Cardiovascular Revascularization Medicine 20 (2019) 403–408

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Overview of the 2018 US Food and Drug Administration Circulatory System Devices Panel meeting on the INCRAFT AAA Stent Graft System

Micaela Iantorno, Kyle D. Buchanan, Nelson L. Bernardo, Rebecca Torguson, Ron Waksman *

Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, United States of America

ARTICLE INFO

Article history:
Received 13 February 2019
Accepted 13 February 2019

Keywords:
Abdominal aortic aneurysm
Endoleak
Stent graft

ABSTRACT

On June 12, 2018, the US Food and Drug Administration (FDA) convened a meeting of the Circulatory System Devices Panel to advise on the safety and effectiveness of the INCRAFT® AAA Stent Graft System for the treatment of abdominal aortic aneurysms (AAA) and to consider a premarket approval application sponsored by Cordis, Inc., for Unique identifier: NCT01664078 based on the results of the pivotal INSPIRATION trial (URL: https://clinicaltrials.gov/ct2/show/NCT01664078). The INCRAFT® AAA Stent Graft System is designed for endovascular repair of infrarenal AAAs with complex aortic anatomies. The stent-graft system utilizes nitinol stent and polyester graft technology in an ultra-low profile delivery system, with the goal of isolating the aneurysmal sac and preventing sac rupture. The multicenter, prospective, non-randomized investigation trial met its primary composite safety and effectiveness endpoints but also showed higher-than-anticipated rates of stent fracture and endoleaks. The committee discussion focused on how these events impact the long-term safety and effectiveness, as well as the benefit/risk profile, of the device. While the panel acknowledged the risk of the device, the panel's final vote supported that the benefits of the INCRAFT AAA Stent Graft System outweigh the risks and that a post-marketing study should be mandated. The FDA approved the device for use in complex access anatomies in December 2018.

1. Introduction

1.1. Abdominal aortic aneurysm

In the US, abdominal aortic aneurysms (AAAs) are found in 4–8% of men and 0.5–1.5% of women, with 200,000 new diagnoses every year [1]. AAAs develop under the coexistence of traditional cardiovascular risk factors and altered connective tissue metabolism, such as fragmentation of the internal elastic membrane and loss of smooth muscle cells in the medial of the aortic wall, all of which lead to weakness of the vessel wall and enlargement over time. The most significant complication of AAA is an aneurysm sac rupture, from which >15,000 patients die annually (1% to 2% of all deaths in the Western world) and is the 15th leading cause of death in people between 60 and 85 years of age [2]. Guidelines recommend periodic monitoring of the aneurysm expansion [3]. The usual threshold for elective repair is an aortic diameter of 5.5 cm in men and 5.0 cm in women [4]. AAAs can be treated in three ways: 1) medical management; 2) open surgical repair (preformed since the 1950s); and 3) endovascular aneurysm repair (EVAR) (first performed in 1987) [5]. Perioperative mortality has significantly decreased over time, from 7% to 2% [6], with average hospital stay of 9 days and full recovery expected in weeks to months.

1.2. Endovascular aneurysm repair

EVAR is performed percutaneously with the patient under local anesthesia and has a perioperative mortality of approximately 1% and a hospital stay of 3 days. Full recovery is expected after a few days to weeks. However, the procedure requires appropriate anatomy for intervention that allows introduction of the stent and anchorage to the walls of the aorta. The use of EVAR has significantly increased over time and is currently performed in the majority of the patients with AAAs undergoing intervention [4]. There are 3 major randomized trials that have compared open repair to EVAR with a follow-up of 7 to 10 years: the U.K. Endovascular Aneurysm Repair 1 (EVAR 1) trial [7], the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial [8], and the Open Versus Endovascular Repair (OVER) Veterans Affairs Cooperative Study [9]. All 3 trials show that EVAR confers an initial survival benefit that disappears over a period of ~4 years because of late ruptures and secondary interventions, with similar mortality over 8 to 10 years. The benefit of EVAR includes faster operative time, high degree of patient

Abbreviations: AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; FDA, Food and Drug Administration; MAE, major adverse event; MI, myocardial infarction.

* Corresponding author at: MedStar Washington Hospital Center, 110 Irving St., NW, Suite 4B-1, Washington, DC 20010, United States of America.
E-mail address: ron.waksman@medstar.net (R. Waksman).

https://doi.org/10.1016/j.carrev.2019.02.018
1553-8389/

acceptance, shorter hospital stay, and lower early mortality. The disadvantages of EVAR relate to higher re-intervention rate, need for repeated surveillance testing that requires IV contrast and radiation exposure, and higher risk of AAA-related death. Secondary EVAR interventions include loss of fixation (migration), inadequate seal (device integrity compromise, endoleak, or sac expansion), and patency-related events (occlusion, stenosis, or graft kink/compression). In two large series, secondary interventions were required in 10% and 27% of patients at just over 2 years of follow-up [10,11].

1.3. Endoleak

An endoleak is defined as persistent blood flow outside the lumen of the graft but inside the aneurysm sac or the adjacent vascular segment treated by the device. In one large series, endoleaks occurred in approximately 20% of patients with a mean follow-up of 15 months [12]. Four types of endoleaks have been classified (Table 1, Fig. 1): Type I endoleaks occur at the proximal or distal anastomosis of the graft; type II endoleaks occur as a result of collateral flow into the aneurysm from branch vessels such as the mesenteric or lumbar arteries; type III endoleaks occur between the modular components of the endograft through tears or defects in the graft; and type IV endoleaks occur through pores in the graft fabric. Types II and IV endoleaks are considered benign and often resolve spontaneously, while types I and III are potentially dangerous and require an additional procedure to repair [7]. Of note, type II endoleaks have been associated with worse outcomes despite being considered benign; however, the mechanism is unclear [13]. Sac expansion is a marker of worse outcomes in patients undergoing EVAR and presents in ~9% of the patients undergoing EVAR [14]. To date, a number of EVAR devices are commercially available, with various composition, structure, and delivery mechanisms [15].

2. Highlights from the sponsor's presentation

2.1. Device description

Dr. Shaden Marzouk, Chief Medical Officer of Cordis, introduced the INCRAFT® AAA Stent Graft System (INCRAFT) by describing the unmet need for an ultra-low profile EVAR device that is easy to use and deliver for a wide range of eligible patients with tortuous iliacs and complex anatomies. INCRAFT was developed by Cordis Corporation for the endovascular treatment of infrarenal AAAs. The device consists of 3 main components, including an in vivo adjustable stent graft assembly and an ultra-low profile delivery system (aortic bifurcate prosthesis, ipsi- and contralateral limbs). Placement of the device is comparable to other marketed devices. Proposed indications are: 1) adequate iliac or femoral vessel morphology; 2) proximal neck length ≥ 10 mm; 3) aortic neck diameters ≥17 mm and ≤31 mm; 4) aortic neck suitable for suprarenal fixation; 5) infrarenal and suprarenal neck angulation ≤60°; 6) iliac fixation length ≥ 15 mm; 7) iliac diameters ≥7 mm and ≤22 mm; and 8) minimum overall AAA treatment length (proximal landing location to distal landing location) ≥128 mm. Most devices used to date have larger delivery systems (≥18 Fr) that are more rigid and difficult to deliver in patients with small and tortuous iliacs (Fig. 2).

Table 1
Endoleak definitions.

Type	Source
Type I	Lack of seal at the proximal (1a) or at the distal end of the graft (1b)
Type II	Retrograde branch flow from collateral vessels (i.e. lumbar, inferior mesenteric arteries)
Type III	Lack of seal between components overlapping (IIIa) or through leaks from graft (IIIb)
Type IV	Porosity of the graft identified during the procedure as a blush of contrast within the sac
Type V	No evidence of leak with aneurysm expansion (unknown etiology)

Dr. Robert Bersin, MD, FSCAI, FACC, Medical Director of Endovascular Services and Structural Heart Services at Swedish Medical Center in Seattle, provided a background on EVAR and introduced the clinical perspective on the device's utility. In consideration of the lower perioperative mortality, shorter hospital stay, and faster return to normal activities, the use of EVAR has almost doubled in the US in the last 10 years [16]. Since the introduction of the device in 1999, the technology has evolved dramatically, from a 27 Fr delivery system in 1999 to 14 Fr in 2012. The benefits of a lower-profile device include more flexibility and ease of use for a device that could potentially treat a patient population with small vessels (especially women). It is, in fact, estimated that 10% of men and 51% of women have an iliac vessel diameter < 6 mm. In the US, only 1 ultra-low profile device is approved and utilizes a polymer-based sealing technology (Fig. 3, Table 2). The limitations of the use of ultra low-profile devices include the use of non-conventional stent-graft technology and employment of injectable polymers for sealing that introduce the potential for failure that is more difficult to treat.

2.2. INSPIRATION trial

Dr. Michael Makaroun, co-Principal Investigator of the INSPIRATION trial at UPMC, presented the study design and the trial's primary results. The device was initially tested in the first-in-human INNOVATION trial, which was performed in Italy and Germany and included 60 patients. The INSPIRATION trial is the pivotal study designed to evaluate the safety and effectiveness of the INCRAFT device. The study is a prospective, multicenter, open-label, single-arm trial that enrolled 190 subjects across 32 sites in the United States (134 subjects at 27 sites) and Japan (56 subjects at 5 sites) from July 2012 to August 2013. The follow-up completed was 4 years as of 2018. Subjects were evaluated at 1 month, 6 months, and 1 year post-procedure, with planned follow-up annually until 5 years post-procedure. The study design was similar to that used in recent studies to support marketing approval for other AAA endovascular grafts, with the exception of longer follow-up planned after the identification of higher frequency of transrenal stent fracture. The population enrolled was typical of the subjects with AAA, being mostly older Caucasian men (90%) with cardiovascular risk factors and lung disease. The enrolled population included patients with challenging anatomy, which makes it difficult to draw comparisons with other endovascular devices because of differences in the baseline characteristic of the patient population. Key inclusion criteria are: (1) proximal aortic neck diameter of 17–31 mm; (2) infrarenal aortic neck length ≥ 10 mm; (3) suprarenal and infrarenal angulation ≤60°; (4) AAA size >5.0 cm or diameter increase >0.5 cm over the previous 6 months; (5) aortic bifurcation diameter > 18 mm; (6) iliac landing zone length ≥ 15 mm and diameter 7–22 mm; and (7) minimum access vessel size ≥5 mm. Key exclusion criteria include: (1) ruptured or leaking AAA; (2) mycotic, dissecting, or inflammatory AAA; (3) vascular injury caused by trauma; (4) significant aortic or iliac mural thrombus, plaque, or calcification; (5) conical aortic neck in seal zone; and (6) any aortic dissection.

The primary safety endpoint analysis at 30 days included death, stroke, myocardial infarction, renal failure (requiring dialysis), respiratory failure (requiring mechanical ventilation), paralysis, bowel ischemia, and procedural blood loss >1000 cc. There were 6 subjects with 7 major adverse events (MAEs, 6/190, 3.2%). One subject died of a myocardial infarction (MI). There was 1 subject with a stroke, and 4 subjects had blood loss of at least 1000 cc. There were no cases of new-onset of renal failure, respiratory failure, paralysis or paraparesis, or bowel ischemia. Secondary safety endpoints include MAEs at 6 months, 1 year, and yearly afterward. The reasons behind failures to meet technical success include the device not being deployed at the intended location in 2 subjects and type I endoleaks at the time of procedure completion in 9 subjects (which resolved at the 1-month follow up). Additionally, there were 2 conversions to open surgery, 3 type I endoleaks, and 7 graft

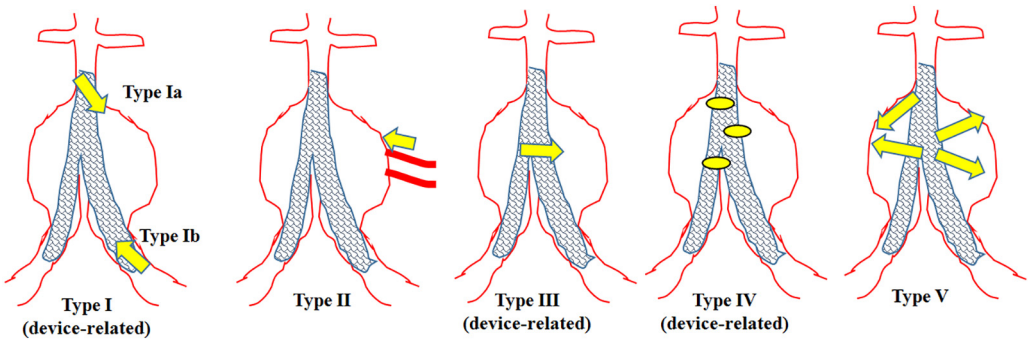

Fig. 1. Endoleak types.

occlusions noted through 1 year. There were no post-operative aneurysm sac enlargements, graft migrations, or aneurysm sac ruptures noted through 1 year. The primary effectiveness endpoint was a composite of periprocedural technical success and the absence of 1-year complications such as aneurysm enlargement, implant migration, conversion to open surgery, aneurysm sac rupture, type I or III endoleak, and graft occlusion. Regarding primary effectiveness endpoints, of 173 patients at 1-year follow-up, 87.9% had successful treatment and periprocedural technical success was 94.1%. Secondary effectiveness endpoints included events at 6 months, 1 year, and yearly afterward. Aneurysm-related mortality was reported in 1 patient (1/190, 0.5%) who died of an acute MI on post-operative day 2. No aneurysm ruptures were reported in the study. Primary effectiveness and safety performance goals were met.

2.3. Identified events of interest

Kenneth Ouriel, MD, MBA, medical monitor for the INSPIRATION study, presented the identified events of interest, which included (1) stent fracture; (2) endoleaks/aneurysm sac enlargement; and (3) occlusions and other patency-related events.

Stent fracture can be described as a discontinuation of the strut in either a cranial or caudal location (Fig. 4). Stent fractures occur in the transrenal portion of the stent, which contributes to the fixation of the endovascular graft to the abdominal aorta and may lead to device migration and type II endoleaks, aneurysm enlargement, and aortic rupture. Dr. Ouriel emphasized that the INSPIRATION trial had to utilize 2 core labs: the first through the end of year 1 and the new one at the beginning of year 2. Core lab 2 retrospectively re-read all the images of year 1. To date, there have been 19 subjects (19/190, 10.0%) identified with at least 1 stent strut fracture in the bare transrenal stent. There have been no clinical sequelae or secondary interventions associated with the observation of transrenal stent fracture(s) reported to date. Of note, core lab 2 read a 4.2% rate of fractures at 1 year compared to the 1.1% identified by core lab 1. The stent fracture rate is higher for the INCRAFT than for other EVAR devices (OVATION 2.5%, ENDURANT 0.7%, and ZENITH 2.6% at 1 year). At 5 years, a total of 38 stent fractures in 19 subjects were identified. Dr. Alan Pelton, PhD, Chief Technical Officer, described a proposed mechanism by which stent fracture occurs and identified cyclic axial compression (i.e., axial length changes in the transrenal aortic region associated with the cardiac cycle) as the root cause. The sponsor has not been able to identify specific risk factors for subjects who are more likely to develop a transrenal stent fracture.

There have been a total of 168 endoleaks of all types observed in the study to date. Of the 168 endoleaks, the majority have been identified as type II (109/168, 64.9%). Type Ia endoleak (at the proximal end) has been observed in 15 subjects, 9 of which were at the time of the procedure (all resolved at 1-month follow-up). A total of 7 subjects had type Ia at follow-up and underwent standard secondary intervention. Type Ib (at the distal end) was observed in 3 subjects. Type II endoleaks (from collateral vessels, n = 109) were observed in 101 subjects, 20 of which (in 16 subjects) were treated with secondary intervention. In 25 subjects, type II endoleak was associated with aneurysm expansion and 12 subjects underwent secondary intervention. Type IIIb endoleak (related to defect in graft material) was observed in 1 subject and treated. No type IIIa endoleaks were observed (related to inadequate seal between graft components). Type IV endoleaks (due to graft permeability) were observed in 33 subjects at the time of the procedure and resolved at 1-month follow-up. One subject was noted to have type V endoleak.

There were a total of 29 subjects with aneurysm expansion noted over the 4-year follow-up. The majority were attributed to type II endoleaks (25/29, 86.21%). Three aneurysm expansions (3/29, 10.34%) were deemed likely attributable to a type I endoleak. One aneurysm expansion (1/29, 3.45%) had no endoleaks observed and was therefore classified as endotension.

Occlusion of the stent was observed in 10 subjects. Two subjects had complete occlusion of the aortic component and both iliac limbs. The other 8 subjects had limb occlusions. All subjects underwent secondary intervention, resolving the occlusion. Stenosis was seen in 16 subjects in the iliac limbs. Seven subjects underwent secondary interventions to resolve the stenoses, and 9 subjects did not require an intervention. The stenosis and occlusions did not recur after the interventions. Secondary interventions completed to address stent graft stenosis or thrombus included the following: conversion to open repair, stent placement, and angioplasty.

There have been no reports of aortic device migration. Five proximal limb migrations were reported. Thirty-five subjects underwent 50 secondary interventions.

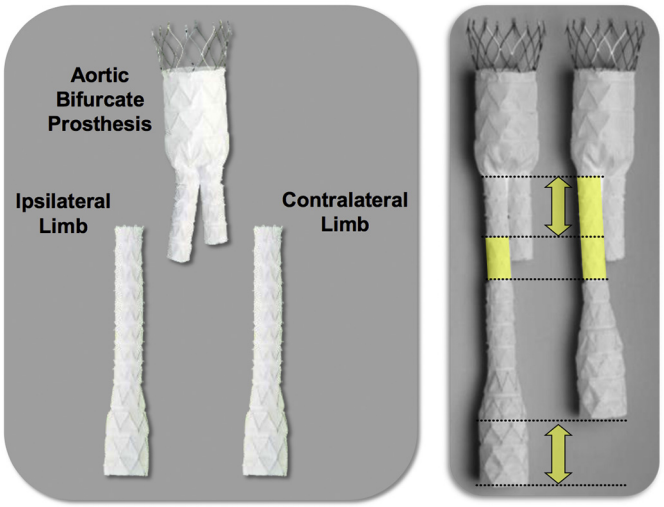

Fig. 2. The INCRAFT device.

Criteria	Ultra Low-Profile	Standard Profile			
	Ovation™	AFX®	Endurant™	Zenith®	Excluder®
					
Year approved	2012	2011	2010	2003	2002
Seal zone material	Polymer	Cobalt chromium	Nitinol	Stainless steel	Nitinol
Delivery profile, min (Fr)	14	19	18	18	18
In situ length adjustment	No	No	Unilateral	No	No
Product matrix	35	127	76	78	59

Fig. 3. Commercially available devices.

2.4. Post-approval study proposal

Dr. Marzouk concluded the sponsor presentation with a proposal for the post-approval study. The INSIRATION and INSIGHT studies will have longer follow-ups, up to 10 and 5 years, respectively. The post-approval study will be a prospective, multi-center, open label study including 30 centers in the US and ~150 patients with the primary endpoint of MAEs at 30 days.

3. Highlights from the FDA presentation

Pre-market approval (PMA) for endovascular grafts is usually based on 1-year effectiveness endpoints. The reported rate of aneurysm-related mortality attributable to INCRAFT device use and lack of aneurysm rupture are consistent with reports from other relevant clinical studies. The FDA raised the issue of the significant rate of complications, such as stent fractures in 10% (19/190), reported in the INSPIRATION trial, which was higher than reported in other device studies. Previously reported rates through 5 years range from 0% to approximately 7% of the patients enrolled. There is currently not a clear understanding of the long-term clinical implications of stent fractures. Clinically significant migration has been reported for early-generation devices that have had fractures. Other issues are related to the incidence of endoleaks, aneurysm expansion, and occlusion. Although caution should be applied in comparing events between endovascular graft studies including different patient populations, the frequency of type Ia and Ib endoleaks during follow-up seems to be higher than the reported rate for other endovascular graft studies (i.e., 5.3% as compared to 0–2%). The frequency of type II endoleaks also is higher than the FDA has seen in most other studies. Moreover, most studies report declining percentages of endoleaks over time, with around 10% for longer-term follow-up, as compared to 36–45% in this study. While the clinical sequelae of type II endoleaks are not clear, 25 out of 29 aneurysm expansions (25/29, 86.21%) were deemed likely attributable to type II endoleak. Similarly, the frequency of patency-related events during follow-up was higher than the rate in other devices, particularly occlusions within 1 year of follow-up (7/189, 3.7% as compared to approximately 1% in the other studies). The rate of secondary interventions (including axillo-bifemoral bypass, conversions to open repair, fem-fem bypass, additional stent grafts, and a variety of other catheter-based interventions) to address patency-related events for the INCRAFT (7.9%, 15/190) was higher than what has been reported for other studies (i.e., rates from 2 to 5%). Other endovascular graft studies reported migrations of the proximal end of the aortic bifurcate component (the highest rate being approximately 2%), with none reported in this study. The Advisory Panel was asked to assess whether the data provide a reasonable assurance of safety and effectiveness and to address the benefit-risk profile of the INCRAFT AAA Stent Graft System when used in accordance with the proposed indications. It is important to note that direct comparisons between endovascular graft designs are not reliable because there are major differences among studies and patient populations.

4. Open public remarks

There was obvious patient appreciation for the device and generally positive remarks from physicians. Mr. William Ward is an 87-year-old electrical engineer who continues to work part-time. After learning he would need repair for a large AAA, Mr. Ward knew that open surgical repair was not an option at his age. He was grateful for the opportunity to receive the INCRAFT device, highlighting that the procedure was successfully performed in a couple of hours with only local anesthetic and safe discharge from the hospital in <48 h. Physicians from around the world with the most experience implanting the device also provided generally positive remarks, and a common theme that the INCRAFT

Table 2
Comparison of indications for use statements with INCRAFT device and commercially available devices.

Criteria	INCRAFT	OVATION	ENDURANT II	AFX	EXCLUDER	ZENITH	Range or limit for commercially available devices
Aortic neck diameter (mm)	17–31	16–30	19–32	18–32	19–32	18–32	16–32
Aortic neck length (mm)	≥10	NA	≥10	≥15	≥15	≥15	≥10
Infrarenal neck angulation (degrees)	≤60	≤60	≤60	≤60	≤60	≤60	≤60
Suprarenal neck angulation (degrees)	≤60	Not specified	≤45	Not specified	NA	≤45	≤45
Iliac fixation diameter (mm)	7–22	8–20	8–25	10–23	8–25	7.5–20	7.5–25
Iliac fixation length (mm)	≥15	≥10	≥15	≥15	≥10	≥10	≥10
Introducer outer diameter (Fr)	AB: 14, 16 IL: 12, 13	AB: 14, 15 IL: 13, 14, 15	AB: 18, 20 IL: 14, 16, 18	AB: 19 IL: 14, 16	AB: 16, 18 IL: 12–18	AB: 18, 20, 22 IL: 14–16	AB: 14 IL:12

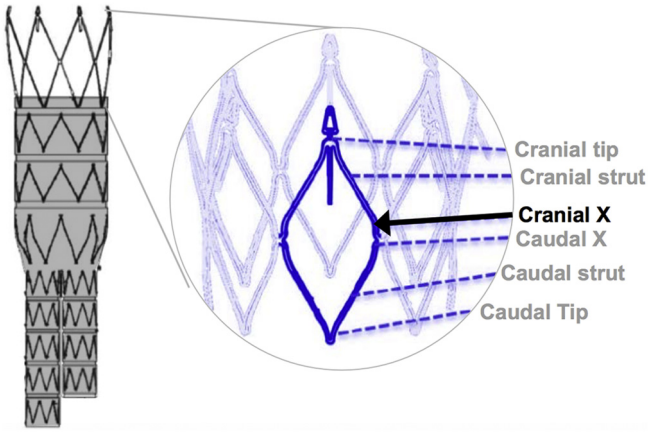

Fig. 4. Stent fracture located to transrenal portion of the stent.

system fulfills an unmet need. Dr. Peter Schneider, a vascular surgeon from Moanalua Medical Center in Honolulu, HI, said the low profile and highly flexible system is beneficial to patients with small vessels, such as women or those of Asian descent, populations that make up a large percentage of his practice.

5. FDA panel questions and deliberations

5.1. Transrenal stent fractures

Following presentations by both the sponsor and FDA, the expert panel deliberated 4 main concerns highlighted by the FDA. The first was in regard to the bare transrenal stent fractures identified in 10% of the INSPIRATION study subjects (19/190) at 5 years. The sponsor stated that there have been no clinical sequelae associated with the observation of stent fractures to-date, namely stent migration or type I endoleaks. As the length of follow-up increases, the number of stent fractures identified also increases. In addition, based on current data, there is no specific patient population or characteristic that has been identified as at risk for such complication. Cordis' bench testing concluded that the reason for such fractures is related to cyclic axial deformation generated by cardiac pulsatility and provided insight into the migration resistance of implants in the presence of such fractures. However, it is not clear how these results translate to the clinical world.

The FDA specifically questioned the panel to comment on whether the lack of known clinical sequelae reported to-date and migration resistance on bench testing are sufficient to mitigate concerns for long-term clinical problems with the observed stent fracture rate. The panel's general consensus was a very low level of concern with regard to stent fracture, concluding the benefits of the device greatly outweigh any risks from stent fracture. The committee and sponsor also noted that zero fractures were identified within the body of the stent graft itself. Panelist Dr. Brandon Propper from San Antonio Military Medical Center on Fort Sam Houston, TX, seemed reassured by the fractures, stating that it is “doing what it's supposed to do,” as the majority of fractures were identified 1-year post-implant after incorporation into the aortic wall and endothelialization.

As noted in the INSPIRATION study, 18 of the 19 subjects with transrenal stent fractures were first identified by the core lab and not the investigational sites, suggesting that patients treated with the INCRAFT device may experience fractures that would not be detected by their regular physicians. The FDA asked the committee whether fracture detection would be needed for appropriate follow-up of patients treated with the device or if standard follow-up would be sufficient. Again, the majority of physicians would not change current follow-up practice given lack of clinical sequelae. However, if complications such as migration, endoleaks, or sac enlargement were identified on standard follow-up, physicians must be diligent in evaluating for the cause.

5.2. Aneurysm expansion

Twenty-nine subjects (15.3%) from the INSPIRATION trial have been observed with aneurysm expansion to date. Three of the 29 (10.3%) were deemed likely attributable to a type I endoleak, while 1 was attributed to endotension. Interestingly, 25 of the 29 were deemed likely attributable to type II endoleaks, which again are caused by retrograde flow from patent branch arteries and traditionally not device-related. There were 101 subjects with type II endoleaks and, therefore, 24.8% were observed to have aneurysm sac expansion. The expansion rate for INCRAFT was higher than that reported for 3 of the currently marketed devices starting at 2 years. Fortunately, there have been no reported ruptures in the study, but the expanding aneurysm sac is at risk for rupture.

The FDA tasked the export panel with commenting on the possible reasons for the observed rate of type II endoleaks and how these subjects should be considered when evaluating the effectiveness of the device. The general consensus was that the type II endoleaks were not device-related, which is in keeping with the definition of type II endoleaks in that there is no theoretical reason for any specific EVAR-device to cause such a phenomenon. In attempts to explain the observation, however, a number of panelists believed it to be a combination of statistical fluke or bad luck and patient selection, postulating that patients with mural thrombus (which is often protective against type II endoleaks) were excluded or the baseline anatomical features of lumbar vessels increased the risk of endoleaks. However, a handful of panelists were concerned that the observed aneurysm sac expansion indicated that the treatment with the INCRAFT device was not effective.

5.3. Benefit-risk analysis

In addition to observation of stent fracture and aneurysm enlargement, the sponsor reported effectiveness-related events, including device occlusions, other patency-related events, and type I endoleaks. Ten subjects with device occlusions and 16 subjects with stent-graft stenoses have been observed in the study to date. All 10 subjects with occlusions and 7 of the 16 subjects with stenoses had secondary interventions to resolve the event and included conversion to open repair, axillo-bifemoral bypass, fem-fem bypass, and relining the INCRAFT device with competitor limbs. In addition, there were 10 subjects with type 1 endoleaks, 3 of which resulted in aneurysm expansion and 8 of whom secondary intervention to resolve the leak. The frequency of type I endoleaks reported through 1 year was twice the highest reported rate for the commercially available devices.

However, the composite primary safety and effectiveness endpoints evaluated at 30 days and 1 year, respectively, were met. Based on the clinical data presented from the INSPIRATION study, including the effectiveness-related observations noted above, the panel generally agreed that the overall benefits outweighed the risks. In addition, the physicians continued to highlight the unmet need the device was providing for a subset of patients with small vessels and complex angulated aorta, saying they were certain that this particular cohort had the most to benefit. All things being equal, in a patient with favorable anatomy, the panel members agreed that the INCRAFT device would not necessarily be their first choice for treatment. The FDA then asked the committee to comment on whether the proposed labeling is acceptable or if warnings or follow-up recommendations should be added. Despite the panel members' agreement that the device is best served for certain subset of patients, they recommended that the labeling remain broad and treatment decision left to the discretion of the surgeon.

5.4. Proposed post-approval study

The sponsor proposed conducting a multicenter, prospective, open-label, observational study to validate the safety and effectiveness of the INCRAFT AAA stent-graft system in routine clinical practice. In addition to long-term follow-up of the 150 INSIGHT study subjects, the study

would enroll approximately an additional 150 de novo subjects at sites around the United States with follow-up through 5 years post-index procedure. The FDA asked the panel to comment on whether any additional study objectives, design features, or surveillance is recommended based on the discussions throughout the day. The panel agreed that the post-approval study is important to evaluate the adverse events identified in the pivotal trial. The physicians agreed that there should be a change of the primary endpoint to some of the more important secondary endpoints outlined in INSIGHT trial. In addition, follow-up imaging needs to be reviewed by participating institutions and the designated core lab to further evaluate incidence and implications of stent fracture while also comparing the sensitivity between imaging specialists. There needs to be careful assessment of endoleaks, how each is treated, and the subsequent outcomes. Finally, the panel agreed that the study must focus on increasing recruitment of female subjects.

6. FDA panel vote

The INCRAFT Stent Graft System is intended for the endovascular treatment of patients with infrarenal abdominal aortic aneurysms with characteristics outlined earlier in the manuscript. After thorough deliberations, the panel voted on the following three questions:

1. On the question whether there is reasonable assurance that the INCCRAFT AAA Stent Graft System is safe for use in patients who meet the criteria specified in the proposed indication, the panel voted 11 “yes” and 4 “no.”
2. On the question of whether there is reasonable assurance that the INCRAFT AAA Stent Graft System is effective for use in patients who meet the criteria specified in the proposed indication, the panel voted 14 “yes”, 0 “no,” and 1 abstained.
3. On the question of whether the benefits of the INCRAFT AAA Stent Graft System outweigh the risks, the panel voted 11 “yes” and 4 “no.”

7. Conclusions

The Circulatory System Devices panel of the FDA Medical Devices Advisory Committee endorsed the premarket approval application for the Cordis INCRAFT AAA Stent Graft System for treating infrarenal abdominal aortic aneurysms. Despite what appeared to be a higher rate of specific adverse events than that reported in a number of other commercially available devices, the overall safety and efficacy composite endpoints were met. The panel thoroughly deliberated the implications of the adverse events, some of which were believed to be attributable perhaps to improved imaging technology, patient selection, and statistical chance. Overall, the consensus was that the device met a specific unmet need for patients with small and tortuous vessels. The panel made recommendations for a high-quality post-market approval study to continue to monitor device performance and further illuminate any important problems with the device.

The open panel meeting served as an important reminder that important EVAR issues are associated with this device. The FDA approved the Cordis device in December 2018. Now, it is essential that operators take time to understand the known benefits and risks of this device to ensure optimal patient care. Despite its interesting design, the Cordis device has not been demonstrated to be a workhorse EVAR device. With thoughtful consideration of its use by the interventionalist, however, it can be a useful tool in the EVAR toolbox. Further study of this device in a well-conducted post-approval study and other venues is necessary to fully understand the role of this device.

Declarations of interest

Ron Waksman: Consultant: Abbott Vascular, Amgen, Biosensors International, Biotronik, Boston Scientific, Corindus, Edwards Lifesciences, Lifetech Medical, Medtronic Vascular, Philips Volcano; Speakers Bureau: AstraZeneca; Grant Support: Abbott Vascular, Biosensors International, Biotronik, Boston Scientific, Edwards Lifesciences.

Nelson L. Bernardo: Conducts training for Cook Medical; Speakers Bureau for Medtronic.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Forsdahl SH, Singh K, Solberg S, Jacobsen BK. Risk factors for abdominal aortic aneurysms: a 7-year prospective study: the Tromso study, 1994–2001. Circulation 2009;119(16):2202–8.
[2] Tang W, Yao L, Roetker NS, Alonso A, Lutsey PL, Steenson CC, et al. Lifetime risk and risk factors for abdominal aortic aneurysm in a 24-year prospective study: the ARIC study (atherosclerosis risk in communities). Arterioscler Thromb Vasc Biol 2016;36(12):2468–77.
[3] Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg 2009;50(4):880–96.
[4] Kent KC. Clinical practice. Abdominal aortic aneurysms. N Engl J Med 2014;371(22):2101–8.
[5] Volodos NL, Karpovich IP, Shekhanin VE, Troian VI, Iakovenko LF. A case of distant transfemoral endoprosthesis of the thoracic artery using a self-fixing synthetic prosthesis in traumatic aneurysm. Grudn Khir (Moscow, Russia) 1988(6):84–6.
[6] Hertzer NR. Current status of endovascular repair of infrarenal abdominal aortic aneurysms in the context of 50 years of conventional repair. Ann N Y Acad Sci 2006;1085:175–86.
[7] Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010;362(20):1863–71.
[8] De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med 2010;362(20):1881–9.
[9] Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg Jr FT, Kohler TR, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med 2012;367(21):1988–97.
[10] Becquemin JP, Kelley L, Zubilewicz T, Desgranges P, Lapeyre M, Kobeiter H. Outcomes of secondary interventions after abdominal aortic aneurysm endovascular repair. J Vasc Surg 2004;39(2):298–305.
[11] Brewster DC, Jones JE, Chung TK, Lamuraglia GM, Kwolek CJ, Watkins MT, et al. Long-term outcomes after endovascular abdominal aortic aneurysm repair: the first decade. Ann Surg 2006;244(3):426–38.
[12] van Marrewijk C, Buth J, Harris PL, Norgren L, Nevelsteen A, Wyatt MG. Significance of endoleaks after endovascular repair of abdominal aortic aneurysms: the EUROSTAR experience. J Vasc Surg 2002;35(3):461–73.
[13] Cieri E, De Rango P, Isernia G, Simonte G, Ciucci A, Parlani G, et al. Type II endoleak is an enigmatic and unpredictable marker of worse outcome after endovascular aneurysm repair. J Vasc Surg 2014;59(4):930–7.
[14] Deery SE, Ergul EA, Schermerhorn ML, Siracuse JJ, Schanzer A, Goodney PP, et al. Aneurysm sac expansion is independently associated with late mortality in patients treated with endovascular aneurysm repair. J Vasc Surg 2018;67(1):157–64.
[15] Kontopodis N, Papadopoulos G, Galanakis N, Tsetis D, Ioannou CV. Improvement of patient eligibility with the use of new generation endografts for the treatment of abdominal aortic aneurysms. A comparison study among currently used endografts and literature review. Expert Rev Med Devices 2017;14(3):245–50.
[16] Suckow BD, Goodney PP, Columbo JA, Kang R, Stone DH, Sedrakyan A, et al. National trends in open surgical, endovascular, and branched-fenestrated endovascular aortic aneurysm repair in Medicare patients. J Vasc Surg 2018;67(6):1690-7.e1.