SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL

November 2, 2021

Via Zoom Videoconference

Attendees:

Chairperson

Richard A. Lange, M.D.
Texas Tech University Health Sciences Center
El Paso, TX

Voting Members

Randall C. Starling, M.D.
Cleveland Clinic
Cleveland, OH

Jason T. Connor, Ph.D.
ConfluenceStat, LLC
Cooper City, FL

James C. Blankenship, M.D.
University of New Mexico
Albuquerque, NM

Keith B. Allen, M.D.
St. Luke's Mid America Heart & Vascular Institute
Kansas City MO

Temporary Non-Voting Members

Keith A. Horvath, M.D.
Association of American Medical Colleges (AAMC)
Washington, D.C.

Ralph G. Brindis, M.D., M.P.H.
AC Wellness Network
San Francisco, CA

Minhaj S. Khaja, M.D., M.B.A.
University of Virginia
Charlottesville, VA

Edwin C. Gravereaux, M.D.
Brigham and Women's Hospital
Boston, MA

Karen Woo, M.D., Ph.D.
University of California
Los Angeles, CA

Alex D. Shepard, M.D.
Henry Ford Health System
Detroit, MI

Joaquin E. Cigarroa, M.D.
Oregon Health & Science University
Portland, OR

Albert G. Hakaim, M.D.
Mayo Clinic
Jacksonville, FL

Matthew T. Menard, M.D.
Brigham and Women's Hospital
Boston, MA.

Industry Representative

Gary J. Jarvis, B.S.
Alfa Medical
Eden Prairie, MN

Patient Representative

Paul T. Conway, B.A.
Conway Strategies Global
Falls Church, VA

Consumer Representative

Jacqueline S. Alikhaani, B.A.
Healthcare Consumer/Volunteer
Los Angeles, CA

Food and Drug Administration

Bram Zuckerman, M.D.
Director, Office of Health Technology 2 (OHT 2: Cardiovascular Devices)
Office of Product Evaluation and Quality

Akinola A. Awojope, Dr.PH, M.P.H.
Designated Federal Officer

CALL TO ORDER
PANEL INTRODUCTIONS

Panel Chairperson Richard A. Lange, M.D., MBA, called the meeting to order at 9:00 a.m. He noted the presence of a quorum and affirmed that the Panel members had received training in FDA device law and regulations. He announced that the Panel would be discussing and making recommendations on information related to the benefit-risk profile of the Endologix AFX endovascular graft system with regard to the risk of Type III endoleaks.

He then asked the Panel members and the FDA staff to introduce themselves.

CONFLICT OF INTEREST STATEMENT
TEMPORARY NON-VOTING MEMBER STATUS STATEMENT
GENERAL ANNOUNCEMENTS

Akinola A. Awojope, Dr.PH, M.P.H., Designated Federal Officer, read the Conflict of Interest statement and reported that conflict of interest waivers had been issued to Drs. Albert Hakaim, Alexander Shepard, and Randall Starling.

He noted for the record that the invited guest speakers, Drs. Rodney White and Gustavo Oderich had acknowledged interests with affected firms.

He announced that Jacqueline Alikhaani, the consumer representative, had been appointed to serve as a temporary non-voting member, and that Gary Jarvis would be serving as the industry representative.

He then made general announcements regarding speaker identification and transcript availability, and introduced Shirley Simson as the press contact.

FDA PRESENTATION PART 1

Overview of Abdominal Aortic Aneurysms and Type III Endoleaks

Robert Lee, M.D., presented an overview of the cause of aneurysms, risk factors, and current therapies, noting that endovascular aneurysm repair now accounts for over 80% of elective AAA repairs in the United States. He provided examples of EVAR device failure modes and reviewed endoleak classification, emphasizing that Type III endoleaks are the primary concern with the AFX platform. He then provided surveillance images showing an AFX-treated aneurysm with sac shrinkage and no endoleak at eight months that went on to rupture four months later. He emphasized that the development of Type IIIb endoleaks from fabric tears cannot be readily anticipated, making prompt detection and reparation very challenging.

Endologix AFX Device Iterations

Aurko Shaw, MTM, outlined the evolution of AFX stent graft technology. He specified that the AFX2 graft is essentially the same as the AFX with Duraply except for changes in the loading process, graft thickness, and the delivery system. He noted that FDA believes there is uncertainty as to whether these changes have adequately addressed Type III endoleak concerns reported in previous iterations of the device.

Endologix AFX Type III Endoleak Risk: Clinical Reports

Dr. Lee summarized five published single-center reports of AFX Type III endoleak safety risks. He noted that the rates of these occurrences are a continuing concern in data sources that cover AFX Duraply and AFX2 outcomes. He reiterated that there is uncertainty as to whether changes implemented by the manufacturer have effectively addressed these risks for the currently available device.

Regulatory History

Mr. Shaw provided information on mitigation measures put forth by Endologix to address Type III endoleaks that included two recalls, a Class II in 2016 and a Class I in 2018. . He further related that an analysis performed by FDA found that Endologix had the highest proportion of medical device reports for Type III endoleaks compared to all other AAA graft manufacturers for the time period of January 1st, 2016 to July 31st, 2021, and noted that FDA has provided updates on the Type III endoleak concerns stemming from the Endologix AFX products.

Additional Information Provided by Endologix

Mr. Shaw then provided a high level analysis and discussed the strengths and limitations of findings from an analysis of complaint data from the Class I recall letter, the LEOPARD trial, the Vascular Quality Initiative, and the Endologix-sponsored multicenter and CMS studies.

Treatment of Patients with AFX Type III Endoleak Device Failures

Dr. Lee acknowledged that there is limited long-term data to provide guidance on the management of patients who have failed AFX devices due to Type III endoleaks. He briefly reviewed some general principles that could be found in a small number of reports. He noted that the endoskeleton design of the AFX device may make it difficult to achieve an adequate seal by overlapping a new component, that the potential for multiple device interactions causes concern, and that FDA believes it is premature to draw conclusions about the durability of the AFX-in-AFX construct.

Benefit-Risk Profile and Conclusion

Mr. Shaw concluded the presentation with a discussion of risk mitigation strategies and benefit-risk considerations. He indicated that AFX with Strata is associated with a higher probability of Type III endoleaks and that there is uncertainty regarding the effectiveness of abatement tactics for addressing this issue with respect to AFX with Duraply and for the AFX2.

Q&A

Questions and Comments from the Panel:

Keith B. Allen, M.D., asked if AFX-in-AFX is an on-label or off-label approach based on FDA's definitions.

Matthew T. Menard, M.D., asked the following questions:

- To what degree was FDA aware of these problems before the reports came out?
- How closely was FDA looking into it and how successful were these efforts?
- Was Endologix providing information about the problems as they were becoming aware of them?
- What are the best estimates as to what the missing numerator is and the scope of the problem?

Paul T. Conway, B.A., Patient Representative, asked what process FDA uses to collect patient insight data, real-world evidence, and patient-reported outcome information.

Alex D. Shepard, M.D., asked for further clarification on the data that was submitted to the FDA regarding the predecessor device (Powerlink).

Answers and Responses from FDA:

Carmen Gacchina Johnson, Ph.D., affirmed that AFX-in-AFX relining is not an on-label indication. She specified that FDA was not aware of this issue until the initial publications came out, and that Endologix had been aware of it several years earlier. She also provided information on data that has been submitted to the FDA regarding the previous iterations of the device, including the predecessor device.

Bram Zuckerman, M.D., indicated that the sponsor's prior management was not as forthcoming regarding the extent of this matter, and that the Agency is seeking assistance in determining what the real scope of the problem is regarding the AFX2 model.

ENDOLOGIX PRESENTATION PART 1

Introduction

Matt Thompson, M.D., stated that the long-term durability issues with the earliest version of the AFX product family have been addressed, that clinical evidence from nearly 3,000 patients treated with AFX2 confirms a favorable performance profile that is comparable to all other EVAR devices, and that the high incidence of Type III endoleak associated with AFX Strata is acknowledged. He pointed out that all endografts have failure modes and durability concerns, that the spectrum of these deficiencies may be different between endografts of various design, and that all relevant insufficiencies should be considered when evaluating endograft performance. He then described the advantages of the AFX design and introduced the speakers for the remainder of the presentation.

AFX System Updates, Management of AFX Strata

Genevieve Dunbar, Senior Director of Regulatory Affairs, advised the Panel of manufacturing, product design, and labeling updates in the AFX category of devices, and presented data supporting the positive impact these changes have had on the occurrence of Type III endoleaks. She affirmed that these products have been continually monitored, that previously identified concerns have been addressed by the AFX2, and that multiple actions have been taken to provide information to physicians to aid in the management of patients who are implanted with the AFX Strata.

AFX Performance Profile

Dr. Thompson provided a synopsis of clinical datasets and real-world evidence from the LEOPARD randomized controlled trial, cohort studies, case reports, and expert opinions. He also presented data from a retrospective analysis of outcomes achieved with AFX2 endografts in five U.S. centers which he indicated showed that the device is performing acceptably in midterm follow-up with no areas of concern and that all aortic-related outcomes were good.

He concluded that the AFX2 is completely differentiated from previous AFX versions by design, manufacturing, and labeling updates; that AFX2 has a performance profile that is similar to other EVAR grafts in all meaningful outcome measures; and that the Type III endoleak rate is less than 1.5% at four years.

Clinical Perspective

Christopher Kwolek, M.D., shared his clinical experience as a vascular surgeon and principal investigator in more than 20 cardiovascular device trials. He related that the majority of patients choose endovascular repair because it is less invasive than open surgery and does not require long hospital stays. He further related that patients who receive EVAR devices require continual follow up, that 30% will need reintervention within 10 years of implant, and that the informed consent process should clearly and comprehensively outline the benefit-risk of all treatment options. He presented a summary of four-year freedom from outcomes results showing that the AFX system is comparable to other EVAR devices across all key endpoints, and highlighted unique properties that make it an important and clinically relevant treatment option.

Q&A

Questions and Comments from the Panel:

Keith A. Horvath, M.D., asked how the decision was made regarding which comparator device would be used in the LEOPARD trial.

Ralph G. Brindis, M.D., M.P.H., asked for further comment regarding FDA's involvement in the LEOPARD trial and on imaging related issues.

Randall C. Starling, M.D., asked if any of the data from the LEOPARD trial has been peer-reviewed and published.

James C. Blankenship, M.D., asked if risk adjustment, propensity matching analysis, or logistic regression has been done to accommodate for differences such as gender and comorbidities.

Minhaj S. Khaja, M.D., M.B.A., asked for information on the amount of overlap that was required in the different devices, and on mitigation strategies.

Mr. Conway asked the following questions:

- Were patients involved in the medical advisory boards?
- What does the company do to communicate risks to patients in an understandable way?

Joaquin E. Cigarroa, M.D., asked for comment and clarification on the design of the LEOPARD trial.

Dr. Horvath asked for an explanation regarding the 20% difference in imaging percentage rates.

Karen Woo, M.D., Ph.D., asked how the inclusion criteria was determined.

Jacqueline S. Alikhaani, B.A., Consumer Representative, asked the following questions:

- Were family members or caregivers included as part of the leadership team for any aspect of the trial?
- What kind of educational materials were provided to patients?
- Were any surveys conducted with patients, family members or caregivers?

Dr. Shepard asked for further comment on proposed IFU updates with regard to Type III endoleaks. He also asked if treatment of large aneurysms, increased surveillance, and highly calcified bifurcations will be addressed in the new indications for use.

Answers and Responses from Endologix:

Dr. Thompson explained that each investigator in the LEOPARD trial had a choice of the three most common commercially available devices in the United States at that time. One device would then be pre-specified for the initial and all subsequent implants.

He clarified that FDA review was not requested at the start of the study, and explained that the trial was designed as a comparative study in its inception to understand the performance of AFX against a randomized group of commercially available proximally fixated grafts, and that it was intended to be a real-world study in terms of patient

recruitment and surveillance where institutions would follow their own standard protocols.

He informed Dr. Starling that the trial is currently under final review by the *Journal of Vascular Surgery*, that the retrospective 405-patient series has been peer reviewed and revised, and that the CMS data was submitted but has not yet been published.

He affirmed that there were no risk adjustments for the retrospective cohort series and the CMS Medicare data,

He informed Dr. Khaja that inadequate overlap was earlier identified as a partial cause for Type IIIa endoleaks, and that evaluation of the current sizing algorithm has shown a reduction in these occurrences.

He acknowledged that patients were not included on the medical advisory board, that there is language in the IFU regarding patient counseling, and that a brochure is made available to patients in the preoperative period.

He clarified that the LEOPARD study's original design was as a comparative study focusing on performance rather than safety, and assured that there are a sufficient number of patients at 4 and 5 years to look at safety issues.

He assured Dr. Horvath that the discrepancy in imaging percentage rates, caused by differences in logistics and processing, is expected to even out towards the end of the trial.

He explained that patients were included in the trial based on a physician opinion that they would be adequately treated and suitable for the AFX or pre-specified comparator device, and that 30% of the patients in both groups would be considered off label pertaining to the anatomical instructions for use.

He confirmed that patients and caregivers were not involved in the design of the trial, and that the study did not use patient-reported outcomes or quality of life measures as endpoints.

He also noted that the surveillance recommendations in the IFU come from discussions with three medical advisory boards and are aligned with guidelines published by the Society of Vascular Surgery and the European Society of Vascular Surgery, and that it has specific warnings and precautions regarding large aneurysms, tortuous aneurysms, and the risk of Type IIIb endoleaks with calcified bifurcation.

OPEN PUBLIC HEARING

Nathan J. Aranson, M.D., discussed the results of a study conducted by the Maine Medical Center on long-term outcomes of the AFX1. He observed that long-term AAA-related complications are significantly higher in patients treated with the AFX1 as compared to conventional endografts, that patients with late-term endoleak or sac growth should be considered for reintervention promptly, and that the risk of mortality is higher with graft explant than it is with relining.

Zachary J. Wanken, M.D., M.S., reviewed the findings of a comparative study done on Strata and non-Strata AFX devices regarding the effect of fabric formulation on outcomes. He noted that most of the reinterventions on Strata-based devices were for Type III endoleak, that one in four patients who were treated with AFX devices suffered a major adverse event within four years of their EVAR procedures, and that relinings, which accounted for more than one-third of reinterventions, were generally performed more than two years post-op.

Kimberly A. Gerling, M.D., presented conclusions from a midterm analysis of AFX devices conducted at Walter Reed National Military Medical Center. The study cohort consisted of 100 patients who underwent endovascular AAA repair with either the Strata, Duraply, or the AFX2 for the period of time between 2011 to the present. Patients with aneurysmal disease were included, while those with incomplete records or aortoiliac occlusive disease were excluded. She reported that the total endoleak rate was 12% for the Strata, 32% for the Duraply, and 23% for the AFX2, and includes all endoleak types. In addition, the most common indication for a major reintervention was either a Type I or III endoleak or an occlusive event in one of the limbs.

Harvey Edward Garrett, Jr., M.D., stated that he has implanted 41 patients with the Strata, that he has only had to reline eight of them, and that there have been no further problems. He further stated that he has done 30 total explants of endovascular aneurysm devices and that of those 30, two were AFX, and that he has only had two Type III endoleaks from over 200 implants with AFX devices since 2007.

Naiem Nassiri, M.D., RPVI, averred that anatomic fixation, externally mounted fabric, a low-profile delivery system, and a novel unibody design are features of the AFX2 platform that make it an exceptional, invaluable, and essential tool that eliminates the need for contralateral cannulation in unfavorable or hostile aortic anatomies. He affirmed that in his practice, Type III endoleaks with the AFX2 have not been a concern in carefully selected patients with appropriate anatomy suitable for the device.

Mark Conrad, M.D., emphasized that there is no single device that is able to handle every anatomy and that it is important to have options when treating patients. He opined that the design of the Endologix graft offers an advantage in several situations, that the endoleak problem has not been unique to the AFX device, and that durability has been compromised with the push for smaller devices.

Art Sedrakyan, M.D., Ph.D., provided information about MDEpiNet and its work in building coordinated registry networks. He presented results from a study of an Australian registry that found early benefits of EVAR as well as a higher risk of mortality starting from Year 1 onwards and that secondary aortic interventions occur more often after EVAR. He further related that a comparison of major device types in Australia found no differences in terms of overall mortality, but that there could be dissimilarities among them with respect to secondary aneurysm repair and aortic interventions.

Diana Zuckerman, Ph.D., spoke on behalf of the National Center for Health Research. She highlighted results and conclusions from FDA's memo stating that there appears to be a higher than expected rate of Type III endoleak with the AFX system regardless of the device iteration. She noted that there is lingering uncertainty about mitigation measures implemented by Endologix and that there are other EVAR devices on the market that have been proven to be safer. She advised the Panel that coordinated registry networks provide useful evidence, and that the CRN for vascular devices can compare the experiences of patients with various types of devices worldwide.

Gary Lemmon, M.D., provided details about Indiana University's failure mode analysis of the Endologix endograft. He reviewed the results of an assessment of 83 Endologix patients in a cohort that also consisted of Cook, Gore, and Medtronic patients. For the Endologix group, there was a total of 38 major adverse events and more than 20 of the reinterventions were for Type III endoleaks. He noted that the Type IIIb endoleak event rate was 9.6% compared to 0.22% reported by the core lab and that these events were sporadic, non-predictable, and occurred anywhere from six to 51 months.

Q&A

Questions and Comments from the Panel:

Mr. Conway asked Dr. Aranson what he tells patients about the device based on the data he has seen at his center. He also asked Dr. Nassiri if the data are flawed based on the outcome that was selected.

Dr. Lange asked Dr. Lemmon to clarify his interactions with the sponsor

Dr. Menard asked if it would be possible to know the conflicts of interest of the open public hearing speakers who were supportive of the graft. **Chairperson Lange** clarified that FDA requested this but OPH speakers are not required to provide this information

Dr. Blankenship requested clarification regarding patient subsets, specifically asking if there are patients that no endovascular alternatives to AFX exist.

Answers and Responses from the Open Public Hearing speakers:

Dr. Aranson informed Mr. Conway of the steps his center takes to proactively contact patients, and **Dr. Lemmon** expounded further on his encounters with the sponsor.

Dr. Nassiri responded to Dr. Blankenship by providing additional details regarding his experience with the AFX2. He specified that it is not his go-to device for typical fusiform aneurysms, but that it does serve a purpose for certain anatomic configurations that would strain the capability of current alternative platforms.

He informed Mr. Conway that he does not think there is any data misrepresentation, but that the discussion needs to be more in depth in terms of how the indications for use are considered for this platform versus others.

CLINICAL RESEARCH GROUPS PRESENTATIONS

Kaiser Permanente

Robert W. Chang, M.D., presented results from a retrospective matched cohort study of patients who received infrarenal EVAR from 2011 to 2017. The treatment of interest was the Endologix group consisting of 491 patients stratified by Strata and Duraply subtypes.

The comparison group was a combination of the three highest-volume commercially available devices used across the system numbering 2,134 patients.

The hazard ratio results for the treatment group were 1.55 for Type I endoleak, 38.84 for Type III endoleak, and 5.76 for risk of revision more than one year out from surgery. In addition, the treatment group had increased risk of requiring conversion to open repair, rupture, and aneurysm-related mortality. Breakout analysis of Strata and Duraply subgroups showed similar findings for the Strata device. An increased risk of Type III endoleaks and revision at three years post-implantation was seen for Duraply.

He then discussed strengths and limitations of the study and concluded that health systems should continue to follow these patients closely to ensure ongoing device integrity.

VQI-VISION

Philip Goodney, M.D., M.S., discussed the methodology used in VQI-VISION datasets and presented findings from an observational cohort study on the effect of device type in EVAR on the long-term risk of reintervention, late aneurysm rupture, and long-term survival. He described the results of the analysis by comparisons of crude data, propensity matched comparisons adjusting for patient characteristics, and Cox proportional hazard models.

He reported that the rate of reintervention was highest for the early generation Endologix device at approximately 40% in seven years; overall survival did not differ by device type and was similar between both generations of AFX devices and all other devices; and late rupture risk was 2.1 times as high in the early Endologix group but was not significant in the late Endologix group. He noted that the analysis demonstrates device-specific variation in the real-world risks of reintervention and late rupture after EVAR, and that signal models suggest that these indications became apparent approximately five years after implantation.

He then concluded that these data suggest that future efforts should consider systematic approaches to monitor, compare, and benchmark long-term EVAR outcomes across devices in real-world practice.

Harvard CMS

Eric A. Secemsky, M.D., M.Sc., presented an analysis comparison of 87,163 Medicare beneficiaries who underwent infrarenal endovascular aneurysm repair with either a unibody or a non-unibody device from 2011 to 2017 with median follow up of over 1200 days. The study used a non-inferiority design with a pre-designated relative margin of 5% and was split into different periods based on graft availability. A sensitivity analysis was also performed to assess the impact of un-measured confounding with the use of falsification endpoints.

He then presented a series of evaluations based on different time points corresponding with graft accessibility, looked at the strengths and weaknesses of the analysis, and made the following conclusions:

- Unibody (AFX) devices failed to meet non-inferiority at the composite endpoint in comparison with non-unibody devices.

- Findings were robust to the evaluation of confounding with the use of falsification endpoints.
- Risks of secondary endpoints persisted in more contemporary time periods, suggesting the possibility of continued risk associated with newer unibody endograft device iterations.

FDA PRESENTATION PART 2

FDA Perspective on New AFX Data Analyses

Dr. Lee reviewed the newly submitted data and made the following conclusions:

- The Kaiser Permanente study showed an increased hazard ratio associated with AFX Duraply versus the comparative EVAR group for Type III endoleaks, aortic reinterventions, aneurysm rupture, and aneurysm-related mortality.
- The VISION-VQI study found no significant difference in the event rate for aortic reinterventions or aortic rupture between the late AFX device versions and the comparator group.
- The SAFE-AAA study showed that there is an increased hazard risk associated with the late AFX unibody versions versus the comparator groups for aneurysm rupture, graft relining, and several clinically meaningful composite endpoints including the composite of aneurysm rupture, graft relining, endograft extension, or conversion to open repair.
- FDA believes that the SAFE-AAA study provides the most robust analysis; it had the largest sample size and longest follow-up, provided the most comprehensive event rate assessments, and used more advanced statistical methodologies.

He stated that despite the new data, there is continued uncertainty as to whether the AFX stent graft design, manufacturing and labeling changes, and the available clinical data have adequately addressed Type III endoleak risks for the AFX2.

ENDOLOGIX PRESENTATION PART 2

Endologix Perspective on Additional Data Provided by Clinical Research Groups and Overall Conclusions

Dr. Thompson clarified that the changes made by Endologix to address Type III endoleaks were clearly identified in the 2014 and 2015 annual progress reports submitted to FDA. He then made the following conclusions regarding the data presented by the clinical research groups:

- Kaiser Permanente:
  - No analyses were made of the 23 patients with AFX2.
  - The company received no details on the AFX Duraply analysis and cannot comment.

- Harvard CMS:
  - The cumulative primary composite endpoint and rupture rates demonstrate that updates to the AFX product family have improved outcomes, and that AFX2 is comparable to non-unibody EVAR devices.

- VQI-VISION:
  - The study provides an extensive dataset that analyzes individual graft performance.
  - The results reveal that updates to the AFX product family have improved outcomes.
  - The data demonstrate that AFX2 has outcomes that are similar to currently available endografts.

He pointed out that the new information shows that AFX2 has a low rate of Type III endoleaks out to four years and that it has an overall safety performance that is similar to other EVAR grafts currently used in the United States.

Q&A

Questions and Comments from the Panel:

Dr. Menard commented that one of the confusing points is the time frames of the analysis of AFX2 versus AFX1 and the other AFX products. He asked Drs. Goodney and Secemsky how easily ththe device iteration data could be completely differentiated in the future, and if it would be possible to go back and use unconventional ways of identifying the exact grafts that were used.

Dr. Cigarroa asked if there are concerns that the exclusion of patients with more extreme peripheral arterial or distal aortic disease may decrease the ability to detect some of the issues surrounding endoleaks, particularly in the LEOPARD trial.

Chairperson Lange asked Endologix to clarify if the Instructions for Use clarifies conditions in which the physician should not use the AFX.

Dr. Brindis asked Dr. Secemsky about the challenges of using solely a CMS claims retrospective analysis.

Dr. Horvath asked Dr. Goodney if the three devices used in the comparator group overlap with the devices used in the LEOPARD trial and if so, to what degree.

Dr. Starling asked for more information on the bench testing. He also asked if FDA provides any specific benchmarks in its discussions with vendors.

Dr. Woo asked FDA to expand upon the reason why the Duraply and the AFX2 are considered to be interchangeable and what the difference between them is.

Jason T. Connor, Ph.D., remarked that the Kaplan-Meier curves usually get huge when there is very little data left. He asked if some other type of modeling was used.

Answers and Responses from the Clinical Research Groups:

Dr. Goodney told Dr. Menard that he is hopeful that the registry integration with claims might serve as an effective way to begin the first steps of a deeper investigation of which grafts were used. **Dr. Secemsky** related that he and his research team attempted to obtain sales data from Endologix to better understand which grafts were the predominant grafts being sold during each period, and that they are also proposing to go back and identify which grafts were placed using Medicare data.

Dr. Goodney told Dr. Horvath that he does not know which devices were included in the LEOPARD trial, and that the three comparator devices used in his group's analysis were the three other major devices that are commonly entered into the VQI registry.

Dr. Secemsky gave his perspective on the challenges of using only a CMS claims retrospective analysis. He noted that the outcome data used for the CMS evaluation is similar to the outcome data used for the VQI assessment. He also addressed comments made about the methods and overall interpretation of the SAFE-AAA study.

Dr. Goodney explained that the sample size his group was allowed to report diminished to a number that was not reportable at later time periods, and that the reintervention and general outcomes for the AFX device seemed very similar to the comparator devices as shown for that time period in the SAFE-AAA analysis at earlier time periods.

Answers and Responses from FDA:

Dr. Lee specified that the LEOPARD trial was not designed to detect events that should be occurring in single digit rates, and that there is a considerable amount of data to suggest that the comparator devices work well in women and in patients with peripheral vascular disease.

Andrew Farb, M.D., responded to Dr. Starling's question by noting that FDA does not have specific benchmarks, but instead looks at the overall rates in considering the benefit-risk. **Dr. Lee** concurred with these points and noted that we view these risks in context.

Mr. Shaw informed Dr. Woo that FDA believes that the major differences between the AFX2 and prior generations are with the delivery system and graft thickness, and clarified that the differences were not expected to change the safety and effectiveness profile of the AFX2 device.

Answers and Responses from Endologix:

Dr. Thompson verified that the three comparator devices in the LEOPARD trial were

the Medtronic Endurant graft, the Gore Excluder, and the Cook Zenith. He also provided additional bench testing results.

Dr. Thompson clarified that the Instructions for Use does not include recommendations for not using the device in certain conditions.

Dr. Thompson clarified the bench testing references made in the Endologix presentation as referring to AFX-in-AFX bench testing. **Arif Iftekhar, Vice President of Research & Development,** informed Dr. Starling that the Strata graft material passed all of the standard specifications that were required at the time in addition to the provisions for the previous generation material, and that the currently marketed AFX2 graft with Duraply also passed with the same results.

GUEST SPEAKER PRESENTATIONS

Gustavo S. Oderich, M.D., focused his discussion on the underreporting of Type IIIb endoleaks. He explained that systematic reviews produce a limited number of publications that have suitable data, and that the epidemiology and risk factors are largely unknown. He stated that many physicians do not want to deal with the paperwork, that imaging can be very inconsistent, and that there is a lack of enforcement regarding reporting of adverse events from regulatory agencies.

Rodney A. White, M.D., presented on the misinterpretation of endoleaks. He showed a slide of an implanted Powerlink with an aberration that eventually resolved which would have been misidentified as a leak under normal circumstances. He explained that with earlier endografts, the flow outside of the stent structure created by the attached fabric would often be misread as endoleaks. He also opined that increased angulation is part of the primary phenomenon with the AFX and Type III endoleaks. He concluded that there is significant pressure by industry to develop lower-profile delivery systems and that in order to get the lower profile, fabrics are getting thinner, less metal is being used, and compromises are made for size reduction.

Q&A

Questions and Comments from the Panel:

Dr. Menard asked Drs. Oderich and White if they have seen similar circumstances where physicians have led the alarm when measures such as complicated aortic repair are not working.

Dr. Allen revealed that he knows of two instances when billowing of the graft fabric was misread as Type III endoleaks. He asked Dr. White if he thinks there is a possibility that some cases are being reported as Type III leaks that are not leaks at all.

Dr. Shepard pointed out that billowing of the graft fabric is entirely different from a Type III endoleak associated with rapid aneurysm expansion or rupture. He asked if either

Dr. Chang or Dr. Lemmon could comment on Dr. White's observations regarding misidentification.

Answers and Responses from the Guest Speakers:

Dr. Oderich stated that he has seen Type IIIb endoleaks with complex fenestrated technology, but not at a rate that was any more alarming than what he has seen with other similar devices. He further stated that the extent of this problem is unknown, and that the imaging quality of CTs can be highly variable.

Dr. White affirmed that it is sometimes seen in other devices where modularity has increased. He cautioned that more parts and less durability creates greater frequency of these occurrences. He also related that he has often had the same experience as Dr. Allen, particularly with the Powerlink.

Answers and Responses from the Clinical Research Groups:

Dr. Chang related that most of the implant surgeons he knows are well aware of the billowing effect, that they are all involved in data entry for the device, and that he is confident that none of the relines performed at his center were due to misreads.

PANEL DELIBERATIONS

Dr. Goodney expounded on his evaluation of the VQI-VISION data and **Dr. Secemsky** addressed concerns about his analysis. He stated that he stands by the endpoints and that the differences can be attributed to a larger representation of U.S. hospitals and patients.

Dr. Chang noted that his study allowed for discernment of Duraply versus Strata and that for the Duraply group, the highest risk was over three years post-implantation.

Dr. Shepard and **Chairperson Lange** asked questions regarding the move from Strata to Duraply, differences in tear propagation and suture retention, and the increased thickness of the AFX2.

Mr. Iftekhar explained that the tolerance was tightened to increase the average thickness of the PTFE layers by 12.5%.

Dr. Shepard pointed out that the sponsor did indicate that these changes were not done in response to a recognition of the Type IIIb endoleaks, but was an attempt to improve the overall performance of the graft.

Ms. Dunbar walked the Panel through a specific timeline of relaying information to FDA and of complaint rates, noting that it became apparent in 2016 that the rates of Type III endoleak were lower with Duraply as compared to Strata.

Questions and Comments from the Panel:

Ms. Alikhaani opined that there needs to be a greater understanding of how patients

feel when these issues are happening.

Dr. Zuckerman asked Dr. Secemsky to provide an estimate of a timeline for the SAFE-AAA Study to provide certainty in their conclusions regarding the outcomes associated with the currently marketed AFX2 device.

Dr. Starling requested information related to patient variables that need to be taken into consideration. He also asked if he should assume that it is impossible to do a randomized clinical trial with the device because there is no comparator.

Dr. Cigarroa asked Dr. Secemsky if he has any concerns that the ability of propensity matching may be flawed due to the unlikelihood of using the device in contrast to one of the others.

Mr. Conway asked Endologix what information they would provide to patients in a shared decision making tool.

Dr. Menard asked Endologix and others if they have used other commercially available grafts to reline AFX grafts. He also asked if there was a way to fill in the gaps of the missing CT data in the LEOPARD trial.

Dr. Zuckerman requested clarification from Endologix regarding the CT imaging requirements outlined in their Instructions for Use. **Dr. Shepard** noted that although the official recommendation for all manufacturers to use annual ultrasound, most manufacturers advise CT scans.

Dr. Allen asked Dr. Zuckerman the state of the current relationship between FDA and Endologix. **Dr. Zuckerman** responded that although it has improved, FDA has tools to ensure that transparency and truthful reporting of data continue to take place.

Answers and Responses from Endologix:

Dr. Thompson acknowledged that patients, families, and caregivers need to play a greater role in the development and evaluation of medical products.

In response to Mr. Conway, he affirmed that the company is open to any methodology that improves shared decision making and dissemination of clinical data to patients and physicians.

In response to Dr. Menard's first question, he noted that in the complaint data, Endologix has noted that other grafts have been used to reline AFX. He noted that the complaint data showed AFX-in-AFX as the most common reintervention, acknowledging the limitations of the complaint data.

In response to Dr. Menard's second question and Dr. Zuckerman's question, he noted that although CT imaging is required as per their Instructions for Use, the LEOPARD trial was a real-world study, not necessarily requiring adherence to the IFU. He also noted that under 65% of patients undergo CT scanning, and that the trial is ongoing, and are expecting more data.

Dr. Kwolek noted that in the LEOPARD trial, medical management is very similar for patients regardless of device used in response to Dr. Starling. He acknowledged the uniqueness of the patient populations treated with AFX2, but stated that patients were randomized between two devices that the physician chose between.

Answers and Responses from the Clinical Research Groups:

Dr. Secemsky noted that they would need three more years of data, and that two years of data should be available soon. In response to Dr. Cigarroa, he stated that it is not uncommon to see imbalances in patient characteristics. He described how propensity weights were applied followed by reevaluation of the balance of these attributes, noting that on all measures, equal distribution was seen after weighting. He explained that falsification endpoints were used to ensure that the balance was accurate and noted that adjustment was not done in the Endologix CMS analysis.

Dr. Goodney informed Dr. Starling that some variations were seen in the VQI registry-based analyses, and provided further detail on the advantages of linking registry data to claims.

FDA QUESTIONS

Mr. Shaw read Question 1A: Please discuss the strength of the evidence that the AFX family of devices (and the AFX2 device in particular) is associated with a clinically meaningful increased rate of Type III endoleaks (considering all Type III endoleaks and Type IIIa and Type IIIb endoleaks).

There was general discussion about the need for more data on the AFX2. **Dr. Allen** commented that removal of the device would have an impact on patient populations who are benefitted by it. He asked if certain controls could be put in place. **Dr. Bram Zuckerman** asked him if he has seen actual data to support the claim that it is a niche device.

Edwin C. Gravereaux, M.D., emphasized the difference between the two types of Type III endoleaks, and noted that there seems to be a learning curve and that more data is needed on graft integrity. **Drs. Menard** and **Woo** identified safety issues and the long-term consequences of EVARs as the most important aspects, while **Dr. Shepard** stressed the need for accurate longitudinal studies on the AFX2.

Mr. Conway stated that he has reservations about the data, **Dr. Starling** affirmed that the risk is clearly defined for the earlier devices, and **Dr. Menard** contended that the device does not fill a critical niche.

Chairperson Lange noted that the Panel believes there is an increased risk of Type III endoleaks with the earlier devices and there is no assurance that the AFX2 has been improved.

Mr. Shaw read Question 1B: Please discuss the effectiveness of the Sponsor's mitigation strategies (including device design and manufacturing changes and updated

instructions for use) to lower the Type III endoleak risk.

Dr. Horvath pointed out that the company never made claims that a Type III endoleak risk was being addressed and that he does not think the modifications were made to specifically resolve the problem. **Drs. Shepard** and **Cigarroa** agreed.

Dr. Gravereaux believed that the sponsor has had a sufficient response to both of the types of Type III endoleaks.

Dr. Khaja remarked that the changes did not appropriately address the issue. **Mr. Conway** and **Ms. Alikhaani** expressed similar sentiments.

Dr. Allen noted that he is unsure if the problems have been fixed with AFX2.

Dr. Cigarroa recommended additional bench testing on the fabric's performance and **Dr. Shepard** commented that the mitigation strategies were really product design improvements.

Chairperson Lange noted that there is not much conviction that these are adequate mitigation strategies. He further noted that the company has been reluctant to admit that the graft should not be used in certain patient populations that have a higher risk of developing endoleaks.

Mr. Shaw read Question 1C: Considering your responses to Questions 1A and 1B, please discuss additional strategies (such as instructions for use or other labeling changes) that could prevent, mitigate, or treat Type III endoleaks that may be associated with the AFX family of devices, particularly the AFX2 device.

A brief discussion occurred regarding situations where the graft should and should not be used, about its use as a niche device, and procedural variations.

Dr. Starling asked the surgeons if they feel that detailed instructions should be provided regarding technique and patient selection.

Drs. Shepard, **Khaja** and **Woo** made the following recommendations:

- better guidance to company reps, surgeons, and interventionists about appropriate candidates for the device (e.g., taking a look at patient anatomy)
- inclusion of Type III endoleak data in the IFU
- mandatory annual CT scans
- appropriate follow-up of imaging and potential reintervention
- educational campaign

Mr. Shaw read Question 2: Please discuss whether the totality of the data (including postmarket data) continue to support that the benefits of the currently available AFX2 device outweigh the risks.

There was general discussion about routine use, niche use, and "no other alternative" use of the device.

Dr. Allen stated that it is important for it to remain on the market for niche populations, but noted that there are concerns about its routine use for general aneurysms. **Dr. Gravereaux** pointed out that those patients in those niche populations could be more susceptible to Type III endoleaks.

Dr. Blankenship noted that this device would have a favorable benefit-risk ratio to hospice or death.

Mr. Conway pointed out that the company had no patient representative in its presentation, that there was no patient and caregiver data, and no patients were included on the medical advisory board. He recommended modification of the IFU to include an informed shared decision making statement in the frontline indication.

Drs. Starling and Dr. Cigarroa agreed with the incorporation of shared decision making in patient/physician discussions. **Dr. Shepard** contended that these discussions usually end with the patient wanting to know what the physician would do. He recommended that the best approach is to have an informed and educated vascular specialist make the decision about which graft to use.

A straw poll was taken by Chairperson Lange. He asked the Panel the following questions:

1. Does the totality of the data show that the AFX2 benefits outweigh the risks?
   He noted that two panelists raised their hands.

2. Do the AFX2 benefits outweigh the risks for niche use?
   He noted that approximately 70% of the panel members agreed.

3. Do the AFX2 benefits outweigh the risks for "no other alternative" use?
   He again noted that there was approximately 70% agreement.

Mr. Shaw read Question 3: Please discuss whether additional clinical data are needed to further evaluate the safety and effectiveness of the AFX family of devices, particularly the AFX2 device. If you conclude that additional clinical data are needed, please discuss key study elements such as registry infrastructure, enrollment criteria, clinical and imaging endpoints, and duration of follow-up.

Dr. Allen encouraged monitoring the data from the CMS claims database and VQI registry. **Dr. Horvath** agreed.

Dr. Zuckerman asked the panelists to weigh in on the idea of an all-comers registry by the company to capture datasets referred to by the vascular surgeons to determine the most useful subgroups for the device.

Dr. Shepard mentioned the cost of surveillance, but also voiced support for the all-corners data collection.

Dr. Allen hesitated at the concept of an all-comers registry and instead suggested a trial for a new specific indication such as occlusive disease.

Dr. Menard agreed but cautioned focusing on occlusive disease. He voiced support for having the device available but acknowledged the red flags. He pointed out that the CMS and VQI datasets have serious flaws and cautioned against putting too much weight on them.

Albert Hakaim, M.D., noted that VQI is a voluntary database

Mr. Conway emphasized the importance of patient-centric data

Chairman Lange summarized the discussion thus far, pointing out discussions regarding long-term follow-up beyond five years, studies of specific patient groups, patient-centric data, quality of life issues, and mandated annual imaging.

Dr. Khaja recommended cross-sectional imaging with an independent core lab to evaluate distraction of stent components and aneurysmal sac growth over different time points.

Dr. Woo suggested looking for ways to collect more granular data.

Dr. Bram Zuckerman posed the following questions to the vascular surgeons:

- If an unfavorable separation of the curves is seen in continued follow-up, would it make any difference in the level of concern?
- What would cause a change in the prevailing opinion that this is still a useful niche device?

The surgeons unanimously agreed that any signal would engender a modified viewpoint.

FINAL COMMENTS

Ms. Alikhaani agreed that additional clinical data is needed. She requested long-term monitoring, improvements in registry use, uniformity of data and data collection, and accessibility of patient-reported outcomes.

Gary J. Jarvis, B.S., Industry Representative, thanked FDA and the sponsor. He stated that more transparency to physicians is never a bad idea and that he would be interested is seeing how off-label use potentially skews the data. He also stressed the importance of effective dialog between patients and their physicians.

Mr. Conway asserted that quality health care relies heavily on patient/physician interaction and good information that includes patient insight data.

Chairperson Lange thanked all of the participants and commended the Panel members for their commitment to grappling with difficult issues pertaining to the health and safety of patients.

Dr. Bram Zuckerman complimented the Panel on doing an excellent job on a very challenging topic. He also thanked Chairperson Lange for his leadership as the Panel chair.

ADJOURNMENT

Chairperson Lange then adjourned the meeting at 5:54 p.m.

I certify that I attended this meeting on November 2, 2021 and that these minutes accurately reflect what transpired.

Akinola A. Awojope -S Digitally signed by Akinola A. Awojope -S
Date: 2022.11.01 12:12:27 -04'00'

Akinola A. Awojope, Dr.PH, M.P.H
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

/S/

Richard A. Lange, M.D., M.B.A.
Chairperson

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