From the Society for Vascular Surgery

Results of the Nellix system investigational device exemption pivotal trial for endovascular aneurysm sealing

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Objective: **The Nellix EndoVascular Aneurysm Sealing system (Endologix, Inc, Irvine, Calif) is a novel approach to abdominal aortic aneurysm (AAA) endovascular repair whereby biocompatible polymer is employed to exclude and to seal the AAA sac. We report 30-day results of the U.S. pivotal trial.**

Methods: **Consecutive, eligible, consenting patients were enrolled at 29 sites in the United States and Europe. Inclusion criteria required an asymptomatic infrarenal AAA, with aortic neck length ≥10 mm and angle to the sac ≤60 degrees, aortic neck diameter of 18 to 32 mm, aneurysm blood lumen diameter ≤6 cm, common iliac artery lumen diameter of 9 to 35 mm, access artery diameter ≥6 mm, and serum creatinine level ≤2 mg/dL. Follow-up at 30 days included clinical assessment and computed tomography angiography evaluation of endoleaks and device integrity as assessed by a core laboratory. The primary safety end point is the incidence of independently adjudicated 30-day major adverse events (MAEs), with success defined as superiority with reference to the Society for Vascular Surgery open repair control group (56%).**

Results: **Between January and November 2014, 150 trial patients having a mean AAA diameter of 5.8 cm were enrolled and treated with the Nellix system with 100% procedural success. One early death (0.7%) occurred secondary to multisystem organ failure. All 149 surviving patients completed 30-day follow-up. There were no aneurysm ruptures, conversions, limb thromboses, stent fractures, or stent kinking. Five early MAEs occurred in four patients (2.7%) and included one death, bowel ischemia (1), renal failure (2), and respiratory failure (1). One (0.7%) secondary intervention to treat inadvertent coverage of a renal artery was performed. The core laboratory identified nine (6%) endoleaks (one type I, eight type II) on 30-day computed tomography angiography. Freedom from MAE was 97.3% (95% confidence interval, 93.3%-99.0%).**

Conclusions: **In selected patients, perioperative outcomes with the Nellix system for endovascular aneurysm sealing are encouraging, with very low 30-day morbidity and mortality and high procedural success. The primary safety end point has been achieved. Longer term follow-up is in progress. (J Vasc Surg 2016;63:23-31.)**

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Whereas endovascular aortic aneurysm repair (EVAR) has significantly reduced perioperative mortality and morbidity of abdominal aortic aneurysm (AAA) treatment in comparison to open surgical repair, long-term results demonstrate a significant need for reintervention, necessitated by problems related to endoleak, migration, and other issues inherent to the EVAR approach. Three well-designed, randomized, controlled trials have demonstrated a significantly lower 30-day mortality rate for EVAR compared with open surgical repair.[1-3] This early mortality benefit was not sustained long term. Moreover, systematic reviews of long-term outcomes demonstrate that the reintervention rate[4] and cost[5] of EVAR are considerably higher than for open repair. Complications necessitating reintervention are chiefly due to endoleaks and migration of endografts.[4] The threat of long-term complications necessitates continued long-term surveillance of EVAR patients, with associated inconvenience, radiation exposure, nephrotoxicity, and expense.

In addition, EVAR is currently limited in applicability by restrictions related to hostile neck and sealing zone anatomies. Up to 50% of AAA patients do not qualify for EVAR

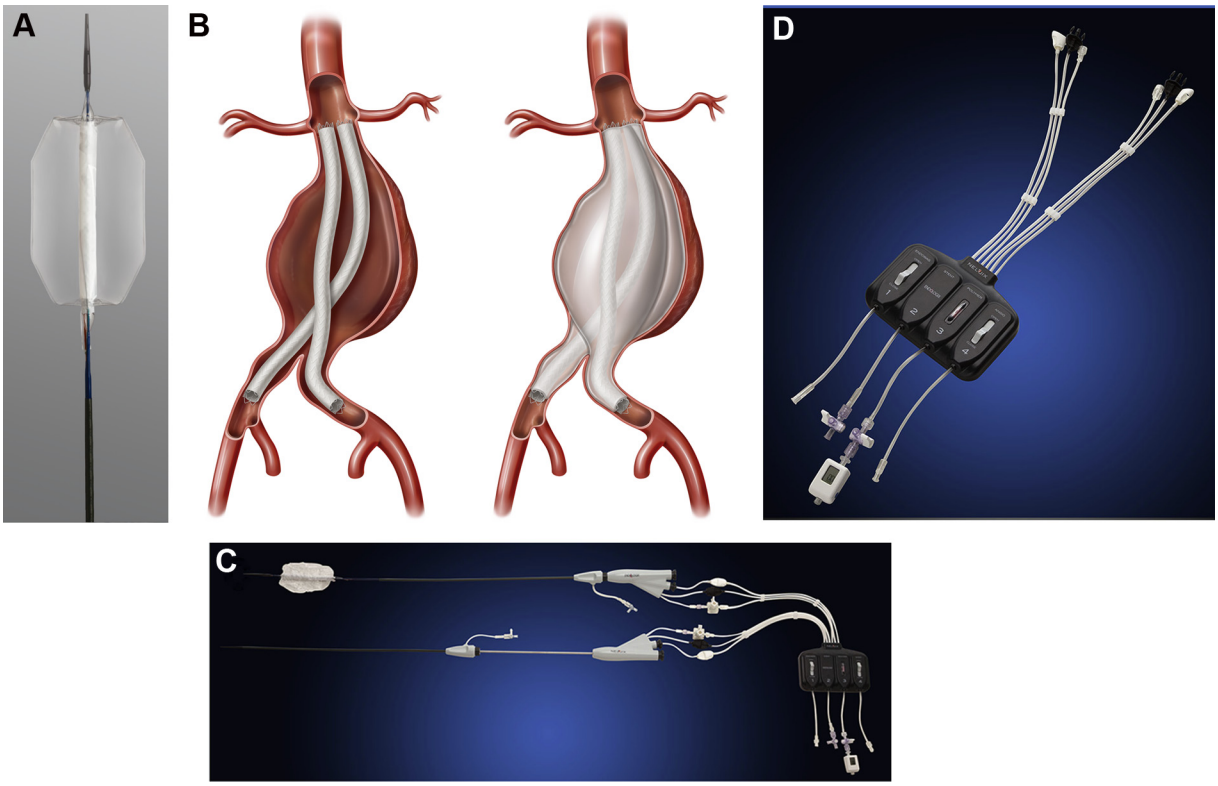

Fig 1. Nellix EndoVascular Aneurysm Sealing (EVAS) system. Each Nellix device **(A)** includes a balloon-expandable cobalt-chromium alloy stent jacketed in expanded polytetrafluoroethylene and surrounded by a polyurethane endobag. Two Nellix devices are deployed in "kissing stent" fashion, ensuring proximal stent alignment, after which polymer is introduced under pressure monitoring to the endobags **(B)**. The delivery system catheter **(C)** outer sheath is 17F in profile (outer diameter). A console **(D)** attaches to two Nellix catheters to facilitate simultaneous endobag preparation, stent deployment, polymer filling, and angiography. An in-line pressure transducer is used to monitor pressure during prefill and polymer fill.

on the basis of the manufacturer's instructions for use (IFU).[6,7] Although physician application beyond the IFU (ie, off-label use) is common in clinical practice,[8] it is associated with inferior short- and long-term results,[9-12] including increased mortality and decreased durability of the repair.[13,14]

Unlike in open surgical repair, the aneurysm sac is not directly treated in EVAR. This allows the EVAR-treated patient to remain at risk from endoleaks related to failure of proximal or distal seals or seals between components, device migration, and frequently unligated side branches (type II endoleak). The significance of type II endoleak may be debated; nonetheless, there is ample evidence that its presence is associated with sac enlargement, aneurysm rupture, open conversion, death, and increased rates of reintervention.[15-19]

The Nellix EndoVascular Aneurysm Sealing (EVAS) system (Endologix, Inc, Irvine, Calif) offers a novel approach to the treatment of AAA. Results with use of an early generation of the device have been reported.[20,21] In contrast to traditional prostheses for EVAR, the device stabilizes and completely seals the aneurysm sac by means of polymer-filled endobags attached to covered stents that span the aortic segment to maintain blood flow to the distal limbs. Simultaneous sealing and fixation are accomplished in this way, obliterating the AAA sac and potential endoleak space.

METHODS

Nellix system and EVAS procedure. The Nellix system for EVAS and its method of implantation have been recently described in detail (Fig 1).[22] In brief, the Nellix system is composed of Nellix catheters, accessory kit with console and pressure transducer, 40-mL dual-chamber cartridge with polyethylene glycol diacrylate polymer (stored frozen at −20°C to −40°C until use), and dispenser. The polymer itself is safe and biocompatible and has been demonstrated in preclinical testing not to polymerize in the presence of blood, avoiding the possibility of embolization if there were to be a disruption of the endobag. The number of polymer cartridges needed for each procedure is estimated from volumetric analysis of the recently performed high-resolution, contrast-enhanced computed tomography angiography (CTA) scan. Within

each Nellix catheter is a premounted balloon-expandable cobalt-chromium alloy stent with expanded polytetrafluoroethylene graft cover and polyurethane Endobag (Fig 1, *A*). These Endobags are capable of filling a blood lumen of up to 6 cm in diameter, including a safety margin. This assembly is preloaded into a 17F (outer diameter) sheath with handle and connector system (for mating with console connectors). There have been multiple iterations of the Nellix device before the generation device used in the investigational device exemption (IDE) trial. Major differences include the change from a stainless steel to a cobalt-chromium stent material and a profile reduction from 19F to 17F outer diameter. Procedurally, two prepared Nellix catheters are advanced through femoral access. After unsheathing and Endobag evacuation, stents are balloon expanded in "kissing" fashion, ensuring proximal alignment of the two stents below the level of the renal arteries. The stents extend caudad into the common iliac arteries, bilaterally, spanning the aneurysm. After stent deployment, a nonheparinized sterile saline prefill of the Endobags is performed in a controlled manner under pressure monitoring to a target nominal fill pressure of 180 mm Hg (or 20 mm Hg above systolic pressure for a hypertensive patient). Being greater than systolic pressure, this ensures that the endobags completely fill the blood lumen space of the aneurysm. Angiographic verification of sealing is performed at this time through the delivery system. The prefill volume is then aspirated; this volume serves to estimate the volume of thawed polymer to be injected. Maintaining awareness of this prefill volume and the target pressure of 180 mm Hg, polymer solution is then dispensed to the endobags in a controlled manner under pressure monitoring. Angiographic verification of sealing is again performed. On filling of the endobags, the polymer cures in approximately 3 to 5 minutes. A "secondary fill" capability exists as a backup if additional polymer is required after initial filling. The cured polymer forms a cast of the flow lumen of the aorta and iliac arteries, maintaining the endograft position and obliterating the sac, sealing off side branches. The delivery systems are then detached from the implant (stents and filled endobags) and are removed. Femoral closure is done in the usual fashion.

Clinical trial design. A prospective, multicenter, single-arm clinical trial of the Nellix system for EVAS was conducted at 29 sites under an IDE approved by the U.S. Food and Drug Administration. Local Institutional Review Board or Ethics Committee approval was obtained before first patient enrollment at each participating site (Appendix, online only).

After written informed consent was obtained, each potential subject underwent screening by the local site and an imaging core laboratory (Cleveland Clinic Peripheral Vascular Laboratory, Cleveland, Ohio) as well as by an independent medical reviewer. High-resolution CTA scanning was required to be performed within 3 months of screening. In addition to anatomic eligibility assessment, each patient underwent a physical examination, review of the medical history, and selected blood laboratory analyses. Inclusion and exclusion criteria are shown in Table I. Patients are to be observed at 1 month, 6 months, 1 year, and then annually to 5 years. At each visit, clinical evaluation and CTA scanning (Fig 2) with core laboratory interpretation are performed. The first patient enrolled at each site is designated a roll-in patient. Subsequently enrolled subjects compose the 150-patient trial cohort, which is the basis of this report.

Table I. Trial inclusion and exclusion criteria

Inclusion criteria
1. Male or female at least 18 years old
2. Informed consent signed and agrees to all follow-up visits
3. Intact AAA ≥5.0 cm, or ≥4.5 cm that has increased by ≥0.5 cm within the last 6 months, or that exceeds 1.5 times the transverse dimension of an adjacent nonaneurysmal aortic segment
4. Anatomically eligible for the Nellix system per IFU:
   a. Adequate iliac/femoral access (diameter ≥6 mm)
   b. Aneurysm blood lumen diameter ≤60 mm
   c. Proximal nonaneurysmal aortic neck:
      i. Length ≥10 mm
      ii. Lumen diameter 18-32 mm
      iii. Angle ≤60 degrees to the aneurysm sac
   d. Most caudal renal artery to each hypogastric artery length ≥100 mm
   e. Common iliac artery lumen diameter 9-35 mm
   f. Ability to preserve at least one hypogastric artery

Exclusion criteria
1. Life expectancy <2 years
2. Psychiatric or other condition that may interfere with the study
3. Participating in another clinical study
4. Known allergy or contraindication to any device material
5. Coagulopathy or uncontrolled bleeding disorder
6. Ruptured, leaking, or infected aneurysm
7. Serum creatinine level >2.0 mg/dL
8. CVA or MI within 3 months of enrollment/treatment
9. Aneurysmal disease of the descending thoracic aorta
10. Clinically significant mural thrombus within the proximal landing zone (minimum 10 mm) of the infrarenal nonaneurysmal neck (>5 mm in thickness over >50% circumference)
11. Connective tissue diseases
12. Unsuitable vascular anatomy that may interfere with device introduction or deployment
13. Pregnant

AAA, Abdominal aortic aneurysm; *CVA,* cerebrovascular accident; *IFU,* instructions for use; *MI,* myocardial infarction.

The primary safety end point is defined as the incidence of major adverse events (MAEs) at 30 days as adjudicated by an independent Clinical Events Committee (CEC). MAEs include all-cause death, bowel ischemia, myocardial infarction, paraplegia, renal failure, respiratory failure, stroke, and procedural blood loss ≥1 L.

Serious adverse events are defined as any adverse events that led to death or serious deterioration in the health of the subject that resulted in life-threatening illness or injury, resulted in a permanent impairment, or required hospitalization or prolongation of an existing hospitalization. An independent Data Safety and Monitoring Board reviewed safety data on a periodic basis.

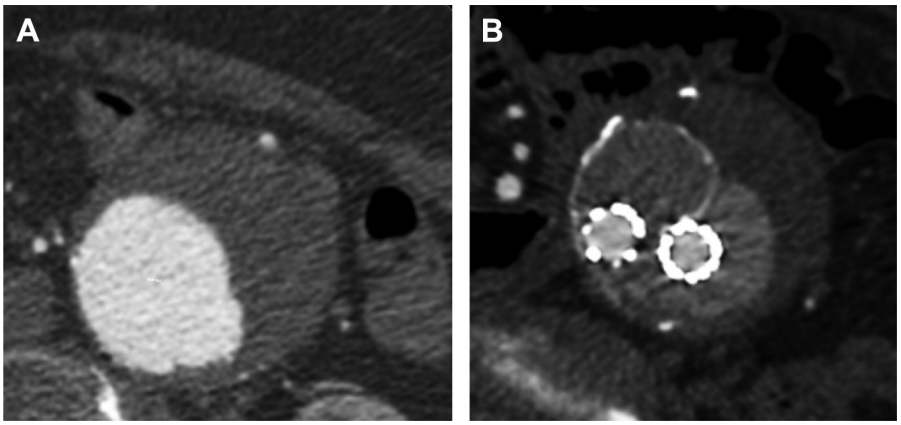

Fig 2. Computed tomography (CT) appearance of an abdominal aortic aneurysm (AAA) before **(A)** and 30 days after **(B)** treatment with the Nellix EndoVascular Aneurysm Sealing (EVAS) device. The enhanced preoperative CT scan shows an AAA with a large flow lumen and mural thrombus. After treatment with the Nellix device **(B)**, CT scan shows residual contrast material within the polymer-filled endobags. The outlines of the two endobags and the two stents are clearly visible.

The primary effectiveness end point is defined as the rate of treatment success at 1 year. Treatment success includes procedural technical success (deployment of the Nellix system in the planned location and without unintentional coverage of both internal iliac arteries or any visceral aortic branches and with the removal of the delivery system) and the absence of the following: AAA rupture; conversion to open surgical repair; endoleak (type I or III) at 12 months; clinically significant migration (>10 mm movement from the first postprocedural CTA scan); aneurysm enlargement (>5-mm-diameter increase from the first postprocedural CTA scan); and secondary procedures through 12 months for resolution of endoleak, device obstruction or occlusion, migration, AAA sac expansion, or device defect.

Statistical analyses. Analyses were performed on an intention-to-treat basis such that all subjects were analyzed on the basis of the attempt to implant the Nellix device during the procedure. The primary safety hypothesis tested is that the rate of MAEs at 30 days in the study population is <56%, the rate of 30-day MAEs in the Society for Vascular Surgery open surgery group, which has been used as the comparison group for EVAR trials seeking Food and Drug Administration approval.[23] The difference in MAE rates will be demonstrated at a significance level of $\alpha = .025$, using a one-tailed exact test. Effectiveness will be tested using the exact binomial distribution based on the hypothesis that the treatment success rate at 1 year exceeds 80%, at a significance level of $\alpha = .05$. The trial sample size of 132 patients was derived from the primary effectiveness end point, presuming a minimum treatment success rate of 88%. To account for deviations from assumptions, a sample size of 150 patients was defined for enrollment. For both primary safety and effectiveness end point analyses, >80% power is provided. Analyses are performed with SAS software version 9.2 (SAS Institute, Cary, NC).

Table II. Patient demographics and medical history

Characteristic	*No. (%)*
Demographics	
Male gender	142 (95)
White race	140 (93)
ASA class 1	3 (2.0)
ASA class 2	38 (25)
ASA class 3	92 (61)
ASA class 4	17 (11)
Medical history	
Angina	16 (11)
Arrhythmia	42 (28)
Cancer	39 (26)
Chronic obstructive pulmonary disease	41 (27)
Congestive heart failure	8 (5)
Coronary artery disease	76 (51)
Diabetes mellitus	26 (17)
Family history of AAA	19 (13)
Hypercholesterolemia	81 (54)
Hyperlipidemia	108 (72)
Hypertension	123 (82)
Liver disease	4 (2.7)
Myocardial infarction	38 (25)
Peripheral vascular disease	44 (29)
Prior coronary artery bypass grafting	26 (17)
Prior defibrillator or pacemaker implant	11 (7.3)
Prior percutaneous coronary intervention	42 (28)
Renal insufficiency	24 (16)
Smoking history	78 (52)
Stroke or transient ischemic attack	18 (14)
Valvular heart disease	14 (9.3)

AAA, Abdominal aortic aneurysm; *ASA,* American Society of Anesthesiologists.

RESULTS

The baseline demographics and medical history of the 150 enrolled trial patients are shown in Table II; aneurysm and vascular characteristics are shown in Table III. This cohort was primarily male (n = 142; 95%) at an average

Table III. Baseline aneurysm and vascular characteristics

Characteristic	*Mean ± SD (range)*
AAA sac diameter, maximum, mm	58 ± 6.2 (44-82)
AAA blood lumen diameter, mm	42 ± 7.8 (22-60)
AAA blood lumen volume, mL	70 ± 33 (24-213)
AAA sac volume, mL	143 ± 53 (63-379)
Aortic neck length, mm	31 ± 14 (10-103)
Aortic neck diameter, mm	25 ± 3.0 (19-32)
Aortic neck angle to sac, degrees	30 ± 14 (3.3-59)
Proportion of aortic neck with thrombus >5 mm in thickness, %	2.3 ± 7.2 (0.0-47)
Renal to right hypogastric artery length, mm	178 ± 22 (102-236)
Renal to left hypogastric artery length, mm	180 ± 22 (113-235)
Right common iliac diameter, maximum, mm	20 ± 5.8 (12-50)
Right common iliac diameter, minimum, mm	11 ± 2.3 (7.5-21)
Left common iliac diameter, maximum, mm	20 ± 6.0 (11-53)
Left common iliac diameter, minimum, mm	11 ± 2.5 (7.6-21)
Right access vessel diameter, minimum, mm	7.7 ± 1.4 (3.6-13)
Left access vessel diameter, minimum, mm	7.8 ± 1.4 (4.9-12)

AAA, Abdominal aortic aneurysm.

Table IV. Procedural characteristics

Characteristic	*Result*
Anesthesia type	
General	109 (73)
Regional	13 (8.7)
Local	28 (19)
Vascular access type	
Bilateral percutaneous ("preclose" technique)	83 (55)
Femoral exposure	67 (45)
Durations	
Fluoroscopy time, minutes	10 (3-65)
Catheter time, minutes	30 (4-114)
Procedure time (skin to skin), minutes	87 (50-205)
Anesthesia time, minutes	158 (50-285)
Volumes	
Contrast medium, mL	120 (39-390)
Polymer fill, mL	75 (29-215)

Results shown as number (% of 150) or median (range).

age of 72 years at the time of enrollment. The mean baseline AAA sac diameter was 5.8 cm. The majority of patients (n = 109; 73%) were American Society of Anesthesiologists class 3 or class 4 at the time of enrollment.

Procedural characteristics are summarized in Table IV. The Nellix device was delivered and deployed in all 150 subjects with removal of the catheter delivery systems. In several patients enrolled with extensive common iliac artery aneurysmal disease, device placement to the iliac bifurcation permitted exclusion of the distal aneurysm while preserving flow to both hypogastric arteries (Fig 3). Device-related serious adverse events occurred procedurally in three patients (2.0%). In the first patient, a renal artery was inadvertently covered by a Nellix device because of malpositioning of the endograft. Delayed filling of the renal artery was observed postoperatively while the patient was in recovery; the patient was returned to the operating room for attempted renal stenting, but the artery was unable to be successfully accessed. In the second patient, procedural damage to one of the endobags occurred secondary to catheter manipulation in calcified anatomy after initial prefill, manifested as blood in the aspirated saline. Polymer filling and the implant procedure were completed; angiographic appearance of the implant verified aneurysm exclusion with a single endobag. The third patient sustained intraoperative iatrogenic disruption of his AAA during the prefill step. On evacuating the prefill from the endobags, the patient's blood pressure was noted to be dropping because of presumed disruption of the aneurysm after pressurization of the sac during the prefill. The procedure was completed uneventfully by injecting polymer into the endobags as planned, achieving seal with no evidence of endoleak. In another patient, inadvertent misalignment of the two Nellix stents proximally was observed, but the procedure was completed without evidence of residual endoleak. One surgical procedure was performed at the time of the Nellix implantation, consisting of iliofemoral bypass to treat a concomitant femoral artery aneurysm. Eight patients received a commercially available covered or uncovered stent to address distal access vessel stenosis or iliac tortuosity. One of these patients also received a covered balloon-expandable stent proximally to correct for stent misalignment (without endoleak). At one site, five patients were prophylactically treated with a self-expanding stent within the distal limb of the Nellix stent to address angulation and tortuosity (not seal). The median hospital length of stay was 1.2 days.

One death (0.7%) occurred on postoperative day 4 in a patient with a history of congestive heart failure, emphysema, uncontrolled diabetes, morbid obesity, and prior pulmonary embolism. The Nellix procedure was completed uneventfully, and she was discharged from the hospital on day 2. She suffered cardiac arrest at home and was found unresponsive; she was admitted emergently to the hospital, where she continued to decline, developing multiorgan failure. CTA found the device intact and patent with no evidence of endoleak. Because of the patient's history and poor prognosis, the family elected no further intervention. All surviving patients completed the 1-month follow-up visit. CEC adjudication identified a total of four patients (2.7%) with five MAEs: death due to multisystem organ failure (1; 0.7%), renal failure (2; 1.3%), bowel ischemia (1; 0.7%), and respiratory failure (1; 0.7%). Freedom from MAE was 97.3% (95% confidence interval, 93.3%-99.0%), significantly less than the 56% MAE rate of the Society for Vascular Surgery open control group. The MAEs of renal failure and bowel ischemia both occurred in the same patient, who developed ischemic colitis and underwent proctocolectomy on postoperative day 1 after EVAS. The patient demonstrated a rise in serum creatinine level, which returned to normal by postoperative day 7 without the need for hemodialysis. The colon specimen was sent for pathologic examination. Both the renal failure and bowel ischemic events were adjudicated by the CEC and found not to be device related.

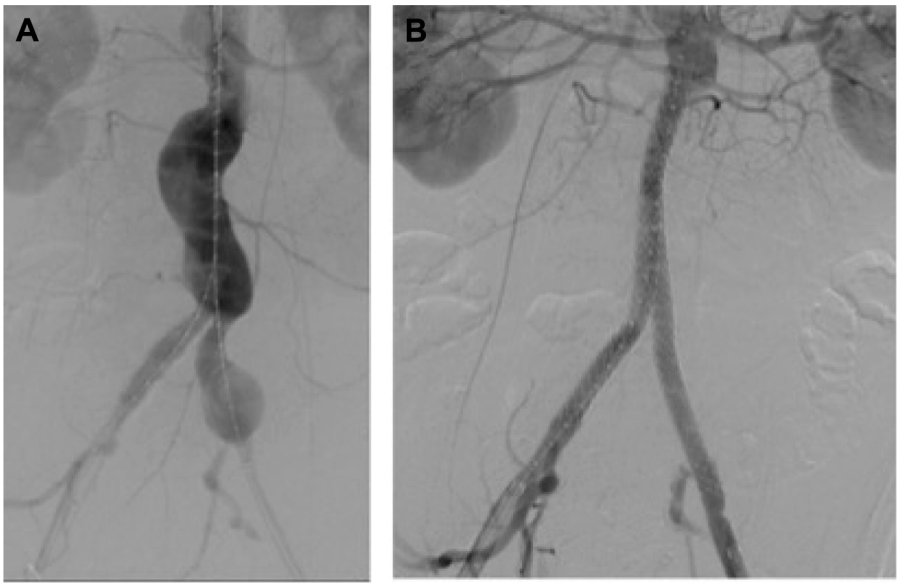

Fig 3. Preservation of the hypogastric artery in an abdominal aortic aneurysm (AAA) patient with concomitant common iliac artery aneurysmal disease. Arteriograms performed before **(A)** and after **(B)** endovascular aneurysm sealing (EVAS) with the Nellix system are shown.

Table V. Thirty-day serious adverse events

Event classification	*No. of patients with event (% of 150)*	*Total events*
Patients with ≥1 serious adverse event	23 (15)	33
Bleeding/anemia	1 (0.7)	1
Bowel related	2 (1.3)	3
Cardiac related	5 (3.3)	5
Malignant neoplasms	3 (2.0)	3
Nellix device[a]	1 (0.7)	1
Neurologic related	1 (0.7)	1
Pulmonary related	4 (2.7)	4
Renal related	2 (1.3)	2
Surgical site wound[b]	3 (2.0)	3
Urogenital related	4 (2.7)	4
Vascular related	4 (2.7)	4
Other[c]	2 (1.3)	2

[a]Blood observed in the endobag evacuation line of the console.
[b]Includes two patients with lymphatic fistulas and one patient with a local groin infection requiring surgical intervention.
[c]Other includes one patient with *Candida* esophagitis and one patient with an elevated international normalized ratio, treated with 2 units of fresh frozen plasma infusion.

Within 30 days, any adverse event was observed in 52 patients (35%). Serious adverse events were observed in 23 (15%) patients (Table V). There was no occurrence of allergic or inflammatory response to polymer. There was no occurrence of aneurysm rupture, open conversion, stent fracture, limb thrombosis or kinking, myocardial infarction, blood loss ≥1 L, paraplegia, or stroke through 30 days.

Endoleaks were reported by the core laboratory in nine patients (6%) on the 1-month CTA scan and included one type Ia endoleak (0.7%; Fig 4), eight type II endoleaks (5.4%; Fig 5), and no type III or IV endoleaks. The type Ia endoleak was associated with stent misalignment procedurally and was treated with coil embolization subsequently. The mean volume of the type II endoleaks was very low (0.16 mL; range, 0.1-0.4 mL). All of the type II endoleaks involved lumbar arteries.

One early secondary intervention (0.7%) was performed subsequent to the index procedure in the aforementioned patient with coverage of a renal artery procedurally. The physician attempted rescue by angioplasty and stenting but was unsuccessful.

DISCUSSION

The Nellix system for EVAS performed well, with 100% procedural technical success and few complications, meeting the primary safety end point. The median procedure time was shorter (87 minutes) compared with that reported for EVAR device trials,[24-27] despite the EVAS procedure being new to the operators. Procedural performance does not require time-intensive steps, such as gate cannulation or placement of multiple components, because the device is not modular or bifurcated. The device was inserted percutaneously in the majority of cases. The right and left limbs are placed simultaneously as balloon-expandable kissing stents. Each limb independently takes the most direct route from renal artery to common iliac artery, unconstrained by attachment to the other limb as occurs in a bifurcated design. This would be expected to reduce kinking and to improve flow characteristics. Procedural planning, too, is simplified by the need only to choose a length for the 10-mm-diameter stents based on

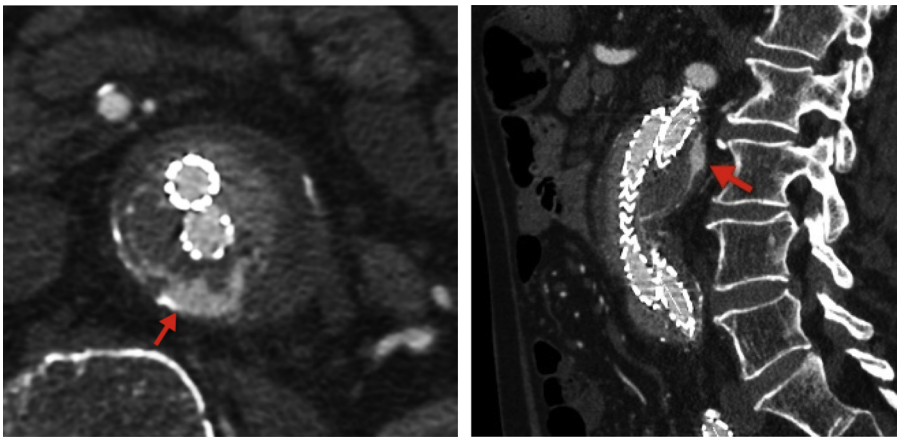

Fig 4. Type Ia endoleak on 30-day computed tomography angiography (CTA). The proximal attachment leak is located posteriorly. Contrast in the endoleak (*arrows*) and in the graft limbs appears much brighter than the residual contrast contained in the polymer-filled endobags.

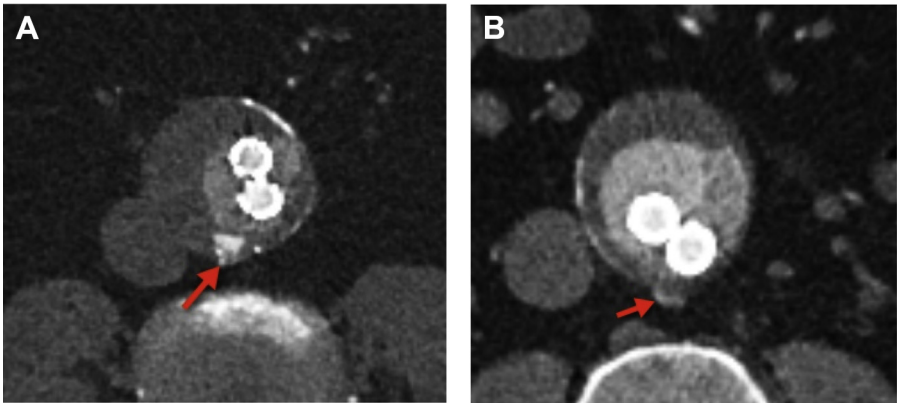

Fig 5. Type II endoleaks. Lumbar to lumbar endoleaks with volumes of 0.4 mL **(A)** and 0.1 mL **(B)** are shown (*arrows*). Faint residual contrast is seen in the polymer within the endobags while bright contrast appears in the regions of blood flow within the graft limbs, in the lumbar arteries, and in the limited endoleak space.

the renal to hypogastric artery length on each side. This also greatly simplifies the inventory necessary to be maintained for treatment of a wide variety of aneurysm anatomies. The EVAS endobags conform to the idiosyncratic anatomy of each individual patient, rather than requiring a large inventory of components, each appropriate for a limited range of anatomic conditions, as in EVAR.

The population of trial patients was challenging, with a mean baseline aneurysm diameter of 58 mm and American Society of Anesthesiologists score of 3 or 4 in the majority. The device proved able to treat a variety of anatomies that are usually considered difficult or impossible for traditional EVAR devices, being indicated for iliac artery lumen diameters up to 35 mm. Investigators were able to successfully treat extensive common iliac artery aneurysm disease while preserving the hypogastric artery, avoiding the risk of claudication and bowel ischemia that has been reported to be associated with hypogastric artery sacrifice (Fig 3).[28]

Several of the adverse events reported illustrate elements of the learning curve for this unique system. Inadvertent coverage of a renal artery may result if movement of the device occurs during polymer injection into the endobags, as was seen in one case. Balloon-expandable stents offer the advantage of precise deployment, but as the endobags expand and fill, movement can be translated to the attached stents. The operator must be vigilant to maintain optimal position of the expanded stents in this dynamic situation.

Similarly, our single patient with a type Ia endoleak also illustrates the importance of maintaining device position while filling the endobags with polymer. A low positioning of the device can result if the endobags displace the stents apart from each other (laterally) while they are fixed in the iliac arteries distally. This lateral displacement while the distal stent is fixed will result in downward movement and relative shortening, with loss of proximal positioning

or alignment, potentially leading to proximal endoleak. This is best avoided by preplanning of the case to account for certain anatomic situations. In more narrow common iliac arteries, it is recommended to keep the stent balloons inflated during saline prefill and polymer fill to maintain proximal stent positioning and alignment. Importantly, Nellix procedural steps that can mitigate the occurrence of type Ia endoleak include confirming angiographic seal after prefill (multiple views may be necessary), sealing to target pressure and volume, and using secondary polymer fill, if needed. In commercial cases outside the United States, remediation of type I endoleak has been performed successfully by endovascular means in Nellix patients by means of embolic materials and glue as well as proximal extension employing parallel graft techniques.[22]

Finally, excessive pressurization of the endobags beyond the IFU transmits pressure to the AAA wall and has the potential to cause iatrogenic aortic disruption, as was observed in one patient. This did not lead to excessive blood loss or adverse outcome, however, as the disruption was simply treated with controlled filling of the endobags with sealing polymer while monitoring both volume and pressure. The EVAS system depends on pressurization of a volume of polymer to achieve adequate seal. This necessary pressurization must be tempered by the risk of iatrogenic rupture with excessive pressurization. Overfilling or overpressurization of an aortic aneurysm can lead to rupture. Careful preoperative volume planning, prefill with saline, and careful attention to pressurization in adherence to the IFU are necessary to avoid this complication. Close monitoring and attention must be paid to the pressure delivered to the aneurysm by means of the in-line pressure-monitoring transducer. A target fill pressure of 180 mm Hg and exceeding the patient's systolic pressure is considered optimal to ensure adequate dissemination of polymer into recesses of the sac and seal zones and to obliterate all potential endoleak spaces.

This obliteration of the aneurysm sac is the essential concept on which the EVAS procedure is based. Filling the entire treatment zone from the infrarenal segment across the aneurysm sac to the distal segment with polymer has the ability to provide secure fixation by using the sac itself to anchor the graft and to prevent migration. Seal is also accomplished by allowing the liquid polymer to take the shape of the aneurysm's seal zones because of the ability of the liquid polymer-filled endobags to assume the shape of the neck, whatever it may be, before curing.

Filling of the aneurysm sac has other advantages. First, we observed a very low rate of any endoleak (6%) at 30 days. Other IDE trials of EVAR devices have reported higher 30-day endoleak rates of 11% to 44%.[24-27,29,30] Injecting polymer to a pressure in excess of systolic pressure allows sealing of proximal and distal attachments (avoidance of type I endoleak) and tamponade of branch vessels arising from the aneurysm sac (avoidance of type II endoleak). Other reports of the Nellix device have also described extremely low rates of endoleak with EVAS to 1 year.[20-22,31] The few type II endoleaks that were detected in our study were of very small volume, ranging from immeasurably small to a maximum of only 0.4 mL. This is significant in that other authors have found that sac expansion is related to endoleak size.[32,33] Furthermore, in EVAS, these endoleaks are bounded by polymer on all sides, potentially preventing transmission of pressure to the aneurysm sac. Other authors have seen frequent spontaneous resolution of type II endoleaks in EVAR and EVAS.[34] Further follow-up is necessary to evaluate the fate and significance of these endoleaks. Endoleaks are known to significantly increase morbidity and mortality after EVAR. Type I endoleak puts patients at continued risk for rupture, with pressurization of the AAA sac. The presence of type II endoleak is associated with aneurysm rupture, open conversion, death, and increased rates of reintervention and can lead to the development of type I endoleak when it produces sac enlargement.[15] These fundamental problems of EVAR are addressed in EVAS by definitive treatment of the aneurysmal sac with elimination of its potential space for endoleaks.

In addition, filling of the sac with polymer stabilizes motion of the endograft. EVAR grafts are subject to the introduction of kinking and conformational change as the aneurysm sac regresses because there is no support to prevent lateral movements of the grafts.[35] This has produced structural failure and stent fracture, pullout of modular graft components, limb stenosis and thrombosis, and dislodgment of attachment sites and is associated with late adverse events.[36,37] Filling the sac with polymer in this way ensures maintenance of graft geometry and decreases motion.

Lowering the frequency of endoleak and stabilizing the sac may result in fewer reinterventions and may provide patients with a more durable endovascular repair of their AAAs. Longer term follow-up is necessary to determine if these benefits of EVAS will accrue and prove the efficacy of EVAS. Because EVAS is reliant on a novel polymer, the long-term behavior and durability of this material need to be demonstrated. The behavior of the aneurysm sac and interactions of aneurysm thrombus with the endobags are also of continuing interest.

CONCLUSIONS

Perioperative outcomes with the Nellix system for EVAS are encouraging, achieving high procedural success with very low endoleak rate, morbidity, and mortality. The primary safety end point has been achieved with a high level of significance. Assessment of the trial effectiveness end point and long-term durability of EVAS is in progress.

AUTHOR CONTRIBUTIONS

Conception and design: JC
Analysis and interpretation: JC, CB, CH, SH, MR, JT, RC, DB
Data collection: JC, CB, CH, SH, MR, JT, RC, DB
Writing the article: JC
Critical revision of the article: JC, CB, CH, SH, MR, JT, RC, DB

Final approval of the article: JC, CB, CH, SH, MR, JT, RC, DB
Statistical analysis: JC
Obtained funding: JC, CB, CH, SH, MR, JT, RC, DB
Overall responsibility: JC

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APPENDIX (online only). Investigational sites and principal investigators

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Allegheny General Hospital	Pittsburgh, Pa	Satish Muluk, MD
Baylor Heart Hospital	Plano, Tex	Javier Vasquez, MD
Baylor Scott and White Healthcare System	Temple, Tex	Clifford Buckley, MD
Baystate Medical Center	Springfield, Mass	Neal Hadro, MD
Carolinas Health Care	Charlotte, NC	Steven Lalka, MD
Christiana Hospital	Wilmington, Del	Ralph Ierardi, MD
Cleveland Clinic	Cleveland, Ohio	Daniel Clair, MD
Froedtert Memorial Lutheran Hospital (Medical College of Wisconsin)	Milwaukee, Wisc	Cheong Jun Lee, MD
Inova Hospital	Fairfax, Va	Homayoun Hashemi, MD
Maine Medical Center	Portland, Me	Christopher Healey, MD
MedStar Health Research Institute	Washington, D.C.	Nelson Bernado, MD
Miami Vascular Institute	Miami, Fla	James Benenati, MD
Nebraska Heart Hospital	Lincoln, Neb	Steve Tyndall, MD
Ohio Health Research Institute	Columbus, Ohio	Mitchell Silver, DO
Providence Sacred Heart Medical Center	Spokane, Wash	Stephen Murray, MD
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