Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting

Endologix AFX
Risk of Type III Endoleaks

November 2, 2021

U.S. FOOD & DRUG ADMINISTRATION

FDA Presentation

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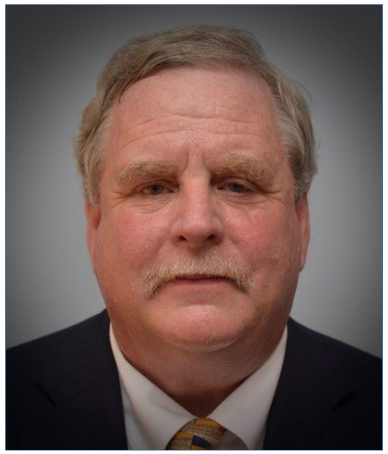
Overview of Abdominal Aortic Aneurysms and Type III Endoleaks



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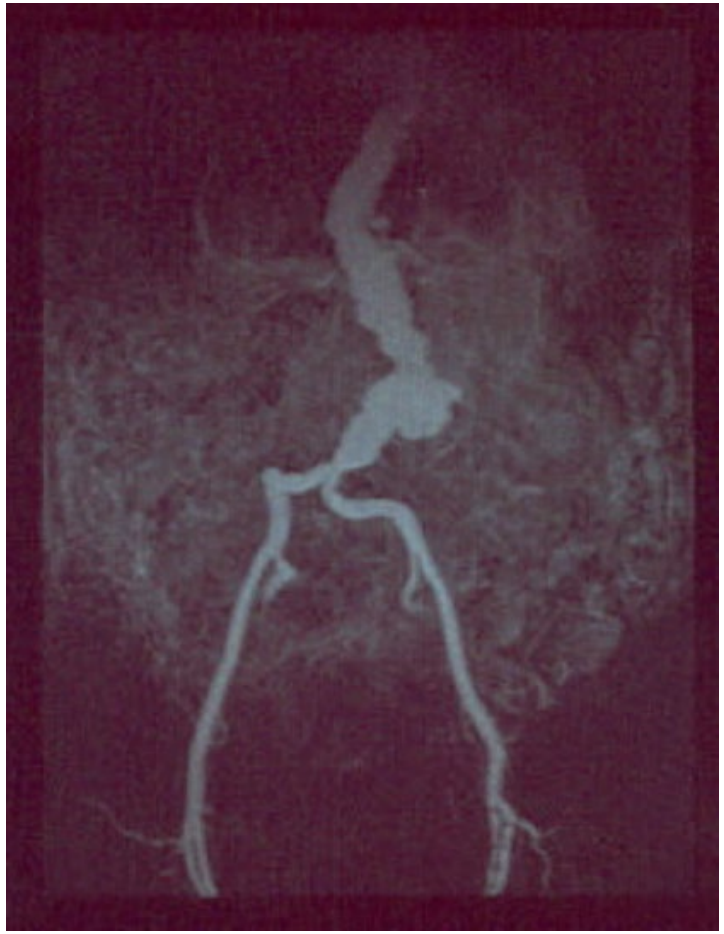
Abdominal Aortic Aneurysm (AAA)

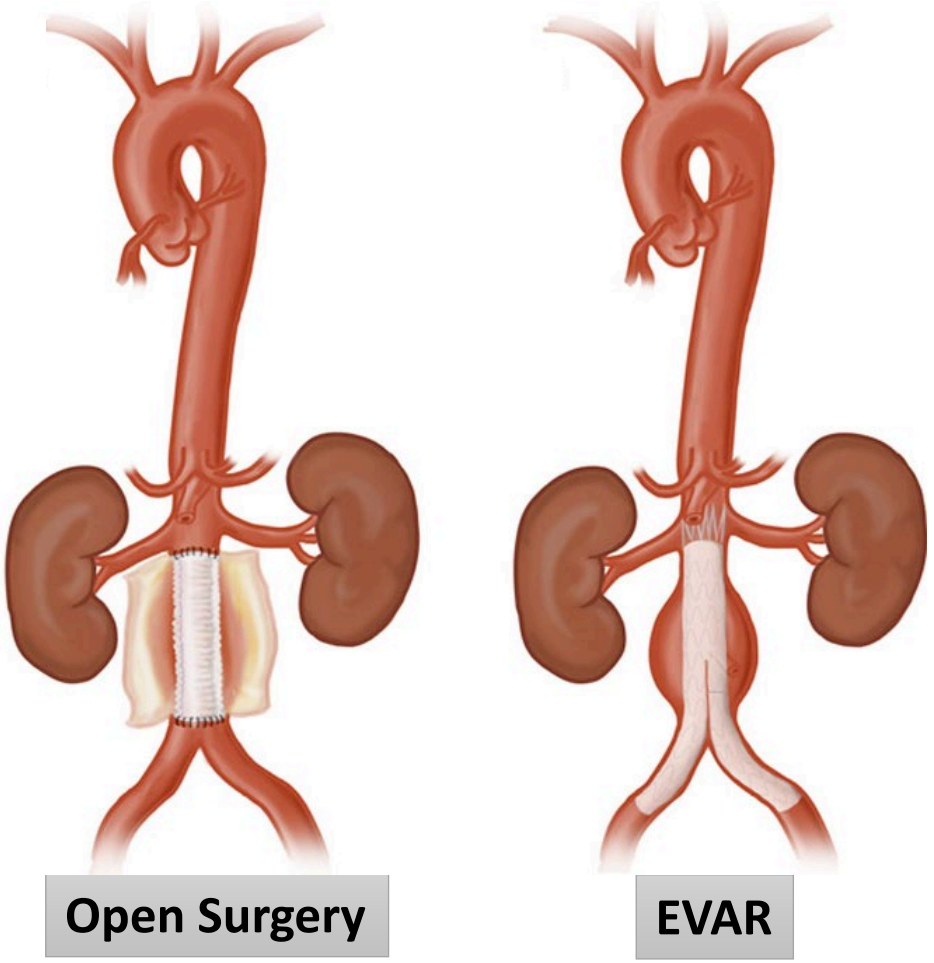
- AAA – structural deterioration of the aortic wall with gradual expansion of the aneurysm sac
  - Enlargement increases risk of rupture
- Risk factors:
  - Age > 65 years old
  - Males
  - Smoking
  - Hypertension
  - Family History of AAA
- Result in an estimated 10,000 deaths each year in the US



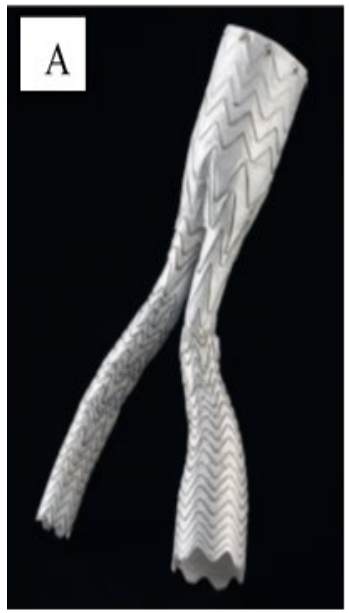
Sakalihasan N, R Limet, OD Defawe. "Abdominal aortic aneurysm". The Lancet. 2005, Vol 365(9470).

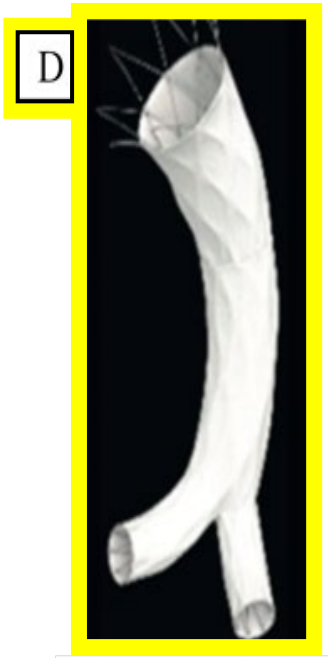
Current Therapies for AAA

- **Medical management** – treatment of risk factors while aneurysm is small and asymptomatic
- **Open surgical repair** – aneurysmal tissue is replaced with a synthetic graft
- **Endovascular aneurysm repair (EVAR)** – a stent graft system is delivered to the aneurysm via catheter
- **EVAR** – now accounts for over 80% of elective AAA repairs in the US



Swerdlow NJ, Wu WW, Schermerhorn ML. “Open and Endovascular Management of Aortic Aneurysms.” Circulation Research. Vol 124 Issue 4. 2019





Design Features of FDA Approved Endovascular Grafts

A: Gore Excluder

B: Cook Zenith Flex

C: Cook Zenith Fenestrated

Endologix AFX

E: Medtronic Endurant II

F: Endologix Alto

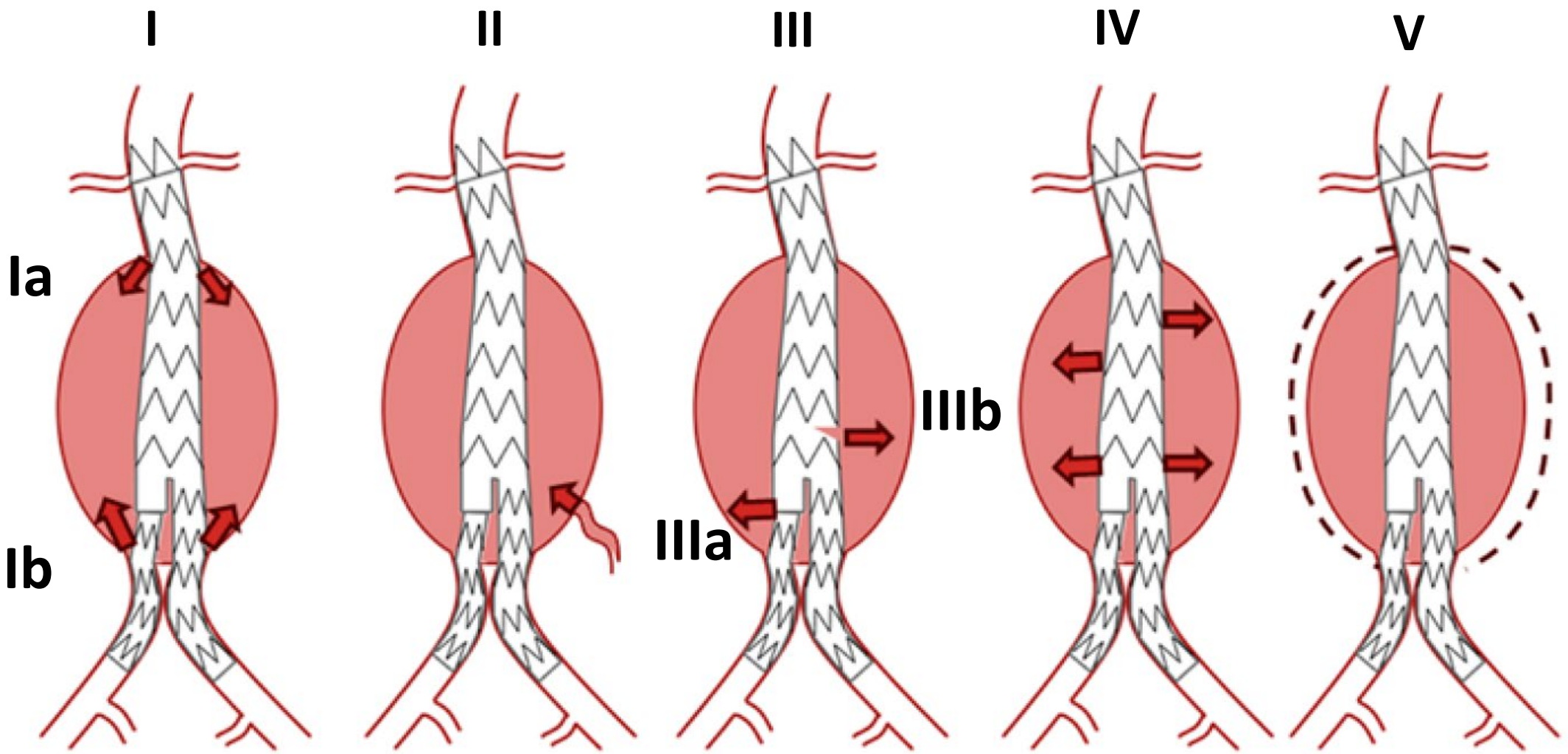
G: Gore Conformable Excluder

H: Bolton Treo

EVAR Device Failure Modes

- Delivery system failures
- Patency-Related events: kinks, compression, thrombosis
- Stent or barb fractures
- Device migration
- Component separation
- Fabric tears or holes
- Aneurysm sac expansion >5 mm

Endoleak Classification



England et. al, EVAR, Ulster Med J 2013;82(1):3-10

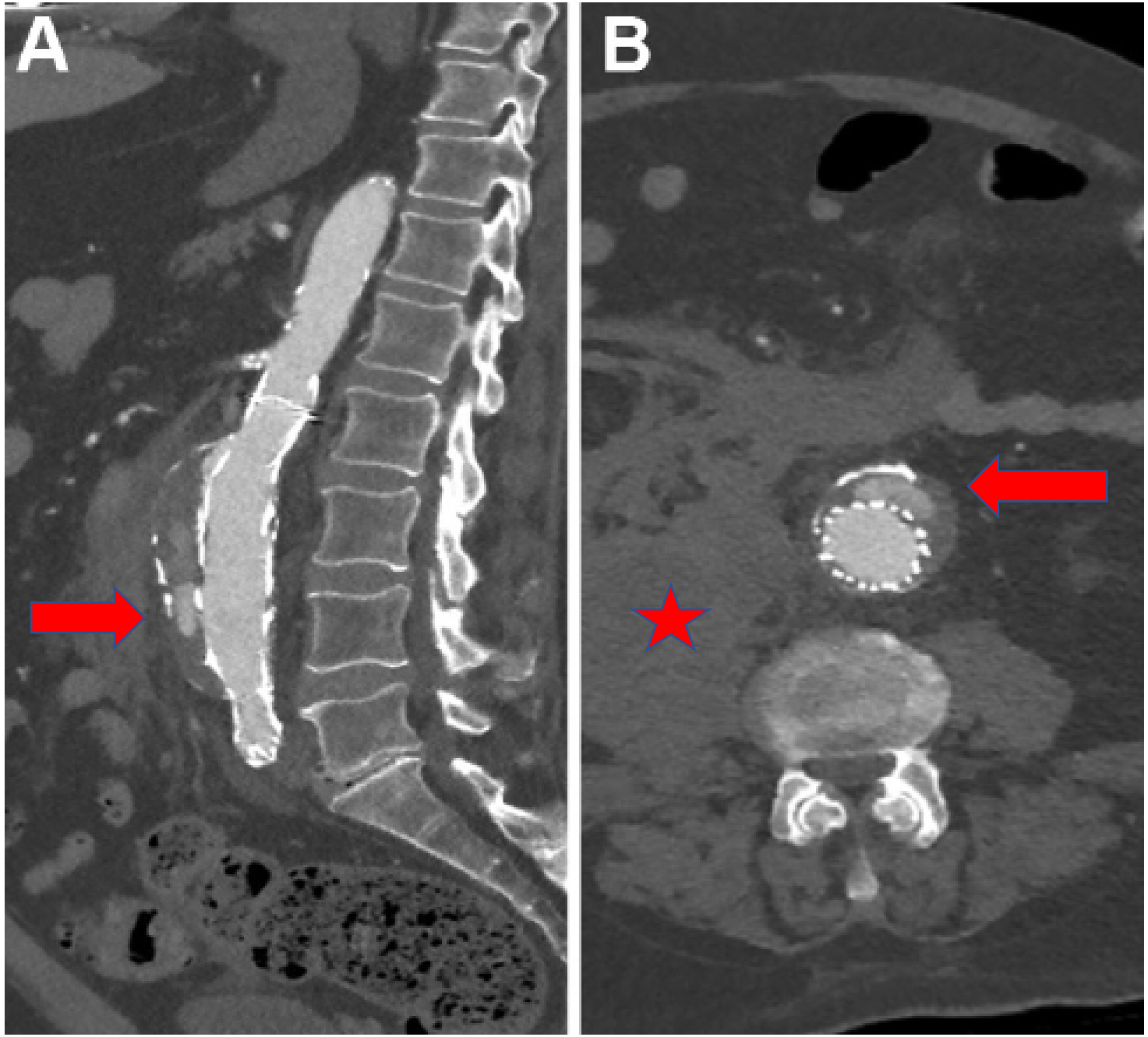
3 months post AFX

37 months post AFX

Type IIIa Endoleak:

AFX Component Separation

Skibba et al, J Vasc Surg 2015;62:868-75.



Type IIIb Endoleak with AAA rupture

Lemmon et al, J Vasc Surg Cases and Innovative Techniques, 2019:5:51

Endologix AFX Device Iterations

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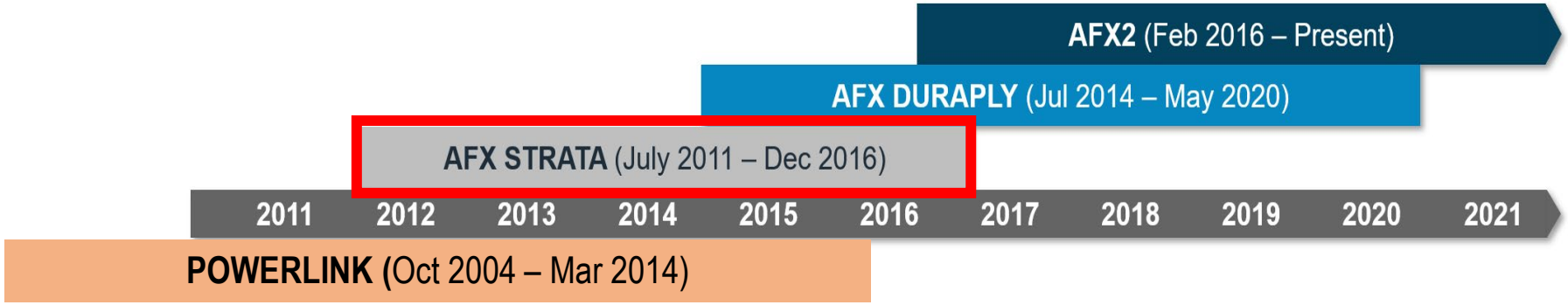
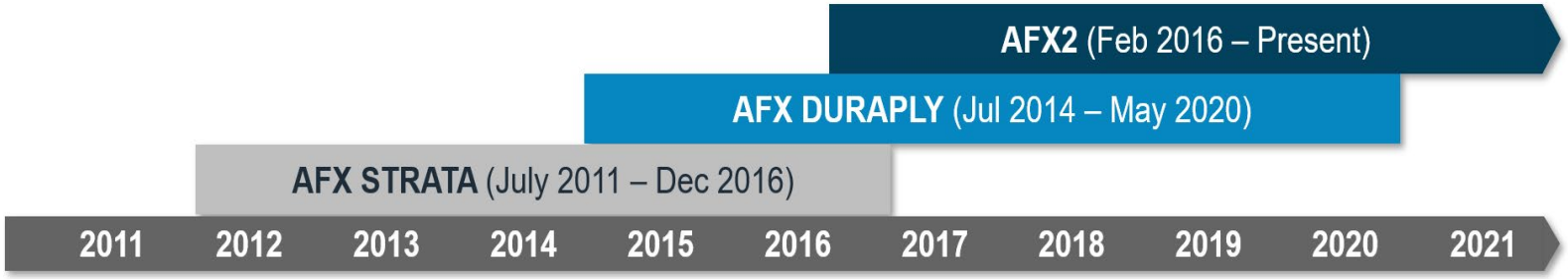
Endologix AFX Stent Graft History



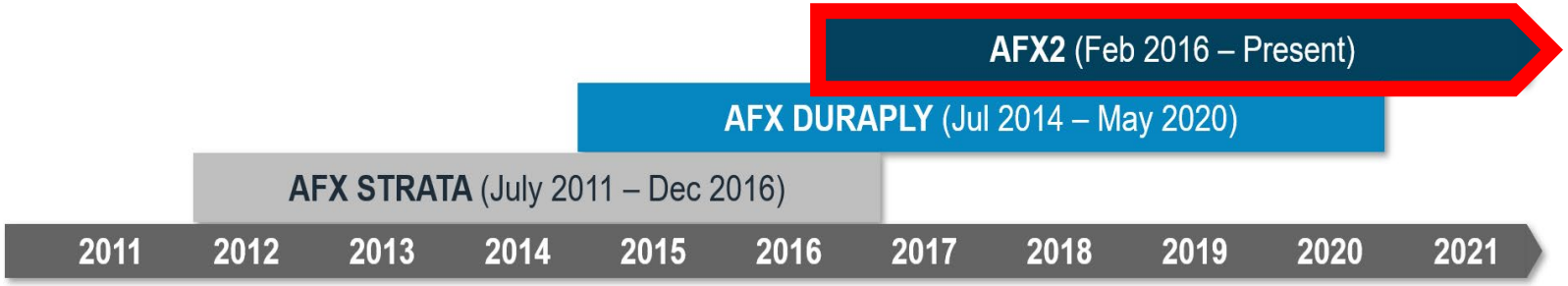
- Powerlink approved October 2004
  - Pre-market bench and animal testing and a clinical study
  - US distribution ceased March 2014
- AFX with Strata approved June 2011
  - New ePTFE sheet extrusion process resulting in reduced wall thickness
  - Pre-market non-clinical testing without a clinical study
  - Device removed from market December 2016 due to Type III endoleaks

Endologix AFX With Duraply

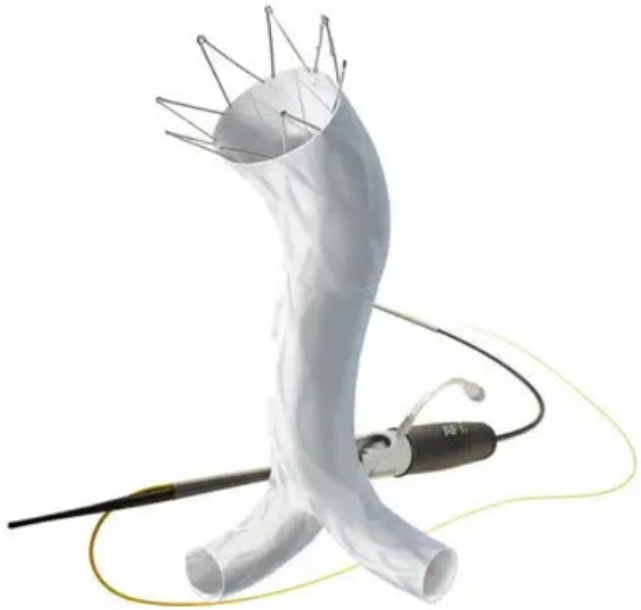


- AFX with Duraply first US sale in July 2014
- New graft processing method of helical wrapping of middle layers to improve tear propagation resistance and suture retention strength
- No changes to graft materials or stent design from AFX with Strata
- AFX with Duraply US distribution halted in August 2018

Endologix AFX2



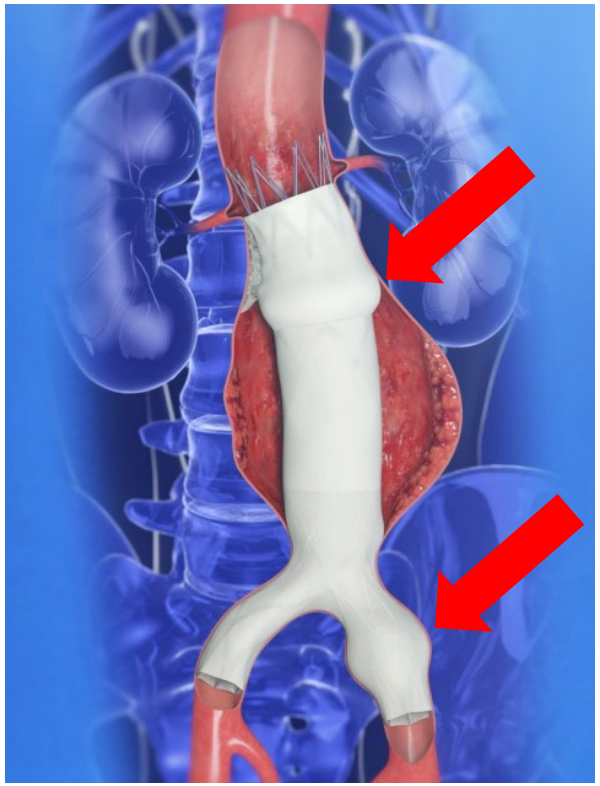
- Approved October 2015
- Changes to delivery system and graft material manufacturing tolerances intended to increase average graft material thickness
- No changes from AFX with Duraply to the stent design or graft processing method
- Modifications to stent graft loading process
- Sizing algorithm



Uncertainty that the device changes included in the AFX2 have addressed Type III endoleak concerns.

Endologix AFX2

- Unique design characteristics
  - Self-expanding metal endoskeleton inside ePTFE graft
  - Graft fabric attached to stent only at superior and inferior ends allows for graft billowing
  - Deployment on native aortic bifurcation with passive anatomic fixation
- Potential benefits (per Endologix)
  - Shorter procedure time
  - Lower peri-operative Type Ia endoleak rate
  - Preservation of native aortic bifurcation
  - Benefits in patients with narrowed aortic bifurcation

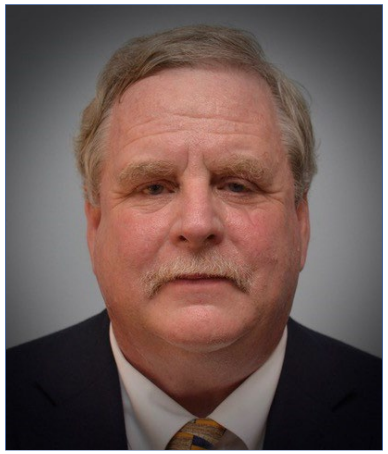


Panel will be asked to assess the clinical value of potential AFX2 benefits

Endologix AFX Iteration Comparison

Device Feature	Powerlink	AFX with Strata	AFX with Duraply	AFX2
Stent Design	Unibody configuration			
Manufacturing Materials	CoCr alloy stent; ePTFE graft material; polypropylene suture			
Graft Material Manufacturing Method	Tube Extrusion	Strata – Sheet Extrusion	Duraply – modified Strata with helical wrapping of middle layers	
Graft Material Thickness	Powerlink	Thinner graft thickness than Powerlink	• Same graft thickness as Strata until 2016 • Followed by manufacturing change in 2016 intended to increase average graft material thickness	Same graft thickness as Duraply after 2016 modification
Delivery System	Powerlink delivery system	AFX delivery system (reduced profile and standalone introducer)		AFX2 delivery system

Endologix AFX Type III Endoleak Risk: Clinical Reports



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Lemmon GW , et al. Failure mode analysis of the Endologix Endograft , J Vasc Surg , 2016.

Powerlink and AFX with Strata

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

**20 of the 24 interventions were for patients with Type III endoleaks*

***7 of the 8 ruptures were in patients with Type III endoleaks*

Lemmon GW , et al. Failure mode analysis of the Endologix Endograft , J Vasc Surg , 2016.

Powerlink and AFX with Strata

Strengths

- Focused outcomes analysis where number of treated patients and number of events are known with a reasonable degree of certainty
- Outcomes in patients treated with Endologix Powerlink and AFX with Strata compared to other commercial AAA devices
- Failure mode analysis relating Type III endoleaks to AFX platform unique design features

Limitations

- CT follow-up compliance not reported
- No data of AFX-Duraply or AFX2

Barleben, et. al. *Lessons Learned from the Largest Cohort of Type III Endoleaks With the Endologix AFX Stent Graft.* J Vasc Surg 2018 Abstract

AFX with Strata

- Authors noted an increased incidence of Type III leaks with early generation AFX devices
- Targeted follow-up of 107 subjects
- Type III endoleak rate 24.3% (26 /107)
- Complete graft relining performed in 22 subjects at average time of 45.2 months (1.6 to 70 months)
  - 4 Type IIIa endoleaks
  - 18 Type IIIb endoleaks

Barleben, et. al., 2018 Abstract
AFX with Strata

Strengths

- Focused review of outcomes where number of treated patients and number of events are known with a reasonable degree of certainty
- Extensive experience treating AFX failures (to be discussed later)

Limitations

- CT compliance was 63.1%
- No data on AFX with Duraply or AFX2 device iterations

Wanken, et. Al., Comparison of Endologix Endografts Made With Strata Fabric Versus IntuiTrak and Duraply Fabrics J Vasc Surg Abstract, 2019

Powerlink, AFX with Strata and AFX with Duraply

- Retrospective single-center chart review of infrarenal aneurysm patients treated with Endologix AFX devices from 2011 to 2015
- Analyzed MAEs (reintervention related to the endograft, aneurysm related death, and aneurysm rupture) stratified by endograft fabric: Strata vs. Powerlink/Duraply cohorts
- 118 patients (67 Strata, 51 Powerlink/Duraply) with median follow-up of 4.7 years

Wanken, et. al., Abstract, 2019
Powerlink, AFX with Strata and AFX with Duraply

- Kaplan-Meier analysis demonstrated that 25% of patients suffered MAEs within 4 years of repair with no significant difference between fabric groups
- Reintervention procedures were required in 26 patients
  - Strata = 22.4% (15/67)
  - Non-Strata (Powerlink and Duraply)= 21.6%, (11/51)
- 12 of the reinterventions were relinings for Type III endoleaks
  - 10 Strata subjects and 2 Non-Strata (Powerlink and Duraply) subjects
- Need for relinings occurred 2 to 5 years post-procedure

Wanken, et. al., 2019 Abstract
Powerlink, AFX with Strata and AFX with Duraply

Strengths

- Focused outcomes analysis where number of treated patients and number of events are known with a reasonable degree of certainty
- Comparative outcomes based on device fabric types
- Four-year follow-up

Limitations

- Retrospective analysis
- No comparator group of non-AFX devices
- CT follow-up rate not specified
- The Powerlink and Duraply groups were combined

Ta TM, et. al. , Six-Year Outcomes of the Endologix AFX1 Endovascular AAA System: 2020 Abstract, J Vasc Surg

AFX with Strata

- Maine Medical Center study of 122 AFX-Strata patients treated 2012 to 2019
- Outcomes compared to 101 patients treated with Gore, Cook and Medtronic devices
- Follow-up longer for the AFX with Strata cohort vs. comparator device group (4.6 vs. 1.8 years, respectively)
- Primary study end point: Freedom from AAA-related major complications (non-type II endoleak, graft relining, or graft explant)

Ta TM, et. al., 2020 Abstract
AFX with Strata

Freedom from	AFX-Strata n=122	Comparator Group* n=101	p value
Any Endoleak	62%	85%	P=0.006
Reinterventions	63%	87%	P=0.001
AAA related major** complications	69%	95%	P=0.001

*Gore, Cook and Medtronic Devices

**Major complications = endoleak excluding Type II, graft relining, or graft explant

Ta TM, et. al. 2020 Abstract
AFX with Strata

Strengths

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

Limitations

- Retrospective analysis
- Duration of follow-up information longer for AFX with Strata vs. comparator devices, and the number of subjects available for follow-up at later time points not provided
- Follow-up CT rate not provided

Chang, et. al. Midterm outcomes for 605 patients receiving Endologix AFX or AFX2 Endovascular AAA Systems in an integrated healthcare system. J Vasc Surg 2019

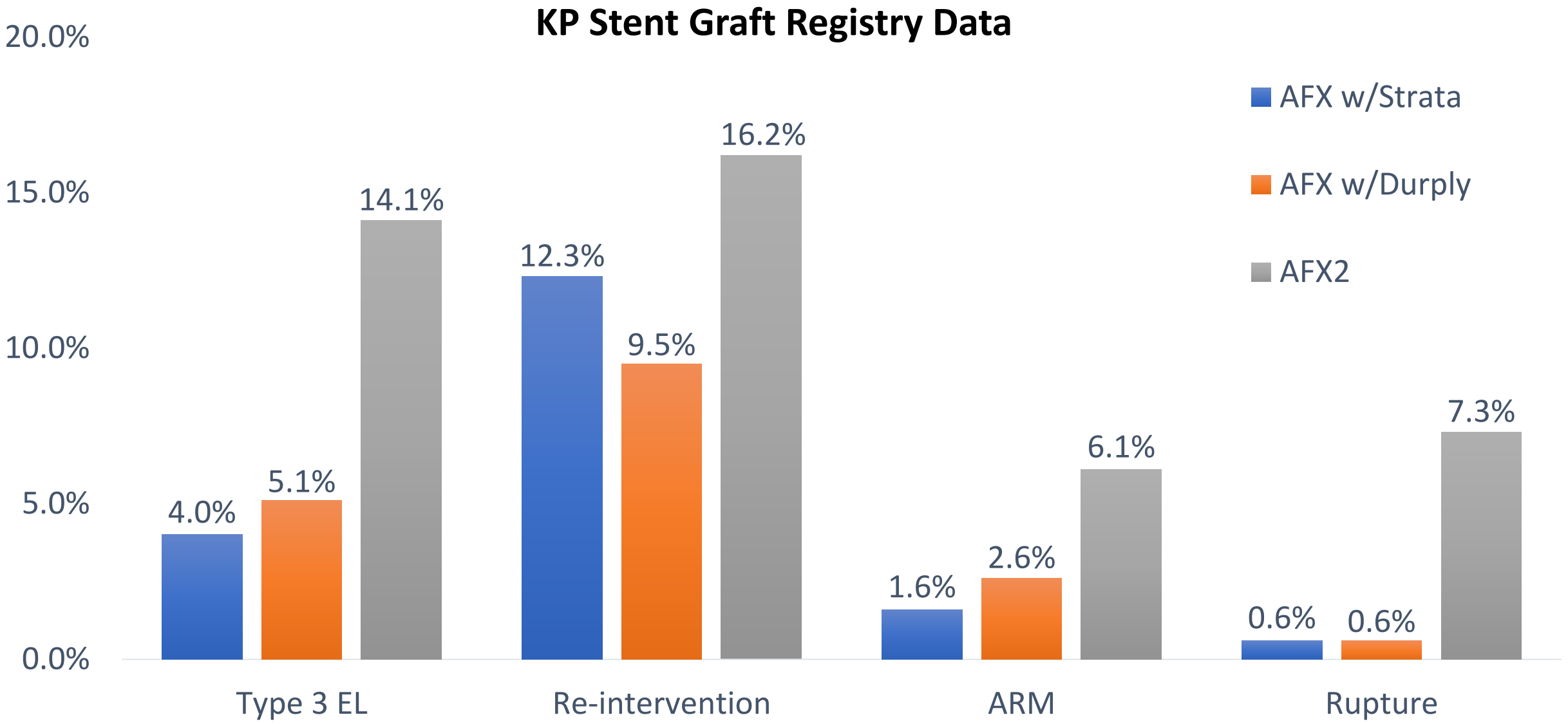
AFX with Strata, AFX with Duraply, and AFX2

Midterm outcomes for 605 patients treated between 2010 and 2017 with Endologix AFX with Strata, AFX with Duraply, or AFX2 devices followed prospectively in the Kaiser Permanente (KP) endovascular stent graft registry

- 375 AFX with Strata (AFX-S)
- 197 AFX with Duraply (AFX-D)
- 33 AFX2

Median postoperative follow-up 3.9 years (maximum 7.3 years)

2-Year Cumulative Incidence Probability



Chang, et. al. 2019 Publication
AFX with Strata, AFX with Duraply, and AFX2

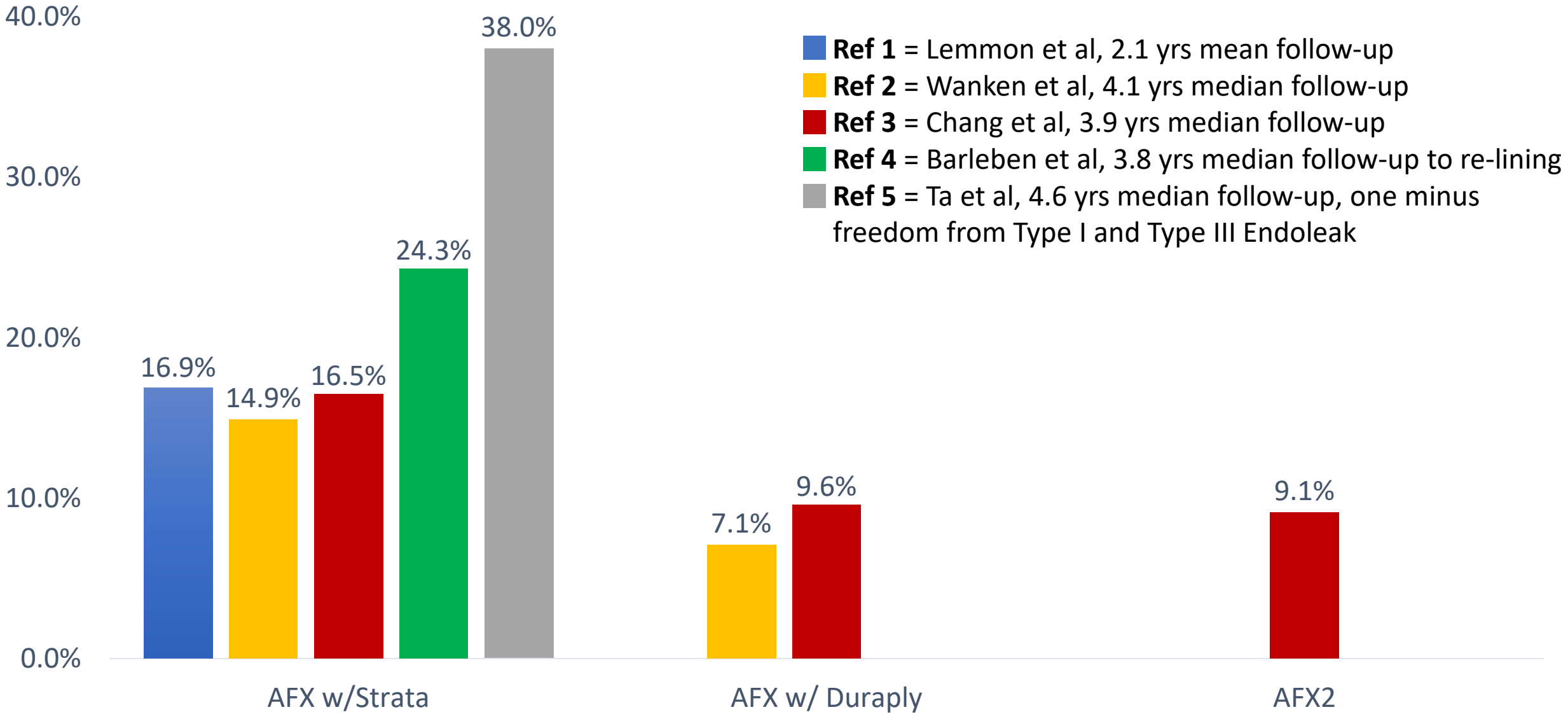
Strengths

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

Limitations

- Small number of patients with AFX2 implants
- No comparator group of non-AFX devices
- Follow-up CT compliance not reported

Summary of Type III Endoleak Rates



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Regulatory History

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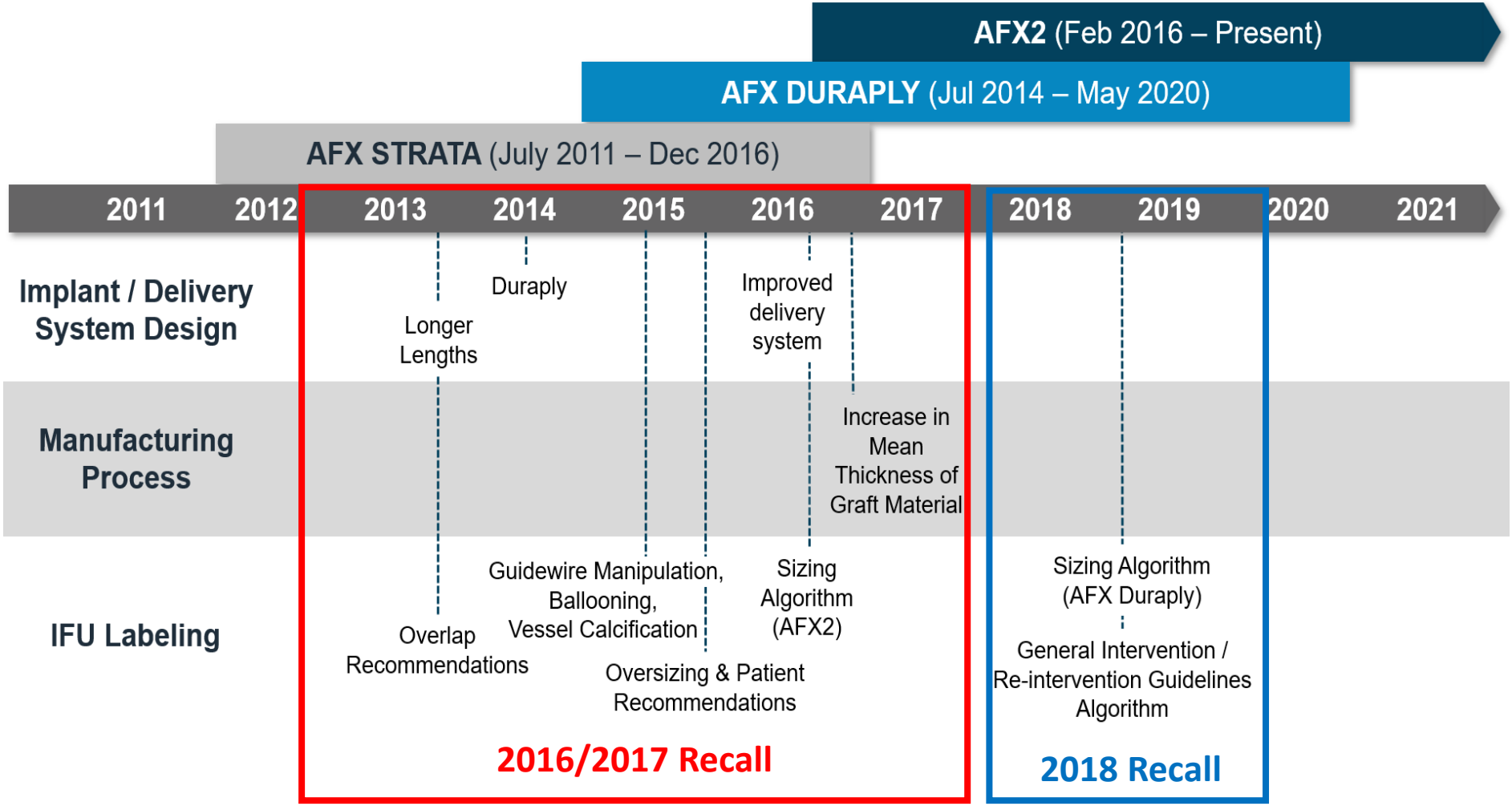
Recalls


AFX2 (Feb 2016 – Present)
AFX DURAPLY (Jul 2014 – May 2020)
AFX STRATA (July 2011 – Dec 2016)
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Implant / Delivery System Design
Manufacturing Process
IFU Labeling
Longer Lengths
Duraply
Improved delivery system
Increase in Mean Thickness of Graft Material
Overlap Recommendations
Guidewire Manipulation, Ballooning, Vessel Calcification
Oversizing & Patient Recommendations
Sizing Algorithm (AFX2)
Sizing Algorithm (AFX Duraply)
General Intervention / Re-intervention Guidelines Algorithm
2016/2017 Recall
2018 Recall

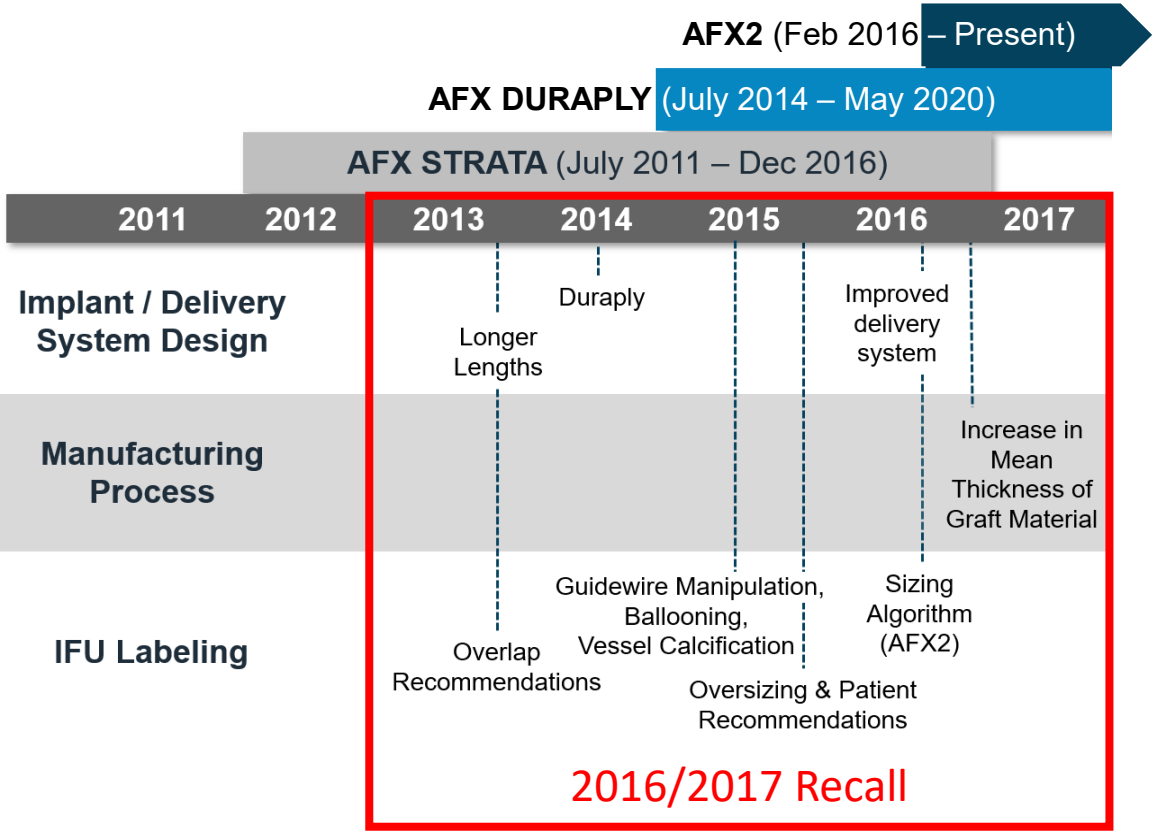
2016/2017 Recall

Endologix submitted a recall package that included a Type III Endoleaks Corrective and Preventative Action Investigation (CAPA) Investigation (initiated 2013)

Clinical Sequalae related to Type IIIa/IIIb Endoleaks from August 2011 to December 2016

	Total	Deaths	Ruptures	Open Surgeries	Secondary Procedures
Type IIIa Endoleak	259	18	28	8	173
Type IIIb Endoleak	186	17	30	17	97

2016/2017 Recall

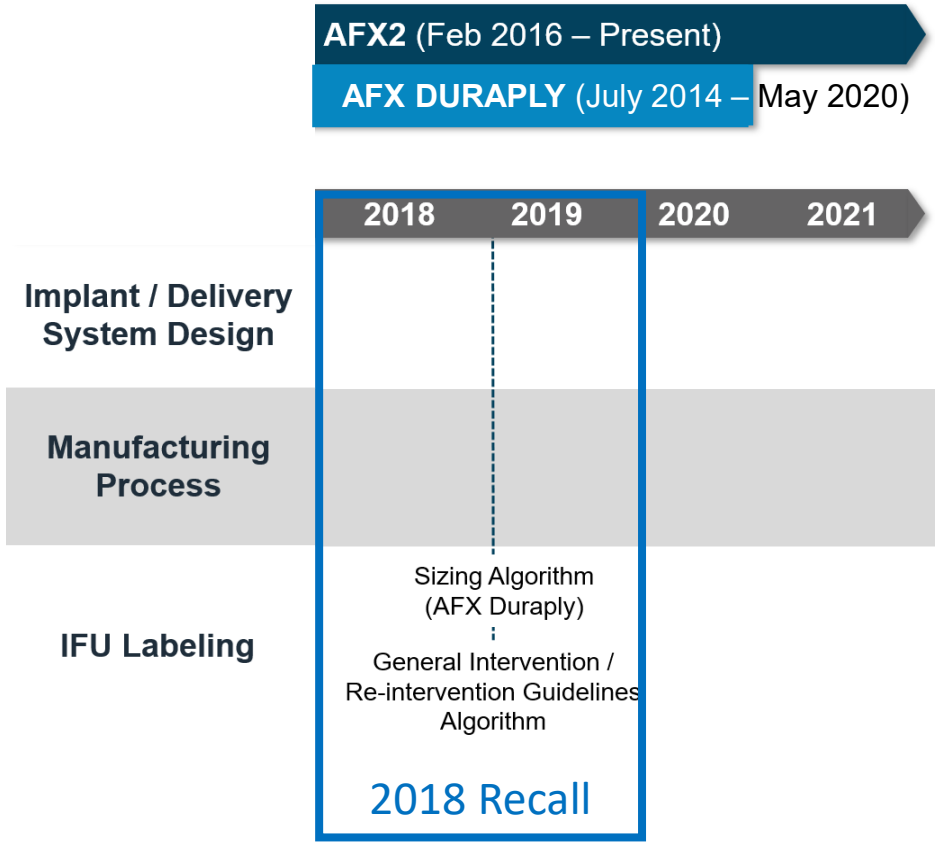


Physician letter December 30, 2016

- Corrective actions implemented between 2013-2016
  - **AFX with Duraply (2014)**
  - **AFX2 changes**
  - IFU updates (2013-2016)
- Product removal
  - **All Strata devices**
  - **Large diameter AFX2** (not shown in graphic)

2018 Recall

- Update on Type III Endoleak reports from November 2016 to August 2018
  - 544 Type III endoleaks, 535 serious/life-threatening injuries, 25 deaths
    - 372 AFX with Strata
    - 129 AFX with Duraply
    - 41 Device not identified
- IFU updates
  - Refining patient surveillance recommendations
  - Sizing recommendations for AFX with Duraply
  - Intervention/reintervention recommendations



FDA Safety Communications

- September 2017 Letter to Health Care Providers
  - Awareness of Type III endoleaks in endovascular graft systems
- June 2018 updated Letter
  - AFX with Strata at greater risk for Type IIII endoleaks
  - Monitor patients who have undergone implantation w/ Strata
- October 2019 Safety Communication
  - Potential for Type III endoleaks occurring with AFX with Duraply and AFX2
- December 2020 Updated Safety Communication
  - New research studies indicate a potential for Type III endoleaks associated with AFX with Duraply and AFX2
  - Announcements of additional data collection and an Advisory Panel meeting

Medical Device Reports (MDRs)

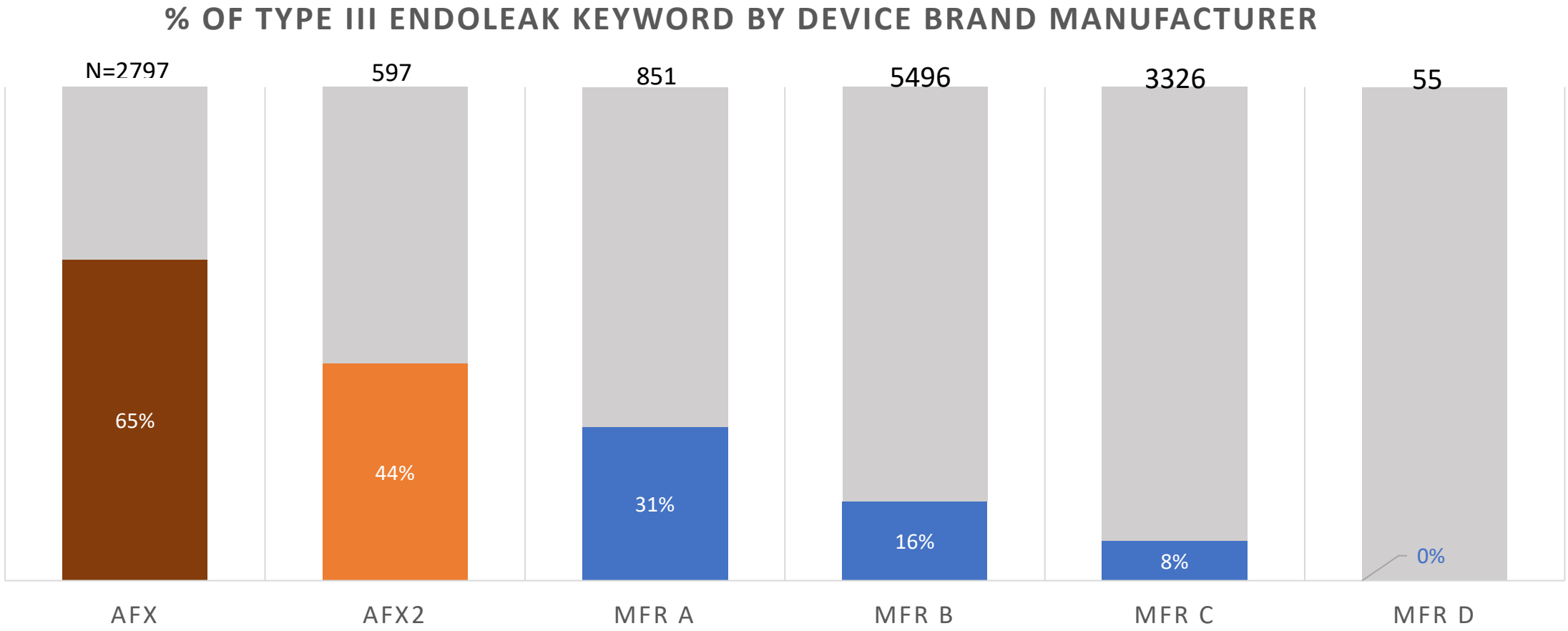
MDR submissions

- Mandatory reporters (manufacturers, importers, and device user facilities)
- Voluntary reporters (health care professionals, patients, and consumers)

Strengths	Limitations
- All stakeholders may submit reports - Ease of trending coded information - Usually relevant timelines reported (date of implant and event) - Can capture longer term events - Allows for narrative event descriptions	- Reports may be incomplete, inaccurate, untimely, unverified, or biased - Events under-reported - Imprecise information coding leads to inefficient event trending - Denominator of devices implanted not available

MDR Analysis

Endologix had the highest proportion of reports for Type III Endoleaks from January 1, 2016 to July 31, 2021



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Additional Information Provided by Endologix

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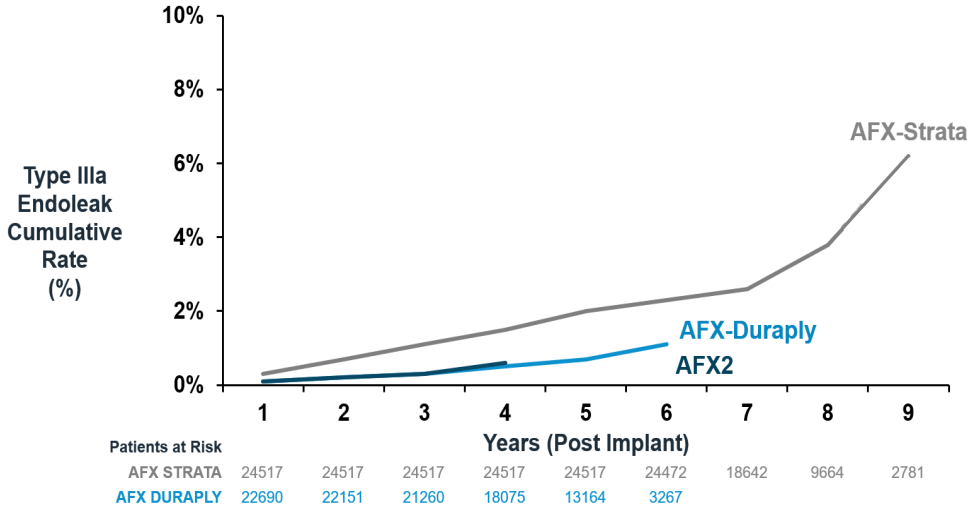
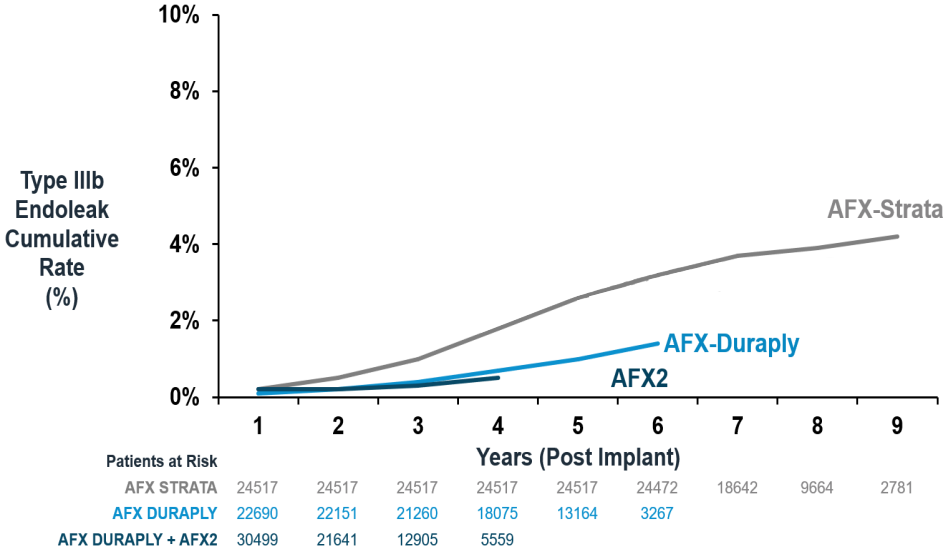
Complaint Data Analysis

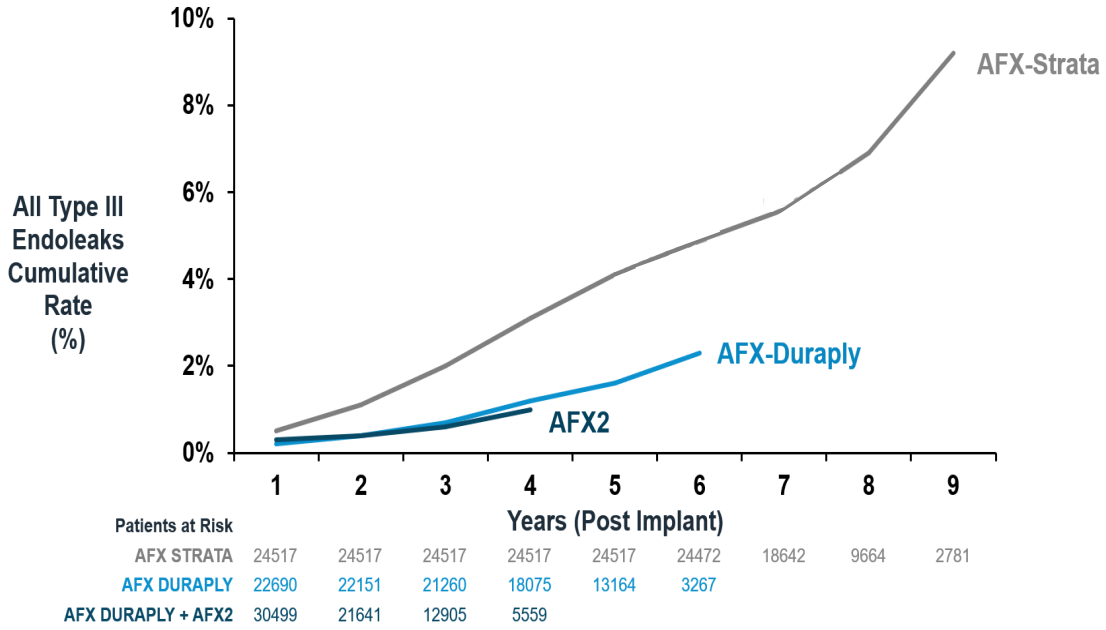
Comparison of complaint data from the Class I Recall Letter to the February 28, 2021 data lock

July 2018 Endologix customer letter for class I labeling recall related to Type III endoleaks	*Sep 22, 2021 Endologix data (sent to FDA July 27, 2021)
Type III Endoleaks - Overall	
Strata – N/A	Strata – 9.2% at 9 years (257/2781)
Duraply – N/A	**Duraply – 2.3% at 6 years (76/3267)**
AFX2 – N/A	**AFX2 – 1.0% at 4 years (57/5559)**
Type IIIa	
Strata – 3.9% at 6 years (141/3614)	Strata – 6.2% at 9 years (173/2781)
Duraply – 0.4% at 3 years (21/4883)	**Duraply – 1.1% at 6 years (35/3267)**
AFX2 – 0.1% at 1 year (5/5868)	**AFX2 – 0.6% at 4 years (33/5559)**
Type III b	
Strata – 2.0% at 6 years (73/3614)	**Strata – 4.2% at 9 years (117/2781)**
Duraply – 0.5% at 3 years (22/4883)	**Duraply – 1.4% at 6 years (46/3267)**
AFX2 – 0.1% at 1 year (5/5868)	**AFX2 – 0.5% at 4 years (28/5559)**

Type III Endoleak Complaint Trends, Bifurcated Device Type September 22, 2021







- AFX with Duraply and AFX2 complaint curves overlap
- AFX with Strata complaints increase substantially starting at 6-years post-procedure for Type IIIa endoleaks and 3-years post-procedure for Type IIIb endoleaks
  - Similar long-term data not yet available for AFX with Duraply and AFX2

Complaint Data Analysis

Strengths

- Event comparison duration starting at t=0 and years post-implant that event occurred

Limitations

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

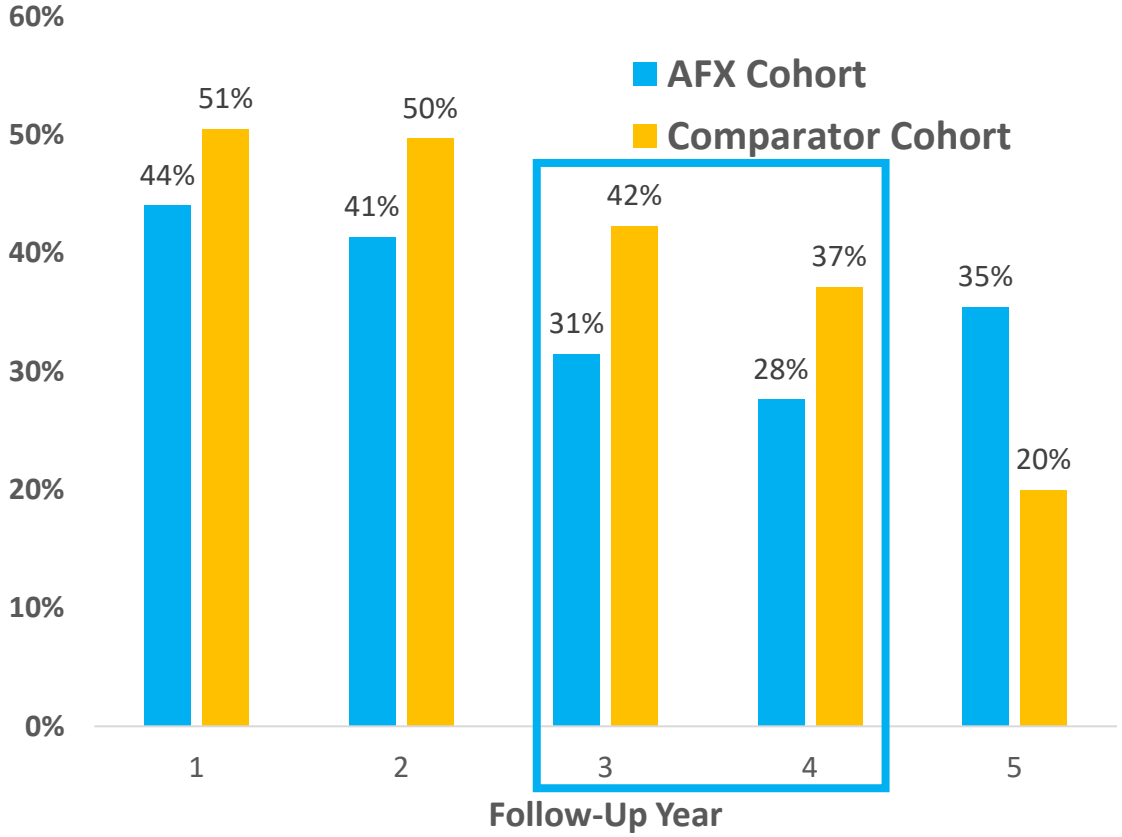
LEOPARD Trial

- Multicenter RCT to compare 5-year outcomes for AFX with Duraply & AFX2 to comparator devices
- No per protocol annual CT imaging
- Enrollment ended 2017
  - 235 AFX subjects
    - 124 AFX with Duraply
    - 111 AFX2
  - 220 comparator device subjects

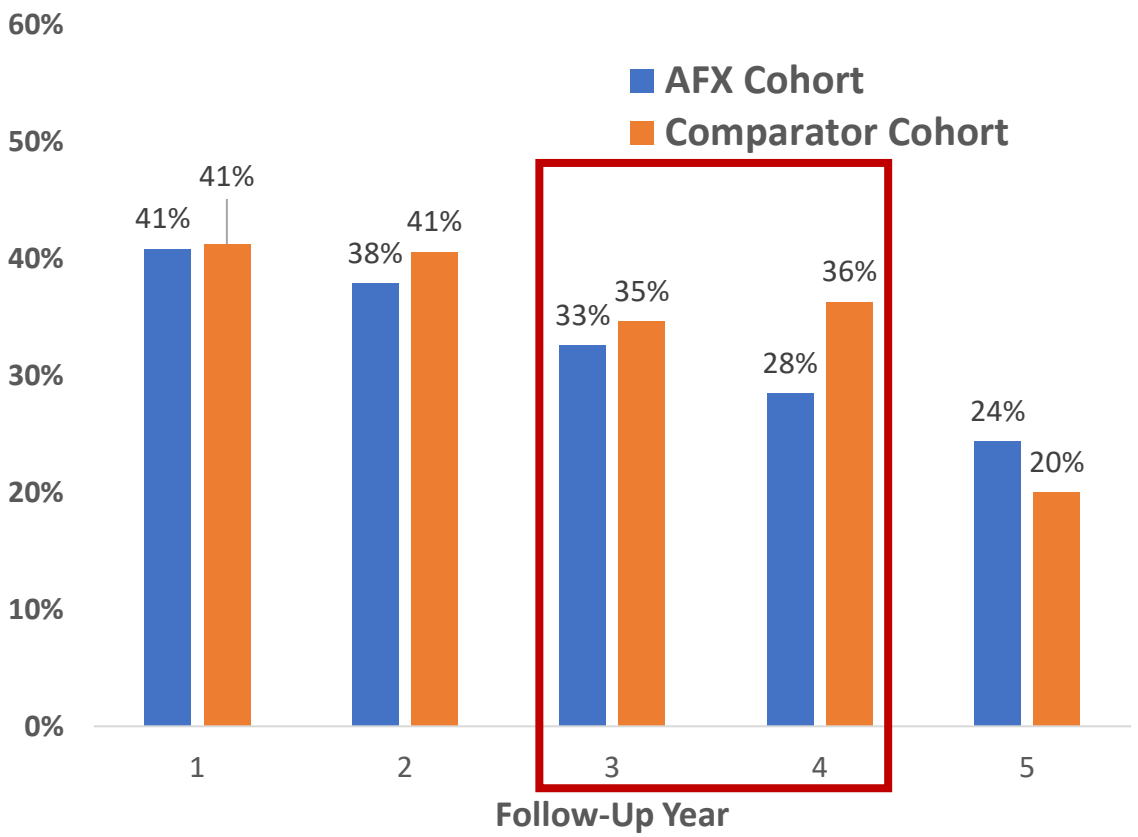
Key Outcome Measures extracted from ARC Through February 28, 2021	AFX/AFX2 with Duraply (n=235)	Comparators (n=220)
Aneurysm Related Mortality (ARM)	5	3
Peri-Operative Mortality	3	0
ARM ≥ 30 Days	2	3
Aneurysm Rupture	2	1
Conversion to Open Surgical Repair	0	4
Device/AAA-Related Re-interventions	25	24
Type III Endoleaks	3	0
Type IIIa Endoleak	**1**	**0**
Type IIIb Endoleak	**2**	**0**
Total	43	35

LEOPARD Trial – Imaging and Clinical Follow-Up

Proportion of Eligible Subjects With Evaluable Endoleak Imaging Reviewed by Core Lab



Proportion of Eligible Subjects With Evaluable Sac Enlargement Imaging Reviewed by Core Lab



Clinical follow-up at 3 and 4 years: Proportion of eligible subjects with missing data

- **AFX cohort: 3 years 14%, 4 years 19%**
- **Comparator cohort: 3 years 11%, 4 years 17%**

LEOPARD Trial

Strengths

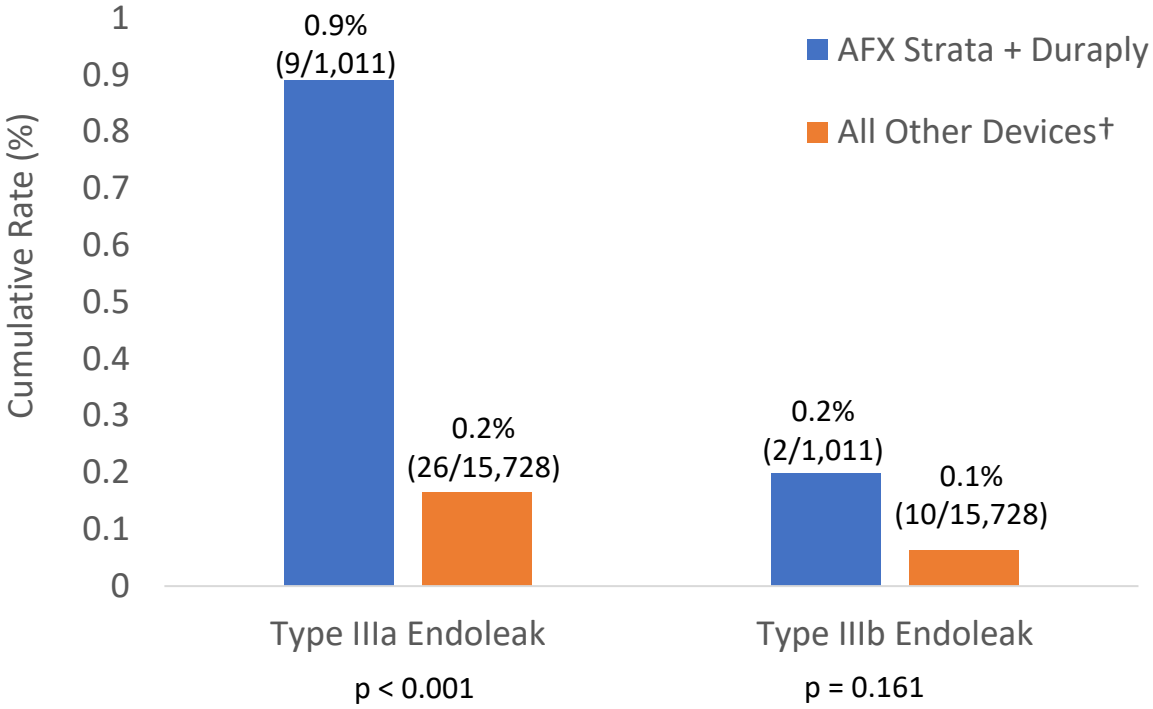
- Multicenter, prospective randomized trial
- Imaging core lab review

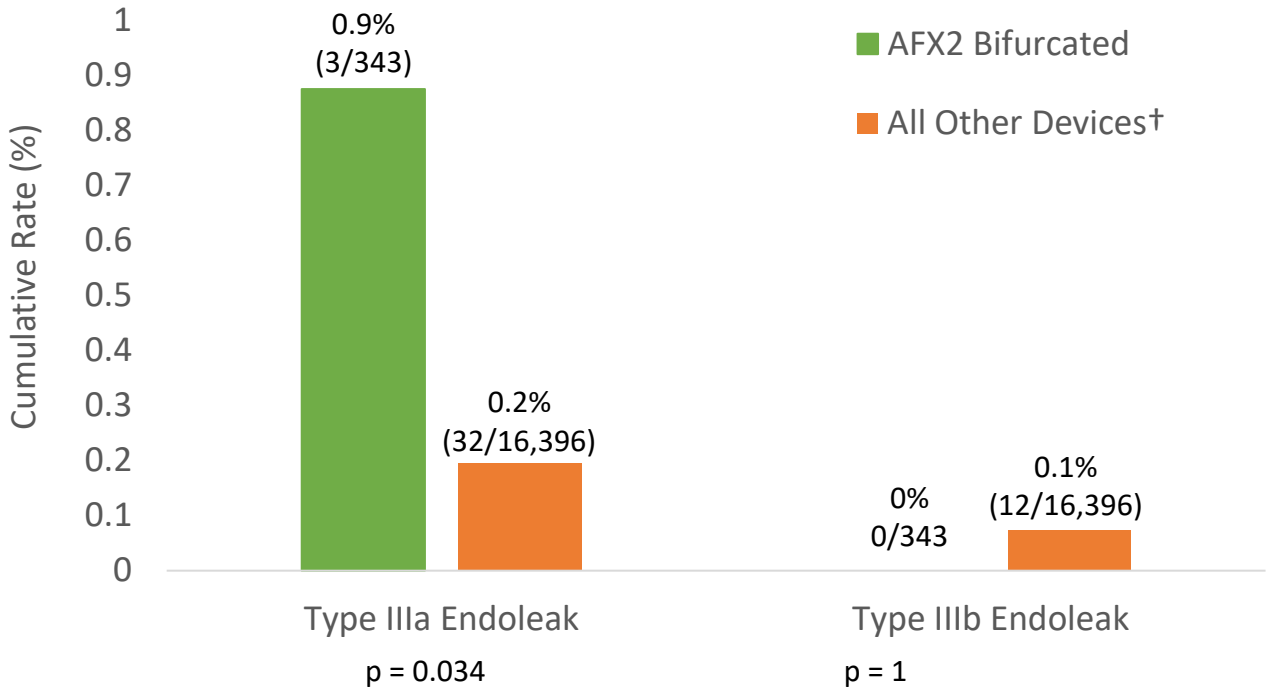
Limitations

- Annual CT scans not required per protocol
- Substantial missing imaging and clinical data
- Limited sample size and longer-term follow up of AFX2 subjects

Vascular Quality Initiative (VQI)

- VQI registry utilizing information from Society for Vascular Surgery
- Compares peri-operative and 1-year outcomes amongst EVAR devices





†"All Other" EVAR devices includes Bolton Treovance, Cook Zenith, Gore CTAG, Gore Excluder C3, Endologix Ovation, Endologix Nellix, Lombard Aorfix, Medtronic Endurant, Medtronic Endurant II, Medtronic Talent and Medtronic Valiant Captiva. For AFX Bifurcated table, Endologix AFX2 is included. For AFX2 table, Endologix AFX with Strata and Duraply are included.

Vascular Quality Initiative (VQI)

Strengths

- 775 participating centers across US and Canada
- Real-world practice and some follow-up information in >70% of cases when patients return for follow-up

Limitations

- No data available beyond 1-year
- Type III endoleak rate of AFX with Strata and AFX with Duraply are combined
- AFX with Strata and AFX with Duraply devices are included in the “All Other Devices” group when comparing results to the AFX2

Endologix-Sponsored Multi-Center Series

Strengths

- Focused outcomes analysis where number of treated patients and number of events are known with a reasonable degree of certainty
- Moderate-sized cohort of 405 AFX2 patients

Limitations

- Five centers selected by the sponsor
- Retrospective study
- No independent event adjudication or core lab analysis
- No comparator group of non-AFX devices
- CT follow-up rate not specified
- Mean follow-up 1.7 years

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%

Endologix-Sponsored Center for Medicare and Medicaid Services (CMS) Study

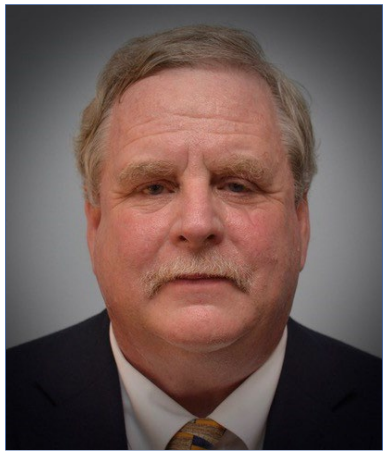
Strengths

- Large sample size
- Comparator group
- Real-world data

Limitations

- Stent graft type could only be identified by CPT (current procedural terminology) codes, allowing for identification of AFX yet not completely stratifying AFX iterations
- No details on number and classification of endoleaks, migration, sac expansion
- Retrospective analysis

Treatment of Patients with AFX Type III Endoleak Device Failures



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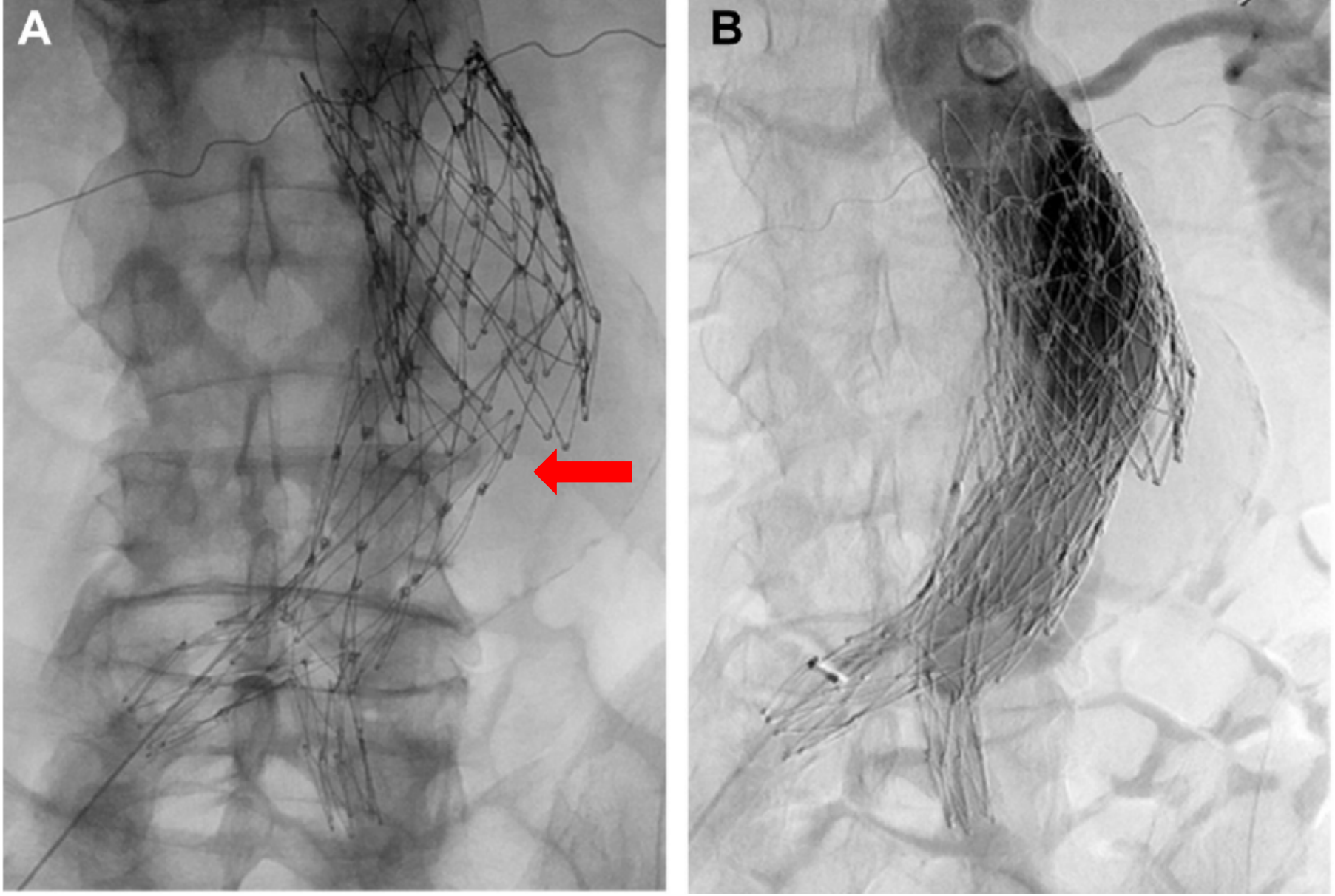
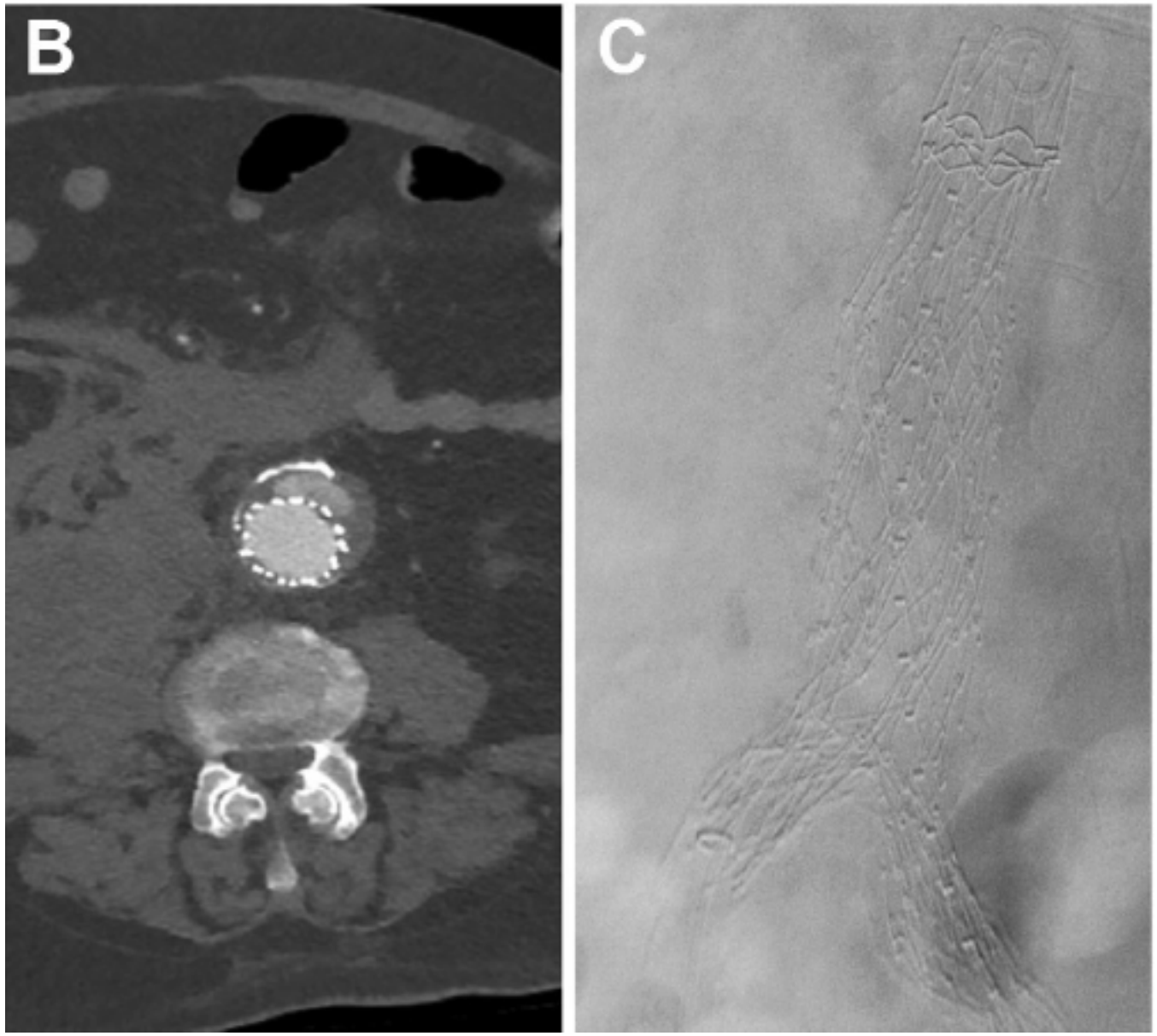


Type IIIa Endoleak Management Post-AFX

Management of late main-body aortic endograft component uncoupling and type IIIa endoleak encountered with the Endologix Powerlink and AFX platforms. Skibba A, et. al, J Vasc Surg 2015;62:868-75.



Type IIIb Endoleak Management Post AFX

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

AFX-in-AFX: Sponsor's Data

- Report provided to FDA on September 22, 2021
- Retrospective analysis of 77 subjects treated with AFX-in-AFX relining identified from complaint data on 360 relinings
  - 76 subjects had complete AFX relining, one with open surgical conversion
- 62 Type IIIb and 13 Type IIIa
- Perioperative mortality following relining 3.9%
- 3 aneurysm related deaths, 95.2% freedom from ARM at 3 years
- Median follow-up 1.7 years

Benefit/Risk Profile and Conclusion

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Risk Mitigation Strategies

Mitigations	Additional Data Collections
Device/Treatment related measures to mitigate risk of Type III endoleaks: • Device design considerations • Device labeling and training considerations • Patient labeling/selection Potential sponsor actions: • Voluntary product recall/removal • Withdrawal of PMA	Postmarket surveillance under Section 522: • Class III device for which failure of the device would be reasonably likely to have a serious adverse health consequence • Class III device intended to be implanted in the human body for more than one year

Benefit/Risk Considerations

- AFX with Strata is associated with an increased risk of Type III Endoleaks
- Uncertainty regarding effectiveness of mitigation strategies to address Type III endoleaks for the AFX with Duraply and AFX2
  - Device design/manufacturing/labeling changes
  - Limited clinical data
- FDA will present our comments on the additional studies presented today in our second presentation

FDA is seeking Advisory Committee input on the benefit-risk profile of the Endologix AFX device family with a focus on the currently marketed AFX2 device