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Endovascular Aneurysm Sealing is Associated with Higher Medium-Term Survival than Traditional EVAR

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Abstract

Background: Endovascular repair (EVAR) is the dominant treatment modality for abdominal aortic aneurysm (AAA). Periprocedural risks are low, and cardiovascular events are the principle determinants of long-term survival. Recently, the concept of endovascular aneurysm sealing (EVAS) has been introduced into clinical investigation. In previous cohort studies EVAS has been associated with a lower all-cause mortality than expected despite device issues. We used a propensity weighted approach to investigate whether EVAS was associated with lower all-cause mortality after aneurysm repair.

Methods: We compared the 333 patients in the Nellix United States Investigational Device Exemption (IDE) to 15,431 controls from the Vascular Quality Initiative (VQI) between 2014-2016 after applying the exclusion criteria from the IDE (hemodialysis, creatinine > 2.0 mg/dL, or rupture). We calculated propensity scores and applied inverse probability weighting to compare risk adjusted medium-term survival using Kaplan-Meier and Cox regression.

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Results: After weighting, patients treated with the Nellix EVAS system experienced higher three-year survival than controls from the VQI (93% vs 88% respectively). This corresponded to a 41% lower risk of mortality for EVAS compared to EVAR (HR 0.59 [0.38 – 0.92], P = 0.02). Subgroup analysis demonstrated that the association between EVAS and higher survival was strongest in the subgroup of patients with aneurysms over 5.5 cm (P for interaction < .001). In this subgroup, EVAS patients experienced half the rate of mortality as those patients treated with EVAR, with three-year survival of 92% compared to 86% (HR 0.5 [0.3 – 0.9], P = 0.02).

Conclusion: In this select group of patients, EVAS was associated with higher medium-term survival than traditional EVAR. Although issues with the device have recently surfaced, this exploratory analysis shows that the concept of sac sealing may hold promise. Further study is needed to confirm this finding and determine whether EVAS is associated with lower rates of cardiovascular events.

Keywords

endovascular aneurysm repair; endovascular aneurysm sealing; AAA; abdominal aortic aneurysm; survival

Introduction:

Following its introduction in 1991, endovascular aneurysm repair (EVAR) rapidly supplanted open surgical repair as the dominant treatment modality for abdominal aortic aneurysms (AAA) due to its low perioperative morbidity and mortality.[1,2] However, the use of EVAR had little effect on long-term mortality, when compared to open repair. As the immediate risks associated with the procedure itself continue to decline, patient factors such as cardiovascular risk are the principle determinants of long-term survival after repair.

Patients with AAA experience high rates of cardiovascular events, and the National Institutes of Health (NIH) considers AAA to be a coronary artery disease (CAD) equivalent.[3] Over a third of deaths following EVAR are due to cardiovascular events, and up to a third of patients undergoing EVAR experience an adverse cardiovascular event within five years.[4,5] Recent data suggest that inflammation plays a crucial role in the progression of atherosclerosis, in particular acute thrombosis.[6,7] While endovascular surgery avoids the inflammatory response of traditional open surgery, the process of sac remodeling and regression necessitates an inflammatory response.[8] In addition to the longer-term process of sac involution, up to 60% of patients develop post implantation syndrome in the acute postoperative period, a systemic inflammatory response of unclear origin characterized by fever, leukocytosis, and elevated markers of inflammation.[9,10] In addition, any ongoing wall stress, either from an incompletely excluded sac or through endotension, may drive a pro-inflammatory cascade.[11,12]

Despite the adverse cardiovascular implications of these inflammatory responses to EVAR, the solution remains unclear. Statins may reduce the inflammation, but results are mixed.[13–16] Recently, however, increased attention has focused on the signaling from the aneurysm sac itself. Aortic wall stress is associated with elevated levels of inflammatory biomarkers such as matrix metalloproteinases that are linked to adverse cardiovascular events.[11,12,17]

Although traditional endografts exclude the aneurysm sac, many sacs remain pressurized either through endoleak or endotension. These pressurized sacs continue to release cytokines, and recent research demonstrates that expanding and even stable aneurysm sacs after EVAR are associated with higher mortality compared to those with sac regression.[18,19] Consequently, several recent efforts have focused on a more active approach towards sac management.

The Nellix endovascular aneurysm sealing (EVAS) system (Endologix, Irvine, CA) represents a novel treatment approach that may hold promise in avoiding or at least blunting this response.[20] Nellix consists of 2 cobalt-chromium ePTFE covered stent grafts surrounded by endobags, which solidify after instillation of a hydrogel polymer to fill the residual sac and fixate the device. By filling the aneurysm sac instead of merely excluding it, EVAS compresses the intraluminal thrombus, avoids sac thrombosis and evolution, and reduces pressure transmission to the sac, thereby possibly reducing sac inflammation. Indeed, early results show decreased postoperative inflammatory markers and a lower incidence of post implantation syndrome.[8] In addition, early results from the EVAS1 Trial showed two-year survival of 94%, which is equivalent or higher than the pivotal trials of other devices such as the Medtronic Endurant (94%), Medtronic Talent (89%), Gore Excluder (87%), Endologix Powerlink (90%), and Cook Zenith (91% for standard-risk patients, 82% for high-risk).[21–24] Several recent reports out of European centers demonstrated that the first generation Nellix device, like many novel products, had significant flaws, with higher than expected rates of migration, proximal endoleak and device failures.[25–27] However, the underlying concept of sac obliteration is an appealing one, despite potential issues with the initial device. With this in mind, we compared the three-year survival following Nellix to a propensity-weighted set of controls utilizing a national registry.

Methods:

Patients:

Nellix: The inclusion and exclusion criteria of the Nellix system investigational device exemption (IDE) and pivotal trial were previously reported.[20] Each patient provided written informed consent, and underwent preoperative eligibility assessment. These patients were followed at 1 month, 6 month, 1 year and then annually with laboratory data and computed tomography angiography (CTA). The Nellix system IDE was approved by the local institutional review board (IRB) at each participating center prior to enrollment of any patients. Each patient signed written informed consent to participate in the Nellix registry. Cause of death was adjudicated by an independent Clinical Events Committee, and an independent Data Safety and Monitoring Board reviewed data on a periodic basis.

Controls: We utilized the Society for Vascular Surgery Vascular Quality Initiative (SVS-VQI) as a control group. The VQI is a cooperative quality improvement initiative developed in 2002 to improve outcomes in vascular surgery, and collects data from 412 centers in 46 states and Canada. Over 200 variables are entered by vascular surgeons and trained nurses. Data include patient demographics, comorbid conditions, perioperative complications, one-

year follow-up, and long-term mortality through linkage to the Social Security Death Index. To match the eligibility criteria for the Nellix IDE, we included only patients undergoing EVAR from 2014-2016, excluded patients on dialysis or with a creatinine > 2.0 mg/dL and those who presented with ruptured aneurysms.

The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and waived the need for further patient consent due to the nature of the design and minimal risk to human subjects.

Variables:

We calculated estimated glomerular filtration rate utilizing the CKD-EPI formula, and categorized chronic kidney disease into none, glomerular filtration rate (GFR) 30-60 and GFR < 30. Coronary artery disease was defined as a history of documented coronary artery disease, previous myocardial infarction, angina, arrhythmia, coronary artery bypass grafting or percutaneous coronary intervention.

Outcomes: Our primary outcome was overall survival in our propensity-weighted cohort. In a secondary analysis, we compared overall survival stratified by aneurysm size. As we hypothesized that aneurysm sac wall stress and remodeling were associated with higher mortality risk, we theorized that any mortality difference would be most pronounced in the subgroup of patients with larger aneurysms who would experience the most risk. Although long-term outcomes such as re-intervention rates are not well documented in the VQI, mortality is well captured due to the linkage with the SSDI, with an error rate of approximately 2.5%. As an IDE cohort under close monitoring by the Food and Drug Administration, mortality in the Nellix cohort is similarly well captured.

Statistical Analysis:

To adjust for baseline demographics, we constructed propensity scores using logistic regression and applied inverse probability weights. With propensity scores, *every patient experiences the outcome of interest* (in this case treatment with EVAR or EVAS). This allows adjustment for more covariates without the risk of overfitting. Propensity weighting offers an advantage over propensity matching in that it retains the entire sample size, and therefore may reduce unmeasured confounding. We generously introduced covariates into our model, including age, race, sex, aortic diameter, surgery year, peripheral vascular disease, hypertension, chronic kidney disease, CAD, prior coronary artery bypass grafting (CABG), prior percutaneous coronary intervention (PCI), diabetes, chronic obstructive pulmonary disease, body mass index, congestive heart failure, preoperative aspirin use, preoperative statin use, presence of one or more iliac aneurysm, family history of AAA, and smoking status. There may be confounding that we are unable to control for such as unsuitability for open repair, and anatomic features such as neck angles, calcified necks, and treatment outside the IFU, as these are not captured by the VQI. Anatomic variables other than diameter are not well captured by the VQI, and therefore we could not control for anatomic criteria other than diameter. We stratified by an age threshold of 80 to balance the age distributions in the two cohorts. The propensity scores enabled us to create inverse probability weights (the inverse of the probability of receiving the treatment that the subject

received). We tested these scores for adequacy of overlap by plotting the distribution of propensity scores in the treated (EVAS) and untreated (controls) groups. Covariate balance/bias reduction was assessed by calculating the absolute standardized differences before and after weighting. After weighting, the standardized differences were all ≤10% (the usual threshold), indicating adequate balance. We then used these weights to compare the risk of primary and secondary outcomes between treatment arms. We constructed weighted Kaplan-Meier survival curves and compared the EVAS patients and controls using the Wald test and weighted Cox regression. For our secondary outcome, we utilized an interaction term between the two treatment arms and aneurysms over 5.5 cm, as well as constructed separate Kaplan-Meier curves based on aneurysm size. Data analyses were performed using STATA 14.2 (StataCorp LP, College Station, TX).

Role of the Industry Source:

The authors did not receive funding from the industry source for this project. The authors had full access to the data, performed all statistical analyses, and had final responsibility for the decision to submit and publish. MLS serves as a member of the Clinical Events Committee for a different Endologix endograft. The methodology and final manuscript were reviewed prior to submission by the executive committee of the SVS Patient Safety Organization.

Results:

Baseline Characteristics:

There were 333 EVAS patients and 15,431 patients in the control group. Baseline characteristics of the EVAS cohort and the controls are shown in Table I. Compared to the EVAR cohort, patients in the EVAS cohort were more frequently male, had larger aortic diameters, more often had a family history of AAA, were twice as likely to have concomitant iliac aneurysms, had higher rates of PVD, were more likely to have undergone PCI previously, and were more likely to be obese, but less frequently had a history of smoking and CHF (all $P < 0.05$). As noted previously, after inverse probability weighting on our propensity score, the standardized differences all were ≤10%.

Medium-term Survival

Crude survival was 93% at three years following EVAS, and 91% following EVAR ($P = 0.5$). After applying inverse probability weighting to account for baseline differences in the two patient populations, EVAS was associated with a significantly higher rate of medium-term survival (93% vs 88%, $P = 0.02$) (Figure 1). This corresponded to a 41% lower risk of mortality for EVAS compared to EVAR (HR 0.59 [0.38 – 0.92], $P = 0.02$).

Use of EVAS in Aneurysms over 5.5cm:

We identified 7,826 (52%) EVAR patients with aneurysms over 5.5 cm, and 212 (64%) EVAS patients. Crude three-year survival in patients with aneurysms over 5.5 cm was 89% following EVAR and 92% following EVAS ($P = 0.32$), and 93% following EVAR and 95% following EVAS ($P = 0.9$) for patients with aneurysms 5.5cm or less. After risk adjustment using propensity weighting, EVAS was more strongly associated with higher survival in the

subgroup of patients with aneurysms over 5.5 cm (P for interaction < .001). There was no difference in survival between patients with aneurysms < 5.5cm treated with EVAS vs EVAR (P = 0.25) (Figure 2). However, in the subgroup of patients with larger aneurysms, EVAS patients experienced half the rate of mortality as those patients treated with EVAR, with three-year survival of 92% compared to 86% (HR 0.5 [0.3 – 0.9], P = 0.02) (Figure 3).

Discussion:

The advent of endovascular techniques for AAA repair reduced perioperative mortality to such a level where its impact on a patient's long-term survival following repair is minimal. Consequently, improvements in the care of patients with aneurysmal disease must increasingly focus on lowering a patient's risk long after the immediate perioperative period. Many potential factors impact long-term survival after repair such as patient comorbidities, procedural complications, and reinterventions, but none more so than cardiovascular events. We found higher three-year survival in patients treated with EVAS, compared to contemporary patients in the VQI. The difference in survival was more pronounced in patients with aneurysms over 5.5cm. Although suggestive, this study is exploratory in nature, and as such should not be used to guide treatment indications or device selection until further studies confirm our hypotheses. Rather, we hope this study will spark future graft development and research, as well as confirmatory studies with cardiovascular endpoints.

This is a retrospective analysis, not a randomized trial, and therefore we can only show association, not causation, and the results should be interpreted with caution. Although early reports showed acceptable results with the EVAS system and lower rates of Type II endoleaks, more recent data from some high-volume European centers show concerningly high rates of graft failure, Type IA endoleak and stent migration.[25–27] It is possible that the mortality difference we found was merely the product of statistical noise, especially given the small size of the EVAS group and the fact that we compared the results of an IDE to the broader EVAR population. There may also be an issue with time lag, as device issues such as proximal endoleak and migration may not result in mortality for several years and not be seen in a mid-term analysis. Indeed, with longer follow-up, any potential benefit from sac obliteration may be overcome by the inherent device issues with migration and Type 1 endoleaks that are uniquely difficult to manage. However, this exploratory analysis shows that while this first-generation device has issues, and should not be used to promote use outside of the recently revised IFU, the underlying concept is worthy of further study.

Patients who undergo endovascular repair experience high rates of adverse cardiovascular events. Underlying cardiovascular disease explains much of this risk, as rates of diagnosed or undiagnosed coronary disease in patients with AAA dramatically exceed the general population, and the NIH actually classifies AAA as a CAD risk equivalent. However, over a third of patients will experience a major adverse coronary event (MACE) within five years after repair, which actually exceeds the event rates in patients with established atherosclerotic disease.[5,28–30] Two factors likely contribute to this excess risk: the inflammatory response required for the remodeling and resorption of the aneurysm sac after the endograft excludes it, and the morbidity of reinterventions after the initial repair.

Over the last decade, a wealth of research established the link between inflammation and atherothrombosis. This culminated in the recent CANTOS study which demonstrated a 17% lower rate of MACE with the use of canakinumab, an interleukin-1β inhibitor.[7] The relationship between AAA, EVAR and inflammation is multifaceted. Disordered inflammation and the action of matrix metalloproteinases (MMPs) in the aortic wall contribute to the development of aortic aneurysms.[31,32] The presence of a AAA is associated with the upregulation of a host of pro-inflammatory markers including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha.[33] After an endograft excludes the aneurysm sac, a complex biological response occurs, related to the compression of intra-luminal thrombus, occurrence of sac thrombosis, changes in sac pressure, and the inflammatory response required to induce fibrosis and regression.[34–37] Inflammation is required to induce the fibrosis responsible for advantageous sac regression after an endograft excludes the aneurysm from aortic pressure. However, this inflammation occurs early, and then subsides as the aortic wall is no longer exposed to preoperative stress levels. Successful, complete sac exclusion results in lower circulating MMP levels than seen prior to repair. [11,12,17,38,39]

However, endoleaks, intraluminal thrombus, and porous endografts transmit pressure to the aortic wall, resulting in ongoing or even accelerated inflammation. The resultant wall stress from an incompletely excluded sac is associated with pathologic inflammation from increased MMP activity.[11,12,17,38,39] Consequently, patients with endoleaks or endotension may be at higher risk of cardiovascular events due to ongoing disordered signaling cascades despite attempted repair. The EVAS system not only excludes the aneurysm sac, but actually seals it with polymer filled endobags. This seal may reduce the wall stress on the aneurysm sac and thus blunt the inflammatory response and resultant cardiovascular risk. Larger aneurysms experience higher wall stress, which may explain the difference in mortality based on aneurysm size. Although the VQI does not capture long-term cardiovascular events or cause of death, further efforts should study whether cardiovascular death drives the lower mortality seen in EVAS patients.

EVAS was initially developed with the goal of sealing the aneurysm sac to reduce/eliminate the possibility of Type II endoleaks, resulting in lower rates of long-term re-interventions. [20,40–42] Indeed, results from the IDE demonstrate the lowest Type II endoleaks ever reported (96.2% freedom from Type II at two years).[43] Endoleaks, and the resultant reinterventions to treat them, likely contribute to ongoing wall stress and long-term mortality, and reducing their incidence is a critical step towards improving endovascular repairs. However, a lower rate of endoleaks does not fully explain the mortality differences we found. Early results from the EVAS device showed that endoleaks still occurred, and Type I endoleaks (both IA and IB) and migration actually occurred at higher rates than anticipated, prompting alteration of the original IFU.[43–48] Our data demonstrate that despite these issues, sealing rather than excluding the aneurysm sac appears to be associated with lower mortality. As previous studies demonstrated no clear improvements in rates of reinterventions, or rupture, and possibly even higher Type I rates in EVAS patients, this mortality difference is unlikely to be due to differences in the rates of reinterventions or rupture.[40,41,45,49] Although further study is needed to test this hypothesis, it lends credence to the theory that the mortality difference is instead due to the impact on aneurysm wall stress, sac remodeling and downstream cardiovascular events. Despite issues with the early EVAS device that are being

addressed in a further IDE trial and ongoing device redesigns, the concept of aneurysm sealing holds promise.

This study must be interpreted in the context of its retrospective design. Patients enrolled in an IDE are a highly selected group of patients treated by a highly selected group of surgeons, and may not be generalizable to the population at large. As with most clinical trials, we don't know how the results of an IDE translate to a more real-world population. With only 333 patients in the EVAS group, we are prone to random statistical variation as well. However, this group of patients appears to have higher survival than other similar IDE populations, including even reports from different devices from the same company.[21–24] Although we cannot make direct statistical comparisons, this does suggest that the results we see here may extend beyond just the careful patient selection process involved in an IDE. In addition, the variable definitions between the two datasets may not be perfectly transferable. There may be confounding that we are unable to control for such as unsuitability for open repair, and anatomic features such as neck angles, calcified necks, and treatment outside the IFU, as these are not captured by the VQI. Despite techniques such as propensity-weighting, residual confounding may remain. In addition, the VQI does not capture cardiovascular events long-term, so any theories regarding mortality are purely theoretical at this point.

Conclusion:

In this selected group of patients, AAA treatment with the Nellix device was associated with higher medium-term survival than traditional EVAR. This analysis is exploratory in nature, and demonstrates an association but not causality. However, this study highlights the potential of endovascular aneurysm sealing despite issues with the first-generation device, and may guide future graft development. Further study is needed to confirm these findings and determine whether EVAS is associated with lower rates of cardiovascular events.

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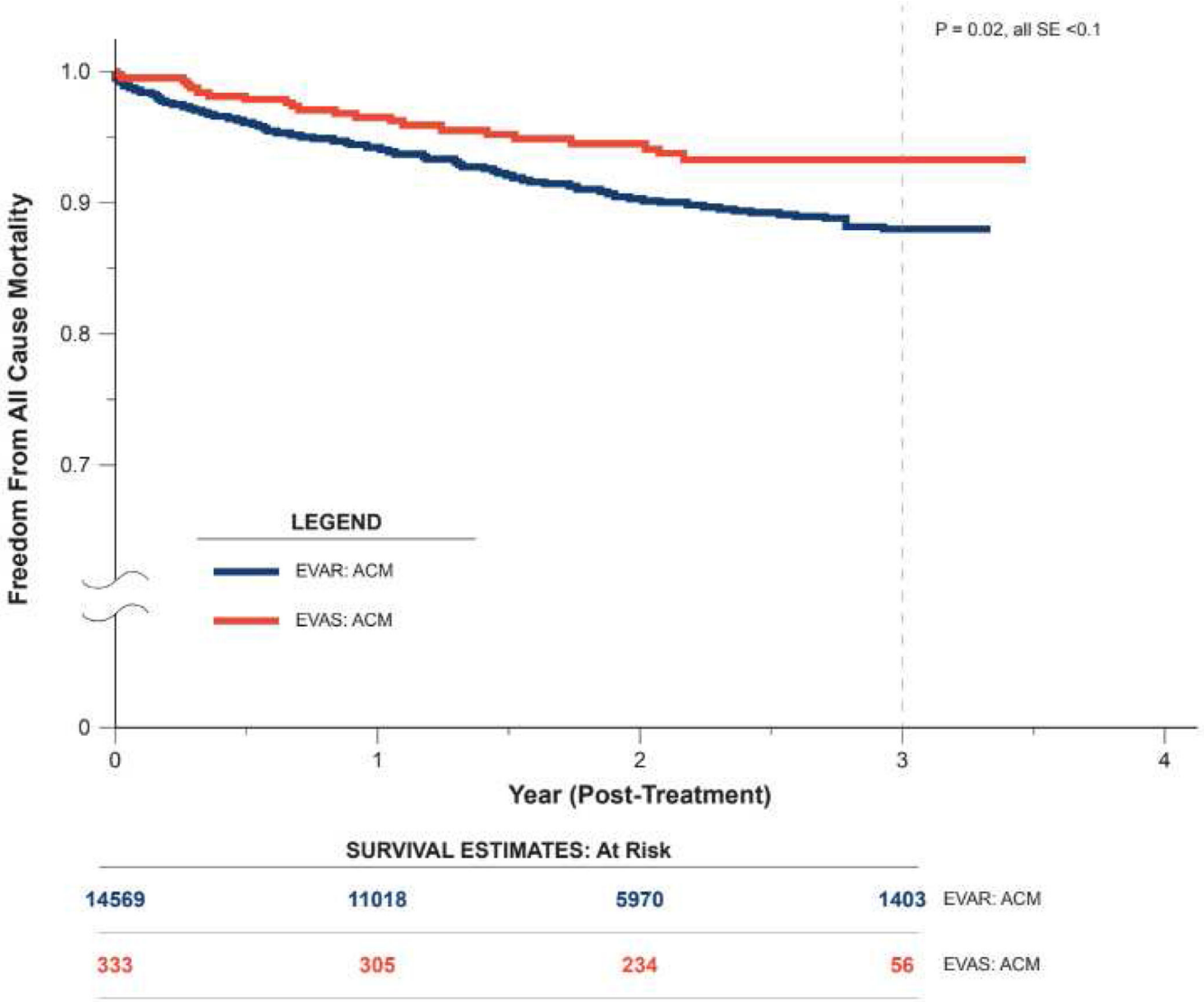

Figure 1.

Adjusted Long-term survival. P = .02, all standard errors < 0.1. *ACM: All-Cause Mortality. EVAR: Endovascular Aneurysm Repair. EVAS: Endovascular Aneurysm Sealing.*

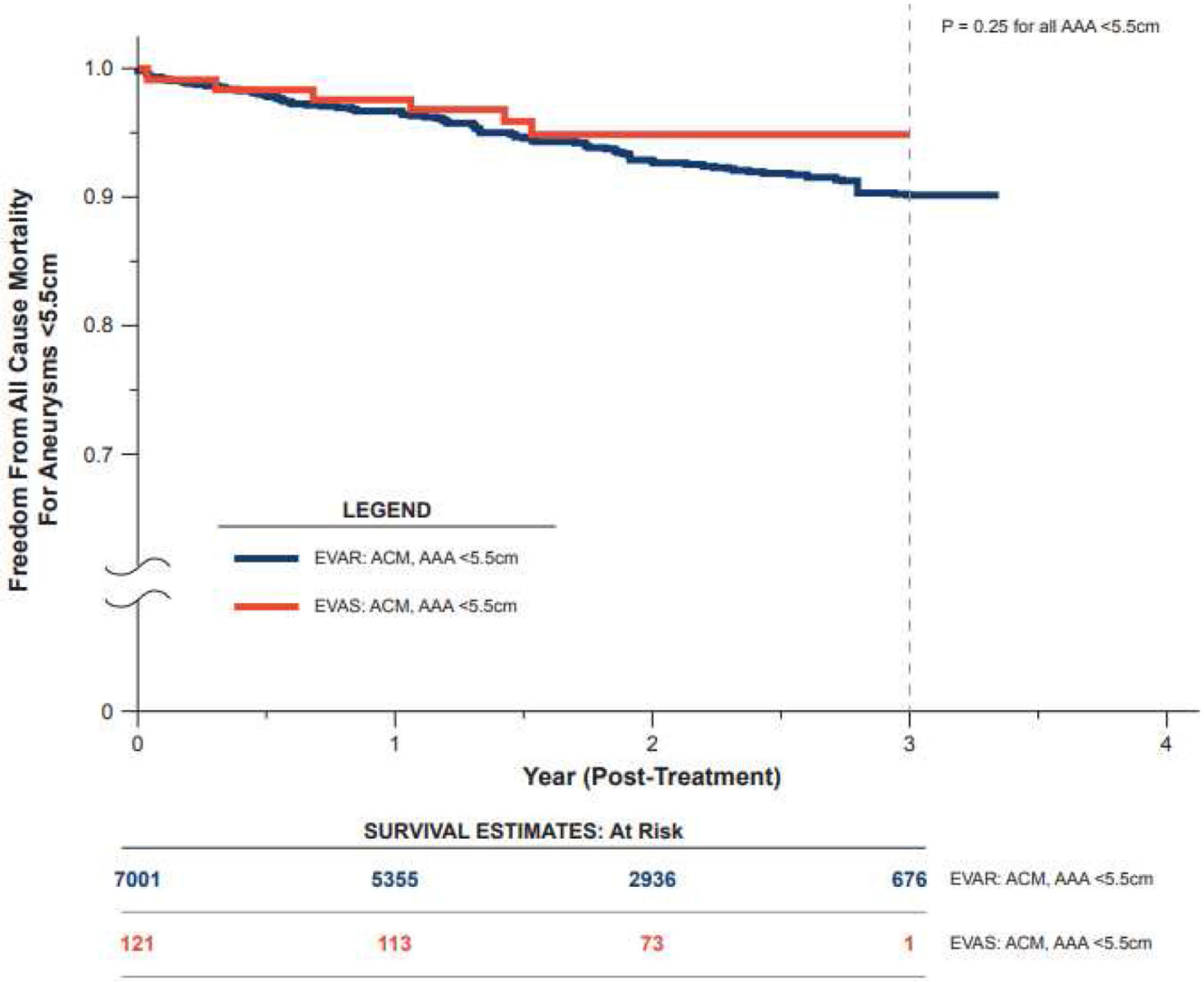

Figure 2.

Adjusted long-term survival in the subgroup of patients with aneurysm diameters < 5.5 cm. P = .25 in this subgroup. All standard errors < 0.1. *ACM: All-Cause Mortality. EVAR: Endovascular Aneurysm Repair. EVAS: Endovascular Aneurysm Sealing.*

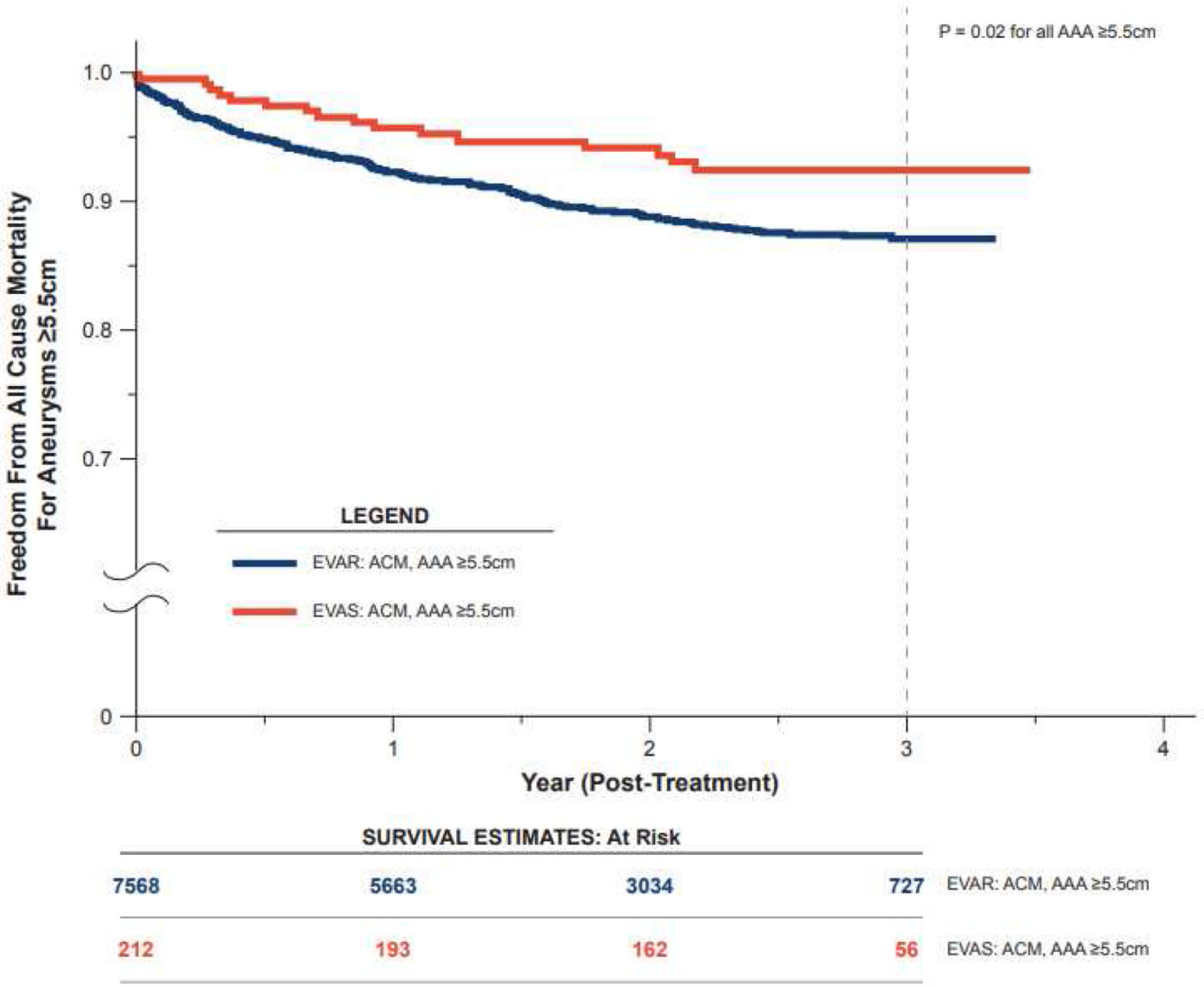

Figure 3.

Adjusted long-term survival in the subgroup of patients with aneurysm diameters ≥ 5.5cm. P < .02 in this subgroup. All standard errors < 0.1. *ACM: All-Cause Mortality. EVAR: Endovascular Aneurysm Repair. EVAS: Endovascular Aneurysm Sealing.*

Table I.

Baseline Characteristics of the Study Population. Control population is from the Vascular Quality Initiative. All absolute standardized differences are <0.1, which is the usual threshold, with lower standardized differences suggesting better balance after weighting. *S.d.: standard deviation. AAA: abdominal aortic aneurysm. COPD: chronic obstructive pulmonary disease. CABG: coronary artery bypass grafting. PCI: percutaneous coronary intervention.*

	Controls (n=15,431)	Nellix (n=333)		Standardized Difference after Weighting
Characteristic	**% except where indicated**		**P**	
Age (mean ± s.d.)	73 ± 8.6	73 ± 8.1	0.26	−0.05
White Race	90	92	0.4	0.1
Male Sex	82	94	<.001	0.09
Aortic Diameter (mean ± s.d.)	56 ± 14	57 ± 6	<.001	0.02
Family history of AAA	8	13	<.01	−0.096
Iliac Aneurysm	25	52	<.001	0.06
Hypertension	83	86	0.14	−0.03
COPD	33	28	0.09	−0.098
Coronary Artery Disease	29	29	0.95	−0.06
Prior CABG	18	18	0.99	0.009
Prior PCI	22	28	0.01	−0.07
Chronic Kidney Disease	31	29	0.44	−0.08
Diabetes	20	22	0.49	0.02
Congestive Heart Failure	11	7	0.01	0.07
Smoking History	87	51	<.001	−0.02
Peripheral Vascular Disease	7	26	<.001	0.005
Body Mass Index (BMI)			<.001	0.06
Underweight	2.5	0.3		
Normal	27	19		
Overweight	38	42		
Obese	28	35		
Morbidly Obese	3	4		
Aspirin	64	68	0.22	0.008
Statin	70	75	0.053	0.05