is limited, the only MAEs reported are deaths with a freedom from ACM of 70.7% at three years and only three deaths were aneurysm-related. One patient underwent an open conversion, this conversion is actually a failed relining that has been immediately converted to open repair and only one (1) patient experienced a rupture 213 days after the relining from this population.

For endoleaks, there were no Type I Endoleaks, Type III Endoleaks, nor any device-related secondary interventions reported after the relining procedure.

These clinical results, along with other types of applicable device data, is suitable for describing the clinical outcomes in the circumstances when an AFX2 device is used in the relining of a previously implanted device in the AFX System family.

REFERENCES

[1] Resnic FS, Matheny ME. Medical Devices in the Real World. N Engl J Med. 2018;378(7):595-7.

[2] Columbo JA, Martinez-Camblor P, O'Malley AJ, Suckow BD, Hoel AW, Stone DH, et al. Long-term Reintervention After Endovascular Abdominal Aortic Aneurysm Repair. Ann Surg. 2021;274(1):179-85

[3] Bradbury AW, Davies AH, Dhesi JK, Hammond CJ, Hampshire M, Jellett K, et al. Recommendations on the Use of Open Surgical and Endovascular Aneurysm Repair for the Management of Unruptured Abdominal Aortic Aneurysm from the Guideline Development Committee Appointed by the UK National Institute for Health and Care Excellence. Eur J Vasc Endovasc Surg. 2021;61(6):877-80.

[4] Machin M, Ulug P, Pandirajan K, Bown MJ, Powell JT. Towards a Core Outcome Set for Abdominal Aortic Aneurysm: Systematic Review of Outcomes Reported Following Intact and Ruptured Abdominal Aortic Aneurysm Repair. Eur J Vasc Endovasc Surg. 2021.

[5] Starnes BW. Multicenter Randomized Clinical Trial of Four Different Devices for Endovascular Aneurysm Repair: Design of the LEOPARD Trial. Journal of Vascular Surgery. 2015;61(61).

[6] Chang RW, Rothenberg KA, Harris JE, Gologorsky RC, Hsu JH, Rehring TF, et al. Midterm outcomes for 605 patients receiving Endologix AFX or AFX2 Endovascular AAA Systems in an integrated healthcare system. J Vasc Surg. 2021;73(3):856-66

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

[8] 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

[9] 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

[10] 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

[11] Jackson BM, Carpenter JP. Devices used for endovascular aneurysm repair: past, present, and future. Semin Intervent Radiol. 2009;26(1):39-43.

[12] White GH, Yu W, May J, Chaufour X, Stephen MS. Endoleak as a complication of endoluminal grafting of abdominal aortic aneurysms: classification, incidence, diagnosis, and management. J Endovasc Surg. 1997;4(2):152-68.

[13] Buth J, Harris PL, Van Marrewijk C, Fransen G. Endoleaks during follow-up after endovascular repair of abdominal aortic aneurysm. Are they all dangerous? J Cardiovasc Surg (Torino). 2003;44(4):559-66.

[14] Stoecker JB, Glaser JD. Review of Type III Endoleaks. Semin Intervent Radiol. 2020;37(4):371-6.

[15] Antoniou GA, Georgiadis GS, Antoniou SA, Kuhan G, Murray D. A meta-analysis of outcomes of endovascular abdominal aortic aneurysm repair in patients with hostile and friendly neck anatomy. Journal of vascular surgery 2013;57:527-38.

[16] Bockler D, Holden A, Krievins D, et al. Extended use of endovascular aneurysm sealing for ruptured abdominal aortic aneurysms. Seminars in vascular surgery 2016;29:106-13.

[17] Prinssen M, Verhoeven EL, Buth J, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. NEnglJMed 2004;351:1607-18.

[18] Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet 2004;364:843-8.

[19] Becquemin JP, Pillet JC, Lescalie F, et al. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. J Vasc Surg 2011;53:1167-73.

[20] Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1863-71.

[21] Lederle FA, Freischlag JA, Kyriakides TC, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med 2012;367:1988-97.

[22] De Bruin JL, Baas AF, Buth J, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1881-9.

[23] Schermerhorn ML, Giles KA, Sachs T, et al. Defining perioperative mortality after open and endovascular aortic aneurysm repair in the US Medicare population. J Am Coll Surg 2011;212:349-55.

[24] Patel R, Sweeting MJ, Powell JT, Greenhalgh RM. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet. 2016;388(10058):2366-74.

[25] Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, et al. Meta-analysis of individual-patient data from EVAR-1, DREAM, OVER and ACE trials comparing outcomes of endovascular or open repair for abdominal aortic aneurysm over 5 years. Br J Surg. 2017;104(3):166-78.

[26] 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(4):328-38.

[27] EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet. 2005 Jun 25-Jul 1;365(9478):2179-86. doi: 10.1016/S0140-6736(05)66627-5. PMID: 15978925.

[28] National Institute for Health and Care Excellence. Abdominal Aortic Aneurysm: Diagnosis and Management. Accessed March 19, 2020. Available at: https://www.nice.org.uk/guidance/ng156.

[29] Dua A, Kuy S, Lee CJ, Upchurch GR, Jr, Desai SS. "Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010." J Vasc Surg 59 (2014): 1512-7.

[30] Kent F, Ambler GK, Bosanquet DC, Twine CP. The Safety of Device Registries for Endovascular Abdominal Aortic Aneurysm Repair: Systematic Review and Meta-regression. Eur J Vasc Endovasc Surg. 2018;55(2):177-83.

[31] van Zeggeren L, Bastos Gonçalves F, van Herwaarden JA, Zandvoort HJ, Werson DA, Vos JA, et al. Incidence and treatment results of Endurant endograft occlusion. J Vasc Surg. 2013;57(5):1246-54; discussion 54.

[32] Jordan WD, Jr., Moore WM, Jr., Melton JG, Brown OW, Carpenter JP. Secure fixation following EVAR with the Powerlink XL System in wide aortic necks: results of a prospective, multicenter trial. JVascSurg 2009;50:979-86.

[33] Avgerinos ED, Dalainas I, Kakisis J, Moulakakis K, Giannakopoulos T, Liapis CD. Endograft accommodation on the aortic bifurcation: an overview of anatomical fixation and implications for long-term stent-graft stability. J Endovasc Ther 2011;18:462-70.

[34] Coppi G, Silingardi R, Tasselli S, Gennai S, Saitta G, Veraldi GF. Endovascular treatment of abdominal aortic aneurysms with the Powerlink Endograft System: influence of placement on the bifurcation and use of a proximal extension on early and late outcomes. J Vasc Surg 2008;48:795-801.

[35] Welborn MB, 3rd, McDaniel HB, Johnson RC, et al. Clinical outcome of an extended proximal seal zone with the AFX endovascular aortic aneurysm system. J Vasc Surg 2014.

[36] DeRubertis BG. Use of an aortic bifurcation-sparing endograft facilitates hypogastric preservation during aortoiliac aneurysm repair. Vascular 2012;20:107-12.

[37] Tadros RO, Faries PL, Ellozy SH, et al. The impact of stent graft evolution on the results of endovascular abdominal aortic aneurysm repair. J Vasc Surg 2014;59:1518-27.

[38] Mezes P, Sallam M, Diamantopoulos A, Taylor P, Ahmed I. Zenith Cook limb Type IIIb Endoleak causing aneurysm rupture five years after EVAR. Vascular 2015;23:319-21.

[39] Giannakakis S, Galyfos G, Geropapas G, et al. Bilateral Type IIIa Endoleak and Disconnection of Both Limbs after Evar with an Endurant II Endograft. Vasc Specialist Int 2016;32:119-23.

[40] Schuurman JP, Fioole B, van den Heuvel DA, de Vries JP. Endovascular therapy for recurrent Type III Endoleak. Vasc Endovascular Surg 2010;44:123-5.

[41] White GH, May J, Waugh RC, Chaufour X, Yu W. Type III and Type IV Endoleak: toward a complete definition of blood flow in the sac after endoluminal AAA repair. J Endovasc Surg 1998;5:305-9.

[42] Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, Mastracci TM, Mell M, Murad MH, Nguyen LL, Oderich GS, Patel MS, Schermerhorn ML, Starnes BW. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018 Jan;67(1):2-77.e2. doi: 10.1016/j.jvs.2017.10.044. PMID: 29268916.

[43] Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, van Herwaarden JA, Holt PJ, van Keulen JW, Rantner B, Schlösser FJ, Setacci F, Ricco JB; European Society for Vascular Surgery. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011 Jan;41 Suppl 1:S1-S58. doi: 10.1016/j.ejvs.2010.09.011. PMID: 21215940.

[44] Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg. 2002;35(5):1048-60.

[45] Bahia SS, Holt PJ, Jackson D, Patterson BO, Hinchliffe RJ, Thompson MM, et al. Systematic Review and Meta-analysis of Long-term survival After Elective Infrarenal Abdominal Aortic Aneurysm Repair 1969-2011: 5 Year Survival Remains Poor Despite Advances in Medical Care and Treatment Strategies. Eur J Vasc Endovasc Surg. 2015;50(3):320-30.

[46] Grima MJ, Boufi M, Law M, Jackson D, Stenson K, Patterson B, et al. Editor's Choice - The Implications of Non-compliance to Endovascular Aneurysm Repair Surveillance: A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2018;55(4):492-502.

[47] Grima MJ, Karthikesalingam A, Holt PJ. Multicentre Post-EVAR Surveillance Evaluation Study (EVAR-SCREEN). Eur J Vasc Endovasc Surg. 2019;57(4):521-6.

[48] Ash J, Chandra V, Rzucidlo E, Vouyouka A, Hunter M. LUCY results show females have equivalent outcomes to males following endovascular abdominal aortic aneurysm repair despite more complex aortic morphology. J Vasc Surg 2020.

[49] Barleben A, Mathlouthi A, Mehta M, Nolte T, Valdes F, Malas MB. Long-term outcomes of the Ovation Stent Graft System investigational device exemption trial for endovascular abdominal aortic aneurysm repair. J Vasc Surg 2020.

[50] Becquemin JP, Haupert S, Issam F, et al. Five Year Patient Outcomes of Endovascular Abdominal Aortic Aneurysm Repair in the ENDURANT France Registry. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2020.

[51] Benveniste GL, Tjahjono R, Chen O, Verhagen HJ, Bockler D, Varcoe RL. Long-Term Results of 180 Consecutive Patients with Abdominal Aortic Aneurysm Treated with the Endurant Stent Graft System. Ann Vasc Surg 2020.

[52] Bergonti M, Teruzzi G, Santagostino G, et al. Third- versus Second-Generation Stent Graft for Endovascular Aneurysm Repair: A Device-Specific Analysis. Ann Vasc Surg 2017;44:67-76.

[53] Beropoulis E, Fazzini S, Austermann M, Torsello GB, Damerau S, Torsello GF. Long-term Results of Thoracic Endovascular Aortic Repair Using a Low-Profile Stent-Graft. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2020:1526602820952416.

[54] Bisdas T, Weiss K, Eisenack M, Austermann M, Torsello G, Donas KP. Durability of the Endurant stent graft in patients undergoing endovascular abdominal aortic aneurysm repair. J Vasc Surg 2014;60:1125-31.

[55] Briggs C, Babrowski T, Skelly C, Milner R. Anatomic and clinical characterization of the narrow distal aorta and implications after endovascular aneurysm repair. J Vasc Surg 2018;68:1030-8.e1.

[56] Buck DB, Soden PA, Deery SE, et al. Comparison of Endovascular stent grafts for abdominal aortic aneurysm repair in Medicare beneficiaries. Ann Vasc Surg. 2018;47:31-42.

[57] Chen PL, Hsu HL, Chen IM, et al. The Impact of Aortic Tortuosity on Delayed Type I or III Endoleak after Endovascular Aortic Repair. Ann Vasc Surg 2017;41:110-7.

[58] de Donato G, Pasqui E, Mele M, et al. The use of a low-profile stent graft with a polymer ring sealing technology combined with bare renal stent (vent technique) in patients with juxtarenal aneurysm not eligible for open surgery and fenestrated endograft. J Vasc Surg 2019.

[59] de Donato G, Setacci F, Bresadola L, et al. Aortic neck evolution after endovascular repair with TriVascular Ovation stent graft. J Vasc Surg 2016;63:8-15.

[60] de Donato G, Pasqui E, Mele M, et al. The use of a low-profile stent graft with a polymer ring sealing technology combined with bare renal stent (vent technique) in patients with juxtarenal aneurysm not eligible for open surgery and fenestrated endograft. Journal of vascular surgery 2020;71:1843-50.

[61] Deery SE, Shean KE, Pothof AB, et al. Three-year results of the Endurant stent graft system post approval study. Ann Vasc Surg. 2018;50:202-208.

[62] Dijkstra ML, van Sterkenburg SM, Lardenoye JW, Zeebregts CJ, Reijnen MM. One-Year Outcomes of Endovascular Aneurysm Repair in High-Risk Patients Using the Endurant Stent-Graft: Comparison of the ASA Classification and SVS/AAVS Medical Comorbidity Grading System for the Prediction of Mortality and Adverse Events. J Endovasc Ther 2016;23:574-82.

[63] Donas KP, Torsello G, Weiss K, Bisdas T, Eisenack M, Austermann M. Performance of the Endurant stent graft in patients with abdominal aortic aneurysms independent of their morphologic suitability for endovascular aneurysm repair based on instructions for use. J Vasc Surg 2015;62:848-54.

[64] D'Oria M, Tenorio ER, Oderich GS, et al. Outcomes after Standalone Use of Gore Excluder Iliac Branch Endoprosthesis for Endovascular Repair of Isolated Iliac Artery Aneurysms. Annals of vascular surgery 2020;67:158-70.

[65] Farber MA, Oderich GS, Timaran C, Sanchez LA, Dawson Z. Results from a prospective multicenter feasibility study of Zenith p-Branch stent graft. Journal of vascular surgery 2019.

[66] Fujimura N, Obara H, Matsubara K, et al. Comparison of early sac shrinkage with third-generation stent grafts for endovascular aneurysm repair. J Vasc Interv Radiol: JVIR. 2016;27(10):1604-1612.e1602.

[67] Fujimura, N., S. Ichihashi, K. Matsubara, S. Shibutani, H. Harada, H. Obara, K. Kichikawa and Y. Kitagawa. "Type IIIb Endoleak Is Not Extremely Rare and May Be Underdiagnosed after Endovascular Aneurysm Repair." J Vasc Interv Radiol 2019, 30: 1393-1399.e1391

[68] Fujimura N, Imazuru T, Matsumura H, et al. Two-Year Results of a Multicenter Prospective Observational Study of the Zenith Spiral-Z Limb Deployed in the External Iliac Artery During Endovascular Aneurysm Repair. Circulation journal : official journal of the Japanese Circulation Society 2020;84:1764-70.

[69] Gallitto E, Faggioli G, Pini R, et al. Endovascular repair of thoraco-abdominal aortic aneurysms by fenestrated and branched endograftsdagger. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2019;56:993-1000.

[70] Gallitto E, Gargiulo M, Freyrie A, et al. Results of standard suprarenal fixation endografts for abdominal aortic aneurysms with neck length </=10 mm in high-risk patients unfit for open repair and fenestrated endograft. J Vasc Surg 2016;64:563-70.e1.

[71] Gentsu T, Okada T, Yamaguchi M, et al. Type II Endoleak After Endovascular Aortic Aneurysm Repair Using the Endurant Stent Graft System for Abdominal Aortic Aneurysm with Occluded Inferior Mesenteric Artery. Cardiovascular and interventional radiology 2019;42:505-12.

[72] Georgiadis GS, Antoniou GA, Argyriou C, et al. Correlation of Baseline Plasma and Inguinal Connective Tissue Metalloproteinases and Their Inhibitors With Late High-Pressure Endoleak After Endovascular Aneurysm Repair: Long-term Results. J Endovasc Ther 2019;26:826-35.

[73] Georgiadis GS, Chatzigakis PK, Kouvelos G, et al. Multicenter Mid-term Results After Endovascular Aortic Aneurysm Repair with the Incraft® Device. Annals of vascular surgery 2020.

[74] Greaves NS, Moore A, Seriki D, Ghosh J. Outcomes of Endovascular Aneurysm Repair using the Ovation Stent Graft System in Adverse Anatomy. Eur J Vasc Endovasc Surg 2018;55:512-7.

[75] Gupta N, Hynes KL, Mahrouyan O, Briggs CS, Azzizadeh A. Polymer leak with the Ovation Abdominal Stent Graft System: Early recognition and treatment. Vascular 2020;28:159-64.

[76] Hammond CJ, Shah AH, Snoddon A, Patel JV, Scott DJ. Mortality and Rates of Secondary Intervention After EVAR in an Unselected Population: Influence of Simple Clinical Categories and Implications for Surveillance. Cardiovascular and interventional radiology 2016;39:815-23.

[77] Han SM, Tenorio ER, Mirza AK, Zhang L, Weiss S, Oderich GS. Low-profile Zenith Alpha Thoracic Stent Graft Modification Using Preloaded Wires for Urgent Repair of Thoracoabdominal and Pararenal Abdominal Aortic Aneurysms. Ann Vasc Surg 2020.

[78] Hernandez Mateo MM, Martinez Lopez I, Revuelta Suero S, et al. Impact of the Repositionable C3 Excluder System on the Endovascular Treatment of Abdominal Aortic Aneurysms With Unfavorable Neck Anatomy. J Endovasc Ther 2016;23:593-8.

[79] Ierardi AM, Tsetis D, Ioannou C, et al. Ultra-low profile polymer-filled stent graft for abdominal aortic aneurysm treatment: a two-year follow-up. La Radiologia medica 2015;120:542-8.

[80] Ioannou CV, Kontopodis N, Georgakarakos E, et al. Routine use of an aortic balloon to resolve possible inflow stenosis induced by the inflatable ring fixation mechanism of the Ovation endograft. La Radiologia medica 2016;121:882-9.

[81] Ioannou CV, Kontopodis N, Kehagias E, et al. Endovascular aneurysm repair with the Ovation TriVascular Stent Graft System utilizing a predominantly percutaneous approach under local anaesthesia. The British journal of radiology 2015;88:20140735.

[82] Irace L, Venosi S, Gattuso R, et al. Initial single-site experience with the Ovation abdominal stent-graft system in patients with challenging aortoiliac anatomy. J Cardiovasc Surg (Torino) 2016;57:846-52.

[83] Iwakoshi S, Nakai T, Ichihashi S, et al. Conformability and Efficacy of the Zenith Spiral Z Leg Compared with the Zenith Flex Leg in Endovascular Aortic Aneurysm Repair. Ann Vasc Surg 2019.

[84] Jetty P, Husereau D, Kansal V, Zhang T, Nagpal S. Variability in aneurysm sac regression after endovascular aneurysm repair based on a comprehensive registry of patients in Eastern Ontario. Journal of vascular surgery 2019.

[85] Kapetanios D, Karkos CD, Pliatsios I, et al. Association Between Perioperative Fibrinogen Levels and the Midterm Outcome in Patients Undergoing Elective Endovascular Repair of Abdominal Aortic Aneurysms. Ann Vasc Surg 2019;56:202-8.

[86] Katsargyris A, Mufty H, Wojs R, Utech G, Verhoeven EL. Single-centre experience with the Gore C3 Excluder stent-graft in 200 consecutive patients. J Cardiovasc Surg (Torino) 2016;57:485-90.

[87] Kawamata H, Tajima H, Ueda T, et al. Long-term outcomes of endovascular aortic aneurysm repair with the Zenith AAA endovascular graft: a single-center study. Japanese journal of radiology 2020;38:77-84.

[88] Krajcer Z, Ramaiah VG, Henao EA, et al. Perioperative Outcomes From the Prospective Multicenter Least Invasive Fast-Track EVAR (LIFE) Registry. J Endovasc Ther 2018;25:6-13.

[89] Le TB, Moon MH, Jeon YS, Hong KC, Cho SG, Park KM. Evaluation of Aneurysm Neck Angle Change After Endovascular Aneurysm Repair Clinical Investigations. Cardiovascular and interventional radiology 2016;39:668-75.

[90] Liao JL, Wang SK, Maijub JG, et al. Perioperative and Long-term Results of Zenith Fenestrated Aortic Repair in Women. Annals of vascular surgery 2020;68:44-9.

[91] Malas MB, Hicks CW, Jordan WD, Jr., et al. Five-year outcomes of the PYTHAGORAS U.S. clinical trial of the Aorfix endograft for endovascular aneurysm repair in patients with highly angulated aortic necks. J Vasc Surg 2017;65:1598-607.

[92] Matsagkas M, Kouvelos G, Peroulis M, et al. Standard endovascular treatment of abdominal aortic aneurysms in patients with very short proximal necks using the Endurant stent graft. J Vasc Surg 2015;61:9-15.

[93] Maudet A, Daoudal A, Cardon A, et al. Endovascular Treatment of Infrarenal Aneurysms: Comparison of the Results of Second- and Third-Generation Stent Grafts. Ann Vasc Surg 2016;34:95-105.

[94] Mazzaccaro D, Malacrida G, Amato B, Alessio Angileri S, Ierardi AM, Nano G. Preliminary experience with the use of ultra-low profile endografts. Diagnostic and interventional radiology (Ankara, Turkey) 2017;23:448-53.

[95] Mazzaccaro D, Occhiuto MT, Stegher S, Righini P, Malacrida G, Nano G. Tips About the Cordis INCRAFT Endograft. Ann Vasc Surg 2016;30:205-10.

[96] Melissano G, Rinaldi E, Mascia D, et al. Single-center mid-term results with the low profile Zenith Alpha Thoracic Endovascular stent-graft. Journal of vascular surgery 2020.

[97] Mirza AK, Sullivan TM, Skeik N, Manunga J. Superior mesenteric artery outcomes after large fenestration strut relocation with the Zenith Fenestrated endoprosthesis. CVIR endovascular 2020;3:54.

[98] Morgan-Bates K, Chaudhuri A. Use of the Ovation Endograft System to Treat Abdominal Aortic Aneurysms With Hostile Anatomy. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2020;60:786-7.

[99] Mufty H, Houthoofd S, Daenens K, Fourneau I, Maleux G. Mid-to long-term outcome results of the Ovation stent-graft. Ann Vasc Surg 2019.

[100] Mwipatayi BP, Anwari T, Wong J, et al. Sex-related outcomes after endovascular aneurysm repair within the Global Registry for Endovascular Aortic Treatment (GREAT). Ann Vasc Surg 2020.

[101] Nishibe T, Iwahashi T, Kamiya K, et al. Clinical and Morphological Outcomes in Endovascular Aortic Repair of Abdominal Aortic Aneurysm Using GORE C3 EXCLUDER: Comparison between Patients Treated within and Outside Instructions for Use. Ann Vasc Surg 2019.

[102] Nishibe T, Dardik A, Koizumi J, et al. Simple renal cyst and its association with sac shrinkage after endovascular aneurysm repair for abdominal aortic aneurysms. Journal of vascular surgery 2020;71:1890-8.e1.

[103] Oderich GS, Farber MA, Schneider D, et al. Final 5-year results of the United States Zenith Fenestrated prospective multicenter study for juxtarenal abdominal aortic aneurysms. Journal of vascular surgery 2020.

[104] O'Donnell TFX, Verhagen HJ, Pratesi G, et al. Female sex is associated with comparable 5-year outcomes after contemporary endovascular aneurysm repair despite more challenging anatomy. J Vasc Surg 2020;71:1179-89.

[105] Oliveira NFG, Bastos Goncalves FM, Van Rijn MJ, et al. Standard endovascular aneurysm repair in patients with wide infrarenal aneurysm necks is associated with increased risk of adverse events. J Vasc Surg 2017;65:1608-16.

[106] Oliveira-Pinto J, Oliveira NFG, Bastos-Goncalves FM, et al. Long-term results after standard endovascular aneurysm repair with the Endurant and Excluder stent grafts. J Vasc Surg 2020;71:64-74.

[107] Orrico M, Ronchey S, Alberti V, et al. Outcomes of endovascular repair of abdominal aortic aneurysms in narrow aortic bifurcations using the ultra-low profile "INCRAFT" device: A retrospective multicenter study. J Vasc Surg 2019.

[108] Pagliariccio G, Gatta E, Schiavon S, et al. Bell-bottom technique in iliac branch era: mid-term single stent graft performance. CVIR endovascular 2020;3:57.

[109] Pecoraro F, Corte G, Dinoto E, Badalamenti G, Bruno S, Bajardi G. Cinical outcomes of Endurant II stent-graft for infrarenal aortic aneurysm repair: comparison of on-label versus off-label use. Diagnostic and interventional radiology (Ankara, Turkey) 2016;22:450-4.

[110] Peters AS, Hatzl J, Bischoff MS, Bockler D. Comparison of endovascular aneurysm sealing and repair with respect to contrast use and radiation in comparable patient cohorts. J Cardiovasc Surg (Torino) 2020;61:67-72.

[111] Pippin K, Hill J, He J, Johnson P. Outcomes of type II Endoleaks after endovascular abdominal aortic aneurysm (AAA) repair: a single-center, retrospective study. Clinical imaging 2016;40:875-9.

[112] Pitoulias GA, Valdivia AR, Hahtapornsawan S, et al. Conical neck is strongly associated with proximal failure in standard endovascular aneurysm repair. J Vasc Surg 2017;66:1686-95.

[113] Pitoulias GA, Torsello G, Austermann M, et al. Outcomes of elective use of the chimney endovascular technique in pararenal aortic pathologic processes. Journal of vascular surgery 2020.

[114] Poublon CG, Holewijn S, van Sterkenburg SMM, Tielliu IFJ, Zeebregts CJ, Reijnen M. Long-Term Outcome of the GORE EXCLUDER AAA Endoprosthesis for Treatment of Infrarenal Aortic Aneurysms. Journal of vascular and interventional radiology : JVIR 2017;28:637-44.e1.

[115] Pratesi G, Pratesi C, Chiesa R, et al. The INNOVATION Trial: four-year safety and effectiveness of the INCRAFT(R) AAA Stent-Graft System for endovascular repair. J Cardiovasc Surg (Torino) 2017;58:650-7.

[116] Ramirez JL, Schaller MS, Wu B, Reilly LM, Chuter TAM, Hiramoto JS. Late graft failure is rare after endovascular aneurysm repair using the Zenith stent graft in a cohort of high-risk patients. J Vasc Surg 2019;70:1456-62.

[117] Reyes Valdivia A, Pitoulias G, Criado FJ, et al. Multicenter European Registry for Patients with AAA Undergoing EVAR Evaluating the Performance of the 36-mm-Diameter Endurant Stent-Graft. Cardiovascular and interventional radiology 2017;40:1514-21.

[118] Rosenfeld ES, Macsata RA, Lala S, et al. Open Surgical Repair of Juxtarenal Abdominal Aortic Aneurysms in the Elderly is Not Associated with Increased Thirty-Day Mortality Compared to Fenestrated Endovascular Grafting. Journal of vascular surgery 2020.

[119] Saha P, Hughes J, Patel AS, et al. Medium-Term Outcomes Following Endovascular Repair of Infrarenal Abdominal Aortic Aneurysms with an Unfavourable Proximal Neck. Cardiovascular and interventional radiology 2015;38:840-5.

[120] Sayed T, El Basty A, Hildebrand D, Bachoo P. Mid-term outcomes of endovascular aneurysm repair in challenging aortic neck anatomy based on experience from the GREAT C3 registry. The Journal of cardiovascular surgery 2020;61:610-6.

[121] Senemaud JN, Ben Abdallah I, de Boissieu P, et al. Intraoperative adverse events and early outcomes of custom-made fenestrated stent grafts and physician-modified stent grafts for complex aortic aneurysms. J Vasc Surg 2019.

[122] Singh MJ, Fairman R, Anain P, et al. Final results of the Endurant Stent Graft System in the United States regulatory trial. J Vasc Surg 2016;64:55-62.

[123] Sirignano P, Capoccia L, Menna D, Mansour W, Speziale F. Pushing forward the limits of EVAR: new therapeutic solutions for extremely challenging AAAs using the Ovation(R) stent-graft. J Cardiovasc Surg (Torino) 2016;57:839-45.

[124] Sirignano P, Mansour W, Capoccia L, et al. Immediate results of the expanding indications for treatment with standard EVAR in patients with challenging anatomies, a multi-centric prospective evaluation - EXTREME Study. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2019.

[125] Sirignano P, Mansour W, Pranteda C, et al. Real-Life Experience with Ovation Stent Graft: Lesson Learned from the First One Hundred Fifty Treated Patients. Ann Vasc Surg 2017;45:253-61.

[126] Sirignano P, Capoccia L, Mansour W, et al. Type 2 Endoleak Incidence and Fate After Endovascular Aneurysms Repair in a Multicentric Series: Different Results with Different Devices? Ann Vasc Surg 2019;56:224-32.

[127] Sobocinski J, Briffa F, Holt PJ, et al. Evaluation of the Zenith low-profile abdominal aortic aneurysm stent graft. J Vasc Surg 2015;62:841-7.

[128] Starnes BW, Dwivedi A, Giglia J, Woo K, Yeh C. Updated outcomes from the TRANSFIX study to evaluate endovascular repair of blunt thoracic aortic injuries with the Zenith Alpha thoracic device. Journal of vascular surgery 2020;71:1851-7.

[129] Storck M, Nolte T, Tenholt M, Maene L, Maleux G, Scheinert D. Women and men derive comparable benefits from an ultra-low-profile endograft: 1-year results of the European OVATION registry. J Cardiovasc Surg (Torino) 2017;58:658-64.

[130] Swerdlow NJ, Lyden SP, Verhagen HJM, Schermerhorn ML. Five-year results of endovascular abdominal aortic aneurysm repair with the Ovation abdominal stent graft. J Vasc Surg 2019.

[131] T Mannetje YW, Broos PP, van Poppel RF, van Sambeek MR, Teijink JA, Cuypers PW. Late single-center outcome of the Talent Abdominal Stent Graft after a decade of follow-up. J Vasc Surg 2016;64:557-62.

[132] T Mannetje YW, Cuypers PWM, Saleem BR, Bode AS, Teijink JAW, van Sambeek M. Comparison of midterm results for the Talent and Endurant stent graft. J Vasc Surg 2017;66:735-42.

[133] Tadros RO, Sher A, Kang M, et al. Outcomes of using endovascular aneurysm repair with active fixation in complex aneurysm morphology. J Vasc Surg 2018;68:683-92.

[134] Teijink JAW, Power AH, Bockler D, et al. Editor's Choice - Five Year Outcomes of the Endurant Stent Graft for Endovascular Abdominal Aortic Aneurysm Repair in the ENGAGE Registry. Eur J Vasc Endovasc Surg 2019;58:175-81.

[135] Trellopoulos G, Georgakarakos E, Pelekas D, Papachristodoulou A, Kalaitzi A, Asteri T. Initial single-center experience with the Ovation stent-graft system in the treatment of abdominal aortic aneurysms: application to challenging iliac access anatomies. Ann Vasc Surg 2015;29:913-9.

[136] Troisi N, Pitoulias G, Michelagnoli S, et al. Preliminary experience with the Endurant II short form stent-graft system. J Cardiovasc Surg (Torino) 2019;60:364-8.

[137] Troisi N, Torsello G, Weiss K, Donas KP, Michelagnoli S, Austermann M. Midterm results of endovascular aneurysm repair using the Endurant stent-graft according to the instructions for use vs. off-label conditions. J Endovasc Ther 2014;21:841-7.

[138] Tsolakis IA, Kakkos SK, Papageorgopoulou CP, et al. Improved effectiveness of the repositionable GORE EXCLUDER AAA endoprosthesis featuring the C3 delivery system compared with the original GORE EXCLUDER AAA endoprosthesis for within the instructions for use treatment of aortoiliac aneurysms. J Vasc Surg 2019;69:394-404.

[139] Unsgard RG, Altreuther M, Lange C, Hammer T, Mattsson E. Five-year results of endovascular aortic repair used according to instructions for use give a good general outcome for abdominal aortic aneurysm. SAGE open medicine 2019;7:2050312119853434.

[140] Vaaramaki S, Salenius JP, Pimenoff G, Uurto I, Suominen V. Systematic Long-term Follow Up After Endovascular Abdominal Aortic Aneurysm Repair With the Zenith Stent Graft. Eur J Vasc Endovasc Surg 2019;58:182-8.

[141] Varkevisser RRB, Swerdlow NJ, Verhagen HJM, Lyden SP, Schermerhorn ML. Similar 5-year outcomes between female and male patients undergoing elective endovascular abdominal aortic aneurysm repair with the Ovation stent graft. J Vasc Surg 2019.

[142] Veraldi GF, Mezzetto L, Vaccher F, et al. Technical Success and Long-Term Results with Excluder/C3 Endoprosthesis in Narrow Aortic Bifurcations: First Italian Multicentre Experience. Ann Vasc Surg 2018;52:57-66.

[143] Verhoeven EL, Katsargyris A, Bachoo P, et al. Real-world performance of the new C3 Gore Excluder stent-graft: 1-year results from the European C3 module of the Global Registry for Endovascular Aortic Treatment (GREAT). Eur J Vasc Endovasc Surg 2014;48:131-7.

[144] Verzini F, Romano L, Parlani G, et al. Fourteen-year outcomes of abdominal aortic endovascular repair with the Zenith stent graft. J Vasc Surg 2017;65:318-29.

[145] Volpe P, Massara M, Alberti A, et al. Preliminary Results of Aorfix Stent Graft to Treat Infrarenal Abdominal Aortic Aneurysms with Severe Proximal Aortic Neck Angulation. Ann Vasc Surg 2017;45:193-8.

[146] Yang G, Zhang M, Muzepper M, et al. Comparison of Physician-Modified Fenestrated/Branched Stent-Grafts and Hybrid Visceral Debranching Plus Stent-Graft Placement for Complex Thoracoabdominal Aortic Aneurysm Repair. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2020;27:749-56.

[147] Yao C, Ning J, Li Z, et al. Parallel Covered Stents Technique in the Treatment of Abdominal Aortic Diseases. Journal of vascular and interventional radiology : JVIR 2020;31:771-7.

[148] Zavatta M, Squizzato F, Balestriero G, et al. Early and Mid-Term Outcomes of EVAR With an Ultra Low-Profile Endograft from the Triveneto Incraft Registry. Journal of Vascular Surgery 2020.

[149] Zettervall SL, Deery SE, Soden PA, et al. Editor's Choice - Renal complications after EVAR with suprarenal versus infrarenal fixation among all users and routine users. Eur J Vasc Endovasc Surg 2017;54:287-93.