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Survival After Endovascular Aneurysm Sealing Compared With Endovascular Aneurysm Repair

Aleksandra C. Zoethout, MD[1,2], Arshad Sheriff, MD[3], Clark J. Zeebregts, MD, PhD[2], Andrew Hill, MD[3], Michel M. P.J. Reijnen, MD, PhD[1,4], and Andrew Holden, MD[3]

Abstract

Introduction: Endovascular aneurysm sealing (EVAS) is a sac-filling device with a blunted systemic inflammatory response compared to conventional endovascular aneurysm repair (EVAR), with a suggested impact on all-cause mortality. This study compares mortality after both EVAS and EVAR. **Materials and Methods:** This is a retrospective observational study including data from 2 centres, with ethical approval. Elective procedures on asymptomatic infrarenal aneurysms performed between January 2011 until April 2018 were enrolled. Laboratory values (serum creatinine, haemoglobin, white blood cell count, platelet count) were measured pre- and postoperatively and at 1 and 2 years, respectively. Mortality and cause of death were recorded during follow-up. **Results:** A total of 564 patients were included (225 EVAS, 369 EVAR), after propensity score matching there were 207 patients in both groups. Baseline characteristics were similar, except for larger neck angulation and more pulmonary disease in the EVAR group. The median follow-up time was 49 (EVAS) and 44 (EVAR) months. No significant differences regarding creatinine and haemoglobin were observed. Preoperative white blood cell count was higher in the EVAR group (p=0.011), without significant differences during follow-up. Median platelet count was lower in the EVAR group preoperatively (p=0.001), but was significantly higher at 1 year follow-up (p=0.003). There were 43 deaths within the EVAS group (20.8%) and 52 within the EVAR group (25.1%) (p=0.293). Of these, 4 were aneurysm related (EVAS n=3, EVAR n=1; p=0.222) and 14 cardiovascular (EVAS n=6, EVAR n=8, p=0.845). For the EVAS cohort, survival was 95.5% at 1 year and 74.9% at 5 years. For the EVAR cohort, this was 93.3% at 1 year and 75.5% at 5 years. No significant differences were observed in causes of death. **Conclusion:** This study showed comparable survival rates through 5 years between EVAS and EVAR with a tendency toward higher inflammatory response in the EVAR patients through the first 2 years.

Keywords

abdominal aortic aneurysm, endovascular aneurysm sealing, endovascular aneurysm repair, survival

Introduction

The Nellix device was commercially introduced in 2013 based on the concept of endovascular aneurysm sealing (EVAS). It consists of dual balloon-expandable stent grafts surrounded by in situ polymer-filled endobags. EVAS differs from conventional endovascular aneurysm repair (EVAR) by completely filling the blood lumen of the aneurysm sac, also termed "active sac management."[1] Even though unforeseen complications have led to the stop of unrestricted sales and commercial use of the device in January 2019, there may be unanticipated benefits to a sac-sealing device.

Open aneurysm repair has been associated with a greater systemic immune response when compared to EVAR,[2] which has been confirmed by increased interleukin (IL)-6 and IL-8 serum levels. Polyester endografts interact with

[1]Department of Vascular Surgery, Rijnstate Hospital, Arnhem, The Netherlands
[2]Department of Surgery, Division of Vascular Surgery, University Medical Center Groningen, University of Groningen, The Netherlands
[3]Department of Radiology, Auckland City Hospital, Auckland, New Zealand
[4]Multi-Modality Medical Imaging Group, TechMed Centre, University of Twente, Enschede, The Netherlands

Corresponding Author:
Aleksandra C. Zoethout, Department of Surgery, University Medical Center Groningen, Hanzeplein 1, Groningen, 9713 GZ, The Netherlands.
Email: sandrazoethout@gmail.com

the aneurysm wall and aneurysm contents, and appear to be correlated with the highest incidence of postimplantation syndrome compared with PTFE (polytetrafluoroethylene) endografts.[2] The major source of IL-6 following EVAR is probably the aneurysm thrombus.[3] Additionally, recent studies[4,5] have shown that the volume of preexisting and new-onset mural thrombus may be a risk factor for the elevation of inflammatory markers after EVAR. A rise in interleukins in the postoperative period may be a valuable predictor of serious complications, including multiorgan failure,[6,7] major cardiac events,[8] and mortality.[9,10]

Berg et al[11] have shown that EVAS is associated with a blunted systematic inflammatory response compared to EVAR and less cardiac events. The blunted systemic inflammatory response after EVAS could be explained by active sac sealing, where the aneurysm sac and associated thrombus is sealed. This could consequently lead to less interleukin release. A recent publication by O'Donnell et al[12] showed a reduction in all-cause mortality in the EVAS group compared to conventional EVAR at 3 years. This analysis included the patients from the US EVAS IDE Trial and EVAR cases from the US VQI Registry. Additionally, AAA (abdominal aortic aneurysms) that do not display sac shrinkage after endovascular treatment have a higher mortality rate, irrespective of reinterventions for endoleak.[13]

In order to assess whether this survival benefit exists in our patient population this study will assess the overall and cardiovascular mortality after both EVAS and EVAR.

Materials and Methods

Study Design

This is a retrospective observational study of EVAS compared to conventional EVAR including data from two centres. Medical ethical approval was granted in both sites. Personal data was anonymized and study codes were used. All information was recorded on a case report form (CRF) and added to the database. A document linking the study code to the patients identifying information was kept separately. Relevant data were obtained by selecting both cases and variables within the preexisting dataset, which complied with our inclusion criteria and CRF variables. Only those patients who had information regarding the type of primary procedure were selected for this study.

The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, 2013) and in accordance with the applicable guidelines, regulations, and acts.

Study Population

Patients were enrolled by database screening and were eligible if they had undergone either an EVAS or EVAR procedure from January 2011 until April 2018. Only those patients who underwent an elective procedure for an asymptomatic infrarenal aneurysm were included. Patients were excluded if they had less than 1-year follow-up after the procedure, required chimney grafts or endoanchors or had distal extensions beyond the common iliac artery. The patients were separated into 2 groups; the EVAS group and the EVAR group that were subjected to propensity score (PS) matching.

Baseline and Follow-up Data

Comorbidities were scored according to the Society for Vascular Surgery (SVS) comorbidity grading scale[14] and based on anesthesiology screening records. Additional parameters for cardiovascular history were collected, including ischemic heart disease (myocardial infarction, stable angina, coronary artery stenting or coronary artery bypass grafting), arrhythmia, and heart failure. Hypertension was defined as known history of hypertension or use of antihypertensive medication. Hyperlipidemia was defined as known history or the use of a statin or elevated lipid levels (low-density lipoprotein, total cholesterol, and triglyceride levels above normal limits for age). Pulmonary status was defined as a history of chronic obstructive pulmonary disease (COPD) or other pulmonary disease. Renal insufficiency was defined as a serum creatinine level of 2.4 mg/dL or higher or dialysis dependency. A patient was considered to have diabetes mellitus (DM) when there was a history of DM or use of antidiabetic medication. Additionally, the ASA (American Society of Anaesthesiologists) score was recorded based on the most recent anaesthesiology assessment.

Aneurysm characteristics were collected from preoperative computed tomography (CT) scan. In one center measurements were performed by 2 investigators (AS, AZ) with the use of 3D vascular planning software (Syngo.via, Siemens, Germany). Diameter measurements were based on the maximum outer-to-outer vessel diameter, orthogonal to the centre lumen line (CLL). In the Dutch center, aneurysm characteristics were extracted from an existing database on all aneurysm patients.

Postoperative follow-up for both EVAS and EVAR was similar in both centres. In one center, EVAR patients received CTA and abdominal X-rays at 1, 6, 12, and 24 months and duplex ultrasound combined with abdominal X-rays annually thereafter. The follow-up after EVAS was the same for the first 2 years but included annual CTA thereafter. In the other centre, both EVAR and EVAS patients were seen 1 month after the procedure and twice a year thereafter. This included a CTA once a year and duplex ultrasound on the other follow-up visit.

Statistical Analysis

To match the EVAS and EVAR cohorts, PS matching was performed. The PS model was based on previously

established factors associated with treatment selection. These included age at procedure, ASA score, cardiovascular history, and maximal aneurysm diameter. After propensity scores were generated for each patient matching was performed. The patients from the EVAS group were matched to the patients from the EVAR group by the statistics program on a "1:1 nearest neighbour" basis with a calliper of 0.01 was used. Patients who could not be matched were deleted from the matched database.

Continuous variables were presented as mean and standard deviation (SD), or as median and interquartile range (IQR) depending on the results of normalcy testing. Normal or skewed distribution was determined by Kolmogorov-Smirnov tests and observation of histograms. Categorical variables were presented as frequencies and percentages. Proportions and nominal variables were compared using the chi-square test or the Fisher exact test in the case of a small sample size. Continuous variables were compared by means of the independent *t* test or the Mann-Whitney *U* test for nonparametric data. Comparison between laboratory results was done with a paired *t* test.

Kaplan-Meier analysis was employed to estimate rates for survival. Curves were compared with the log-rank test. Datasets were truncated when the standard error exceeded 10%. The threshold of statistical significance was $p<0.05$. All statistical analysis was performed using IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, NY, USA), boxplots were made with Microsoft Excel version 2019 (Microsoft Corporation, Redmond, WA, USA).

Results

Baseline Characteristics Before Propensity Score Matching

A total of 564 patients were included in the study, of which 225 (37.9%) had undergone EVAS and 369 (62.1%) had undergone EVAR. Overall baseline characteristics are presented in Table 1 and the preoperative anatomical characteristics in Table 2. Patients who underwent EVAS (mean age 74.7 years) were significantly older than the patients who underwent EVAR (mean age 73.1 years) (p=0.017). Additionally, the infrarenal neck angle was significantly larger in the EVAR group (EVAS 34.0°, EVAR 40.0°), no other significant differences between the 2 groups were observed.

Baseline Characteristics After Propensity Score Matching

Propensity score matching was performed to ensure the groups were as comparable as possible. After PS matching was performed, there were 207 patients in the EVAS group and 207 patients in the EVAR group. Despite an overall well matched cohort there remained 2 variables with a significant difference between the 2 groups, these include medical history of pulmonary disease (EVAS n=69, EVAR n=109; p=0.000) and aortic neck angulation (EVAS=34.0°, EVAR=42.0°; p=0.000).

Blood Test Values Over Time

The lab values for all 4 time points for both the EVAS and the EVAR group are shown in Table 3 and Figure 1. The preoperative white blood cell (WBC) count was higher in the EVAR group compared with the EVAS group. During follow-up there were no significant differences in WBC count although there was a trend toward higher values in the EVAR-treated patients at all time points. Platelet count was lower in the EVAR group preoperatively, and became significantly higher at 1 year follow-up.

Survival

Within the matched cohort, there were 95 (22.9%) patients who died. This included 43 deaths within the EVAS group (20.8%) and 52 deaths the EVAR group (25.1%) and (p=0.293). The median time to death was 29 months (IQR 20–46) for the EVAS group and 37 months (IQR 13–69) for the EVAR group (p=0.413). For those patients who did not pass away, the median time of follow-up was 49 (IQR 30–61) and 44 (IQR 18–77) months, respectively. The causes of death are displayed in Table 4 with the only significant difference being that there were more (n=15) unknown causes of death within the EVAR group compared with the EVAS group (n=4) (p=0.011).

Survival analysis (Figure 2) showed no difference in all-cause mortality between the 2 groups (log-rank p=0.668) for the entire follow-up period. For the EVAS cohort, survival was 95.5% at 1 year, 89.5% at 2 years, 85.8% at 3 years, 79.6% at 4 years, and 74.9% at 5 years. For the EVAR cohort, this was 93.3% at 1 year, 87.9% at 2 years, 84.3% at 3 years, 79.3% at 4 years, and 75.5% at 5 years. Additionally, no significant difference was observed when only those cases with an aneurysm diameter $\geq$5.5cm were selected for survival analysis (log-rank p=0.668).

Discussion

The present study did not find any difference in mortality between EVAS- and EVAR-treated patients. The EVAR-treated patients did have a trend toward higher inflammatory markers. The current data conflict with the earlier publication by O'Donnell et al.[12] They gave grounds to believe that EVAS would provide a survival benefit by actively managing the aneurysm sac as a survival benefit at 3 years was observed. Also, after correction for aneurysm size of greater than or equal to 5.5 cm no survival benefit

Table 1. Baseline Characteristics Prior to Endovascular Procedure Before and After Propensity Score Matching.[a]

	Unmatched Cohort			Matched Cohort		
	EVAR	EVAS	p	EVAR	EVAS	p
Number of patients	369	225	NA	207	207	NA
Age at procedure (y)	73.1 (8.0)	74.7 (7.2)	0.017*	74.4 (7.4)	74.5 (7.2)	0.909
Height (cm)	174.5 (9.0)	173.7 (8.5)	0.305	174.2 (9.2)	174.0 (8.5)	0.799
Weight (kg)	82.5 (15.5)	81.9 (17.3)	0.669	82.4 (16.4)	82.1 (17.3)	0.886
BMI (kg/m^2)	26.9 (4.2)	27.0 (4.6)	0.870	27.0 (4.5)	27.0 (4.6)	0.901
Gender			0.185			0.122
Male	312 (84.6)	199 (88.4)		172 (83.1)	183 (88.4)	
Female	57 (15.4)	26 (11.6)		35 (16.9)	24 (11.6)	
Cardiac disease						
Myocardial infarction	96 (26.0)	67 (29.8)	0.319	57 (27.5)	57 (27.5)	1.000
Myocardial stenting	62 (16.8)	43 (19.1)	0.576	34 (16.4)	39 (18.8)	0.519
CABG	51 (13.8)	36 (16.0)	0.466	33 (15.9)	28 (13.5)	0.488
Stable angina	36 (9.8)	17 (7.6)	0.344	19 (9.2)	15 (7.2)	0.465
Arrhythmia	62 (16.8)	32 (14.2)	0.403	36 (17.4)	32 (15.4)	0.596
Congestive heart failure	28 (75.9)	11 (4.9)	0.198	16 (7.7)	11 (5.3)	0.320
Hypertension	274 (74.3)	179 (79.6)	0.141	45 (21.7)	42 (20.2)	0.717
Hyperlipidemia	276 (74.8)	166 (73.8)	0.063	38 (18.4)	53 (25.6)	0.177
Pulmonary disease	114 (30.9)	74 (32.9)	0.776	109 (52.7)	69 (33.3)	0.000*
Renal disease	118 (32.0)	57 (25.3)	0.081	61 (29.5)	55 (26.6)	0.511
Diabetes mellitus	73 (19.8)	33 (14.7)	0.114	39 (18.8)	31 (15.0)	0.294
Smoking	162 (43.9)	90 (40.0)	0.177	89 (43.0)	82 (39.6)	0.275
ASA class			0.225			0.157
2	165	87 (38.7)		71 (34.3)	84 (40.6)	
>2	(44.7)					
Unknown	200 (54.2)	137 (60.9)		136 (65.7)	123 (59.4)	
	4 (1.1)	1 (0.4)				

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CABG, coronary artery bypass grafting; EVAR, endovascular aneurysm repair; EVAS, endovascular aneurysm sealing; NA, not applicable.
[a]Continuous variables are presented as mean and standard deviation (SD), or as median and interquartile range (IQR) depending on the results of normalcy testing. Categorical variables are presented as frequencies and percentages.
*Significant difference.

Table 2. Preoperative Anatomical Characteristics Before and After Propensity Score Matching.

	Unmatched Cohort			Matched Cohort		
	EVAR	EVAS	p	EVAR	EVAS	p
Infrarenal neck length (mm)	27.8 (20.0–38.8)	26.8 (15.8–38.1)	0.151	27.0 (19.3–39.1)	27.0 (15.5–38.5)	0.356
Aortic neck diameter	23.0 (21.0–25.0)	22.7 (20.2–25.0)	0.073	23.7 (21.0–25.2)	22.7 (20.2–25.0)	0.050
Neck angulation (deg)	40.0 (27.0–52.3)	34.0 (22.0–46.0)	0.002*	42.0 (30.0–56.8)	34.0 (23.0–46.0)	0.000*
Maximum AAA diameter	58.0 (54.0–64.0)	57.0 (54.0–62.6)	0.296	57.0 (23.0–63.0)	57.0 (54.0–63.0)	0.947
Maximum right CIA diameter	15.1 (13.0–20.0)	16.0 (13.0–18.3)	0.642	16.0 (14.0–20.0)	16.0 (13.0–18.5)	0.180
Maximum left CIA diameter	15.0 (13.0–18.8)	16.0 (13.0–19.5)	0.491	16.3 (13.7–21.0)	15.7 (12.8–19.1)	0.056

Abbreviations: AAA, abdominal aortic aneurysm; CIA, common iliac artery; EVAR, endovascular aneurysm repair; EVAS, endovascular aneurysm sealing.
*Significant difference.

was observed in our cohort. Additionally, no significant difference was observed in the incidence of cardiovascular mortality. However, there appears to be a presence of nonproportional hazards with a higher EVAS survival at 1 to 3 years but a lower survival at 4- and 5-year follow-up, without any significant differences. This might be explained

Table 3. Laboratory Values for Each Time Point.

	EVAR	EVAS	p
Creatinine (mmol/L)			
Preoperative	89 (76–101)	92 (79–106)	0.094
Postoperative	85 (72–101)	90 (75–108)	0.190
1 year	97 (82–118)	98 (82–118)	0.754
2 years	95 (75–120)	98 (87–118)	0.408
Hemoglobin (mmol/L)			
Preoperative	8.7 (8.1–9.2)	8.7 (8.0–9.2)	0.931
Postoperative	7.5 (6.6–8.2)	7.5 (6.7–8.2)	0.868
1 year	7.9 (7.3–9.0)	8.4 (7.7–9.2)	0.111
2 years	8.2 (7.3–8.7)	8.5 (7.4–9.0)	0.201
White blood cell count ($\times 10^9$/L)			
Preoperative	7.6 (6.5–9.2)	7.1 (6.2–8.6)	0.011*
Postoperative	10.2 (8.6–13.0)	9.6 (7.8–11.9)	0.061
1 year	8.1 (7.2–9.2)	7.4 (6.1–9.1)	0.058
2 years	7.5 (5.7–10.3)	6.9 (5.9–8.6)	0.412
Platelet count ($\times 10^9$/L)			
Preoperative	233 (191–285)	214 (181–250)	0.001*
Postoperative	184 (147–220)	170 (142–202)	0.209
1 year	244 (207–299)	207 (170–254)	0.003*
2 years	220 (183–262)	206 (169–224)	0.094

Abbreviations: EVAR, endovascular aneurysm repair; EVAS, endovascular aneurysm sealing.
*Significant difference.

by the trend toward a lower inflammatory response which only provides a benefit at early follow-up. At longer follow-up, however, there has been shown to be higher failure of EVAS due to endoleaks, migration, and even rupture.

The only significant difference in cause of death was that there were markedly more patients with an unknown cause of death in the EVAR group, which may have indirectly influenced the incidences of the other causes of death. It may be possible that due to the novelty and reported complications of the EVAS device clinicians have been more stringent with investigating the causes of death in this group.

In this study, there were 3 cases of aneurysm related mortality in the EVAS group and one in the EVAR group. Two of the EVAS patients died after a reintervention and 1 patient had aortitis. The EVAR patient had brief hypotension with a known endoleak and aneurysm growth but no treatment was wanted, the patient was discharged and died at home. In the current study, we also found no significant differences in the incidences of oncological deaths, gastrointestinal deaths and deaths due to multiorgan failure. Interestingly, previous research[12] has shown an opposite finding, with a lower incidence of oncological deaths after EVAS compared with EVAR.

Previous studies[11,12] have postulated that a survival benefit of EVAS over EVAR could have been related to a lower systemic inflammatory response. In order to measure this we evaluated blood test values over time, including creatinine, hemoglobin, WBC count, and platelet count. Both creatinine and haemoglobin values showed no significant differences between the 2 groups. As could be expected creatinine values increased slightly over time indicating some decrease in renal function. Haemoglobin levels dropped postoperatively but were back at preoperative levels at 1- and 2-year follow-up in both cohorts. In this study, WBC count and platelet count were used to measure inflammatory response. With a lower preoperative WBC count in EVAS and no further significant differences in WBC count, the postulation could be made that there is a tendency toward, relatively, a higher immune response to EVAR compared with EVAS. Additionally, a lower platelet count, both preoperatively and at 1 year, after EVAS compared with EVAR was found. This trend might hint toward a decreased inflammatory response after EVAS compared with EVAR but must be interpreted with care.

There are several limitations to this study that should be acknowledged. First of all, this was a relatively small cohort, especially when compared with earlier research on the same topic where a total of 784 patients were included.[12] This was a retrospective study, and even though propensity score matching has been performed to achieve comparable groups, this is not equivalent to a randomized controlled study. Since data were collected retrospectively, there was a limited access to blood tests for inflammatory markers and only creatinine, hemoglobin, WBC count, and platelet count was included. No interleukins or other inflammatory

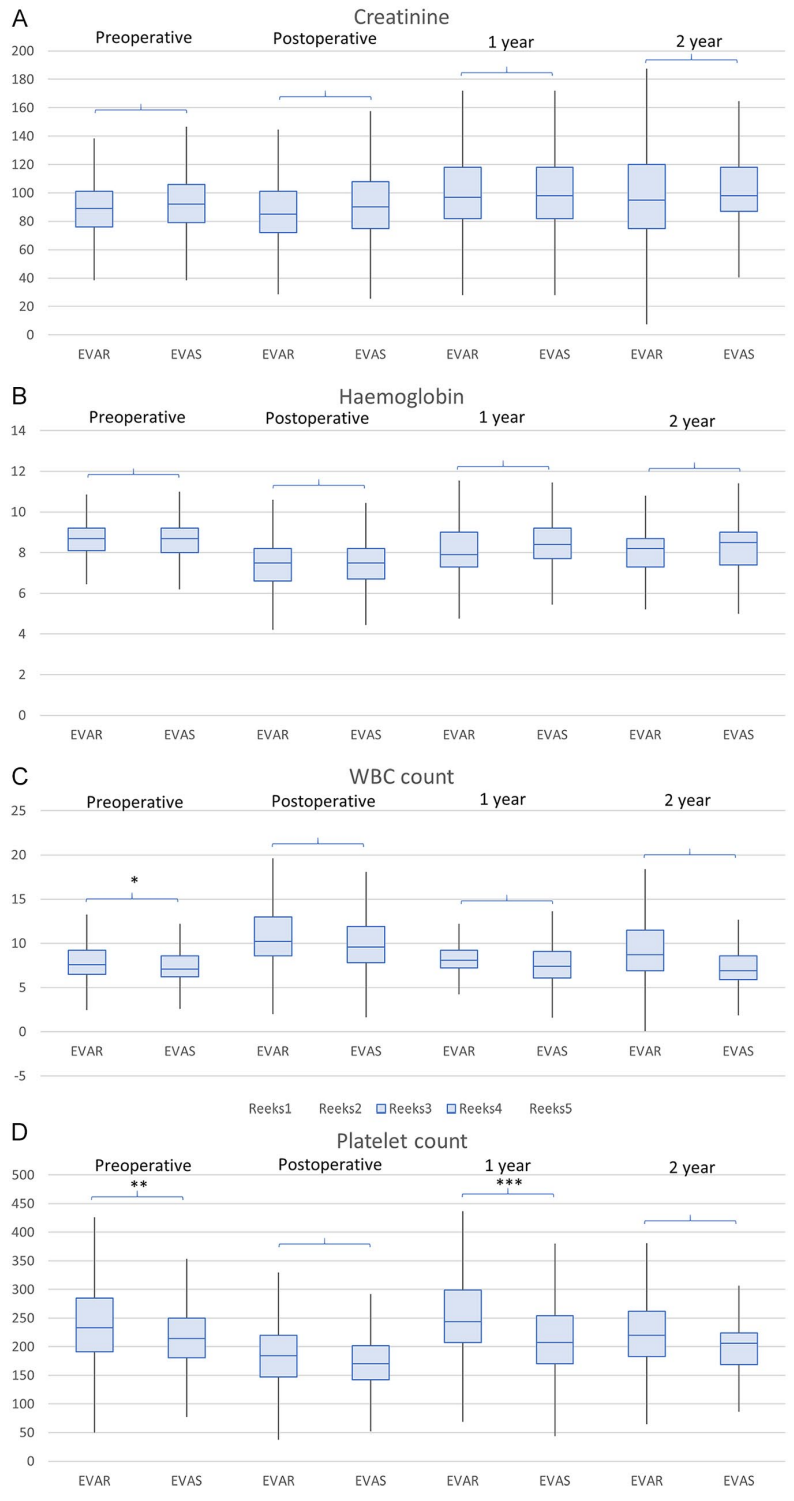

Figure 1. Boxplots of lab values at different time points, significance is marked with *, with *p=0.011, **p=0.001, ***p=0.003. (A) Creatinine values over time. (B) Hemoglobin values over time. (C) White blood cell count over time. (D) Platelet count over time.

Table 4. Causes of Death.

Cause of Death	EVAR	EVAS	p
Aneurysm related	1	3	0.222
Cardiovascular	8	6	0.845
Infectious	5	4	0.959
Renal	2	1	0.673
Oncological	10	12	0.318
Pulmonary	5	3	0.645
Multiorgan failure	3	5	0.306
Neurological	1	2	0.449
Traumatic	1	1	0.892
Gastrointestinal	0	2	0.116
Unknown	15	4	0.011*

Abbreviations: EVAR, endovascular aneurysm repair; EVAS, endovascular aneurysm sealing.
*Significant difference.

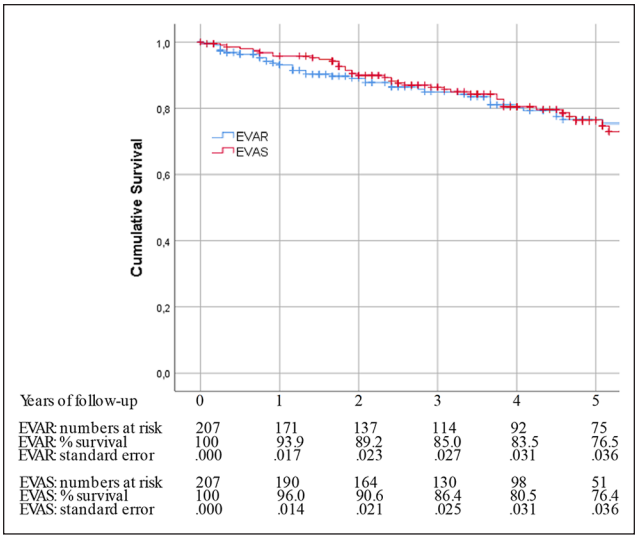

Figure 2. Survival analysis including total mortality.

markers were collected because this is not part of standard clinical practice. Additionally, it is important to note that many patients had a relatively short duration of follow-up with 75 of 207 EVAR patients and 51 of 207 EVAS patients at 5-year follow-up. As has been described the survival analysis shows a slight survival benefit in the short term but a disadvantage at longer follow-up for EVAS. As such, longer follow-up might reveal a further disadvantage for EVAS. More extensive and longer studies are necessary to show if this is indeed the case. Also, there might be a selection bias associated with the inclusion criteria of follow-up data of 1 year or longer. Additionally, in 1 center, patients who were alive were asked for their consent prior to participation and in 16 cases the patient was either not contactable or did not give consent. For those patients in this centre for whom no cause of death was known the death certificate was obtained.

Conclusion

This study shows that, contrary to earlier research, there is a comparable survival rate at 5 years between EVAS and EVAR. However, there is a tendency toward higher increase in values of WBC count and platelet count in the first 2 years of follow-up in EVAR patients compared with EVAS patients. A larger number of patients with a more complete follow-up including laboratory markers is warranted.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Michel M. P. J. Reijnen and Andrew Holden are members of the Endologix Scientific Advisory Board.

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ORCID iDs

Aleksandra C. Zoethout https://orcid.org/0000-0002-5562-190X
Michel M. P. J. Reijnen https://orcid.org/0000-0002-5021-1768
Andrew Holden https://orcid.org/0000-0002-8170-4960

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