Analysis of new diagnostics and technologies in endovascular aortic aneurysm repair
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Anatomical predictors for endoleaks or migration after endovascular aortic aneurysm sealing.
Abstract

Purpose: To identify preoperative anatomical aortic characteristics that predict seal failures after endovascular aneurysm sealing (EVAS) and compare the incidence of events experienced by patients treated within vs outside the instructions for use (IFU).

Methods: Of 355 patients treated with the Nellix EndoVascular Aneurysm Sealing System (generation 3SQ+) at 3 high-volume centers from March 2013 to December 2015, 94 patients were excluded, leaving 261 patients (mean age 765 ± 8 years; 229 men) for regression analysis. Of these, 83 (31.8%) suffered one or more of the following events: distal migration ≥5 mm of one or both stent frames, any endoleak, and/or aneurysm growth >5 mm. Anatomical characteristics were determined on preoperative computed tomography (CT) scans. Patients were divided into 3 groups: treated within the original IFU (n=166), outside the original IFU (n=95), and within the 2016 revised IFU (n=46). Categorical data are presented as the median (interquartile range Q1, Q3).

Results: Neck diameter was significantly larger in the any event cohort versus the control cohort (23.7[21.7-26.3]mm vs 23.0[20.9-25.2]mm, P=0.022). Neck length was significantly shorter in the any event cohort (15.0[10.0-22.5]mm vs 19.0[10.0-21.8]mm, P=0.006). Maximum AAA diameter and the ratio between maximum AAA diameter and lumen diameter in the any event group were significantly larger than the control group (P=0.041 and P=0.002, respectively). Regression analysis showed aortic neck diameter, neck length and ratio between maximum AAA diameter and lumen diameter as significant predictors for any event (P<0.05). Of the 261 patients included, 166 patients were treated inside the original IFU, and 46 were inside the IFU 2016. Of the 261 patients 83 suffered from an event (31.8%), In the inside the original IFU group 52 out of 166 patients suffered an event (31.3%) compared to 13 out of 46 patients inside the IFU 2016 group (28%).

Conclusion: Large neck diameter, short aortic neck length, and the ratio between the maximum AAA and lumen diameters are preoperative anatomical predictors for the occurrence of migration (≥5 mm), any endoleak, and aneurysm growth (>5 mm) after EVAS. Even under the refined 2016 IFU, more than a quarter of patients suffered from an event. Improvements in the device seem to be necessary before this technique can be implemented on a large scale in endovascular AAA repair.
Introduction
The Nellix EndoVascular Aneurysm Sealing (EVAS) System (Endologix Inc., Irvine, CA, USA) is a technique for exclusion of an abdominal aortic aneurysm (AAA), developed to potentially reduce the need for type I and II endoleak–associated reinterventions. It consists of 2 polymer-filled endobags that surround 10-mm balloon-expandable stent frames. The proximal, uncovered stent of the frames must be deployed 5 mm above the lower border of the lowest renal artery orifice. The endobags are filled in situ with polymer and occupy the aortic cavity to provide a total seal of the aneurysm. Early results showed a high technical success rate and a low incidence of complications. At midterm follow-up, differences in clinical outcomes were observed in favor of patient treated inside instructions for use (IFU). Dedicated root cause analysis traced lateral bending of the stents into the surrounding aortic thrombus as a potential cause for EVAS failure, and a recent study also showed that positioning of the sealing top of the endobags flush distally to the renal arteries may be challenging. This led to a refinement of the IFU in 2016. The aim of this study was to identify independent preoperative anatomical characteristics that could predict EVAS failure in order to optimize patient selection. Moreover, the effect of the refinement of the 2016 IFU on complication rate was investigated.

Methods
Study design
The primary purpose of the study was to find independent preoperative anatomical characteristics for post-EVAS migration (≥5 mm) of one or both stent frames, any endoleak, and/or aneurysm growth (>5 mm), collectively referred to as “any event.” Moreover, the complication rate after refinement of the IFU was compared to the rate in the cohort treated under the original IFU. Patients for this retrospective analysis were derived from the Dutch Endovascular Aneurysm Sealing Study (DEVASS) database, which has been previously used to analyze the clinical 2-year outcome of EVAS. The database was interrogated to identify patients treated with the Nellix (generation 3SQ+) from March 2013 to December 2015 in 3 high volume Dutch (endo)vascular centers. Of 355 patients identified during this period, 61 patients were excluded due to nonelective EVAS procedures (Figure 10.1). Another 30 patients were excluded due to missing computed tomography (CT) scans or symptomatic or ruptured AAA, the latter being excluded because no proper anatomical measurements could be performed.
at the pre-EVAS CT scan. Symptomatic AAAs were excluded because not all lengths of Nellix devices were available off the shelf, and adjunctive procedures had to be performed in some of these patients (such as iliac extensions with a regular endograft limb). Another 3 patients with noncontrast preoperative CT scans were excluded from the analysis. The remaining 261 patients (mean age 76 ± 8 years; 229 men) were included in the regression analysis. Of these, 166 patients were treated inside the original IFU and 46 were inside the 2016 IFU. Among all 261 patients, 83 (31.8%) had any event during follow-up; the remaining 178 patients without an event constituted the control group.

Retrospective chart review is not within the scope of the Dutch law governing research involving human subjects, so a waiver of the Dutch central ethics board was obtained (file number 2015-2131) for this study. Personal data were anonymized and handled in compliance with the Dutch Personal Data Protection Act.

**Figure 10.1:** Flowchart of patient inclusion for regression analysis. AAA, abdominal aortic aneurysm; CH-EVAS, chimney endovascular aneurysm sealing; CIAA, common iliac artery aneurysm; CT, computed tomography; EVAS, endovascular aneurysm sealing.
**Measurement protocol**

Measurements were performed on a 3Mensi o vascular workstation (version 8.1; Pie Medical Imaging BV, Bilthoven, the Netherlands) by an independent experienced observer (J.B.). A center lumen line (CLL) was drawn semiautomatically starting 40 mm above the lowest renal artery orifice up to both iliac artery bifurcations and adjusted manually if necessary. The following anatomical characteristics were determined on the preoperative CT scan: aortic neck diameter at the level of the lowest renal artery (baseline), neck length from the lowest renal artery to the distal end of the neck (10% increase in aortic diameter as compared to baseline), suprarenal and infrarenal angulation, maximum AAA diameter, maximum aortic flow lumen diameter, infrarenal neck thrombus thickness and circumference, infrarenal neck calcification thickness and circumference, right and left common iliac artery (CIA) minimum and maximum lumen diameters, and right and left CIA maximum diameters.

At all postoperative CT scans, neck diameter, neck length, proximal end of each stent frame position, and maximum aneurysm diameter were measured. All postoperative CT scan measurements were compared with the first postoperative CT scan to discern potential migration (≥5 mm), any endoleak, and/or aneurysm growth (>5-mm increase of the maximum AAA diameter). If any event was not conclusive on the postoperative CT scans, 3 experienced vascular surgeons (J.H., M.R., J.V.) reached a consensus.

**Refined IFU 2016**

The following characteristics are in the 2016 IFU: (1) infrarenal neck length ≥ 10 mm, (2) proximal neck diameter change ≤10% (original IFU ≤20%), (3) proximal neck diameter 18 to 28 mm (original IFU 18 to 32 mm), (4) infrarenal neck angulation ≤60°, (5) aneurysm blood lumen diameter ≤60 mm, (6) the ratio of the maximum AAA diameter to maximum aortic blood lumen diameter <1.4 (hereafter referred to as the diameter ratio; this parameter was not in the original IFU), (7) iliac artery lumen diameter 9 to 20 mm (original IFU 9 to 32 mm), (8) distal iliac artery seal zone length ≥10 mm with a maximum diameter of 25 mm (not in the original IFU), and (9) femoral access >7 mm.

**Statistical analysis**

Differences in anatomical characteristics were calculated with a one-way analysis of variance (ANOVA), and risk factors for any event were identified. Input parameters for the backward stepwise binary logistic regression model were neck...
diameter, neck length, supra- and infrarenal neck angulation, maximum AAA lumen diameter, maximum AAA diameter, the diameter ratio, infrarenal neck thrombus thickness and circumference, infrarenal neck calcification thickness and circumference, right and left CIA minimum and maximum lumen diameter and right and left CIA maximum diameter. All variables except for infrarenal neck thrombus and calcification are included in the EVAS 2016 IFU.

Independent variables were compared using the Pearson’s correlation test to reduce the effects of multicollinearity. If variables had a correlation coefficient (R) >0.7, only one variable with the highest beta and lowest p-value in the one-way ANOVA was used in the final regression model. Backwards stepwise binary logistic regression eliminated variables with the least significance until the significance of all remaining variables was <0.05.

The sensitivity and specificity of each variable in the final regression model were expressed with receiver operator characteristics (ROC) curves. The ROC curves were used to determine cutoff points for significant independent predictors for migration, endoleak, and/or aneurysm growth.

Data were tested for normality using the Shapiro-Wilk test. Variables with a skewed distribution were presented as the median (interquartile range Q1, Q3). All tests were 2-sided, and p<0.05 was considered significant. Statistical analysis was performed with SPSS software (version 23; IBM Corp, Armonk, NY, USA).

**Results**

Median CT follow-up was 24.2 months (17.2, 34.9) for the any-event group vs 26.9 months (14.3, 37.3) for the control group (p=0.192). Any of the 3 prespecified events occurred at a median 22.8 months (11.8, 29.5). Table 10.1 shows the results of the baseline anatomical characteristics of the any-event and control groups. Median neck diameter was significantly larger in the any-event cohort [23.7 mm (21.7, 26.3)] vs the control cohort [23.0 mm (20.9, 25.2), p=0.022]. Median neck length was significantly shorter in the any-event cohort [15.0 mm (10.0, 22.5)] vs controls [19.0 mm (10.0, 21.8), p=0.006]. The maximum AAA diameter and the diameter ratio in the any-event group were significantly larger than the control group (p=0.041 and p=0.002, respectively).

**Regression Analysis**

There were high correlations between AAA lumen diameter and the diameter ratio (R=0.742), neck thrombus thickness and circumference (R=0.797), neck calcification thickness and circumference (R=0.700), the right CIA maximum
Table 10.1. Anatomical characteristics.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 178)</th>
<th>Any event (n = 83)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter at lowest renal artery, (mm)</td>
<td>23.0 [20.9 - 25.2]</td>
<td>23.7 [21.7 - 26.3]</td>
<td>0.022</td>
</tr>
<tr>
<td>Neck length, (mm)</td>
<td>19.0 [10.0 - 31.8]</td>
<td>15.0 [10.0 - 22.5]</td>
<td>0.006</td>
</tr>
<tr>
<td>Suprarenal angulation, (deg)</td>
<td>13.8 [8.0 - 21.9]</td>
<td>11.9 [7.4 - 19.1]</td>
<td>0.130</td>
</tr>
<tr>
<td>Infrarenal angulation, (deg)</td>
<td>20.7 [11.7 - 36.8]</td>
<td>22.9 [11.6 - 33.8]</td>
<td>0.947</td>
</tr>
<tr>
<td>Maximum AAA lumen diameter, (mm)</td>
<td>43.0 [37.7 - 48.7]</td>
<td>40.0 [36.0 - 48.1]</td>
<td>0.107</td>
</tr>
<tr>
<td>Maximum AAA diameter, (mm)</td>
<td>57.3 [54.2 - 62.0]</td>
<td>58.3 [55.3 - 64.3]</td>
<td>0.041</td>
</tr>
<tr>
<td>Ratio between AAA maximum and lumen diameter</td>
<td>1.3 [1.2 - 1.5]</td>
<td>1.4 [1.3 - 1.7]</td>
<td>0.002</td>
</tr>
<tr>
<td>Neck thrombus thickness, (mm)</td>
<td>0.0 [0.0 - 0.0]</td>
<td>0.0 [0.0 - 2.0]</td>
<td>0.086</td>
</tr>
<tr>
<td>Neck thrombus circumference, (deg)</td>
<td>0.0 [0.0 - 0.0]</td>
<td>0.0 [0.0 - 82.0]</td>
<td>0.108</td>
</tr>
<tr>
<td>Neck calcification thickness, (mm)</td>
<td>0.0 [0.0 - 1.5]</td>
<td>0.0 [0.0 - 1.5]</td>
<td>0.843</td>
</tr>
<tr>
<td>Neck calcification circumference, (deg)</td>
<td>0.0 [0.0 - 40.8]</td>
<td>0.0 [0.0 - 35.0]</td>
<td>0.686</td>
</tr>
<tr>
<td>Right minimum CIA lumen diameter, (mm)</td>
<td>10.0 [9.0 - 11.8]</td>
<td>10.0 [9.1 - 11.7]</td>
<td>0.579</td>
</tr>
<tr>
<td>Left minimum CIA lumen diameter, (mm)</td>
<td>10.0 [9.0 - 11.5]</td>
<td>9.6 [9.0 - 12.0]</td>
<td>0.357</td>
</tr>
<tr>
<td>Right maximum CIA lumen diameter, (mm)</td>
<td>15.6 [12.2 - 18.8]</td>
<td>16.0 [13.4 - 18.2]</td>
<td>0.324</td>
</tr>
<tr>
<td>Left maximum CIA lumen diameter, (mm)</td>
<td>15.2 [13.0 - 18.3]</td>
<td>15.0 [12.0 - 17.8]</td>
<td>0.141</td>
</tr>
<tr>
<td>Right maximum CIA diameter, (mm)</td>
<td>17.1 [13.9 - 20.9]</td>
<td>17.1 [14.5 - 20.5]</td>
<td>0.616</td>
</tr>
<tr>
<td>Left maximum CIA diameter, (mm)</td>
<td>16.6 [14.5 - 19.9]</td>
<td>16.4 [13.4 - 19.8]</td>
<td>0.363</td>
</tr>
</tbody>
</table>

Abbreviations: AAA, abdominal aortic aneurysm; CIA, common iliac artery.

\textsuperscript{a}Data shown as median (interquartile range Q1, Q3).

lumen diameter and the right CIA maximum and minimum lumen diameters (R=0.836 and R=0.702, respectively), the left CIA maximum diameter and left CIA maximum and minimum lumen diameters (R=0.888 and R=0.734, respectively), and the left CIA maximum and lumen diameters (R=0.714). All other variables were R<0.7.

In the next step, the following highly intercorrelated variables were excluded from the regression analysis as they had the highest p-values in the one-way ANOVA: the AAA lumen diameter, neck thrombus circumference, neck calcification thickness, right and left minimum CIA lumen diameters, right CIA maximum lumen diameter, and left CIA maximum diameter. This left the following parameters for entry into the final regression analysis: neck diameter, neck length, supra- and infrarenal angulation, maximum AAA diameter, the diameter ratio, neck thrombus thickness, neck calcification circumference, left CIA maximum lumen diameter, and right CIA maximum diameter.
The regression model (Table 10.2) and ROC curve (Table 10.3, Figure 10.2) showed that the aortic neck diameter ($p=0.006$), neck length ($p=0.001$), and the diameter ratio ($p=0.011$) were significant predictors for any event. Every 1-mm increase in neck diameter amplified the risk of any event by 14.7%. Every 1-mm shorter neck length increased the risk of any event by 3.8%. Infrarenal angulation and left CIA maximum lumen diameter were identified as predictors in the regression model as well; however, the areas under the ROC curve showed a random classification.

The area under the ROC curve of the final model was 0.714 (95% CI 0.646 to 0.781, $p<0.001$), which was better than any of the individual variables in the final model (Table 10.3, Figure 10.2). The optimal cutoff values were 21.3 mm for neck diameter, 18.5 mm for neck length, and 1.35 for the diameter ratio. The sensitivity and specificity of the cutoff values were 0.827 and 0.335 for neck diameter, 0.272 and 0.491 for neck length, and 0.691 and 0.509 for the diameter ratio.

**IFU groups Comparison**

Among the 166 patients treated inside the original IFU group, 52 (31.3%) suffered an event compared to 13 (28.3%) of 46 patients who were in the 2016 IFU group ($p=0.690$). The complications in the 13 2016 IFU patients were migration ($n=4$), endoleak ($n=3$), aneurysm growth ($n=1$), migration and endoleak ($n=1$), migration, endoleak and aneurysm growth ($n=1$), or endoleak and aneurysm growth ($n=3$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>OR*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck diameter</td>
<td>0.137</td>
<td>0.049</td>
<td>1.147</td>
<td>0.006</td>
</tr>
<tr>
<td>Neck length</td>
<td>-0.039</td>
<td>0.012</td>
<td>0.962</td>
<td>0.001</td>
</tr>
<tr>
<td>Ratio between AAA maximum diameter</td>
<td>1.434</td>
<td>0.040</td>
<td>4.197</td>
<td>0.011</td>
</tr>
<tr>
<td>and lumen diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrarenal angulation</td>
<td>0.021</td>
<td>0.010</td>
<td>1.021</td>
<td>0.039</td>
</tr>
<tr>
<td>Left maximum CIA lumen diameter</td>
<td>-0.087</td>
<td>0.040</td>
<td>0.917</td>
<td>0.030</td>
</tr>
<tr>
<td>Constant</td>
<td>-4.427</td>
<td>1.352</td>
<td>0.012</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: AAA, abdominal aortic aneurysm; CIA, common iliac artery.

*aOdds ratio indicates the increase in any event per unit increase. Every 1-mm increase in neck diameter amplifies the risk of any event by 14.7%. Every 1-mm of shorter neck length increases the risk of any event by 3.8%.
**Figure 10.2:** Receiver operating characteristic (ROC) curves of the variables in the final binary logistic regression model. The final model of the regression analyses provides the best sensitivity and specificity. AAA, abdominal aortic aneurysm; CIA, common iliac artery.

**Table 10.3:** Area under the receiver operating characteristics curves of the final regression model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>95% CI</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck diameter</td>
<td>0.590</td>
<td>0.515 to 0.665</td>
<td>0.038</td>
<td>0.021</td>
</tr>
<tr>
<td>Neck length</td>
<td>0.398</td>
<td>0.328 to 0.469</td>
<td>0.036</td>
<td>0.009</td>
</tr>
<tr>
<td>Ratio between AAA maximum and</td>
<td>0.621</td>
<td>0.546 to 0.696</td>
<td>0.038</td>
<td>0.002</td>
</tr>
<tr>
<td>lumen diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrarenal angulation</td>
<td>0.504</td>
<td>0.428 to 0.579</td>
<td>0.039</td>
<td>0.924</td>
</tr>
<tr>
<td>Left maximum CIA lumen diameter</td>
<td>0.442</td>
<td>0.366 to 0.519</td>
<td>0.039</td>
<td>0.140</td>
</tr>
<tr>
<td>Final regression model</td>
<td>0.714</td>
<td>0.646 to 0.781</td>
<td>0.034</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Abbreviations: AAA, abdominal aortic aneurysm; AUC, area under the curve; CI, confidence interval; CIA, common iliac artery.

**Discussion**

In the current study, preoperative aortic neck diameter, neck length, and diameter ratio were preoperative predictors for migration, any endoleak, and aneurysm growth after EVAS. Moreover, despite IFU refinement, more than a quarter of
patients had complications over time, an observation similar to that recently reported by Zerwes et al.\textsuperscript{8}

Previous studies\textsuperscript{9,10} demonstrated caudal and lateral displacement of the EVAS endosystem, which might be due to the instability of intraluminal thrombus within the aneurysm sac. A larger ratio between the maximum AAA and lumen diameters might reflect the potential for this instability to adversely affect the endobags and stent frames, especially in patients with large sac thrombus volumes. Studies have shown that intraluminal thrombus cannot be addressed as a rigid structure and might change over time.\textsuperscript{11-13} This sponge-like effect in combination with a larger AAA diameter might result in bending of the stent frames into the thrombus and parting of the stent frames, which can make the EVAS configuration unstable. A low amount of polymer surrounding the stent frames in small flow lumens might also induce instability into the EVAS configuration.

The definition of migration in this study is not in concert with the standard of migration for EVAR proposed by the Society of Vascular Surgery (>10 mm or clinical consequences).\textsuperscript{14} However, recent studies\textsuperscript{15,16} suggested that a more conservative approach to migration in EVAS would be prudent owing to the lack of active proximal fixation on the Nellix device. Thus, if migration of 3 to 4 mm is documented, it is likely that further migration will occur. Since 1- to 3-mm migration is difficult to distinguish on a CT scan, this current study used a $\geq$ 5-mm threshold for migration.

In 2013, when EVAS was a novel technology, it was thought that it was widely applicable and provided an additional solution for AAAs that could not be treated by EVAR.\textsuperscript{17} Results from the current regression analyses and earlier root cause analyses showed that patient selection needs to be stricter. The percentage of complications in the current DEVASS cohort is higher than was anticipated. For stricter patient selection, a refined 2016 IFU was developed. One of the main new criteria was the “thrombus” ratio of the maximum aneurysm to maximum blood lumen diameters, which excluded patients with relatively high amounts of thrombus in the aneurysm sac.\textsuperscript{8} This ratio was significantly different between the control and any-event cohorts and a predictor in the regression analyses. It is therefore an important parameter to consider during patient selection.

Nonetheless, results from this study showed that despite IFU refinement, more than a quarter of patients developed a complication during midterm follow-up. These results are not in line with a previous report of the 2-year outcomes, which described lower complication rates.\textsuperscript{5} However, the discrepancy is caused by a difference in the definition of migration (>10 mm in the 2-year study vs $\geq$ 5 mm in this analysis) and longer follow-up in the current report. A substantial
proportion of the complications have occurred after 2 years, which is illustrated by the median 22.8 months between the EVAS procedure and the occurrence of any event in our analysis.

In April 2016, a second-generation device was introduced. One of the major changes was attachment of the endobag to the stent frame distally, which may improve iliac sealing. Long-term follow-up needs to provide information on the durability of this new generation device. So far, though, migration is the most frequent EVAS-associated complication, thus the sac-anchoring mechanism of the current Nellix endosystem seems not to be sufficient. Lack of anchoring pins in the aortic wall and no suprarenal fixation are reasons why migration resistance of the Nellix endosystem is low in some patients.

Another failure mechanism is bowing of the stent frames during follow-up, which can cause lateral displacement of the endobags in the aneurysm sac, especially in patients with a large aortic thrombus load. This lateral displacement will cause gaps and type Ia endoleaks in between the 2 Nellix endobags.

**Limitations**

This was a retrospective analysis with a median follow-up of only 2 years. More complications may occur with longer follow-up, which could increase the number of events in patients in the control cohort.

**Conclusion**

Large neck diameter, short aortic neck length, and the diameter ratio between the aneurysm sac and lumen (thrombus ratio) are preoperative anatomical predictors of migration (≥5 mm), any endoleak, and aneurysm growth (>5 mm) after EVAS. A quarter of patients meeting the refined 2016 IFU criteria still suffered one or more of these events. Additional improvements in the device seem to be necessary before this technique can be implemented on a large scale in endovascular AAA repair.
References


