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Outcomes after treatment of complex aortic abdominal aneurysms with the fenestrated Anaconda endograft

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ABSTRACT

Objective: To date, information on the fenestrated Anaconda endograft is limited to case series with a small sample size. This study was performed to assess the technical and clinical outcome of this device in a large international case series.

Methods: All worldwide centers having treated more than 15 complex abdominal aortic aneurysms (AAA) or type IV thoracoabdominal aortic aneurysm patients with the fenestrated Anaconda endograft were approached. Main outcome parameters were procedural technical success, postoperative and follow-up clinical outcome for endoleaks, target vessel patency, reintervention rate, and patient survival.

Results: Three hundred thirty-five consecutive cases treated between June 2010 and May 2018 in 11 sites were included. Patients were treated for a short neck infrarenal (n = 98), juxtarenal (n = 191), suprarenal AAA (n = 27), or type IV thoracoabdominal aortic aneurysm (n = 19). Mean age was 73.6 ± 4.6 years (292 male). Endografts contained a total of 920 fenestrations, with a mean of 2.7 ± 0.8 fenestrations per case. Technical success was 88.4% (primary, 82.7%; assisted primary 5.7%). In 6.9% of cases, a procedural type IA endoleak was observed, spontaneously disappearing in 82.6% during early follow-up. The development of a type IA endoleak was associated with greater neck angulation (odds ratio [OR], 0.94; $P = .01$), three fenestrations (OR, 42.7; $P = .01$) and the presence of augmented proximal rings (OR, 0.17; $P = .03$). Median follow-up was 1.2 years (interquartile range, 0.4-2.6). The mean estimated glomerular filtration rate deteriorated from 67.6 ± 19.3 mL/min/1.73 m^2 preoperatively to 59.3 ± 22.7 mL/min/1.73 m^2 at latest follow-up ($P = .00$). The freedom from AAA growth were 97.9 ± 0.9% (n = 190) and 86.4 ± 3.0% (n = 68), with a freedom from AAA rupture of 99.7 ± 0.3% (n = 191) and 99.1 ± 0.7% (n = 68), at 1 and 3 years, respectively. The endoleak-free survival, excluding spontaneously resolved procedural endoleaks, at 1 and 3 years was 73.4 ± 2.6 (n = 143) and 65.6 ± 3.4% (n = 45), respectively. The target vessel patency at one and three years were 96.4 ± 0.7% (n = 493) and 92.7 ± 1.4% (n = 156), respectively. A total of 75 reinterventions were done in 64 cases (19.1%), of which 25 cases for an endoleak. The reintervention-free survival at 1 and 3 years were 83.6 ± 2.2% (n = 190) and 71.0 ± 3.7% (n = 68), respectively. No deaths during procedure, extending within 24 hours postoperatively, were observed. Within 30 days 14 patients (4.2%) died and during follow-up another 39 patients (11.6%) died. Three deaths were considered AAA related (one rupture, one endograft infection, and one bilateral renal artery occlusion). The estimated cumulative survival at 1 and 3 years were 89.8 ± 1.8% (n = 191) and 79.2 ± 3.0% (n = 68), respectively.

Conclusions: The custom-made fenestrated Anaconda endograft is a valuable option for the treatment of a complex AAA. A procedural type IA endoleak is seen relatively frequently, but spontaneously resolves in most cases. (J Vasc Surg 2020;72:25-35.)

Keywords: Abdominal aortic aneurysm; Fenestrated Anaconda; FEVAR; Endovascular

Since the introduction of endovascular aneurysm repair (EVAR) for the treatment of aortic abdominal aneurysm (AAA), a shift toward endovascular treatment was seen globally.[1,2] A more proximal extension of the AAA jeopardizes the ability to achieve seal of the infrarenal device below the renal arteries (RAs). Suprarenal deployment

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of an endovascular device with fenestrations in the main body and subsequent stenting of these fenestrations has enabled enlargement of the proximal sealing zone and preservation of flow to the visceral arteries.[3,4]

Complex cases, including AAAs involving the visceral arteries, seem to have a lower mortality risk when treated by fenestrated EVAR (FEVAR) compared with open surgery.[5,6] Increased experience made FEVAR one of the primary treatment options for complex AAA repair, subsequently leading to an increase in complexity including the use of three or four fenestrations.[7] In recent years, the custom-made fenestrated Anaconda endograft was introduced (Terumo Aortic, Inchinnan, Scotland, UK) for the treatment of patients with anatomy unsuitable for standard EVAR. The treatment with this specific fenestrated endograft showed an acceptable technical success rate (85.0%-95.0%), a high target vessel patency at 1 year (97.2%-99.0%), and a high reintervention-free survival at 1 year (91.0%-96.5%) in several case series, all with a relatively small sample size.[8-11]

The goal of the current study was to assess technical and clinical outcomes of the fenestrated Anaconda in a large subset of patients treated in multiple centers globally. Study parameters were technical outcome, clinical outcome, number of endoleaks, target vessel patency, and survival rates, including freedom from AAA rupture.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective, multicenter, international cohort study
- **Key Findings:** In 335 patients, complex abdominal aortic aneurysm was treated with the fenestrated Anaconda endograft, with a technical success of 88.4%, with a 30-day mortality rate of 4.2% and a reintervention rate of 19.1% during a median follow-up of 1.2 years. In 6.9% of patients, a procedural type IA endoleak was observed, spontaneously disappearing later in 82.6%.
- **Take Home Message:** Treatment of a complex abdominal aortic aneurysm with the fenestrated Anaconda endograft is a valuable option and a procedural type IA endoleak mostly disappears spontaneously.

METHODS

All consecutively treated patients with the custom-made bi-iliac or uni-iliac fenestrated Anaconda for AAA or type IV thoracoabdominal aortic aneurysm repair, were eligible for inclusion, including cases after previous AAA repair. At the initiation of the study, an estimate of 2200 cases worldwide were treated with the fenestrated Anaconda. The cutoff value of the learning curve with the fenestrated Anaconda is unknown. To overcome learning curve bias, the minimum number of patients treated with the device was set at 15 patients. All centers globally having treated patients with the fenestrated Anaconda, and meeting the 15 cases threshold, were approached to participate, potentially, 843 cases in 24 centers. Data were center reported, collected retrospectively in a validated online data management system (OpenClinica, LLC, Waltham, Mass), and analyzed anonymously. A waiver was granted by the review boards per participating country, The Netherlands reference number M16.203416, Germany reference number 18-268, the United Kingdom IRAS reference number 225488, and Canada reference number REB17-0510.

Study design. Preoperative patient characteristics were gathered and the risk factors age, hypertension, renal function, cardiac status, and pulmonary status were scored from 0 to 3 according to the Society of Vascular Surgery – American Association of Vascular Surgery medical comorbidity grading system. ASA scores were gathered and renal function was measured by the estimated glomerular filtration rate (eGFR) and checked with the Cockcroft-Gault formula.[12,13] Information about prior AAA treatment and aortic anatomy were collected. Operation specifics, including endograft design, were gathered. Procedural technical success was achieved in successful endovascular access, the fenestrated endograft was deployed, and the fenestrations stented as planned, in the absence of a type I or III endoleak. Additionally, there was no conversion to open repair or death extending within 24 hours after the operation. Assisted primary technical success was achieved if technical success was achieved with additional endovascular treatment, within 24 hours.[14] Adverse events, reinterventions, and deaths are reported separately for the first 30 days postoperative period and the follow-up after 30 days. Major adverse events were defined as death, reintervention, life-threatening disease, or disease resulting in significant disability. Estimated cumulative analysis was calculated for freedom from AAA growth, freedom from endoleaks, target vessel patency, reintervention-free survival, freedom from AAA rupture, freedom from AAA-related mortality, and overall patient survival. AAA growth was defined as an AAA increase surpassing the 5% threshold described by Chaikof et al.[14] Endoleaks were presented as described by Jain et al.[15] A target vessel adverse event was defined as stent fracture, stent kinking, or stent stenosis or occlusion. Stenosis of visceral arteries or limbs was based on the SVS guidelines for peripheral artery disease and simplified by differentiating between occlusion and stenosis, therefore the simplified scoring being occlusion, stenosis (25%-99% circumferential stenosis of the vessel diameter) and no occlusion (none to ≤25%).

Endograft design. The fenestrated Anaconda (Fig 1) is a custom-made device containing two proximal nitinol rings, with three or four pairs of proximal hooks for

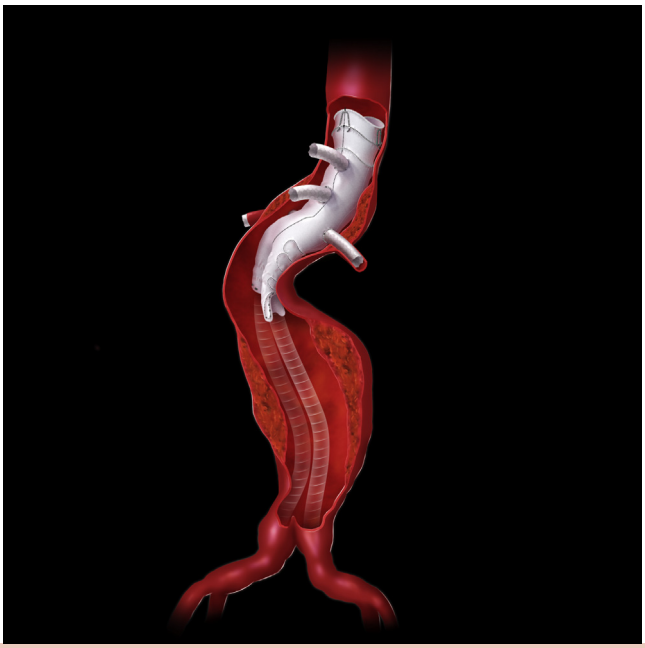


Fig 1. The fenestrated Anaconda endograft with four fenestrations for the celiac trunk, the superior mesenteric artery and both renal arteries (RAs). In this case a bi-iliac endograft is presented with two parallel proximal rings and four pair proximal hooks.

fixation to the aortic wall. The proximal rings are either parallel or convergent from dorsal to anterior (augmented) to allow adequate sealing between two proximate arteries. The rings are oversized by up to 25%, creating a saddle shape to apposite the rings to the aortic wall and provide a proximal seal. The unsupported part allows an unlimited number of nitinol reinforced fenestrations. After deployment of the proximal part through the femoral artery, repositioning throughout the procedure is possible, and additional access from the contralateral side or cranially allows cannulation and stenting of the fenestrations.

Statistics. Categorical variables were presented with frequencies and percentages. Continuous variables were tested for normal distribution by Q-Q plots and presented with the mean and standard deviation, or in case of skewed data median and interquartile range (IQR). Continuous data were analyzed with the Student *t*-test or the Mann-Whitney *U* test, when appropriate. Paired continuous data was analyzed with the paired Student *t*-test. Survival analysis was done with Kaplan-Meier curves, and cut-off once 10% of the numbers were at risk.[16] To predict renal function at latest follow-up, a multiple linear regression analysis was performed with preoperative patient characteristics. To predict endoleaks, a multiple regression analysis was performed with anatomic characteristics and endograft design. In linear regression analysis the B, and in the logistic regression analysis the odds ratio (OR) were reported, both with the 95% confidence interval (CI). Confounding was considered in a B change of 10% in the multiple regression analysis. A *P* value of less than .05 was considered statistically significant. Statistical analysis was done with IBM SPSS Version 23.0.0.3 (Armonk, New York).

RESULTS

A total of 11 sites reported 335 consecutive cases treated between June 2010 and May 2018, which was 39.7% of the intended sample size. In the other 13 sites the clinicians did not respond or did not want to participate. The Supplementary Table (online only) shows the number of cases per participating site over time. Median number of cases per site was 21 (IQR, 16-42).

The preoperative patient characteristics are described in Table I and the aortic anatomy in Table II. One patient was on hemodialysis for renal insufficiency and excluded in the analysis for renal function. Details on the endograft design are described in Table III. A total of 920 fenestrations were used, indicating a mean of 2.7 per case. The median follow-up was 1.2 years (IQR, 0.4-2.6 years).

Procedural results. General anesthesia was used in 96.7% and regional in 3.3% of cases. Access was gained by cut-down in the groin in 91.6% of the cases, with an additional cranial access in 42.0% from the subclavian artery (11.6%), the axillary artery (19.1%), or the brachial artery (11.3%). The mean procedural time was 272 ± 100 minutes and mean contrast used was 43 ± 27 g. No deaths during the procedure, or within 24 hours postoperatively, were observed. One conversion and open surgical repair was performed, because rotation of the endograft prevented stenting of the right RA and thrombosis of the iliac limbs.

Technical success was 88.4% (primary technical success of 82.7% and assisted primary of 5.7%). There were 39 technical failures (11.6%); in 32, technical failure was related to type IA (n = 22 [6.6%]), type IB (n = 4 [0.9%]), or type IIIC (n = 6 [1.2%]) endoleak. In one case, there was both a type IA and IIIC endoleak (0.9%). One technical failure was a conversion with explantation (referred to elsewhere in this article). In another case it was impossible to cannulate a RA, without a visible endoleak. In another case it was impossible to cannulate the celiac artery and a proximal cuff was placed to seal this fenestration, without clinical sequela. In another case, the tortuous iliac arteries prevented advancement of the sheath containing the endograft and the procedure was aborted. In a next case, with a neck length of 15 mm, but angulated, barrel shaped, and with mural thrombus, there was a failure to stent the superior mesenteric artery and left RA. Open surgical repair was not preferred because multiple preoperative comorbidities (Society of Vascular Surgery – American Association of Vascular Surgery score of 1.5). The fenestrated endograft was collapsed, repositioned and released into the

Table I. Preoperative patient risk factors

	No.	Mean ± SD	Percent
Age,[a] years	335	73.6 ± 4.6	
0 (<55)	1		0.3
1 (55-69)	83		24.8
2 (70-79)	185		55.2
3 (>80)	66		19.7
Gender			
Male	292		87.2
Female	43		12.8
ASA score			
I	0		0.0
II	107		31.9
III	221		63.0
IV	17		5.1
V	0		0
Hypertension[a]	335		
0 (no medication)	70		20.9
1 (controlled, 1 drug)	108		32.2
2 (controlled, 2 drugs)	124		37.0
3 (uncontrolled, >2 drugs)	33		9.9
Comorbidities (none SVS/AAVS)	335		
Hypercholesterolemia	217		64.8
Diabetes mellitus	66		19.7
Peripheral artery disease	70		20.9
Cerebrovascular disease	45		13.4
Plasma creatinine,[a] μmol/L	335	67.6 ± 19.3	
0 (<105)	235		70.1
1 (110-215)	91		27.2
2 (220-520)	8		2.4
3 (>520, dialysis)	1		0.3
Cardiac status[a]	335		
0 (asymptomatic)	180		53.7
1 (remote MI)	104		31.0
2 (stable angina, recent MI)	48		14.3
3 (unstable angina, heart failure)	3		0.9
Pulmonary function of predicted (%)[a]	335		
0 (asymptomatic, >80)	231		69.0
1 (65-80)	82		24.5
2 (50-65)	19		5.7
3 (<50)	3		0.9
SVS/AAVS grading score (0-3)[a]	335	0.72 ± 0.40	

AAVS, American Association Vascular Surgery; *ASA*, American Society of Anesthesiologists; *MI*, myocardial infarction; *SD*, standard deviation; *SVS*, Society of Vascular Surgery.
[a]Higher category corresponds with higher postoperative morbidity and mortality risk according to the SVS/AAVS grading system by Chaikof et al.[12]

Table II. Preoperative aortic anatomic characteristics

	No.	Mean ± SD	Percent
Anatomic aneurysm location	335		
Infrarenal	98		29.3
Juxtarenal	191		57.0
Suprarenal	27		8.1
Type IV thoracoabdominal	19		5.7
Aneurysm type	335		
Fusiform	315		94.0
Saccular	20		6.0
Previous treatment	10		
Open surgical repair (para-anastomotic)	5		1.5
EVAR	5		1.5
Aortic neck angle[a]	270	23 ± 16	
Diameter at SMA, mm	275	26 ± 3	
Diameter at RAs, mm	275	27 ± 5	
Aneurysm diameter, mm	335	62 ± 10	
Aortic tortuosity index[b]	249	1.1 ± 0.1	
Aortic most acute angle[a]	255	27 ± 17	
Mycotic aneurysm	10		3.0
Iliac most acute angle right[a]	252	56 ± 29	
Iliac most acute angle left[a]	253	52 ± 30	
Iliac tortuosity index right[b]	243	1.3 ± 0.2	
Iliac tortuosity index left[b]	243	1.3 ± 0.2	

EVAR, Endovascular aneurysm repair; *RAs*, renal arteries; *SD*, standard deviation; *SMA*, superior mesenteric artery.
[a]Degrees; straight was considered 0° counting toward 180° in more angulation.
[b]Length of the artery divided by the length of a straight line between origin and the end of the artery.

AAA sac and left there. Subsequently, a standard Endurant endograft (Medtronic, Minneapolis, Minn) was deployed alongside the fenestrated endograft and left there, sealing the AAA. The last failed patient died within 24 hours of myocardial infarction.

In 18 cases (5.4%) with two or more lumbar arteries of more than 4 mm in diameter on preoperative CTA, a spinal drain was used as a preventative measure. In another four cases (1.3%), spinal cord ischemia was noted postoperatively and a spinal drain was used. On the preoperative CTA, there were multiple lumbar arteries of greater than 4 mm in diameter in one and in a second case only very small lumbar arteries were seen on preoperative CTA. The anatomy of the lumbar arteries were unavailable in the remaining two cases. In two cases, the sensory disorder disappeared. In one case, spinal injury presented as sensorimotor paralysis. During follow-up the paralysis disappeared, but a

Table III. Endograft design

	No.	Percent
Proximal ring design		
Parallel	177	52.8
Augmented	158	47.2
No. of proximal hooks		
3	153	45.7
4	182	54.3
No. of fenestrations		
1	12	3.6
2	132	39.4
3	123	36.7
4	65	19.4
5	3	1.5
Target vessel stents[a]		
Atrium Advanta V12[b]	318	97.0
LifeStream[c]	3	0.9
BeGraft[d]	1	0.3
Atrium Advanta V12[a] + LifeStream[b]	5	1.5
Atrium Advanta V12[a] + BeGraft[c]	1	0.3
Iliac design		
Bi-iliac	322	96.1
Uni-iliac	13	3.9
	Mean	**SD**
Oversizing of proximal rings	19.6[a]	3.7
Fenestrations per case	2.7	0.8

SD, Standard deviation.
Oversizing is presented as percentage above aortic diameter.
[a]In seven cases, the target vessel stents were unknown.
[b]Maquet GmbH & Co KG, Rastatt, Germany.
[c]BARD Peripheral Vascular Inc., Tempe, Ariz.
[d]Bentley Innomed GmbH, Hechingen, Germany.

neuropathic pain disorder remained. In the fourth case, the spinal injury presented as paraplegia, and after spinal drain the paraplegia disappeared, but a sensory disorder remained. The number of events for spinal cord ischemia was too low for regression analysis.

Renal function. The mean eGFR deteriorated to 65.2 ± 22.0 mL/min/1.73 m^2 postoperatively ($P = .00$) and further to 59.3 ± 22.7 mL/min/1.73 m^2 at the latest follow-up ($P = .00$). In the regression analysis, the preoperative patients characteristics presented in Table I were used. In the univariate regression analysis, the eGFR at latest follow-up was statistically significantly associated with preoperative eGFR (B = 0.830; 95% CI, 0.711-0.949; $P = .00$) and age at operation (B = −.692; 95% CI, −1.133 to −0.250; $P = .00$). After backward multivariate selection only preoperative eGFR was associated with eGFR at latest follow-up. No confounders were found.

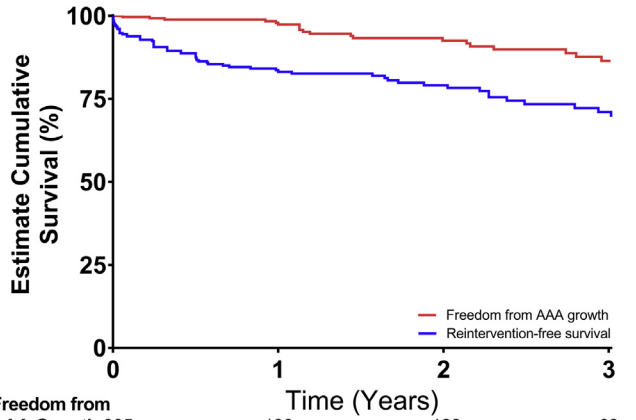
Within 30 days, there were 32 cases (9.6%) of renal infarction noted. In these cases, the eGFR deteriorated from 71.4 ± 16.8 mL/min/1.73 m^2 to 56.2 ± 23.1 mL/min/1.73 m^2 postoperatively ($P = .01$). One of the patients with a renal embolus became permanently dialysis dependent and another with a renal embolus became temporarily dialysis dependent. In three cases (0.9%), there was a bleeding from a renal branch during surgery necessitating coiling. In another three cases (0.9%), an accessory RA was intentionally overstented. In a seventh case, a renal thrombus occurred that was accepted, without further sequela. In the remaining cases, the infarction was most likely the consequence of an embolus. Six patients became permanently dialysis dependent, and one patient was already dialysis dependent preoperatively. Four patients became dialysis dependent, but the eGFR recovered sufficiently during follow-up and dialysis was stopped.

Four of the newly dialysis-dependent patients had newly diagnosed renal infarction, without stent or RA stenosis, and became dialysis dependent thereafter. In a fifth patient, the endograft migrated distally leading to occlusion of the RAs. The remaining five renal failure cases had an already borderline eGFR preoperatively.

Rupture and aneurysm size. The freedom from AAA growth were 97.9 ± 0.9% and 86.4 ± 3.0%, with a freedom from AAA rupture of 99.7 ± 0.3% and 99.1 ± 0.7%, at 1 and 3 years, respectively (Fig 2). The mean aneurysm size decreased from 61.7 ± 9.6 mm to 55.9 ± 12.1 mm ($P = .00$). Aneurysm size during follow-up remained stable in 96 (28.6%), growth was noted in 28 (8.4%), shrinkage in 181 (54.0%), and in 30 cases (9.0%) no follow-up aneurysm size was available. There was no difference in aneurysm size change during follow-up between cases that had a procedural type IA endoleak or these without such an endoleak ($P = .23$).

In 20 cases with aneurysm growth, an endoleak was observed. This concerned a procedural type IA endoleak, a type IB endoleak at 3 months, three spontaneously resolved procedural type II endoleaks, four treated type II endoleaks, five closely followed for a persistent type II endoleaks, a spontaneously resolved procedural type IIIC, and a treated unclear endoleak. In two cases with aneurysm growth, a type IA endoleak had spontaneously disappeared, but a type IC in one and a type II endoleak in the other occurred during follow-up. One patient had a procedural type II endoleak and developed a type IA endoleak and aneurysm growth. During follow-up, a type IB and type II endoleak with aneurysm growth was treated in another case. The last patient had a combined type IB and II endoleak during follow-up, and was scheduled for treatment.

In the remaining cases, no endoleak was noted, but an increase was observed from 4 to 13 mm over a period of 3 months to 6 years, and these patients were followed closely.



Freedom from AAA Growth	335	190	122	68
Survival (%)	100	97.9	92.5	86.4
SE (%)	0	0.9	2.0	3.0
Reintervention-free Survival	335	168	97	52
Survival (%)	100	83.6	79.1	69.6
SE (%)	0	2.2	2.7	3.7

Fig 2. Estimated cumulative survival for freedom from abdominal aortic aneurysm (*AAA*) growth and reintervention-free survival. Number at risk and Kaplan-Meier survival analysis with standard error are presented. AAA growth was considered in case of AAA size increased above the 5% threshold.[15] *SE,* Standard error.

Endoleaks. At completion angiography, 103 endoleaks in 101 cases were detected (Table IV). There were 23 procedural type IA endoleaks (6.9%), of which 13 had disappeared spontaneously at 30 days (56.5%) and six others thereafter (26.1%). In the spontaneously disappeared type IA endoleak cases, no returning type IA endoleak was observed during follow-up. There were two reinterventions for type IA endoleak. At latest follow-up, three type IA endoleaks were still present, without clinical consequences. In one newly developed type IA endoleak, treatment was planned because of an additional increase of the aneurysm diameter.

In the multivariate regression analysis to predict type IA endoleak, the anatomic variables presented in Table II and the endograft design presented in Table III were used. In the univariate regression analysis statistically significant predictors for a type IA endoleak were neck angle (OR, 0.94; 95% CI, 0.90-0.99; $P = .01$) and three fenestrations (OR, 8.0; 95% CI, 1.2-53.6; $P = .03$). In the multivariate regression analysis, with backward selections, predictors for type IA endoleak were neck angle (OR, 0.94; 95% CI, 0.90-0.99; $P = .01$), three fenestrations (OR, 42.7; 95% CI, 3.0-610.2; $P = .01$) and the presence of augmented proximal rings (OR, 0.17; 95% CI, 0.04-0.80; $P = .03$). No confounders were found. The sample sizes of type IB and type IC were too low for statistical regression analysis.

Fifty new endoleaks in 39 cases were observed during follow-up. Consequently, there were 153 endoleaks in 140 cases (Fig 3). In 26 cases, a reintervention for an endoleak was performed (Table IV).

Target vessel patency. A total of 37 adverse events with target vessels occurred between 4.0 days and 4.4 years postoperatively (Fig 4). There were 13 target vessel adverse events within 30 days (Table V). In all these cases, a balloon-expandable covered stent was used for the fenestrations. In one case, the left RA stent kinked slightly during endograft placement, and a second balloon-expandable covered stent was placed, resulting in left renal infarction and a decrease in eGFR from 108.9 to 50.7 mL/min/1.73 m^2. During follow-up after 30 days, 13 target vessel adverse events were treated by expectant observation, without clinical consequences. In another 11, target vessel adverse events a reintervention was performed (Table V).

Reintervention-free survival. A total of 69 reinterventions were performed in 64 cases (Fig 5; Table V). The endoleak-related interventions are separately described in Table IV. No difference was seen in iliac tortuosity ($P = .21$) and most acute iliac angle ($P = .50$) between occluded and nonoccluded iliac limbs.

Survival. Within 30 days, there were 14 procedure-related deaths (4.2%). During follow-up, another 39 patients (11.6%) passed away. Consequently, a total of 53 patients died during follow-up (Fig 5). Six cases were lost to follow-up.

There were two known AAA ruptures (Fig 5); one was the aborted case and, in the second case, a coil embolization at 4 months for a type II endoleak was performed. After reintervention, the patient left the hospital with fever against advice and presented at the emergency department 10 months later with an infected endograft and ruptured AAA.

In one case, there was dilation of the proximal landing zone and distal migration of the endograft. An explantation was performed at 27 months, but the patient died after multiorgan failure. In another case, the RAs occluded owing to endograft migration at 11 months and the patient became dialysis dependent. Another 5 months later, there was proximal aneurysm enlargement, but the patient decided he wanted to stop treatment, resulting in device-related death (Fig 5).

Major adverse events. Within 30 days 14 deaths were reported, and in two of these cases a reintervention was performed before death. Another 16 reinterventions were done, resulting in 30 major adverse events (9.0%) within 30 days postoperatively.

During follow-up, another 39 patients died; in three of these cases, a reintervention was done during follow-up. Another 48 reinterventions were done during follow-up, resulting in 117 overall major adverse events (34.9%) at a median follow-up of 14.4 months. All deaths and reinterventions are described in detail in Table V.

Table IV. Endoleaks

Endoleak	Completion angiography	30 day postoperative				Last follow-up (median, 14.4 months)			
		New	Successfully treated	Disappeared	Present	New	Successfully treated	Disappeared	Present
Type IA	23 (6.9%)	1	1	13	10	1	1	6	4
Type IB	4 (1.2%)	2	1	2	3	3	3	0	3
Type IC	0 (0.0%)	0	0	0	0	1	1	0	0
Type II	68 (20.6%)	22	1	36	53	12	8	33	24
Type IIIC	7 (2.1%)	2	1	4	4	5	7	1	1
Unclear	1 (0.3%)	0	0	1	0	1	1	0	0
Total	103	27	4	56	70	23	21	40	32

Endoleaks at completion angiography, and on computed tomography angiography within 30 days and at last follow-up in 335 treated cases. Number of cases are presented with percentage. Endoleaks are described by Jain et al.[16] No type IIIA or type IV endoleaks were seen. All treatments successfully sealed the endoleaks.

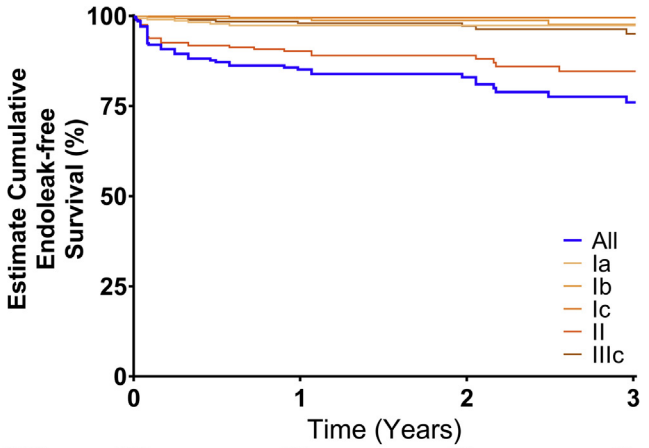
DISCUSSION

This study shows the technical and clinical outcomes of the fenestrated Anaconda endograft for the treatment of complex AAA. The study included 335 cases from 11 different experienced vascular centers globally, and as such reflects the current international practice.

The current study shows a relatively high incidence of intraoperative type IA endoleak at completion angiography. Interestingly most of these endoleaks spontaneously disappear during follow-up and the necessity for reinterventions is very low. This may be related to the design of the endograft. The proximal nitinol rings need time to fully expand into their saddle shape, eventually sealing the type IA endoleak.[17] The Anaconda endograft for infrarenal AAA repair has the same design, and the procedural type IA endoleaks of 8.2% were directly and successfully treated by ballooning.[18] In FEVAR, the clinician might await a full expansion of the proximal rings, because there is a risk of crushing the intraluminal target vessel stent during ballooning after the completion angiography. In our study, there was only one case of AAA growth observed 3.6 years postoperatively owing to a newly developed type IA endoleak. In the remaining cases, no type IA endoleak-related clinical consequences were noted, nor was there a difference noted in aneurysm size change during follow-up, but results in the long term remain unknown. Close observation of these patients is therefore indicated.[19]

The technical success rate was impacted by the rate of intraoperative endoleaks. These endoleaks seemed to have no clinical significance in the majority of patients and once disappeared, results were comparable to the fenestrated endograft from Cook Medical (Bloomington, Ind).[20-22]

Target vessel patency rates over time are very similar to earlier reported case series. These studies also have similar outcome for reintervention-free survival and are primarily based on results from few cases per center. The expectation is that, with experience with the fenestrated Anaconda, results will continue to improve.[10,11,23] Our study includes all first treated cases per center and worldwide with the fenestrated Anaconda and in seven centers fewer than 25 cases were treated to date. Although the learning curve was not investigated in our study, a learning curve effect may have impacted outcomes.



All ELs	335	143	90	45
Survival (%)	100	73.4	71.6	65.6
SE (%)	0	2.6	2.7	3.4
Type Ia EL	335	168	117	64
Survival (%)	100	95.1	95.1	95.1
SE (%)	0	1.3	1.3	1.3
Type Ib EL	335	192	121	66
Survival (%)	100	98.7	98.2	97.1
SE (%)	0	0.6	0.8	1.4
Type Ic EL	335	193	123	68
Survival (%)	100	99.6	99.6	99.6
SE (%)	0	0.4	0.4	0.4
Type II EL	335	156	99	50
Survival (%)	100	81.4	80.2	76.3
SE (%)	0	2.2	2.3	2.9
Type IIIc EL	335	190	121	67
Survival (%)	100	97.1	96.3	94.2
SE (%)	0	1.0	1.3	2.0

Fig 3. Estimated cumulative endoleak (*EL*)-free survival. Excluding spontaneously resolved procedural endoleaks. All endoleaks combined and separated are presented. Number at risk, Kaplan-Meier survival analysis with standard error (*SE*) are presented.

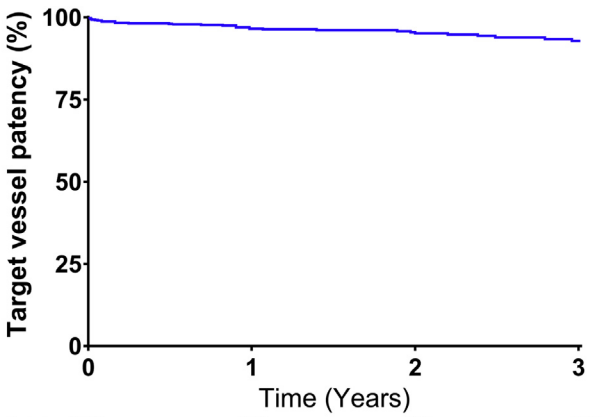


Fig 4. Estimated cumulative target vessel patency. Number at risk and Kaplan-Meier survival analysis with standard error (*SE*) are presented.

A direct comparison of the fenestrated Anaconda with other available fenestrated endografts may not be appropriate. The considerations for choosing a specific endograft were not available to the researchers, but can be based on anatomic features, clinician preference, and/or the difference in production time. The unsupported body of the fenestrated Anaconda enables an unlimited number of fenestrations unrestricted by struts and may have a better applicability in certain anatomic cases. Alternatively, the device cannot be combined with branches, limiting its applicability in others. The reason of choosing the fenestrated Anaconda can be the higher flexibility of the endograft and the iliac limbs, consequently using it in more challenging anatomies.[24-26] A comparative study with similar groups, including anatomic features, will be necessary to properly characterize difference in performance between fenestrated endografts.

In this study, overall renal function gradually decreased, and a significant percentage of renal infarction was observed, even in patients with patent RAs. Renal infarction has been reported up to 26% of patients after FEVAR.[27] Although mostly without clinical consequences, two cases in our study became permanently dialysis dependent after renal infarction. A decrease in renal function is likely related to intraoperative microembolization, but may also be related to increasing age, low preoperative renal function, and the use of contrast agents.[27-30] Special care should be taken to decrease contrast loads in patients with an already borderline renal function, and to minimize reposition of the graft deployment.

The 30-day mortality of 4.2% in this study is comparable with prior results of 3.0% to 7.0% with the fenestrated Anaconda, but slightly higher than the reported 0.7% to 3.4% with the Zenith fenestrated.[10,11,21-23,31,32] In our large series, in five cases the reason for death was a thromboembolic event, and the risk of thromboembolic events might be higher with the fenestrated Anaconda. A comparative analysis will not be feasible because the low incidence of thromboembolic events in all reported studies. The reported studies with the Zenith fenestrated included large cohorts from the same center, whereas this study and the studies from Colgan et al[10] and Midy et al[11] include multiple centers with a limited number of cases. As a result, the experience gained with the Zenith fenestrated in the large single centers are much larger compared with the experienced gained with the fenestrated Anaconda in the multiple small centers. However, the latter may represent more real-world data.

The recently reported perioperative mortality in open surgical repair for perirenal and previsceral aortic pathology of 8.8% still favors FEVAR.[11,32] Most results in open surgical repair are based on combined infrarenal and suprarenal clamping, and these results are similar to these in our study.[33] Suprarenal and perivisceral clamping leads to higher postoperative morbidity and long-term mortality compared with infrarenal clamping.[34-36] The results with FEVAR in our study compared with an open surgical repair group with suprarenal clamping and support the benefit of FEVAR. A review by Rao et al[37] did not show this difference, and they attributed their results to different preoperative characteristics and anatomy between groups. Until comparative studies containing similar FEVAR and open surgical groups are available, the choice between the two should be weighed by experience and the preference of the patient and clinician.

The retrospective nature and the voluntary submission of cases are the main limitations of this study. Complete datasets for all cases was not available, no core-lab imaging analysis was done, and site self-reporting may have led to patient selection or outcome bias. Furthermore, only 39.7% of all the potential cases were included, which might have resulted in a further selection bias. Although 5-year follow-up was available for some cases, the median follow-up was 1 year, and a long-term follow-up study needs to be completed.

CONCLUSIONS

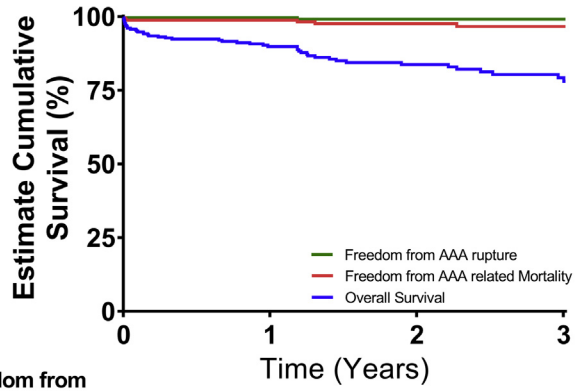
The custom-made fenestrated Anaconda endograft is an effective option for the treatment of complex abdominal aortic aneurysm. A procedural type IA endoleak is seen relatively frequent, but due to the evolving interaction between the proximal rings and the aortic neck spontaneously resolves over time in most cases.

Special thanks goes to S. Mylonas, Cha-ney Kim and C. Findlay for their application to their National Review Boards.

Table V. Overview of complicated course after treatment

	Within 30 days postoperatively	Last follow-up (median, 14.4 months)
Target vessel adverse events	**13 (1.4%)**	**24 (2.6%)**
Stenosis	CA: 1, SMA: 2, RA: 4	CA: 1, SMA: 4, RA: 6
No clinical consequences	2	7
Successfully treated	1	4
Renal infarction	1	–
Visceral organ ischemia	3	–
Occlusion	SMA: 2, RA: 3	CA: 1, SMA: 1, RA: 6
No clinical consequences	2	5
Successfully treated	–	3
Renal infarction	2	–
Visceral organ ischemia	1	–
Kinked stent	RA: 1	SMA: 1, RA: 1
No clinical consequences	–	1
Successfully treated	1	1
Stent fracture	–	RA: 3
Successfully treated	–	3
Reinterventions	18 (5.4%)	51 (15.2%)
Target vessel balloon angioplasty	2	1
Target vessel stent relining	1	9
Bowel resection	4	–
Proximal extension	–	2
Open surgical repair		
Endograft occlusion	1	1
Endograft migration	–	2
Endograft relining	–	1
Iliac limb thrombectomy/balloon angioplasty	6	15
Femorofemoral crossover bypass	–	4
Iliac-femoral bypass	–	1
EndoAnchors for type IA EL	1	–
Balloon angioplasty for type IA EL	–	1
Amplatzer plug for type IB EL	1	–
Iliac limb extension for type IB EL	–	3
Coil embolization for type II EL	1	8
Reflairing target vessel for type IIIC EL	1	3
Mortality	14 (4.2%)	39 (11.6%)
Ruptured aortic aneurysm	1	1
Endograft migration	–	1
Visceral artery occlusion	3	–
Visceral embolism	2	–
Renal failure	–	3
Cerebral event	–	2
Myocardial infarction	1	7
Respiratory failure	1	6
Malignancy	1	9
Necrotizing fasciitis	1	–
Unknown	4	10

–, None observed; *CA*, celiac artery; *EL*, endoleak; *RA*, renal artery; *SMA*, superior mesenteric artery.
Adverse events in 920 target vessels, reinterventions and deaths in 335 cases. The endoleaks were described in detail in Table IV.



Freedom from AAA Rupture	335	191	123	68
Survival (%)	100	99.7	99.1	99.1
SE (%)	0	0.3	0.7	0.7
Freedom from AAA related Mortality	335	191	123	68
Survival (%)	100	98.8	97.6	96.6
SE (%)	0	0.6	1.0	1.4
Overall survival	335	191	123	68
Survival (%)	100	89.8	83.7	79.2
SE (%)	0	1.8	2.4	3.0

Fig 5. Estimated cumulative survival for freedom from abdominal aortic aneurysm (*AAA*) rupture, freedom from AAA-related mortality (AAA-related mortality: ruptured AAA cases and endograft related deaths) and overall survival. Number at risk and Kaplan-Meier survival analysis with standard error (*SE*) are presented.

AUTHOR CONTRIBUTIONS

Conception and design: AN, CJ, MR
Analysis and interpretation: AN, CJ, MR
Data collection: AN
Writing the article: AN
Critical revision of the article: AN, CJ, MR
Final approval of the article: AN, CJ, MR
Statistical analysis: AN
Obtained funding: CJ, MR
Overall responsibility: MR

REFERENCES

1. Bacharach JM, Wood EA, Slovut DP. Management of aortic aneurysms: is surgery of historic interest only? Curr Cardiol Rep 2015;17:105.
2. Budtz-Lilly J, Venermo M, Debus S, Behrendt CA, Altreuther M, Beiles B, et al. Assessment of international outcomes of intact abdominal aortic aneurysm repair over 9 years. Eur J Vasc Endovasc Surg 2017;54:13-20.
3. Park JH, Chung JW, Choo IW, Kim SJ, Lee JY, Han MH. Fenestrated stent-grafts for preserving visceral arterial branches in the treatment of abdominal aortic aneurysms: preliminary experience. J Vasc Interv Radiol 1996;7:819-23.
4. Stanley BM, Semmens JB, Lawrence-Brown MM, Goodman MA, Hartley DE. Fenestration in endovascular grafts for aortic aneurysm repair: new horizons for preserving blood flow in branch vessels. J Endovasc Ther 2001;8:16-24.
5. Dijkstra ML, Tielliu IF, Meerwaldt R, Pierie M, van Brussel J, Schurink GW, et al. Dutch experience with the fenestrated Anaconda endograft for short-neck infrarenal and juxtarenal abdominal aortic aneurysm repair. J Vasc Surg 2014;60:301-7.
6. Gupta PK, Brahmbhatt R, Kempe K, Stickley SM, Rohrer MJ. Thirty-day outcomes after fenestrated endovascular repair are superior to open repair of abdominal aortic aneurysms involving visceral vessels. J Vasc Surg 2017;66:1653-8.
7. Starnes BW, Caps MT, Arthurs ZM, Tatum B, Singh N. Evaluation of the learning curve for fenestrated endovascular aneurysm repair. J Vasc Surg 2016;64:1219-27.
8. Kotelis D, Schleimer K, Jalaie H, Grommes J, Jacobs MJ, Kalder J. Operative and midterm outcomes of the fenestrated Anaconda stent-graft in the endovascular treatment of juxtarenal, suprarenal, and type IV thoracoabdominal aortic aneurysms. J Endovasc Ther 2016;23:930-5.
9. Blankensteijn LL, Dijkstra ML, Tielliu IFJ, Reijnen MM, Zeebregts CJ. Midterm results of the fenestrated Anaconda endograft for short-neck infrarenal and juxtarenal abdominal aortic aneurysm repair. J Vasc Surg 2017;65:303-10.
10. Colgan FE, Bungay PM, Burfitt N, Hatrick A, Clarke MJ, Davies AH, et al. Operative and one year outcomes of the custom-made fenestrated Anaconda aortic stent graft - a UK multicentre study. Ann Vasc Surg 2017;46:257-64.
11. Midy D, Becquemin JP, Mialhe C, Frisch N, Martinez R, Caradu C, et al. Results of the French multicentric study of ANACONDA™ fenestrated endografts in the treatment of complex aortic pathologies (EFEFA registry). Ann Vasc Surg 2017;43:151-65.
12. Riley R, Holman C, Fletcher D. Inter-rater reliability of the ASA physical status classification in a sample of anaesthetists in Western Australia. Anaesth Intensive Care 2014;42:614-8.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
14. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg 2002;35:1048-60.
15. Jain AK, Oderich GS, Tenorio ER, Karkkainen JM, Mendes BC, Macedo TA, et al. Natural history of target vessel endoleaks after fenestrated-branched endovascular aortic repair. J Vasc Surg 2018;67:e53-4.
16. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002;359:1686-9.
17. Koenrades MA, Klein A, Leferink AM, Slump CH, Geelkerken RH. Evolution of the proximal sealing rings of the Anaconda stent-graft after endovascular aneurysm repair. J Endovasc Ther 2018;25:480-91.
18. Freyrie A, Gargiulo M, Rossi C, Losinno F, Testi G, Mauro R, et al. Preliminary results of Anaconda aortic endografts: a single center study. Eur J Vasc Endovasc Surg 2007;34:693-8.
19. van Marrewijk C, Buth J, Harris PL, Norgren L, Nevelsteen A, Wyatt MG. Significance of endoleaks after endovascular repair of abdominal aortic aneurysms: the EUROSTAR experience. J Vasc Surg 2002;35:461-73.
20. Verhoeven EL, Katsargyris A, Bekkema F, Oikonomou K, Zeebregts CJ, Ritter W, et al. Editor's choice - Ten-year experience with endovascular repair of thoracoabdominal aortic aneurysms: results from 166 consecutive patients. Eur J Vasc Endovasc Surg 2015;49:524-31.
21. Verhoeven EL, Katsargyris A, Oikonomou K, Kouvelos G, Renner H, Ritter W. Fenestrated endovascular aortic aneurysm repair as a first line treatment option to treat short necked, juxtarenal, and suprarenal aneurysms. Eur J Vasc Endovasc Surg 2016;51:775-81.
22. Wang SK, Gutwein AR, Gupta AK, Lemmon GW, Sawchuk AP, Motaganahalli RL, et al. Institutional

experience with the Zenith Fenestrated aortic stent graft. J Vasc Surg 2018;68:331-6.
23. Falkensammer J, Taher F, Uhlmann M, Hirsch K, Strassegger J, Assadian A. Rescue of failed endovascular aortic aneurysm repair using the fenestrated Anaconda device. J Vasc Surg 2017;66:1334-9.
24. Rodel SG, Zeebregts CJ, Huisman AB, Geelkerken RH. Multicenter Angulated Neck Study with the Anaconda study participants. Results of the Anaconda endovascular graft in abdominal aortic aneurysm with a severe angulated infrarenal neck. J Vasc Surg 2014;59:1495-501.
25. Lin J, Wang L, Guidoin R, Nutley M, Song G, Zhang Z, et al. Stent fabric fatigue of grafts supported by Z-stents versus ringed stents: an in vitro buckling test. J Biomater Appl 2016;28:965-77.
26. Rodel SGJ, Zeebregts CJ, Meerwaldt R, van der Palen J, Geelkerken RH. Incidence and treatment of limb occlusion of the Anaconda endograft after endovascular aneurysm repair. J Endovasc Ther 2019;26:113-20.
27. Burke LM, Conyers JM, Burke CT, Dixon R, Yu H, Kim J, et al. Incidence and clinical significance of renal infarct after fenestrated endovascular aortic aneurysm repair. AJR Am J Roentgenol 2017;208:885-90.
28. Saratzis A, Bath MF, Harrison S, Sayers RD, Mahmood A, Sarafidis P, et al. Long-term renal function after endovascular aneurysm repair. Clin J Am Soc Nephrol 2015;10:1930-6.
29. Saratzis A, Nduwayo S, Sarafidis P, Sayers RD, Bown MJ. Renal function is the main predictor of acute kidney injury after endovascular abdominal aortic aneurysm repair. Ann Vasc Surg 2016;31:52-9.
30. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. Adv Chronic Kidney Dis 2016;23:19-28.
31. Sveinsson M, Sobocinski J, Resch T, Sonesson B, Dias N, Haulon H, et al. Early versus late experience in fenestrated endovascular repair for abdominal aortic aneurysm. J Vasc Surg 2015;61:895-901.
32. Varkevisser RRB, O'Donnell TFX, Swerdlow NJ, Liang P, Li C, Ultee KHJ, et al. Fenestrated endovascular aneurysm repair is associated with lower perioperative morbidity and mortality compared with open repair for complex abdominal aortic aneurysms. J Vasc Surg 2019;69:1670-8.
33. Hwang D, Park S, Kim HK, Lee JM, Huh S. Reintervention rate after open surgery and endovascular repair for nonruptured abdominal aortic aneurysms. Ann Vasc Surg 2017;43:134-43.
34. Sarac TP, Clair DG, Hertzer NR, Greenberg RK, Krajewski LP, O'Hara PJ, et al. Contemporary results of juxtarenal aneurysm repair. J Vasc Surg 2002;36:1104-11.
35. Chong T, Nguyen L, Owens CD, Conte MS, Belkin M. Suprarenal aortic cross-clamp position: a reappraisal of its effects on outcomes for open abdominal aortic aneurysm repair. J Vasc Surg 2009;49:873-80.
36. Karthikesalingam A, Grima MJ, Holt PJ, Vidal-Diez A, Thompson MM, Wanhainen A, et al. Comparative analysis of the outcomes of elective abdominal aortic aneurysm repair in England and Sweden. Br J Surg 2018;105:520-8.
37. Rao R, Lane TR, Franklin IJ, Davies AH. Open repair versus fenestrated endovascular aneurysm repair of juxtarenal aneurysms. J Vasc Surg 2015;61:242-55.

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Supplementary Table (online only). Total number of included cases per participating site, and treated cases per year

	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Royal Derby Hospital, Derby, United Kingdom[a]	2	8	11	9	13	11	11	11	–	76
University of Calgary, Calgary, Canada	0	0	2	4	12	10	8	3	3	42
University Hospital Cologne, Köln, Germany[b]	–	–	–	–	–	–	–	–	–	58
Norfolk and Norwich University Hospitals, United Kingdom[a]	0	0	0	4	8	9	11	3	–	35
Rijnstate, Arnhem, The Netherlands	0	0	0	8	4	4	6	–	–	22
Universitätsklinikum Regensburg, Regensburg, Germany[a]	0	0	0	4	4	4	4	–	–	16
Medisch Spectrum Twente, Enschede, The Netherlands[a]	0	3	1	3	2	1	6	–	–	16
Evangelisches Krankenhaus Mülheim, Mülheim and der Ruhr, Germany[a]	0	0	0	4	4	9	0	–	–	17
University Medical Center Groningen, Groningen, The Netherlands	0	2	1	2	5	0	3	4	4	21
Marien-Hospital Witten, Witten, Germany[a]	0	1	7	2	2	0	5	–	–	17
Hull University Teaching Hospitals NHS Trust, Kingston upon Hull, United Kingdom	0	0	0	1	2	7	3	0	2	15

[a]The time for inclusion of cases extended from 2017 into 2018, the latest cases from early participating sites were therefore not available.
[b]The local ethical board did not approve supply of treatment date in one site, therefore year of treatment was not available.