From the Society for Vascular Surgery

Refinement of anatomic indications for the Nellix System for endovascular aneurysm sealing based on 2-year outcomes from the EVAS FORWARD IDE trial

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ABSTRACT

Background: The Nellix System (Endologix, Inc, Irvine, Calif) for endovascular aneurysm sealing (EVAS) is a novel approach to abdominal aortic aneurysm treatment and conceptually different from endovascular aneurysm repair, whereby polymer is employed to fill and actively manage the abdominal aortic aneurysm sac. One-year safety and effectiveness results of the Nellix pivotal trial demonstrated encouraging outcomes with very low morbidity and mortality and high procedural and treatment success. Two-year imaging revealed a signal of migration, leading to a field safety notification issued by the manufacturer on October 21, 2016, and a dedicated root cause analysis, resulting in refinements to the instructions for use (IFU). We report the 2-year results of the investigational device exemption pivotal trial stratified according to the new and original criteria for selection of patients.

Methods: Comprehensive engineering evaluations, statistical analyses, and clinical assessments were conducted looking at patients enrolled in the pivotal trial (N = 150), roll-in cohort (N = 29), and continued access program (N = 154). All patients in all cohorts were treated on-IFU at the time of enrollment. Logistic regression models supported the mechanism that migration with Nellix is associated with a small aortic flow lumen relative to a large aneurysm thrombus burden and large aortic neck diameters. Based on these findings, refinements to the IFU criteria were applied, excluding patients with a thrombus index (maximum aneurysm sac/maximum flow lumen diameter) >1.4, aortic neck diameter >28 mm, and aortic neck conicity (>10% diameter change along the infrarenal neck) and requiring a 10-mm distal seal zone in the iliac artery.

Results: Freedom from all-cause mortality at 2 years was 94%. Patient outcomes were then stratified on the refined morphologic criteria and analyzed retrospectively. Two-year freedom from composite endoleak was high among both cohorts (95% on-IFU vs 92% off-IFU). Freedom from migration was 97.7% on-IFU vs 93.2% off-IFU ($P = .0125$). Freedom from aneurysm enlargement was 98.1% on-IFU vs 93.5% off-IFU (*P* value is not available because of failure of log-rank test assumptions). Composite freedom from migration, type IA endoleak, or aneurysm expansion was 95.9% among the on-IFU cohort vs 85.1% in the off-IFU cohort ($P = .0017$).

Conclusions: Consistent with the introduction of a novel therapy, the presentation of failure modes of EVAS over time was inevitable. Using detailed imaging as well as engineering and statistical analysis, we were able to understand risk factors for adverse events specific to EVAS and defined those patients best suited for Nellix. With this EVAS-specific approach to defining IFU, on-IFU patients were identified as those with large aneurysms with little thrombus that would be prone to type II endoleaks and sac expansion with traditional devices. When treated with Nellix, these patients were predicted to experience exceptional results, especially with regard to a low composite endoleak rate and low all-cause mortality. (J Vasc Surg 2018;68:720-30.)

Keywords: Nellix; Endovascular aneurysm sealing; EVAS

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The Nellix System (Endologix, Inc, Irvine, Calif) for endovascular aneurysm sealing (EVAS) is a novel approach to abdominal aortic aneurysm (AAA) treatment and conceptually different from endovascular aneurysm repair (EVAR), whereby polymer is employed to fill and actively manage the AAA sac. The 30-day safety and 1-year effectiveness end points of the Nellix pivotal trial were achieved and demonstrated encouraging outcomes with very low morbidity and mortality and high procedural and treatment success at 1 year.[1] Two-year imaging revealed a signal of migration, leading to a field safety notification issued by the manufacturer on October 21, 2016, and a dedicated root cause analysis, resulting in refinements to anatomic indications within the instructions for use (IFU) by proximal neck diameter constraints and criteria based on the aneurysm sac to flow lumen diameter ratio. We report the 2-year results of the investigational device exemption (IDE) pivotal trial stratified according to the new and original criteria for selection of patients.

METHODS

The Nellix System for EVAS, the EVAS procedure, and the EVAS FORWARD IDE trial design with its 1-year results have recently been described in detail.[1,2] In brief, the EVAS FORWARD IDE trial is a prospective multicenter single-arm clinical trial conducted at 29 centers with IDE approval from the Food and Drug Administration. Institutional Review Board approval of the protocol and informed consent of the patients were obtained at all participating sites. Eligible patients were accrued between 2014 and 2016 to the trial in its roll-in (N = 29), pivotal trial (N = 150), and continued access (N = 154) cohorts. All three cohorts were treated on-IFU using identical inclusion and exclusion criteria, namely, an infrarenal AAA with maximum sac diameter ≥5.0 cm or ≥4.5 cm that has increased by ≥0.5 cm within the last 6 months, adequate iliac or femoral access compatible with the required delivery systems (diameter ≥6 mm), aneurysm blood lumen diameter ≤60 mm, proximal nonaneurysmal aortic neck of length ≥10 mm and lumen diameter of 18 to 32 mm, angle ≤60 degrees to the aneurysm sac, and common iliac artery lumen diameters between 9 and 35 mm. Patients underwent computed tomography angiography imaging and clinical evaluations at intervals of 1 month (30 ± 14 days), 6 months (180 ± 30 days), 1 year (365 ± 60 days), and annually postoperatively (±90 days). Images were analyzed by an imaging core laboratory (Cleveland Clinic Peripheral Vascular Laboratory, Cleveland, Ohio). Clinical and computed tomography angiography-determined morphometric data were entered into a database. Data were continuously monitored for detection and analysis of adverse events, including migration, sac enlargement, and endoleaks, and risk factors for these events were identified by statistical analysis. Data updated as of March 20, 2017, are included in this analysis; as of this date, median follow-up was 763 days with 186 participants having reached 730 days, and 184 had a 2-year follow-up.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective evaluation of a prospective investigational device exemption clinical trial
- **Take Home Message:** Two-year results of endovascular sealing with the Nellix endograft using revised instructions for use (thrombus index <1.4, aortic neck diameter ≤28 mm, aortic neck conicity ≤10%, iliac sealing zone ≥10 mm) demonstrated significantly higher composite freedom from migration, type IA endoleak, or aneurysm expansion.
- **Recommendation:** The authors recommend using the revised instructions for use for treatment of aneurysms with the Nellix device. Patients with a large aneurysm and a small amount of thrombus will likely have the best results.

Table I. Demographics of the patients

ID	No.	Result
Age, years	333	73 ± 8
Sex		
Male	333	312 (94)
Female	333	21 (6)
Race		
White	333	306 (92)
Nonwhite	333	27 (8)
ASA class		
1 or 2	333	89 (27)
3, 4, or 5	333	244 (73)
SVS class		
0 or 1	333	307 (9)
2, 3, or 4	333	26 (8)
Height, cm	333	177 ± 8
Weight, kg	333	92 ± 19
Calculated BMI, kg/m^2	333	29 ± 5

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *ID*, identifier; *SVS*, Society for Vascular Surgery.
Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

Clinical and engineering analysis. Clinical review by a panel of physician experts, engineers, and statisticians was performed for all cases in which an adverse event had been observed, examining all available clinical and imaging data. Laboratory analysis of the mechanism of migration was conducted after its detection in the clinical data emerged. Testing included mechanical testing and computational fluid dynamic analysis.

Table II. Aneurysm characteristics

ID	No.	Result[a]
Maximum sac diameter, mm	333	56.8 ± 6.0 (40.8, 82.1)
<50 mm	23	7%
≥50, <60 mm	231	69%
≥60, <70 mm	65	20%
≥70, 70 mm	14	4%
AAA blood lumen diameter, mm	333	42.4 ± 7.5 (22.4, 59.9)
AAA sac volume, mL	333	137.5 ± 47.4 (38.1, 378.8)
Sac thrombus volume, mL	333	68.2 ± 35.6 (14.1, 225.6)
AAA blood lumen volume, mL	333	69.3 ± 29.9 (19.2, 218.3)
Nonaneurysmal neck length, mm	333	31.6 ± 14.1 (10.1, 103.1)
Maximum neck diameter at lowest renal, mm	333	25.6 ± 3.1 (19.6, 38.4)
Left common iliac artery diameter, maximum, mm	333	19.5 ± 5.3 (11.1, 53.1)
Left common iliac artery diameter, minimum, mm	333	11.1 ± 2.4 (7.5, 31.1)
Right common iliac artery diameter, maximum, mm	333	20.0 ± 5.6 (12.1, 50.4)
Right common iliac artery diameter, minimum, mm	333	11.2 ± 2.2 (7.5, 21.1)
Lowest renal to right hypogastric length, mm	333	177.5 ± 21.7 (101.5, 247.3)
Lowest renal to left hypogastric length, mm	333	179.1 ± 21.9 (112.9, 248.4)
Right access vessel minimum diameter, mm	333	7.7 ± 1.3 (6.0, 13.0)
Left access vessel minimum diameter, mm	333	7.7 ± 1.4 (4.9, 12.4)
Infrarenal proximal neck circumference with mural thrombus >5-mm thick, %	331	2.4 ± 7.3 (0.0, 47.0)
Aortic neck angulation, degrees	333	30.4 ± 13.4 (3.3, 59.7)

AAA, Abdominal aortic aneurysm; *ID*, identifier.
[a]Presented as mean ± standard deviation (minimum, maximum) or percentage when applicable.

Statistical analysis. Descriptive tables for demographics and aneurysm characteristics for the study population were created, presenting either the frequency or mean (standard deviation) when applicable. When outcomes were dependent on imaging, tables were created by using the number of evaluable computed tomography scans at each visit as the denominator. Kaplan-Meier analysis was used to provide 2-year overall survival and freedom from aneurysm-related mortality rates. When Kaplan-Meier analysis was used, observations were considered censored at the time of withdrawal, on loss to follow-up, or on the day of cutoff date used in the analysis. To support the investigative efforts into late adverse events, statistical modeling was implemented to identify useful predictors. Anatomic, demographic, and medical history variables identified as potential clinical risk factors and that reached statistical significance through univariate analysis were placed into a stepwise backward elimination logistic regression model with 5-mm migration set as the dependent variable. To maximize the number of events evaluable by the model, migration of 5 mm instead of 10 mm was used to determine event observations. To guard against overfitting of the data, the final model was limited to 3 variables to stay within the rule of using approximately 1 predictor per 10 events. The analysis was restricted to only those with a baseline and follow-up image for comparison as patients were located at various follow-up stages at the time of the initial analysis. Once predictor variables were identified, interaction was evaluated among the predictors. Utility of the model was evaluated through goodness of fit testing by the Hosmer-Lemeshow test and inspection of the resulting receiver operating characteristic curve. Kaplan-Meier analyses of the adverse events were stratified by IFU status to illustrate the application of the refined IFU. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Demographics

Clinical characteristics of the combined cohorts (N = 333) are shown in Table I. Anatomic features of their aneurysms are described in Table II.

Two-year outcomes

Mortality and rupture. All-cause mortality through 2 years was 5.7% (19 patients). The Kaplan-Meier freedom from all-cause mortality estimate was 93.8% (Fig 1, *A*). The Kaplan-Meier freedom from aneurysm-related mortality estimate was 98.6%, and the freedom from rupture estimate was 99.4% (Fig 1, *B*), which included two early deaths and AAA ruptures reported in follow-up. The details of these patients have been reported previously.[1]

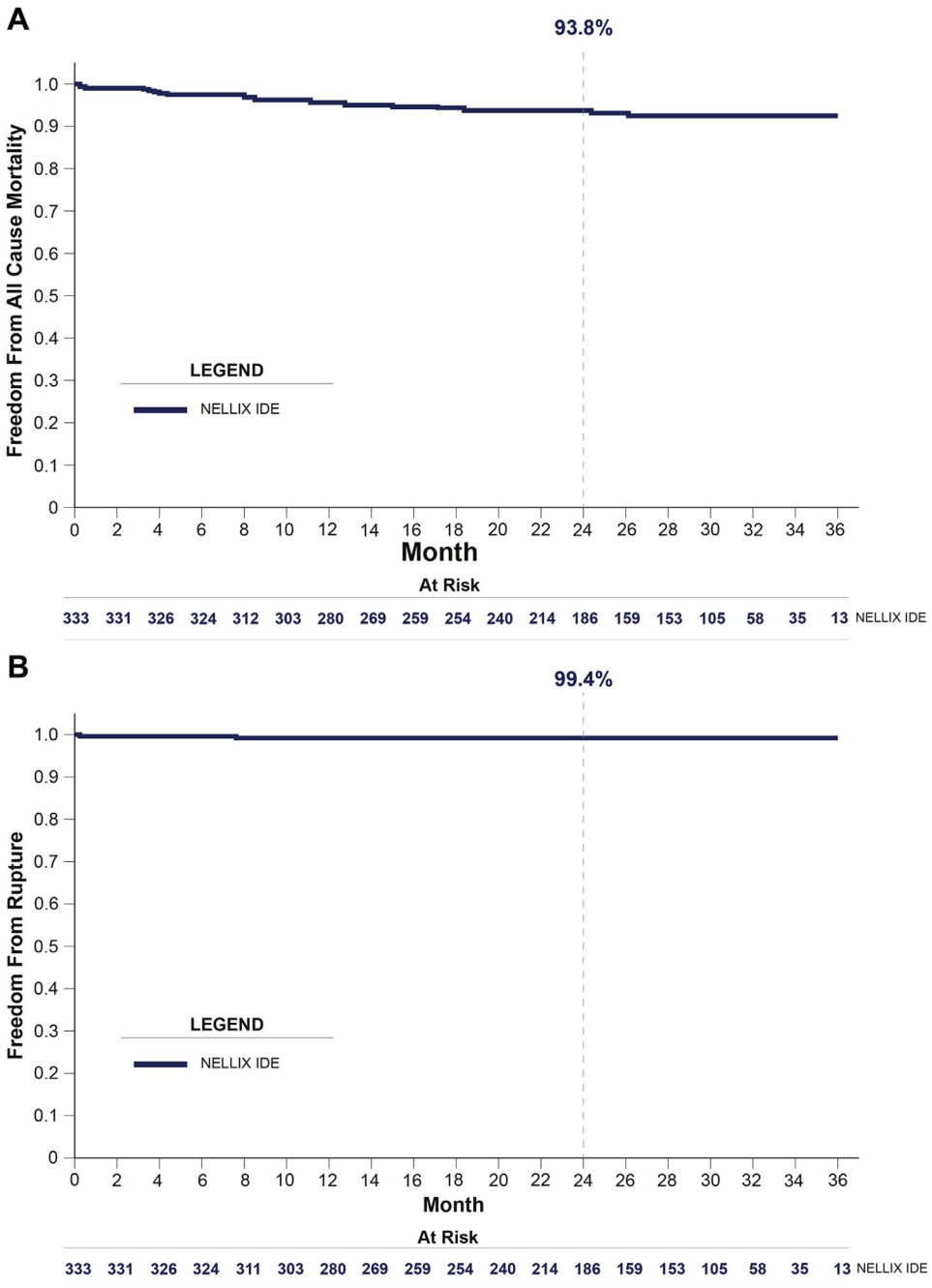

Fig 1. Kaplan-Meier freedom-from analysis, entire cohort (N = 333). **A,** Freedom from mortality. **B,** Freedom from rupture. *IDE,* Investigational device exemption.

Statistical analyses. The logistic regression model selected three preoperative anatomic features that were predictive of 5-mm migration (Table III). The thrombus index (the ratio of maximal aneurysm diameter to maximal flow lumen diameter), neck area (derived from the neck lumen diameter), and neck angle were found to be statistically significant risk factors for migration. Included together in a multivariable approach, these three variables provided good model fit per the Hosmer-Lemeshow test (nonsignificant *P* value). A receiver operating characteristic curve generated for the multivariable model had an area under the curve of 0.86, suggesting good predictive accuracy. These risk factors were consistent with clinical and engineering understandings of the migration mechanics and thus supported the use of preoperative imaging morphometric features to select patients at low risk for events.

Migration. Migration (>10 mm) was observed in 20 (6.0%) patients at the time of analysis. Of these, three (15%) were also associated with a type IA endoleak.

Table III. Binomial logistic regression analysis

Multivariable analysis[a]		
Factor for 5-mm migration	**OR**	**95% CI**
Thrombus index (sac diameter/lumen diameter)	40.52	7.03-233.70
Neck area, cm^2	2.30	1.38-3.81
Neck angle, degrees	1.07	1.03-1.11

CI, Confidence interval; *OR*, odds ratio.
[a]Hosmer-Lemeshow goodness of fit (*P* value is nonsignificant).

However, for one of these three patients, the type IA endoleak was observed in imaging before the finding of 10-mm migration.

Clinical review of these cases revealed that the common imaging feature of these migrations was bending of one or both stents, leading to shortening (Fig 2). Stents were observed to bend into adjacent thrombus in regions of minimal surrounding support by the aortic wall or polymer. Bending resulted in the proximal stent's moving distally.

Engineering analysis by mechanical testing and computational fluid dynamic analysis demonstrated that the stent's ability to resist bending forces (Fig 3) was insufficient to avoid buckling when the stent was not buttressed by sufficient surrounding thickness of polymer. The less polymer surrounding the stents, the less resistant they are to lateral bending. Conversely, the less thrombus present, the more polymer can be introduced, providing support for the stents.

Bending was the result of the downward force of flowing blood acting on the shelf presented by the polymer-filled endobags at the proximal aspect of the implant and the lateral force of blood flowing along the outside bend of any curvature of the stents. As the stent bends, it is pulled down (caudal migration). Stents continue to bend until coming to rest against the aortic wall or the proximal forces reach equilibrium with thrombus compressibility. The larger the aortic neck, the larger the size of the shelf and resulting downward force applied to the implant.

The migration phenomenon is related to several factors that work in concert to displace the device. The model was developed through evaluation of baseline risk factors and provides odds ratios (Table III) for several of the leading predictors. It can be seen that each of these factors is significantly associated with migration; however, the relative magnitude of each contributing factor suggests that thrombus burden is the most important.

Given these understandings, a threshold for thrombus burden was determined in an effort to separate patients at risk for migration from those at low risk. This threshold aimed to achieve a balance between sensitivity and false-negative calls without the complexity of a predictive statistical model. The ratio of aneurysm sac to flow lumen diameter (thrombus index) provides a simple way to gauge the thrombus burden and thus risk of migration. Using this index, a threshold of <1.40 reduced the incidence of migration.

Sac enlargement and sac morphologic changes. Compared with the 1-month baseline, AAA sac diameter increased >5 mm in 21 (12.5%) patients, remained stable (<5-mm change) in 136 (81.5%) patients, and decreased in 10 (6%) patients evaluable at the 2-year imaging window. Among those 21 patients with sac expansion, 5 type I endoleaks (23.8%) were observed at or before the time of enlargement.

The incidence of aneurysm enlargement initially made little sense in the context of a low endoleak incidence. Investigation of these patients revealed that large iliacs were a common finding for all these cases when proximal endoleaks were not a factor. Aneurysm enlargement in the absence of migration or endoleak occurred exclusively in patients with iliac diameter >20 mm.

Further clinical review of these cases revealed incomplete treatment of the iliac aneurysms as the most distal sections of the endobags were in contact with an aneurysmal portion of the iliac artery, surrounded by thrombus only, without direct apposition to healthy arterial wall (Fig 4). This absence of a healthy distal seal zone likely provided the opportunity for endotension by transmitting arterial pressure from the iliac artery's flowing blood through the thrombus layer adjacent to the endobag back into the AAA sac.

Endoleak. Endoleaks by type and follow-up interval are reported in Table IV. At the 2-year visit, endoleak prevalence was 1.9% for type I, 0.6% for type II, and 0% for type III or type IV among patients with an evaluable computed tomography scan. The Kaplan-Meier estimate of freedom from any endoleak was 95.1% at 24 months; from type IA endoleaks, 97.5%; and from type II endoleaks, 96.6%. Type IA endoleak was associated with large proximal aortic neck diameter (>28 mm) and irregular neck shape (change in neck diameter >10% for length of >10 mm).

Secondary procedures. Secondary procedures were performed in 35 (10.5%) patients as of the data cut for treatment of endoleaks (7 type IA, 2 type IB, 1 unknown type), migration (4), sac expansion without evidence of endoleak (1), AAA rupture (1), limb occlusion (17), stent infection (2), inadvertent renal artery coverage (1), and other (2). One patient with sac expansion was treated with distal extensions. Patients may have had multiple interventions and thus be counted in categories simultaneously, and eight patients had their first secondary procedure after 2 years. The Kaplan-Meier estimate of freedom from device-related secondary intervention was 91.1% at 2 years (Fig 5).

Surgical conversion. Surgical conversion occurred in 11 (3.3%) patients, including 1 with migration, 2 with migration and a type IA endoleak, 2 with isolated type IA endoleak, 1 with type IA endoleak and sac enlargement, 1 with

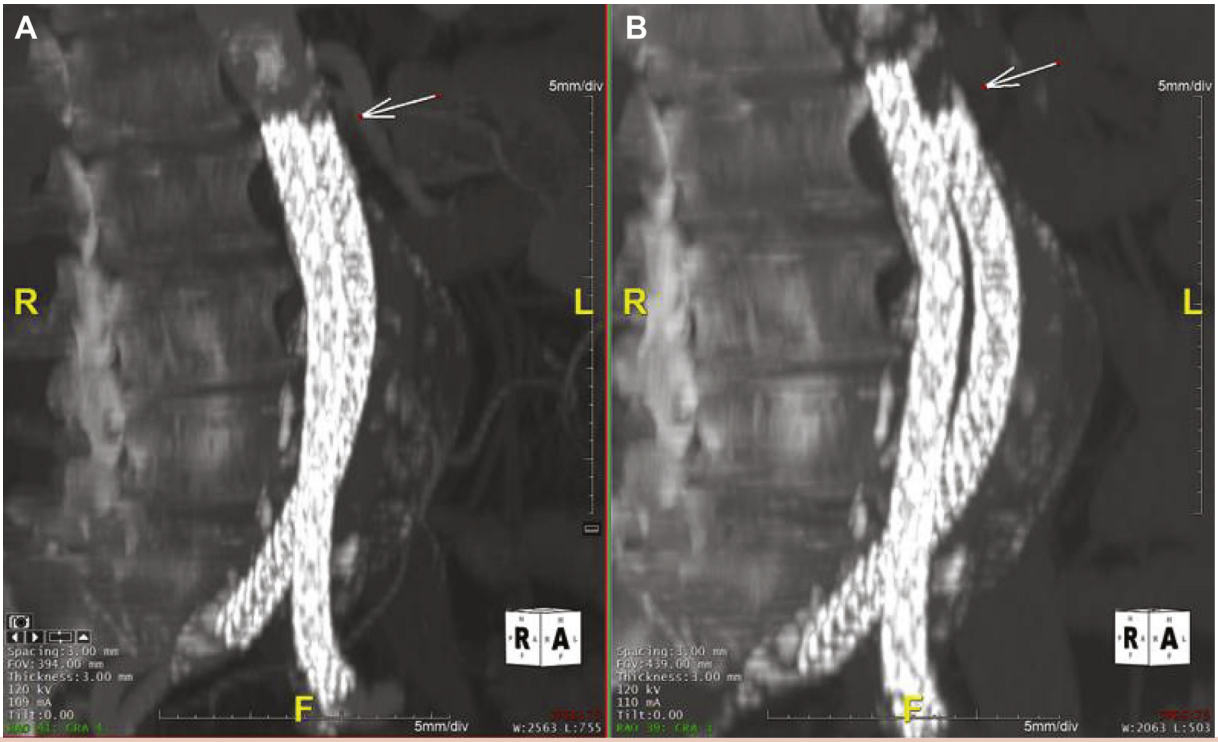

Fig 2. Migration mechanism: lateral displacement and bending. **A,** Initial postplacement computed tomography scan of the Nellix stents shows alignment of the tops of both stents (*arrow*). **B,** Follow-up computed tomography scan shows stent bending and lateral displacement leading to caudal migration of the right iliac limb (*arrow*).

isolated sac enlargement, 1 with stent infection, 1 with wound infection, and 2 with other reasons. The Kaplan-Meier estimate of freedom from surgical conversion was 98.0% at 2 years (Fig 6).

Retrospective development of revised IFU and prospective application: freedom-from analysis

A data cut was performed in October 2016 to investigate the adverse event phenomenon. At that time, 58 patients had evaluable imaging for migration within the 2-year follow-up visit window. Based on findings from clinical, engineering, and statistical vantages, revised IFU based on anatomic selection criteria were created to optimize selection of patients leading to reduction in migration, sac enlargement, and type I endoleak rates. IFU refinements include exclusion of patients with a thrombus index (maximum aneurysm sac/maximum flow lumen diameter) >1.4, aortic neck diameter >28 mm, and aortic neck conicity (>10% diameter change along the infrarenal neck) and the addition of a 10-mm distal seal zone requirement in the iliac artery. Note that although neck angle was found to be a third significant predictor for migration events, the revised IFU were not modified in this regard as control of the more influential variables appears effective in mitigating adverse events while also being relatively easy to obtain. The IFU, which were developed on the results of these 58 patients, were prospectively applied to the remaining patients as they subsequently passed the 2-year mark.

The impact of adoption of the new IFU on freedom-from survival for clinical end points is shown in Fig 7. Of the total cohort, suitability for the new on-IFU classification applied to 131 (39%) patients.

Freedom from migration (Fig 7, *A*) was 97.7% in the on-IFU group and 93.2% in the off-IFU group ($P = .0125$). Freedom from sac enlargement (Fig 7, *B*) was 98.1% in the on-IFU group and 93.5% in the off-IFU group. Freedom from type IA endoleak (Fig 7, *C*) was 99% in the on-IFU group and 96.6% in the off-IFU group ($P =$ NS). Freedom from device-related secondary intervention (Fig 7, *D*) was 95.9% in the on-IFU group and 88.1% in the off-IFU group ($P = .0066$). Freedom from conversion (Fig 7, *E*) was 98.5% in the on-IFU group and 97.7% on the off-IFU group. When statistical assumptions required for the log-rank test were not met, *P* values are not reported. Note that for all freedom-from curves where images are used, imaging dates tend to cluster around the protocol-defined visit windows, leading to deflections in the curve around these time points.

Six cases have been identified in which adverse outcomes have been identified despite meeting of refined IFU criteria. These include two patients with isolated migration; two patients with isolated aneurysm

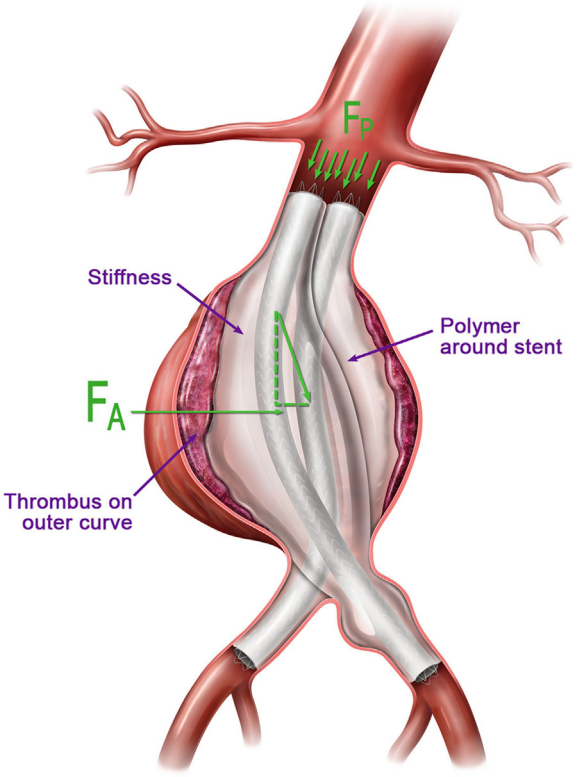

Fig 3. Mechanisms of bending and lateral displacement. Factors shown in *green* favor caudal migration, whereas factors shown in *blue* resist migration. The chief force favoring migration is the shelf force (F_P), whereby the caudally flowing pulsatile blood impacts the shelf of the endobag filled with polymer adjacent to the Nellix stents at the proximal aspect of the implant. The larger the aneurysm neck diameter, the greater the shelf area and force. The drag induced by blood flow around curved portions of the stents provides a lateral vector component (F_A) that can produce buckling. These forces are resisted by the stent's stiffness, the thickness and distribution of the polymer surrounding the stents, the adjacent vessel wall, and the surrounding thrombus.

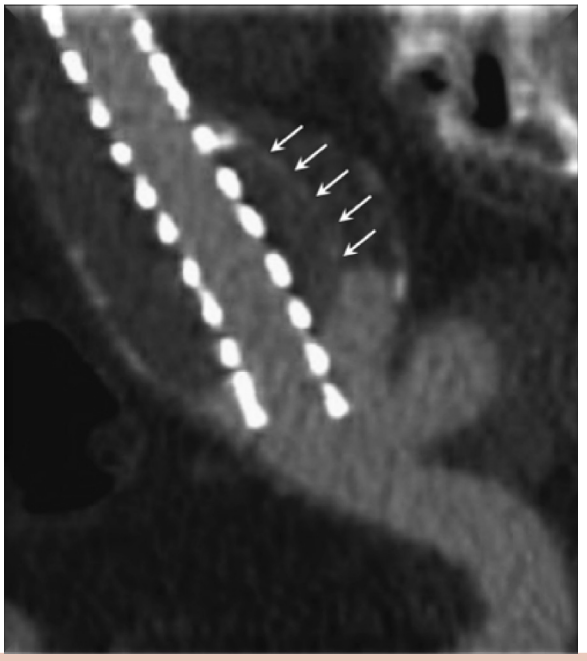

Fig 4. Sac enlargement due to distal sealing into iliac artery aneurysm thrombus. The root cause of aneurysm enlargement was found to be placement of distal endobags into iliac artery aneurysm thrombus. The distal Nellix stent is shown, ending at the bifurcation of the iliac artery, with the endobag (*arrows*) sealing into iliac artery aneurysm thrombus that is in communication with the aortic aneurysm sac. This allowed retrograde transmission of pressure into the aortic aneurysm sac through thrombus, creating endotension. The original Nellix instructions for use (IFU) did not stipulate a distal iliac seal zone in normal artery. The refined IFU now require a distal seal zone of ≥10 mm of iliac artery that is 9 to 20 mm in diameter.

enlargement; one patient with both migration and aneurysm enlargement; and one patient with migration, type IA endoleak, and aneurysm enlargement. In five of these six cases, technical issues during the index procedure have been identified as the cause (three underfilled endobags, one low placement of the stents, and one misalignment of the stents). In the remaining case, no immediate explanation for the adverse event has been identified.

DISCUSSION

EVAS, a novel approach to the treatment of aneurysm disease, is still in its infancy. Important observations have emerged from the IDE data that have greatly contributed to our understanding of EVAS and resulted in a refinement of the Nellix System's IFU. Early assumptions about EVAS predicted that filling of the aneurysm alone would be sufficient to ensure adequate aneurysm treatment. Our findings and the previous findings of others do not support this concept, however, but rather suggest the importance of both a proximal and distal seal zone and the necessity of a healthy AAA neck.

Aneurysm enlargement is commonly noted in EVAR, with a reported prevalence ranging from 21% to 41% at 5 years.[3,4] We noted aneurysm enlargement in association with a lack of distal iliac seal zone. Sealing of the aneurysm in thrombus, with lack of endobag apposition to the iliac artery wall, can lead to retrograde pressurization of the aneurysm sac by endotension through thrombus, as has previously been noted in Nellix patients.[5]

Each of these learnings has been incorporated into the revised IFU by requiring a smaller diameter (28 mm rather than 32 mm before), a more parallel (≤10% diameter change rather than ≤20% before) proximal AAA neck, and, for the first time, a 10-mm distal iliac artery seal zone in healthy (20-mm-diameter maximum) artery. Large AAA neck diameters have been associated with poor outcomes in EVAR, particularly with respect to

Table IV. Endoleaks

Endoleaks (core laboratory)							
Time point	**No.**	**Type IA**	**Type IB**	**Type II**	**Type III**	**Type IV**	**Unknown**
1 Month	320	3 (0.9)	0	9 (2.8)	0	0	0
New		3	0	9	0	0	0
Persistent		N/A	N/A	N/A	N/A	N/A	N/A
6 Months	291	2 (0.7)	0	2 (0.7)	0	0	1 (0.3)
New		1	0	0	0	0	1
Persistent		1	0	2	0	0	0
1 Year	253	2 (0.8)	2 (0.8)	3 (1.2)	0	0	1 (0.4)
New		2	2	2	0	0	0
Persistent		0	0	1	0	0	1
2 Years	160	3 (1.9)	0	1 (0.6)	0	0	1 (0.6)
New		3	0	0	0	0	1
Persistent		0	0	1	0	0	0

N/A, Not applicable.
Values are reported as number (%).

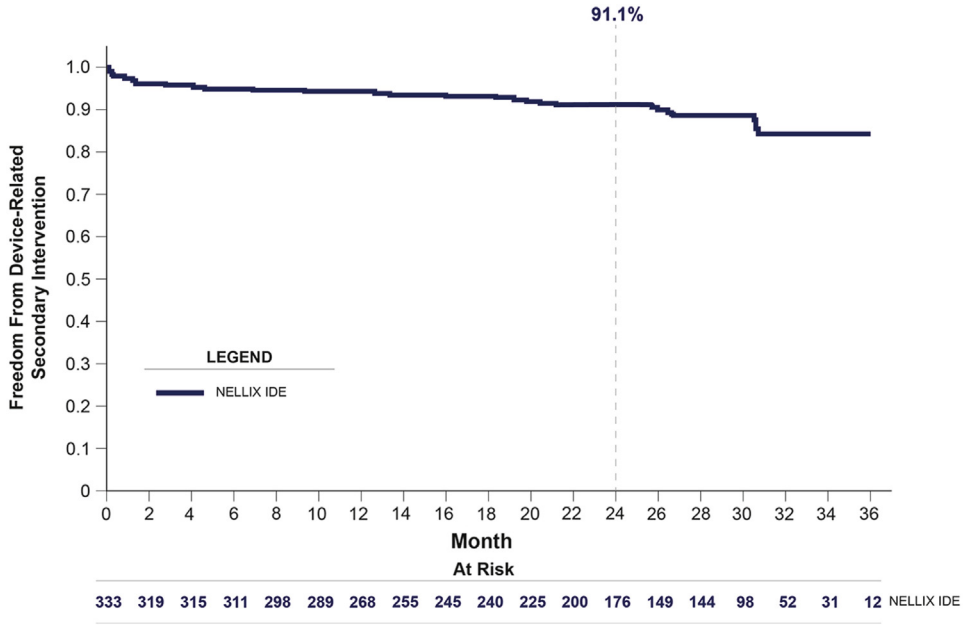

Fig 5. Kaplan-Meier estimate of freedom from device-related secondary intervention. *IDE,* Investigational device exemption.

type IA endoleak and sac enlargement.[6] Whereas type IA endoleak has not been a prevalent failure mode for EVAS, the restriction of the IFU to neck diameters of 18 to 28 mm may provide further benefit. Although there was no direct variable for aortic neck conicity, the IFU refinement of a ≤10% diameter change was introduced as imaging analysis showed that in some of the patients in whom the neck technically met the definition of 20% diameter change, the devices were landing in inadequate necks.

We and others have noted migration in Nellix patients.[1,7] An important lesson learned from the 2-year IDE data has been the need for sufficient polymer to support the Nellix stents to avoid migration of the prosthesis. The root cause of Nellix stent migration has been traced to lateral bending of the stents into surrounding soft thrombus. The ability of the stents themselves to resist bending forces is low, requiring polymer support.

Bending is induced by two caudally directed forces, the force of pulsatile pressure applied to the top of the

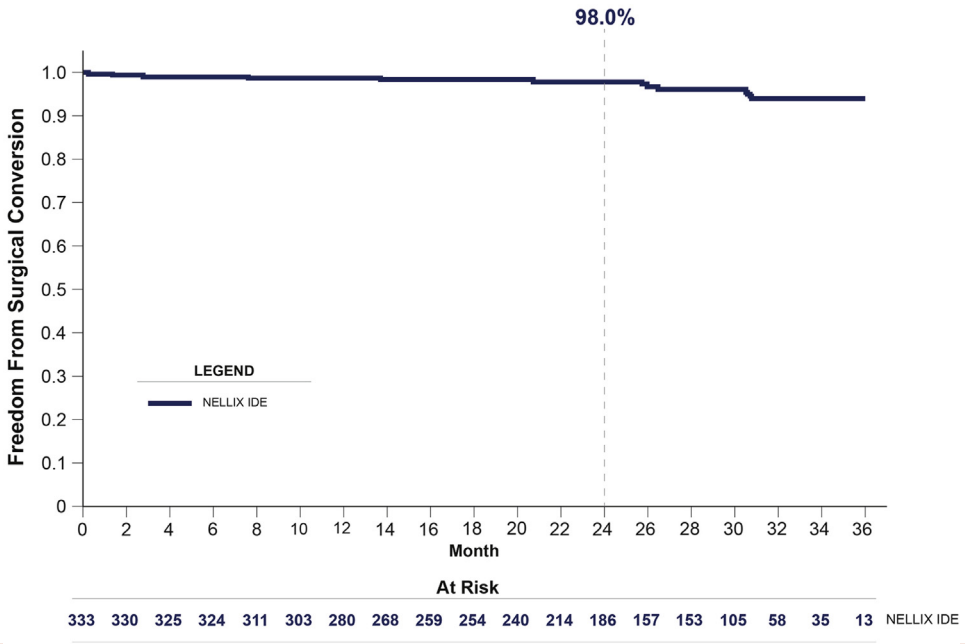

Fig 6. Kaplan-Meier estimate of freedom from surgical conversion. *IDE,* Investigational device exemption.

prosthesis (shelf force) and the force of blood dragging on the wall of curved portions of the stents. The shelf force is unique to EVAS because of the configuration of the top of the endograft, consisting of two stents surrounded by polymer-filled endobags. The shelf provided by the endobags provides a high resistance and strong downward force that contributes to migration. The size of the shelf increases with increasing aneurysm neck diameter. Neck diameter was identified as an independent predictor of migration, leading to the reduction in the maximum treatable neck diameter in the IFU from 32 mm to 28 mm.

Larger polymer volumes mitigate lateral bending of the stents. The introduction of the novel thrombus index into the revised IFU is to ensure that sufficient polymer is provided. This index is the ratio of the maximal aneurysm diameter to maximal flow lumen diameter. An index <1.4 provided a substantial reduction in migration incidence among the IDE patients (Fig 4).

The refined IFU were determined after 2-year experience was gained with 58 patients. The retrospectively determined IFU changes were then prospectively applied to the IDE cohort as patients continued to enter the 2-year follow-up. The results have remained unchanged without any further modification of the IFU, demonstrating consistently improved rates of migration and aneurysm enlargement for the on-IFU patients. This prospective application of the revised IFU has provided confidence in the choice of criteria for selection of patients necessary to achieve excellent clinical results with EVAS.

This analysis poses a limitation and caution of the new findings because patients were prospectively enrolled and treated on-IFU and then analyzed retrospectively against a revised set of anatomic inclusion criteria. A prospective confirmatory study is planned to validate the retrospective findings. The revised IFU criteria are also significantly more restrictive in applicability to infrarenal AAA patients, with only 39% of our original IDE cohort meeting the requirements. It is hoped that with future developments of EVAS devices, broader applicability can be achieved to make these results more generally available to AAA patients. However, the current iteration of the device has an important role in the treatment of AAAs. Endoleaks, the Achilles heel of EVAR, are low, with 97.4% freedom from type IA endoleak and 97% freedom from type II endoleak. Endoleaks have been identified as the root cause of many adverse events and as necessitating many secondary procedures associated with traditional EVAR.[8-10] Filling of the aneurysm sac with polymer, obliterating the potential space for endoleaks, is an advantage of this technique. Patients with a low thrombus burden and large flow lumen have historically had high rates of type II endoleaks and sac expansion when treated with traditional EVAR.[11,12] These are precisely the patients who have good outcomes with the Nellix System. In addition, the results achieved in these patients are excellent at 2 years with respect to overall mortality (6%) and provided 99% freedom from rupture.

Further research may explain the potential relationship between EVAS and changes to aortic intraluminal thrombus, postoperative inflammatory response, and improved clinical outcomes including all-cause and cardiovascular mortality.

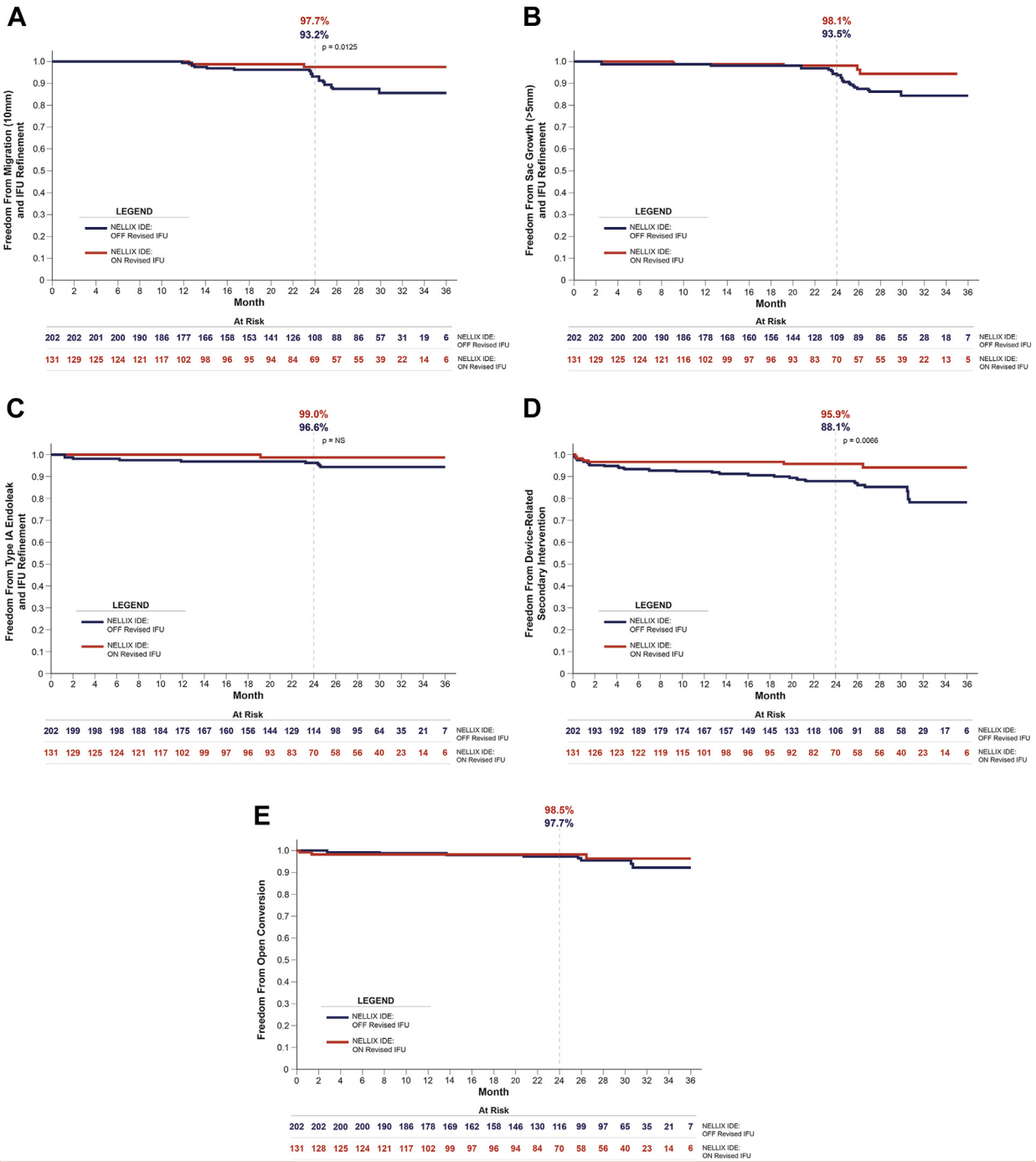

Fig 7. Freedom-from analysis stratified according to on and off refined instructions for use (*IFU*). **A,** Freedom from migration. **B,** Freedom from aneurysm enlargement. **C,** Freedom from type IA endoleak. **D,** Freedom from device-related secondary intervention. **E,** Freedom from conversion. *IDE,* Investigational device exemption.

CONCLUSIONS

Consistent with the introduction of a novel therapy, the presentation of failure modes over time is inevitable. Using detailed imaging, engineering, and statistical analysis, we have been able to understand risk factors for adverse events specific to EVAS and to define those patients best suited for Nellix. With this EVAS-specific approach to defining IFU, on-IFU patients treated with Nellix are predicted to experience exceptional results, especially with regard to a low composite endoleak rate and low all-cause mortality.

AUTHOR CONTRIBUTIONS

Conception and design: JC
Analysis and interpretation: JC
Data collection: JC, JL, JT, SH, CH, CB, HH, RC

Writing the article: JC
Critical revision of the article: JC, JL, JT, SH, CH, CB, HH, RC
Final approval of the article: JC, JL, JT, SH, CH, CB, HH, RC
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: JC

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DISCUSSION

Dr Jon Matsumura (*Madison, Wisc*). Nice presentation, Jeff, and I really appreciate your bringing this to the meeting in this way so we can discuss it openly. With the change to the ratio 1.4 in the instructions for use (IFU) and prior limits for some large aneurysms, what is the percentage of patients in the study who meet the new IFU, and what is your estimate of the percentage of patients who could be treated with other devices?

Dr Jeffrey P. Carpenter. In the investigational device exemption trial, the on-IFU group represents 39% of the total, so it does place a significant restriction on the patients we would now consider candidates for Nellix.

It's not surprising that issues would arise in a first-generation device and a novel disruptive technology. For that 39% that are on-IFU, the results that are achievable are the best ever reported in an investigational device exemption aneurysm trial. The possibility of eliminating endoleak and reducing reinterventions addresses the shortcomings of endovascular aneurysm repair and is very attractive with the polymer-based endovascular aneurysm sealing solution. This is a first attempt, and as further iterations of the device come along, it will likely become more broadly applicable.

APPENDIX (online only).

Investigative sites and principal investigators.

Investigative site	Location	Principal investigator
Cooper University Hospital	Camden, NJ	Jeffrey P. Carpenter, MD (Global PI) Jose Trani, MD (Site PI)
Addenbrooke's Hospital Cambridge University	Cambridge, United Kingdom	Paul Hayes, MD
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 Frank Arko, MD
Christiana Hospital	Wilmington, Del	Ralph Ierardi, MD
Cleveland Clinic	Cleveland, Ohio	Daniel Clair, MD Lester Lee Kirksey, 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
Minneapolis Hospital	Minneapolis, Minn	Timothy Sullivan, MD Elliot Stephenson, 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
Rijnstate Hospital	Arnhem, The Netherlands	Michel Reijnen, MD, PhD
Sacred Heart Hospital	Pensacola, Fla	Stuart Harlin, MD Huey McDaniel, MD
San Diego VA Hospital	San Diego, Calif	John Lane, MD
Spectrum Health	Grand Rapids, Mich	Robert Cuff, MD
St. Elizabeth's Hospital	Brighton, Mass	Nikhil Kansal, MD
St. Luke's Episcopal Hospital	Houston, Tex	Zvonimir Krajcer, MD
St. Vincent Healthcare	Billings, Mont	Kevin Bruen, MD
St. Vincent's Heart Center of Indiana	Indianapolis, Ind	Sajjad Hussain, MD
Tucson Medical Center/PIMA Vascular	Tucson, Ariz	Luis Leon, MD
University Hospital	Heidelberg, Germany	Dittmar Böckler, MD, PhD
University of Pittsburgh Medical Center	Pittsburgh, Pa	Michel Makaroun, MD
Yale New Haven Hospital	New Haven, Conn	Jeffrey Indes, MD Timur Sarac, MD