U.S. FOOD & DRUG ADMINISTRATION

Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting

General Issues Panel – Real World Surveillance of AAA Endovascular Stent Grafts

November 3, 2021

U.S. FOOD & DRUG ADMINISTRATION

FDA Presentation

Circulatory Systems Devices Panel of the Medical Devices Advisory Committee Meeting

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Background and Current Status of Endovascular AAA Repair

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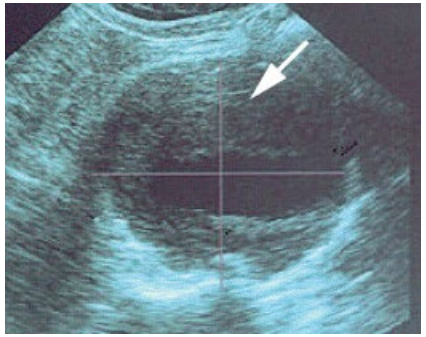
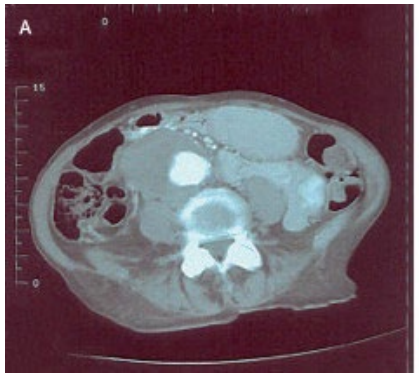
Presentation Outline

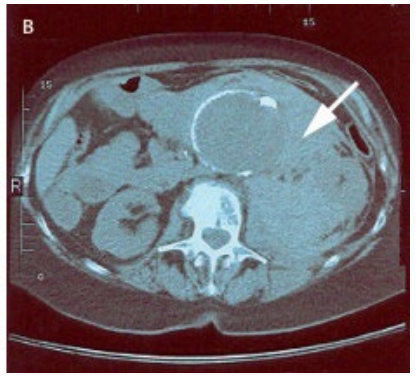
- Overview of Abdominal Aortic Aneurysms and Therapies
- History and Current Status of Endovascular AAA Repair
- Currently FDA Approved AAA Endovascular Grafts
- Benefits and Disadvantages of EVAR
- Current Realities
- EVAR Outcomes of Interest
- Current Regulatory Paradigm for EVAR Devices
- Role of Long-term Surveillance

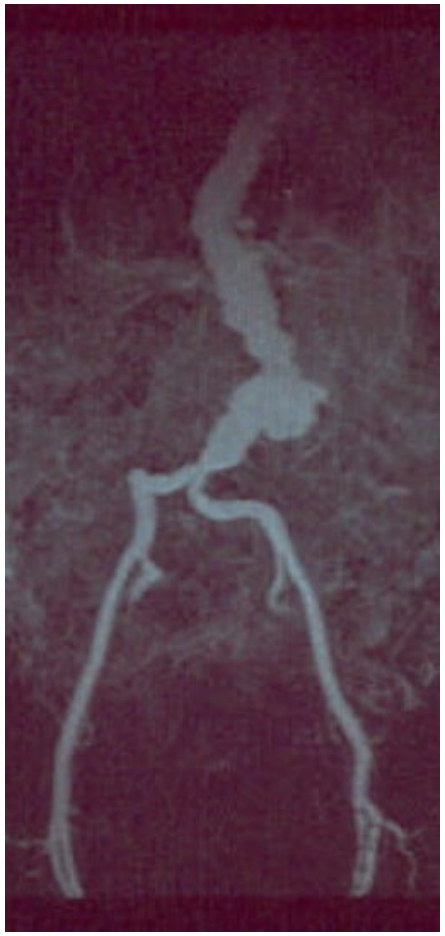
Abdominal Aortic Aneurysms

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





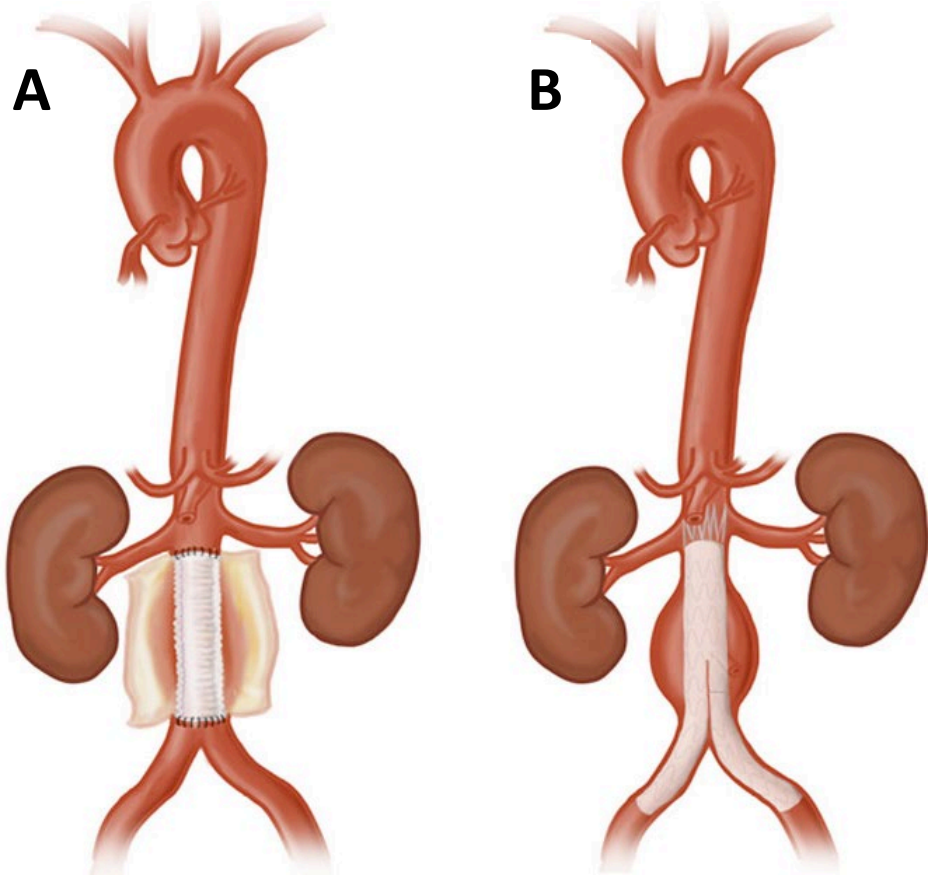




Sakalihasan N, R Limet, OD Defawe. "Abdominal aortic aneurysm". The Lancet. 2005, Vol 365(9470).

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 (A)
- **Endovascular aneurysm repair (EVAR)** – a stent graft system is delivered to the aneurysm via catheter (B)



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

History of EVAR

- Endovascular abdominal aortic aneurysm repair was initially described by Volodos in **1986**
- Juan Parodi in **1991** published his experience with retrograde deployment through the femoral arteries of a stent-anchored, Dacron-prosthetic graft that would act to depressurize the aneurysm sac and thus reduce the risk of aneurysm rupture
  - EVAR was born
  - Early stent grafts were tubular (**aorto-aortic**)
  - First unibody bifurcated (**aorto-bi-iliac**) stent developed in **1993**
- Regulatory approval for the first abdominal aortic stent-graft occurred in **1996 in Europe and in the US in 1999**

EVAR Market in the US

- EVAR has been widely accepted in the US as approximately 80% of aneurysms are so repaired.
  - >50% of global market share
- In 2012, approximately 47,000 EVARs performed in the US
  - The US EVAR endograft market has continued to grow by approximately 8% per year.
- Open surgery rates have consistently declined from 2004 to 2015.

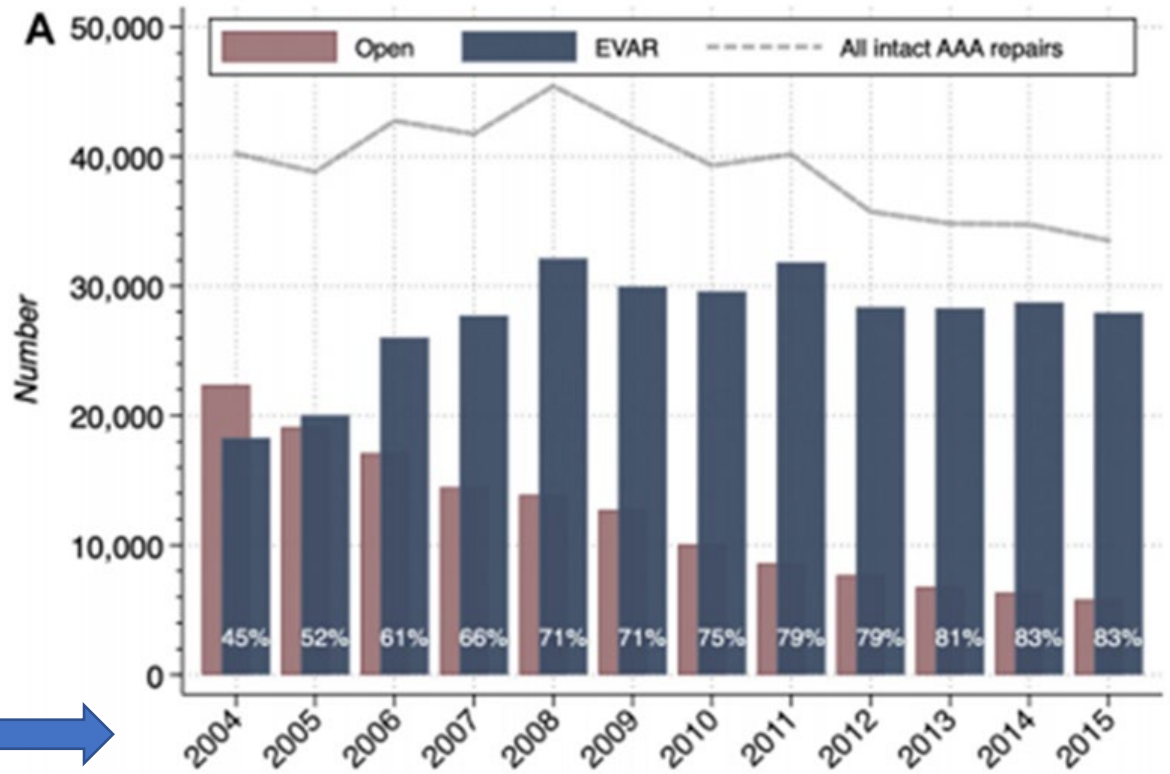


Figure 3: Comparison of Open Repair vs EVAR by Year

Dansing KD, Varkevisser RRB, et al. Epidemiology of endovascular and open repair for abdominal aortic aneurysms in the United States from 2004 to 2015 and implications for screening. J Vasc Surg 2021;74:414-24.

FDA Approved Endovascular Grafts

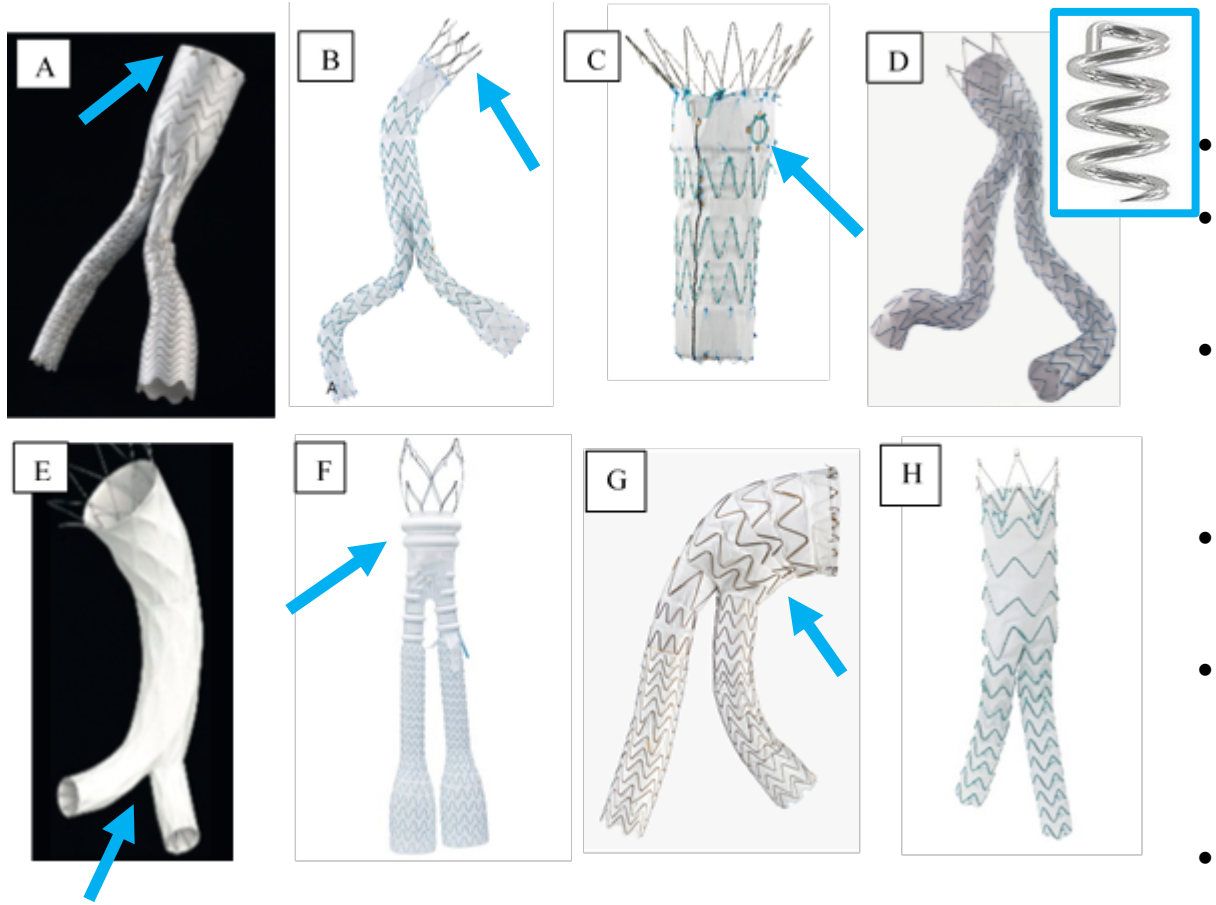
*Table 1: AAA endovascular grafts currently marketed in the US**

Sponsor	Device Name	Year of Original PMA Approval	Currently Marketed Iteration[13]
W. L. Gore and Associates, Inc	Excluder AAA Endoprosthesis	2002	Excluder AAA Endoprosthesis
Cook, Inc	Zenith AAA Endovascular Graft	2003	Zenith Flex AAA Endovascular Graft & Zenith Fenestrated AAA Endovascular Graft**
Endologix, LLC	Powerlink System	2004	AFX2 Endovascular AAA System
Medtronic Vascular	Endurant Stent Graft System	2010	Endurant II & IIs Stent Graft System**
Trivascular, Inc / Endologix, LLC	Ovation Abdominal Stent Graft System**	2013	Alto Abdominal Stent Graft System**
W. L. Gore and Associates, Inc	Excluder Conformable AAA Endoprosthesis	2020	Excluder Conformable AAA Endoprosthesis
Bolton Medical Inc (a Terumo Aortic Company)	TREO Abdominal Stent Graft System	2020	TREO Abdominal Stent Graft System

**The Cordis US Corporation Incraft AAA Stent Graft System is PMA approved (2018) but is not yet marketed in the US.*

*** These devices have unique device designs and approved indications to treat more challenging proximal anatomies.*

Design Features of Endovascular Grafts



***Commercially available devices**: A, Gore Excluder. B, Cook Zenith Flex. C, Cook Zenith Fenestrated. D, Medtronic Endurant II. E, Endologix AFX2. F, Endologix Alto. G, Gore Excluder Conformable. H, Bolton TREO.*

- The modern version of stent-graft design is a **fully supported bifurcated modular graft**
- Several designs have **barbs** to provide **active fixation**.
- Most current stent-graft designs have **suprarenal stents to inhibit downward migration and Type I endoleak.**
- Another device allows for extension of the proximal seal zone into the visceral segment by incorporating **fenestrations** into the design.
- One device with suprarenal fixation is approved for use with **adjunctive endoanchor fixation.**
- **One device is designed for passive fixation**, whereby the flow divider of the stent-graft sits directly on the aortic bifurcation.
- One stent graft design has unique **polymer-filled sealing rings** intended to create enhanced seal in the aortic neck.
- Another device offers **angulation control** to achieve conformability and seal.

Evolving Learnings: Long-term Device Performance

Failure modes impacting long-term device performance

- Iliac limb stenoses/occlusions
- Stent graft migrations
- Fabric tears
- Fabric porosity
- Stent or barb fractures
- Loss of proximal or distal seal
- Modular stent graft separations

Consequences

- Vascular injury
- **LE ischemia due to thrombo-embolic events**
- Branch vessel coverage/thrombosis
- Dissection (creation or extension)
- **Endoleaks (I and III)**
- **Continued aneurysm sac expansion**
- **Need for re-interventions to prevent rupture**

Peri-Operative Benefits of EVAR

Benefits of EVAR over open surgical repair are **peri-operative** (30 day) and include:

- High degree of patient acceptance
- Shorter operative times
- Reduced operative blood loss
- Lower major operative complications
- Elimination of intensive care unit stays
- Reduced hospital length of stay
- Rapid recovery
- Selective use of local anesthesia
- **Lower mortality rates**
  - Reduced 30-day mortality (EVAR-I, Dream, and OVER trials)
  - A review of 79,932 Medicare patients confirmed these results are representative of current outcomes, with an overall peri-operative mortality of 5.2% for open repair and 1.6% for EVAR

Chaikof E, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018; 67(1):2-77.
Schermerhorn M, et al. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. N Engl J Med 2015;373:328-338.

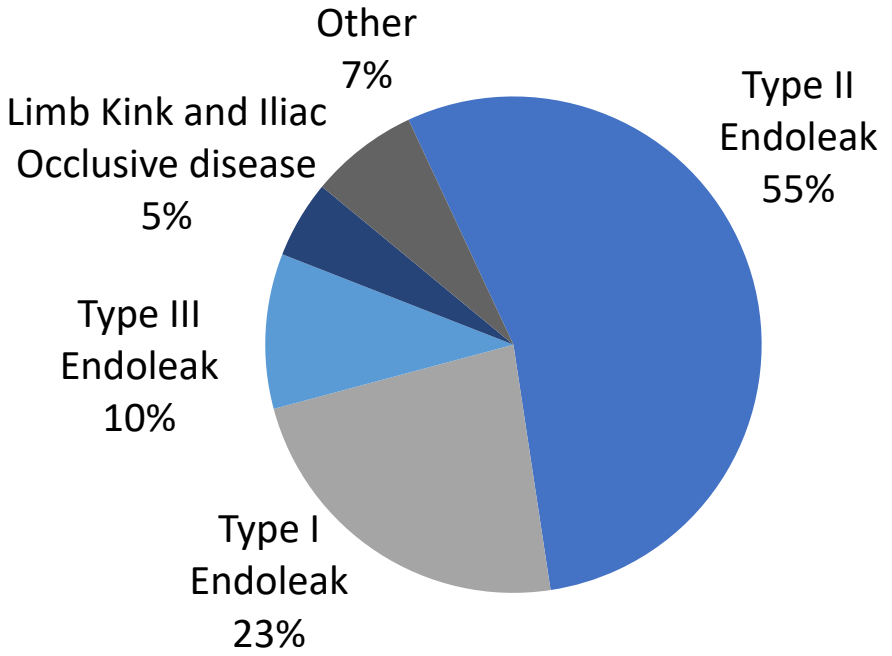
Longer-Term Disadvantages of EVAR

- Higher re-intervention rates **(EVAR-1, Dream, and Over Trials)** related to:
  - Device patency
  - Aneurysm sac expansion
  - Endoleaks
- Peri-operative survival advantage of EVAR not maintained over time
  - **Long-term survival similar after 3 years**
- Need for long-term imaging follow-up with radiation and intravenous contrast
- Higher risk of late aneurysm-related death post-EVAR
- A review of **79,932 Medicare** patients through 8 years of follow-up:
  - Aneurysm rupture EVAR 5.4% vs. open surgery 1.4%
  - Aneurysm-related reinterventions EVAR 18.8% vs open surgery 3.7%
  - Similar long-term all cause mortality

Chaikof E, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018; 67(1):2-77.
Antoniou G, et al. Endovascular vs. Open Repair for Abdominal Aortic Aneurysm: Systematic Review and Meta-analysis of Updated Peri-operative and Long Term Data of Randomized Controlled Trials. Eur J Vasc Endovasc Surg (2020) 59, 385-397
Schermerhorn M, et al. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. N Engl J Med 2015;373:328-338.

Longitudinal Outcomes of EVAR

- Retrospective review of a 16-year EVAR experience (1,835 EVARs performed between 2000-2016) from the University of Pennsylvania: Overall re-intervention rate was 7.5%.
- Reinterventions were performed as far out as 8 years following EVAR
  - 80%: ≤2 re-interventions
  - 13%: 3 re-interventions
  - 7%: ≥4 re-interventions
- Mean time to first re-intervention 2.3 ± 2.5 years
- Most common causes of re-intervention
- Most common cause of open conversion and explant:
  - Type II endoleak and sac expansion



Fairman AS et al. Characterization and outcomes of reinterventions in Food and Drug Administration-approved versus trial endovascular aneurysm repair devices. J Vasc Surg. 2017 67(4): 1082-1090.

Current Realities

- Long-term disadvantages of EVAR are not specific to individual devices
- Long-term follow-up pivotal study outcomes
  - Aneurysm-related mortality at 5 years: 1% - 2.5%
  - Aneurysm rupture: 0 - 2.3%
  - Conversion to open surgery: 0 - 3.8%
  - Aneurysm sac expansion at 5 years: 4.3% - 5.8%
- Current US practice demonstrates liberal use of EVAR
  - Anatomic inclusion/exclusion applicability for EVAR based on device IFUs ≈ 50%
  - EVAR use anatomies outside the IFU is predictive of sac enlargement and late rupture
- Rates of readmissions and multiple re-interventions ≈ 7% - 20%

Medtronic Endurant, Zenith AAA, and Zenith Fenestrated Instructions for Use and annual clinical updates
Oderich et al. Final 5-year results of the United States Zenith Fenestrated prospective multicenter study for juxtarenal abdominal aortic aneurysms. J Vasc Surg. 2020 Vol 73(4).
Sternbergh et al. Redefining postoperative surveillance after endovascular aneurysm repair: Recommendations based on 5-year follow-up in the US Zenith multicenter trial. S Assoc Vasc Surg. 2008 Vol 48 (2).

Current Realities

- Follow-up imaging surveillance noncompliance ≈ 60% with gaps 3-4 years after EVAR
- Rates of sac enlargement at 5 years ≈ 41%
- Endoleak occurs in 1/3 of all EVARs
- Type I, II, III Endoleaks may develop years after EVAR*
  - Need for long-term follow-up of patients with EVAR devices
- Type II endoleaks:
  - Persistent Type II endoleaks (15%) may result in sac expansion (25%) and require multiple re-interventions
  - Delayed Type II endoleaks occur and may result in sac expansion
  - In up to 60% of patients treated for Type II endoleak, aneurysms continue to expand
  - Effective treatment of Type II endoleak remains a challenge post-EVAR

**Chaikof E, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018; 67(1):2-77.*
See FDA Executive Summary for references regarding rates reported

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Current Regulatory Paradigm for AAA Endovascular Devices

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Pre- and Post-Market Balance

- FDA's mission is to protect public health and promote innovation
  - Adequate information for reasonable assurance of safety and effectiveness
  - Avoid a data burden so high that innovative devices do not get to market in a timely fashion
- FDA balances pre- and post-market data to make regulatory decisions for new AAA devices
  - Pre-market data: typically, one-year clinical data and supportive non-clinical data
  - Post-market data: longer-term clinical data

Pre-market Evaluation to Support a New AAA Device

- Non-clinical data
- Clinical data
  - Study Design:
    - Multi-center prospective, single-arm clinical study
    - Samples size of 150 to 200 patients at 25 to 40 investigational sites
  - 30-day composite primary safety endpoint
  - 12-month composite primary effectiveness endpoint
  - Secondary safety and effectiveness endpoints through 5 years

Pre-market Evaluation to Support a New AAA Device

30-Day Composite Primary Safety Endpoint	1-Year Primary Effectiveness Endpoint

• AAA related mortality
• Myocardial infarction
• Stroke
• Renal failure
• Respiratory failure
• Paraplegia
• Bowel ischemia
• Procedural blood loss of 1000 cc or greater
	• Technical success at the conclusion of the procedure
	• Absence of the following through 1 year:
	  • Aneurysm enlargement
	  • Device Migration
	  • Device integrity issues
	  • Conversion to open surgical repair
	  • Aneurysm Rupture
	  • Type I and III endoleaks
	  • Device occlusion

Pre-market Evaluation to Iterative Device Changes

- Devices frequently undergo changes following approval
- Evidence to support a change to an approved AAA device
  - Non-clinical data alone may be sufficient to support approval
    - E.g., minor change to the delivery system
  - Significant changes may require non-clinical and clinical data
    - E.g., expansion of indications for use
    - E.g., change in mechanism of delivery system

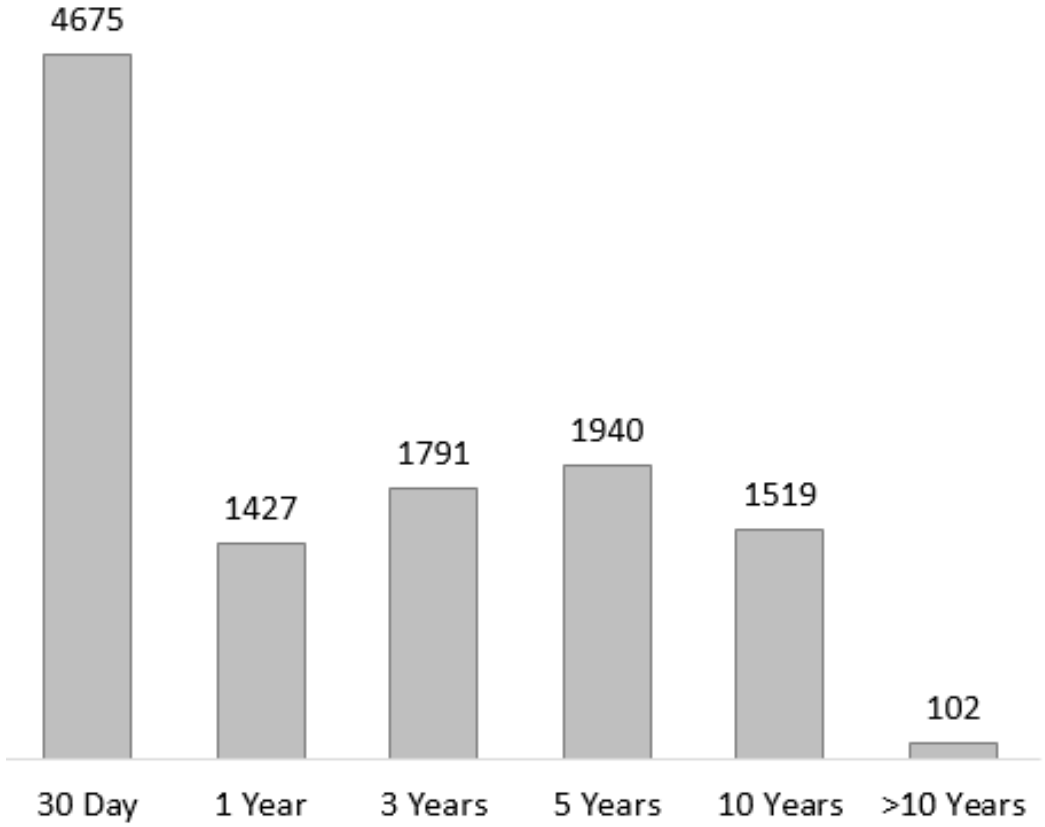
Post-market Evaluation

Both new and modified devices have post-commercialization requirements:

- **Continued follow-up** of pivotal study subjects through 5 years
- New **post-approval studies** may be required as a condition of approval
  - Real-world data collection
  - Clinical data on a subset of patients experiencing specific events
  - Information on the translation of pivotal study results to real world use
- Annual clinical update to physician users

Medical Device Reports (MDRs)

- MDRs are submitted by:
  - Mandatory reporters (manufacturers, importers, and device user facilities)
  - Voluntary reporters (health care professionals, patients, and consumers)
- Figure reflects number of MDRs for all approved AAA devices sorted by time to event occurrence
- Available data shows that long- term events continue to occur



Time to Event Occurrence

Medical Device Reports (MDRs)

Strengths	Limitations
- All stakeholders may submit reports - Ease of trending coded information - Usually reports relevant timelines (date of implant and event) - Can capture longer term events - Allows for narrative description of the event	- Reports may be incomplete, inaccurate, untimely, unverified, or biased - Events are under-reported - Denominator of devices implanted is not available - Imprecision in coded information means trending is time-intensive

Role of Long-term Surveillance

- Current regulatory paradigm may not capture:
  - Real-world use of devices
  - Long term outcomes (5 years and beyond)
  - Iterative device changes implemented post-market
- Considerations for a surveillance platform:
  - Long-term data collection of key outcomes of interest following EVAR
    - Clinical events
    - Imaging surveillance
  - High level of data quality
    - Data monitoring and auditing
    - High levels of follow-up compliance/reduce missing data

Surveillance Outcomes of Interest

Imaging-based Assessments	Clinical Assessments
Loss of Device Integrity	All-cause mortality
Aneurysm Size	AAA-related mortality
Endoleak	EVAR Reintervention
Device Occlusion/Stenosis	Aneurysm rupture
Device Migration	Conversion to open repair

Key outcomes that are clinically meaningful and feasible to capture through real-world surveillance.

Resources and Mechanisms for Real World Surveillance

- Real-world data resources:
  - Medical Device Reports (MDRs)
  - Single-site and regional health system database
  - Literature publications
  - Claims-based and registry-based sources
- Regulatory Mechanisms:
  - Condition of PMA approval
  - Post-market surveillance order (522 order)

Key attributes a real-world surveillance infrastructure should incorporate

Strategies to incentivize relevant stakeholders to participate in real-world data collection.

EVAR Device Regulatory Paradigm Summary

- FDA applies least burdensome principles and pre- and post-market balance
  - Allows for timely device approval based on a reasonable assurance of safety and effectiveness
- Current regulatory paradigm for new AAA devices:
  - 1-year safety and effectiveness pivotal study data for marketing approval
  - 5-year follow-up of pivotal study subjects collected post-market
  - New enrollment post-approval studies, as needed
- Long term real-world outcomes of interest are not adequately captured
- Several mechanisms exist to facilitate real-world data collection

Conclusion of FDA Presentation

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FDA Conclusions

- Pivotal study outcomes at 5-years and long-term real-world data indicate significant adverse clinical events continue to occur post-EVAR
- There is uniform agreement that long-term follow-up is indicated post-EVAR
- While surveillance is critical to understanding long-term real world device performance, clinical and imaging outcomes have been challenging to capture by current surveillance methods
- EVAR patients and physicians would benefit from knowing the rates of important clinical adverse events to an adequate degree of precision
  - For this, large numbers of patients followed post-market are needed
- A high quality robust post-market surveillance system is aligned with FDA's mission to protect public health and our TPLC approach to device regulation

Questions for the Panel

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Questions for the Panel

Question 1:

Please discuss the safety and effectiveness of endovascular stent grafts in the treatment of abdominal aortic aneurysms stratified by near-term and long-term outcomes.

Questions for the Panel

Question 2a:

Available long-term data demonstrate that adverse events continue to accrue post-EVAR. Please discuss which of the following real-world clinical outcomes should be assessed in a long-term EVAR surveillance system:

- All-cause mortality
- Aneurysm-related mortality
- Aortic rupture
- Aortic reinterventions
- Others

Questions for the Panel

Question 2b:

Although imaging outcomes are collected in pre-market and FDA-required post-market studies, these studies have a modest sample size, and it is challenging to collect serial imaging data in real-world surveillance. Please discuss the importance and feasibility of the capturing the following imaging outcomes in real-world surveillance:

- Endoleaks
- Loss of device integrity
- Aortic enlargement
- Device migration
- Device patency

Questions for the Panel

Question 3:

Please discuss whether strengthening existing real-world surveillance is needed to evaluate long-term real-world EVAR performance.

Questions for the Panel

Question 3a:

If so, please discuss the key attributes that should be included in a real-world surveillance infrastructure to assure high quality and clinically useful long-term EVAR device evaluation (e.g., enrollment strategies to address potential selection bias, data monitoring and auditing, event adjudication, core labs, major endpoints, statistical analysis plan).

Questions for the Panel

Question 3b:

Please discuss the frequency and duration of surveillance for patients post-EVAR that would be clinically meaningful and feasible to capture through a real-world surveillance infrastructure, including recommendations for patients who undergo aortic reintervention.

Questions for the Panel

Question 3c:

Please discuss strategies that can incentivize relevant stakeholders to participate in real-world data collection on a routine basis.

Questions for the Panel

Question 3d:

Please comment on how device manufacturers, health care systems, professional societies, individual providers, and other stakeholders should collaborate to maximize long-term follow-up compliance and data quality on EVAR device performance.

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Thank You

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Clarifying Questions from Panel for FDA

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Combined Industry Presentation

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Combined Physician Presentation

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Clarifying Questions from Panel

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Relevant Infrastructure Presentation

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Clarifying Questions from Panel for OCEA

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Lunch Break

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Invited Guest Speaker Presentations

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Clarifying Questions from Panel for Guest Speakers

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Open Public Hearing

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15 Minute Break

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Panel Deliberations

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Summary of Panel Deliberations

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