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Does Aorto-Iliac Anatomy Affect Endovascular Aortic Aneurysm Repair Durability With The New Generation Endografts?

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Abstract

Introduction:

Endovascular aneurysm repair (EVAR) has become the main treatment for abdominal aortic aneurysm, accounting for more than 90% of all AAA treatments in recent studies. Despite of a significant enhancement in new generation endografts, EVAR durability is still questioned. Anatomical features of the AAA play a central role in EVAR success and they were assessed in many papers but only few tried to put them together.

The aim of this study was to evaluate all known anatomical features as potential risk factors for the freedom from reintervention (FFR) taking into account the new generation endografts currently in use.

Materials and Methods:

This study was a retrospective monocentric study including consecutive patients treated by standard EVAR from 2012 to 2018 in elective setting. Patients' clinical characteristics were collected. All currently reported anatomic factors including aortic neck and iliac arteries proprieties were examined and registered using the pre-operative AngioCT imaging (patients lacking imaging were excluded). Patients were followed up by Duplex scan every 6 months while AngioCT was performed in case of AAA growth or endoleak suspicion. The primary endpoint was to define the anatomical risk factors affecting the FFR after EVAR. The secondary endpoint was to define the outcomes of standard EVAR by new generation endografts.

Statistical analysis was performed using Kaplan-Meir survival function, Log-rank test and Cox-regression analysis for univariate and multivariate analysis. The p value $< .050$ (two tailed) was considered statistically significant.

Results:

A total of 653 patients treated by standard EVAR were included. The mean age was 75.6 ± 8 years with a male gender prevalence (90.2%). More than 96% of patients has ASA score ≥3. The mean preoperative AAA diameter was 57.3 ± 12 mm. The deployed endograft type was: 241 (36.9%) Cook-Zenith; 121 (18.5%) Medtronic Endurant; 184 (28.2%) Gore Excluder and 107 (16.4%) Vascutek Anaconda. Intra-operative adjunctive maneuvers were necessary in 177 (27.1%) cases, represented by 17 (2.6%) proximal cuff deployment and 160 (24.5%) iliac limb and axis stenting. The perioperative mortality was 1.4%, while systemic complications occurred in 61 (9.3%). The mean length of hospital stay was 4 ± 2 days. Within hospital stay, 18 (2.8%) patients required reintervention.

The mean follow-up was 34 ± 11 months. Patient survival at 6, 12, 24 and 48 months were 94.4%, 92%, 85.8% and 74.9%, respectively. Freedom from reintervention was 98.4%, 97.4%, 96% and 87.3% at 6, 12, 24 and 48 months, respectively.

Graft related complications occurred in 116 (17.8%) cases: 11 (1.7%) endoleak type Ia, 11 (1.7%) endoleak type Ib, 82 (12.6%) endoleak type II, 2 (0.4%) endoleak type III and 1 (0.2%) endoleak type V. Iliac limb occlusion occurred in 10 (1.5%) cases.

Univariate analysis showed that aortic neck diameter was a significant risk factor for FFR, as larger diameters correlated to higher incidence of reintervention (P=0.001). Aortic neck severe angulation >60° was highly correlated to the need for reintervention (P=0.001). The maximum aneurysm diameter was also associated with higher incidence of reinterventions (P<0.001). Infrarenal aortic length (IRAL) measured as distance between the most distal renal artery and the aortic bifurcation level, was associated with lower FFR (P=0.002). Similarly, the mean aorto-iliac length (MAIL) measured as the sum of distance between the most distal renal artery and iliac bifurcation in both sides divided by two, resulted a negative factor for FFR (P=0.002).

At the multivariate analysis of anatomical features, aortic neck diameter (HR 1.18; CI:1.02-1.37, P=0.03) and MAIL (HR 1.02; CI:1.01-1.04, P=0.01) were confirmed as significant risk factors for FFR.

Conclusion:

This was a retrospective, 7 years real-world study focused on the analysis of anatomic risk factors predisposing for graft-related reinterventions at mid-term. Patient survival and freedom from reintervention are satisfactory and compatible with other studies results. Aortic neck diameter and the mean aorto-iliac length resulted the main risk factors for FFR.

As a side finding, Statin therapy demonstrated a protective effect against iliac limb occlusion and persistent type II endoleak with higher rates of FFR.

The two proposed parameters (infrarenal aortic length and mean aorto-iliac length) resulting significant factors are not described before and need further investigations.

Does Aorto-Iliac Anatomy Affect Endovascular Aortic Aneurysm Repair Durability With The New Generation Endografts?

Introduction:

Background

Abdominal Aortic Aneurysm (AAA) is defined as an increase of the aortic diameter for more than 1.5 folds the normal diameter. Generally, for infra-renal aorta a 3 cm antero-posterior diameter is considered as an aneurysm. AAA prevalence increases with age and is highly influenced by smoking as the principal risk factor. The global prevalence was estimated at about 2275 per 100,000 population with a fourfold male versus female ratio [1,2].

AAA disease is usually clinically silent with catastrophic consequences in case of rupture, as it was associated with more than 80% mortality)[3]. Thus, population screening by abdominal ultrasonography (US), especially in men aged > 55 years is recommended by current guidelines[4]. The risk of aneurysm rupture was found correlated to the maximum diameter with a significant increase at the threshold of 5.5cm in men. The annual rupture risk of aneurysms measuring 5.5-6cm in diameter is about 9.4% and it increases up to 32.7% in aneurysms measuring > 7cm[5].

Traditionally, AAA is treated by open surgical repair which requires a large laparotomy to expose the abdominal aorta and iliac axises allowing hemostatic control by cross clamping and subsequent implant of a graft to substitute the diseased aortic tract. This technique is still recommended by current guidelines as a first choice in patients with a long life expectancy and fit for surgery[4]. However, open surgical repair is associated with a relatively high post-operative morbidity and mortality ranging between 3.0 – 7.5%[6-9]. Furthermore, as the general population is aging with enhanced life expectancy even in old and frail patients, less invasive treatment of AAA gained a crucial role. Endovascular aortic aneurysm repair (EVAR) is a mini invasive technique first proposed by Volodos et al.[10] and Parodi et al.[11] with good safety and effectiveness results. EVAR functioning concept is based on aneurysm sac exclusion from blood flow by means of catheter delivered endovascular graft (endograft) which realizes proximal and distal sealing and fixation. In figure 1, AngioCT images of commonly used endografts with supra and infra-renal fixation systems.

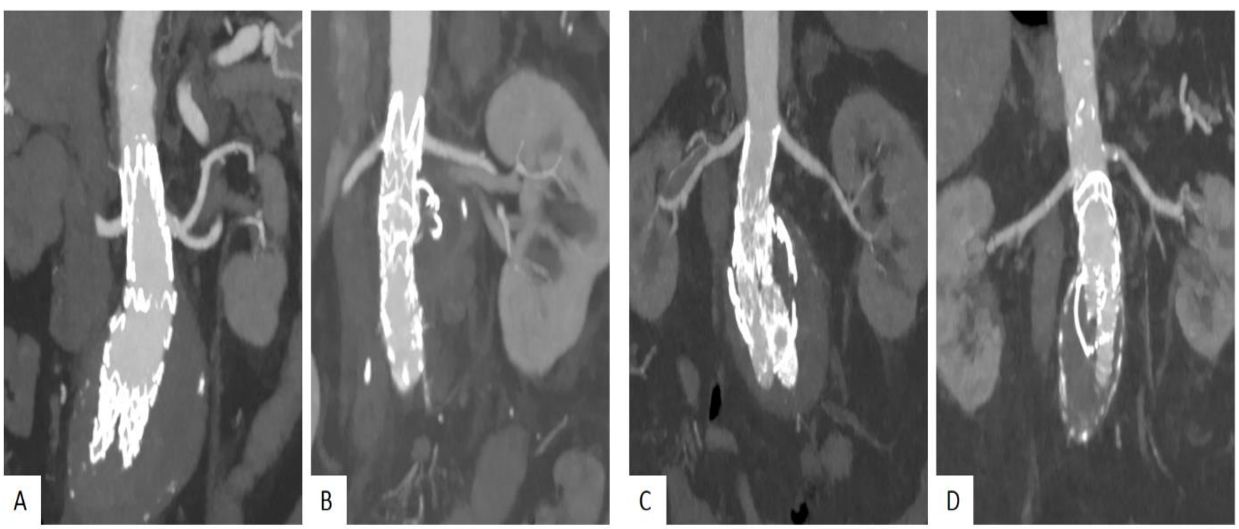

Figure 1: AngioCT images of four commonly used endografts with suprarenal fixation (A, B) and infrarenal fixation (C,D). A:Cook Zenith Alpha (Cook Medical, Bloomington, IN, USA), B:Medtronic Endurant (Medtronic, Minneapolis, MN, USA), C:Gore Excluder C3 (W.L.Gore & Associates, Flagstaff, AZ, USA), D:Vascutek Anaconda (Vascutek, a Terumo company, Inchinnan, UK).

Endograft biomechanical characteristics

The endograft functioning is dependent on the capacity to realize sealing at proximal and distal landing zones represented by healthy arterial segments. The proximal landing zone is called the aortic neck which is the healthy aortic segment between the most caudal renal artery and the aneurysm. The distal landing zone is usually represented by a healthy common iliac artery tract. Sealing is the capacity of the endograft to adhere to the healthy aortic wall preventing blood flow from passing in between. Further, the endograft must realize fixation which is the capacity to maintain position and resist columnar forces causing endograft migration.

The endograft is composed of 2 principal components, the stent which form the skeleton and the tissue. The majority of currently used endografts is bi-modular or tri-modular endografts (composed by a main body and 2 iliac limbs). Table 1 includes a brief description of the mainly used endografts.

The stent can be made by different materials with particular features each. Current materials are represented by stainless steel, Nitinol (alloy of nickel and titanium) and Crom cobalt alloy. Nitinol is the principal material used in recent endoprosthesis due to high flexibility, smaller diameter and high self-expanding capacity.

Currently available endografts are made with one of two tissue materials type; polytetrafluoroethylene (PTFE) or polyethylene terephthalate (PET; as Dacron). These materials are also used in open surgery with good results in terms of biocompatibility, patency (low thrombogenicity), endurance and low permeability.

Table 1: The main EVAR endografts types, characteristics and use requirements.

EVAR device type	**Range for Neck diameter (mm)**	**Range for Neck length (mm)**	**Maximum treatable neck angulation (°)**	**Range for Iliac artery diameter (mm)**	**Range for Iliac artery length (mm)**	**Stent material type**	**Graft material**	**Number of modules**	**Supra-renal fixation**
Zenith® (Cook Medical Technologies, USA)	18-32	15	60	7.5-20	10	Stain-less steel	PET	3	Yes
Endurant® (Medtronic Vascular, USA)	19-32	10	60	8-25	15	Nitinol	PET	2	Yes
Anaconda® (Terumo, Vascutek, UK)	17.5-31	15	90	8.5-21	20	Nitinol	PET	3	No
Excluder® (W.L. Gore & Associates, USA)	19-32	15	60	8-25	10	Nitinol	PTFE/FEP	2	No
AFX® (Endologix, USA)	18-32	15	60	10-23	15	CCA	PTFE	1	Yes
Incraft® (Cordis Corporation, USA)	17-31	10	60	7-22	10	Nitinol	PET	3	Yes
Ovation® (Trivascular, USA)	16-30	10	60	8-25	10	Nitinol	PTFE	3	Yes

Current EVAR indications

Asymptomatic AAA of 5.5cm in diameter in men and 5cm in women should be considered for treatment[4]. Further, guidelines recommend treatment in case of rapid growing AAA defined as a diameter increase rate of 1 cm per year. On the other hand, symptomatic AAA with smaller diameters should be treated promptly.

Currently, EVAR represents the technique of choice in case of moderate/high risk patients with acceptable life expectancy and a suitable anatomy, while open repair remains the technique of choice in fit patients with long life expectancy in elective setting.

However, in case of emergent treatment for ruptured AAA with a suitable anatomy, endovascular treatment represents the first choice approach as it was found associated with a significantly lower rate of peri-operative mortality compared to open approach[12].

Anatomical suitability for EVAR

The gold standard imaging to evaluate AAA anatomy is a thin slice (ideally 1mm) computed tomography angiography (CT Angio) to be performed before EVAR planning. The CT Angio should then be processed using dedicated softwares with the possibility to perform a center lumen line analysis allowing precise diameters and lengths measurements.

There are specific criteria to consider in the anatomy and morphology of the aortic neck and iliac arteries to evaluate feasibility of endovascular repair. These criteria are detailed by manufacturers of the different endografts within the instruction for use (IFU). The IFU criteria are based on in vitro experiments to estimate EVAR efficacy and durability. Anatomical aspects to consider such as neck width, length, angulation and the presence of calcification or thrombosis in the neck affect directly EVAR proximal sealing and fixation capacity. Iliac artery diameter, length angulation and iliac arteries calcification and navigability affect distal sealing and implantability of the endograft (table 1).

Endovascular compared to Open aneurysm repair

Considering the good EVAR efficacy and mini invasiveness it became frequently used to treat AAA around the world with a numerical tendency for EVAR indication over open repair. In the USA, EVAR treatment reached more than 75% in all treatments for AAA in the last years[13].

To answer the question about which approach is best many studies were performed. In particular, four randomized controlled studies gave solid data and contributed to our current knowledge[7,8,14,15].

Starting in the UK where the EVAR-1 trial was performed, followed by DREAM trial performed in Netherlands and Belgium, ACE trial in France and OVER in the USA, all the studies demonstrated early benefit of EVAR over open in perioperative mortality. A meta-analysis of individual patient data including the above mentioned trials was performed by Powel et al.[16] which concluded by confirming EVAR advantage in terms of mortality, in the first postoperative 6 months, while no significant difference was detected at 3 years.

In all studies EVAR was associated with higher reintervention rate compared to open repair and the most reported EVAR complication was endoleak type II.

EVAR complications and reintervention

EVAR treatment is effective but it is characterized by higher rates of reinterventions to deal with different types of complications encountered during the follow-up. Reintervention rate was reported about 20% with associated increased mortality[6]. These complications can be divided into endograft related and intervention related.

The intervention related complications are:

- Surgical /percutaneous access complications such as artery dissection/thrombosis, hematoma, pseudoaneurysm and surgical access infection. The incidence of this type of complication is about 3%[17].
- Myocardial infarction was reported in about 7-9% of cases[18].
- Renal function deterioration mainly due to contrast medium was reported in 13% of cases[18].

The endograft related complications are:

1. Endoleaks: The most frequent complication of EVAR and a cause for reintervention is represented by endoleaks[19]. The definition of an endoleak is the persistence of aneurysm sac perfusion which may lead to diameter growth and AAA rupture[20].

The sac perfusion can occur due to different mechanisms described as different types of endoleaks[20]:

- Endoleak Type I: Is considered as a serious complication associated with high risk of aneurysm rupture due to the direct sac perfusion meccanism. It is caused by the lack of sealing at proximal (Typ Ia) or distal (Type Ib) landing zones.
- Endoleak Type II: It is the most frequent type of endoleaks. In this type, the sac perfusion is determined by patent lumbar and/or inferior mesenteric arteries that continue to fill the aneurysm sac.
- Endoleak Type III: This endoleak describes structural failure of the endograft. Sac perfusion can originate between endograft components in the overlapping segments (e.g. between mainbody and iliac limb), known as type IIIa or it can occur due to endograft perforation, known as type IIIb. The reported incidence was 3-4.5% in older studies[21].

- Endoleak Type IV: It is a type of endoleak observed in old generation endografts which were characterized by fabric porosity.
- Endoleak Type V: Called also Endotension and it describes a continuous sac growth without identified origin. It could be attributed to inadequate diagnostic sensibility.

2. Endograft migration. This type of complication occurs when the endograft fails to maintain the initial deployment position due to lack of fixation in proximal or distal landing zones or it can be associated with the aneurismatic disease progression causing aortic neck or iliac arteries dilation and subsequent loss of sealing/fixation mechanism. Endoleak type I is the direct manifestation of this type of complication.

3. Ischemic complications:

- Acute limb ischemia due to endograft iliac limb occlusion or endograft thrombosis with incidence of 5-7%[22].
- Bowel ischemia due to inferior mesenteric artery occlusion or hypogastric arteries coverage is a rare but highly lethal complication with incidence of about 1-3%[23].
- Spinal cord ischemia is rare in EVAR with low incidence (0.21%)[24] but still a serious complication to take into account when informing the patient about treatment risks.
- Renal artery accidental coverage

4. Endograft infection. It represents a rare complication (1%)[25], sometimes associated with an aorto-enteric fistula[26]. Treatment is based on total endograft explantation with high perioperative morbidity and mortality.

The aim of this study was to analyze different anatomical factors associated with the EVAR durability in new generation endografts.

Materials and methods:

Study design and population:

This was a single center, retrospective study of a prospectively collected data on patients who underwent endovascular treatment of infrarenal abdominal aortic aneurysm by EVAR. The study included all consecutive patients treated between 2012 and 2018, as they were treated by currently available endografts. Demographic and clinical characteristics of all patients were collected as shown in table 2.

All patients were treated based on current guidelines indications by bi-trimodular EVAR including supra- or infrarenal fixation endografts.

Patients treated by a non-standard aorto-bi-common iliac artery EVAR, such as aorto-uniliac, chimney, hypogastric embolisation/coverage or iliac branched endografts were excluded. In addition, patients treated in emergency settings for AAA rupture were also excluded.

Imaging and anatomical features:

All patients underwent pre-operative thin-slice CT angiography of thoraco-abdominale aorta. The CT angiograms were analysed in 2D and 3D reconstructions to evaluate morphology and angulations in the pararenale, infrarenal aorta and iliac vessels. Diameters of aortic neck and iliac arteries, lengths and angulations were evaluated on a center-lumen line analysis using a dedicated software (3mensio, Vascular Imaging, Bilthoeven, The Netherlands). For landing zones, the presence of thrombus or calcification was registered as severe in case > 50% of the circumference was affected. Chaikof's criteria[27] were used to classify the severity of aortic neck and iliac arteries anatomical features including length, diameter, thrombus, calcification, occlusione and tortuosity. Furthermore, the aortic neck shape was considered as cylindrical, taper (diameter gradual reduction by 2mm at the first 1 cm distal to inferior renal artery) or reversed taper (diameter gradual increase by 2mm at the first 1 cm distal to inferior renal artery).

Table 2: Patients demographics and clinical characteristics.

Patient demographics	**N = 653**
Age	75.6 ± 7
Male gender	589 (90.2%)
Patient comorbidities	
Hypertension	535 (81.9%)
Dyslipidemia	397 (60.8 %)
Chronic obstructive pulmonary disease	244 (37.4%)
Active smoker	190 (29.1%)
Obesity	111 (17%)
Coronary artery disease	208 (31.9%)
Atrial fibrillation	77 (11.8%)
Cerebro-vascular Insufficiency	79 (12.1%)
Peripheral arterial occlusive disesase	48 (7.4%)
Diabetes mellitus	103 (15.3%)
Chronic renal failure	252 (38.6%)
Dialysis	7 (1.1%)
ASA Classification	
ASA 3	466 (71.4%)
ASA 4	128 (19.6%)

Endografts

The endografts used were Cook Zenith Flex/Cook Zenith Alpha (Cook Medical, Bloomington, IN, USA), Medtronic Endurant (Medtronic, Minneapolis, MN, USA), Gore Excluder C3 (W.L.Gore & Associates, Flagstaff, AZ, USA) and Vascutek Anaconda (Vascutek, a Terumo company, Inchinnan, UK). Treatment according to the instructions for use (IFU) or out of IFU was taken into account.

Follow-up

All patients were followed at three, six, and 12 months, and yearly thereafter by Duplex ultrasonography. At each control, accurate evaluation of sac diameter, renal arteries and hypogastric arteries patency, presence of endoleak were evaluated. Endograft patency and position were examined. In case of endoleak detection, an ultrasound-contrast enhanced US was performed to define the endoleak type. In all cases of complications and sac diameter growth a CT Angio was performed.

Endpoints

The primary endpoint was to evaluate the impact of the pre-operative anatomical features of the aortic neck and iliac artery landing zones on the risk of endograft failure at mid-term follow-up in patients treated by new generation EVAR. Endograft failure was defined as a need for reintervention for endograft related complication, excluding graft infection. The post-operative time period without the need for reintervention due to graft related complications is called Freedom from Reintervention (FFR).

The secondary endpoint was to define the outcomes of standard EVAR by new generation endografts based on current indications in a high volume vascular surgery center.

Statistical analysis

Descriptive and frequency analysis were performed. Continuous variables were expressed as mean ± standard deviation and categorical variables as number (percentage). Chi square and fisher's exact tests were used. Kaplan–Meier time to event analysis was used to evaluate survival and freedom from reintervention (FFR). Log-Rank test was used to compare Kaplan-Meir time curves. In this analysis, reintervention for endograft infection was excluded. Cox linear regression was used for univariable analysis, reporting β coefficients and 95% confidence intervals (CI). A p value < .050 (two tailed) was considered statistically significant. Factors having statistical significance (p < .050) in the univariable analysis were to be entered into a Cox multivariable model. The statistical analysis was performed using SPSS Statistics software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY).

Results:

In the study period between january 2012 and december 2018, a total of 653 elective EVAR were included. The mean age was 75.6 ± 8 years with a male gender majority 587 (90.2%) patients. The population was characterized by a high American Society of Anesthesiologists (ASA) score, as more than 96.2% of patients had a score of ≥3. The mean preoperative

AAA diameter was 57.3 ± 12 mm. Clinical pre-operative characteristics are reported in table 2. In 231 (35.4%) of treated patients there was at least 1 criteria of aortic neck severity. Anatomical caracteristicas are summarized in table 3.

Procedure and Perioperative Results

Locoregional anesthesia was used in 378 (57.9%) procedures while general anesthesia was used in 235 (36%) cases. Aorto-bi-iliac endografts were implanted in 648 (99.2%) cases, while an aorto-aortic tubular endograft was deployed in 5 (0.8%) patients. Suprarenal fixation was used in 362 (55.4%) cases and infra-renal fixation used in 291 (44.6%) cases. The deployed endograft type was as follows: 241 (36.9%) Cook Zenith Flex/Low profile/Alfa; 121 (18.5%) Medtronic Endurant; 184 (28.2%) Gore Excluder C3/conformable and 107 (16.4%) Vascutek Anaconda. In 60 (9.2%) cases a total percutaneous procedure was adopted and a percutaneous closure system was used for hemostasis at the end of procedure.

Aneurysm sac embolization by coils was performed in 182 (27.9%) cases presenting risk factors for type II endoleak as described by Mascoli et al.[28]

Intra-operative adjunctive maneuvers were necessary in 177 (27.1%) cases, represented by 17 (2.6%) proximal cuff deployment and 160 (24.5%) iliac limb and axis stenting.

At the end of the procedure an intraoperative control angiography detected 2 (0.3%) cases of endoleak type IIIa at the overlapping segment between iliac limb and the gate, treated by relining and 143 (21.9%) type II endoleaks. In one case, a type Ia endoleak verified due to main body infolding with a suprarenal fixation device. This case was treated 3 days later by surgical conversion and endograft removal without significant perioperative complications.

A total of 166 (25.4%) patients were transferred to the ICU for the postoperative observation period with a mean of ICU stay time of 1.2 days.

Table 3: Aorto-iliac anatomical features of treated patients.

Anatomic Feature	**Mean± std. deviation/ Frequency (%)**
Aortic neck diameter	23.6 ± 3 mm
Aortic neck length	24 ± 10 mm
Patients with wide neck > 28mm	66 (10.1%)
Patients with short neck < 15mm	160 (24.5 %)
Taper neck	13 (2%)
Reversed taper neck	70 (10.7%)
B-Angle > 60°	124 (19%)
Severe neck calcification > 50%	17 (2.6%)
Severe neck thrombosis > 50%	84 (12.9%)
Chaikof criteria for aortic neck	
- 1	168 (25.7%)
- 2	108 (16.5%)
- 3	231 (35.4%)
Maximum aneurysm diameter	57.3 ± 12 mm
Infrarenal aortic length (IRAL)	110 ± 23 mm
Right common iliac diameter	16.6 ± 8 mm
Left common iliac diameter	15.3 ± 7 mm
Right common iliac length	59.2 ± 27 mm
Left common iliac Length	59.7 ± 25 mm
Mean aorto-iliac length (MAIL)	169.7 ± 25 mm
Severe iliac calcification	33 (5.1%)
Severe iliac tortuosity	45 (6.9%)
Short iliac arteries < 2cm	10 (1.5%)
Inferior mesenteric artery patency	254 (38.9%)
Number of patent lumbar arteries	2.9 ± 2.3
Number of patent accessory renal arteries	0.2 ± 0.45
Hypogastric artery occlusion	36 (5.6%)

In-hospital complications and reintervention

The perioperative mortality was 1.4%. Nine patients died due to: acute myocardial infarction in 4 cases, respiratory insufficiency in 2 cases, multiorgan failure in 1 case, gastric massive hemorrhage in 1 case and cerebral post-traumatic (falling) hematoma in 1 case.

Systemic complications occurred in 61 (9.3%) patients: cardiac arrhythmia (including atrial fibrillation) in 5 cases, renal function deterioration in 6 (0.9%) cases with 1 case who needed hemodialysis treatment, pleural effusion in 12 cases, anemia in 9 cases, acute lower limb ischemia treated by thromboembolectomy in 3 cases, acute femoral artery thrombosis in 2 cases treated by patch plasty, microembolization to lower limb treated conservatively in 1 case, pneumonia in 13 cases, surgical access site hematoma and lymphocele in 10 cases.

Endograft related complications detected at the Duplex scan before discharge, occurred in 4 cases (0.6%) including: 1 case of type Ib endoleak treated by iliac limb extension; 1 case of type IIIa treated by relining; 1 case of iliac limb occlusion treated by mechanic thrombectomy and relining; 1 case of renal artery stenosis caused by endograft compression on the plaque at renal artery ostium treated by renal artery stenting.

The mean length of hospital stay was 4 ± 2 days. Within hospital stay, 18 (2.8%) patients required reintervention.

Early and midterm results

The mean follow-up was 34 ± 11 months. Patient survival at 6, 12, 24 and 48 months were 94.4%, 92%, 85.8% and 74.9%, respectively. Freedom from reintervention(FFR) was 98.4%, 97.4%, 96% and 87.3% at 6, 12, 24 and 48 months, respectively (figure 2). A total of 37 (5.7%) reinterventions were performed to treat graft related complications. The treatment type in relation to the type of endoleak is specified in the table 4. In 10 cases (1.5%) an open conversion was performed with EVAR explant. The main cause of graft failure and the need for open conversion was endoleak type II and type Ia (4 and 3 cases, respectively).

Table 4: Graft related complications and type of reintervention.

Graft related complication	**Frequency (%)**	**Reintervention approach**	**Main Reintervnetion procedure type**	**Endograft explant**
Endoleak type 1a	11 (1.7%)	72.7% endovascular	Proximal cuff with/without chimney (54.5%)	3 (27.3%)
Endoleak type 1b	11 (1.7%)	81.8% endovascular	Iliac limb extension (54.5%)	1 (9%)
Endoleak type II	82 (12.6%)- 6 (1%) cases needed reintervnetion	67% open	Endograft explantation	4 (67%)
Endoleak type III	2 (0.4%)	100% endovascular	Relining	0 (0%)
Endotension	1 (0.2%)	100% open	Endograft explantation	1 (100%)
Iliac limb occlusion	10 (1.5%)	50% open	Fem-fem cross-over bypass (50%)	1 (10%)

Graft related complications occurred in 116 (17.8%) cases as follows: 11 (1.7%) endoleak type Ia, 11 (1.7%) endoleak type Ib, 82 (12.6%) endoleak type II, 2 (0.4%) endoleak type III and 1 (0.2%) endoleak type V. Iliac limb occlusion occurred in 10 (1.5%) cases.

Risk factors for FFR:

At univariate analysis of risk factors for FFR, some pre-operative anatomical features resulted significantly. Aortic neck diameter was a significant risk factor for FFR, as larger diameters correlated to higher incidence of reintervention with a HR of 1.2 (P=0.001). Aortic neck severe angulation >60° was highly correlated to the need for reintervention with a HR of 3 (P=0.001). The maximum aneurysm diameter was also associated with higher incidence of reinterventions with a HR of 1.04 (P<0.001). Another two particular anatomical features associated with lower FFR were the infrarenal aortic length (IRAL) measured on segmented imaging between the most distal renal artery and the aortic bifurcation level and the mean aorto-iliac length (MAIL) arteries (the sum of distance between the most distal renal artery and iliac bifurcation in both sides divided by two). IRAL was associated with a HR of 1.02 (P=0.002) while MAIL was associated with a HR of 1.03 (P=0.002). In addition, the number of patent accessory renal arteries originating from aneurysm sac and aortic neck was a significant risk factor for reintervention (HR 1.79 , P=0.03). On the other hand, other important anatomical features for EVAR functionality such as aortic neck length and iliac arteries diameter did not show significant association with the FFR at the univariate analysis (P=0.10 and P=0.14, respectively).

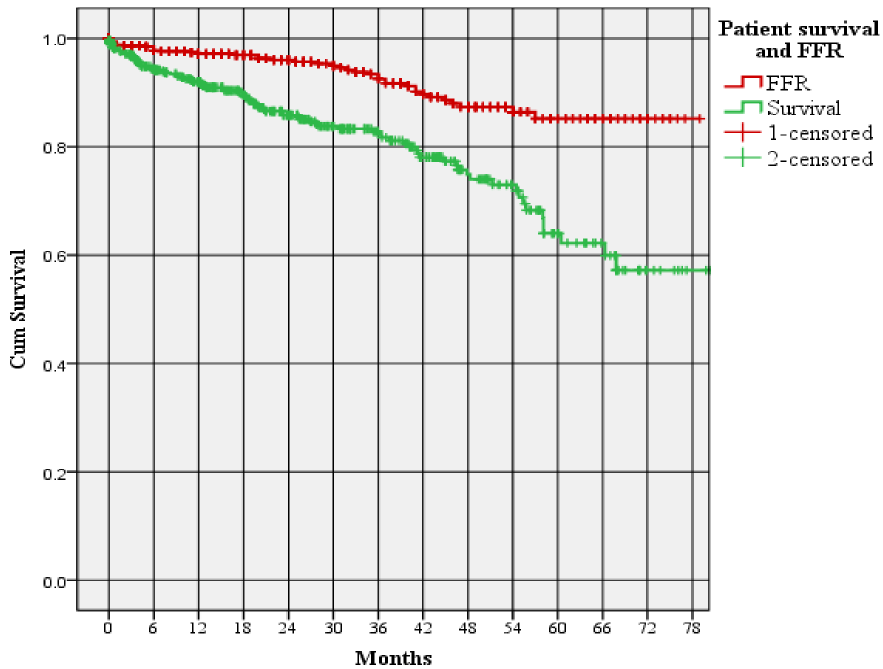

Figure 2: Patients survival and Freedom From Reintervention (FFR) Kaplan-Meier survival curves.

Analyzing non-anatomical features at univariate analysis, oral anticoagulation therapy was a significant risk factor for the FFR with a HR of 2.7 (P=0.01). Statin therapy resulted in a significant protective factor against reintervention with a HR of 0.45 (P=0.05).

At the multivariate analysis of anatomical features, aortic neck diameter (HR 1.18; CI:1.02-1.37, P=0.03) and MAIL (HR 1.02; CI:1.01-1.04, P=0.01) were confirmed as significant risk factors for reintervention.

As many literature reports indicated aortic neck diameter of 28mm as a risk factor, it was used in this analysis. The log-rank test (figure 3) shows a significant increase in risk of FFR loss in patients with an aortic neck diameter of 28mm or greater with P=0.005.

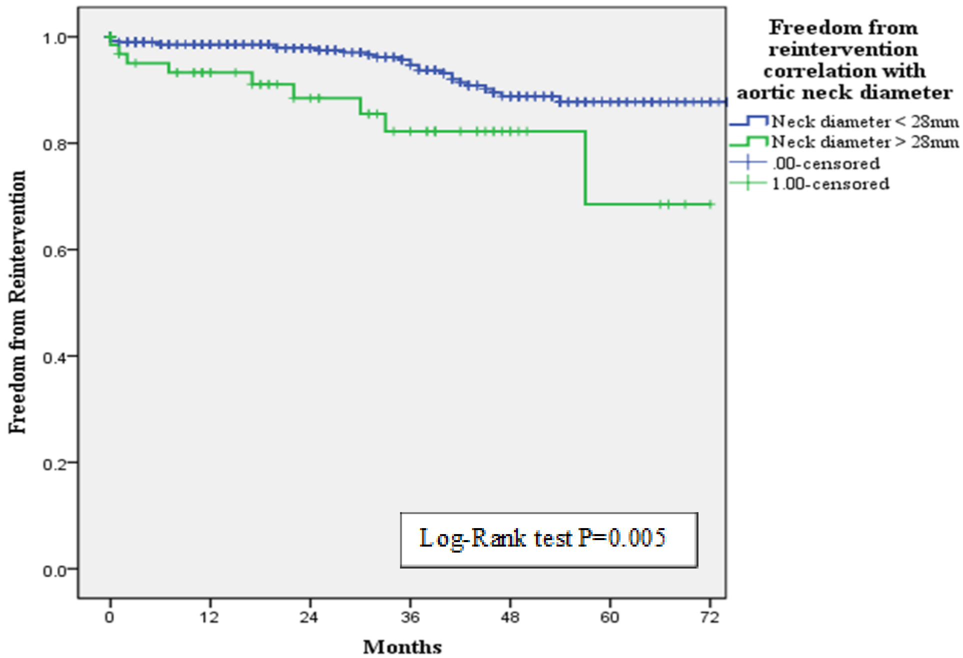

Figure 3: Aortic neck diameter effect on freedom from reintervention.

To better define MAIL and a cut-off value, a ROC curve analysis was performed with an area under the curve of 0.65 (P=0.013). The cut-off value was found to be 170mm with 73.1% sensitivity and 51.2% specificity.

Applying the cut-off value a Log-Rank test was run with a significant difference between the groups, with P=0.006 (figure 4).

As the major causes for reintervention are represented by endoleak type IA (29.7%), endoleak type II (21.6%) and iliac limb occlusion (27%) a specific analysis of factors leading to each type of complication was performed.

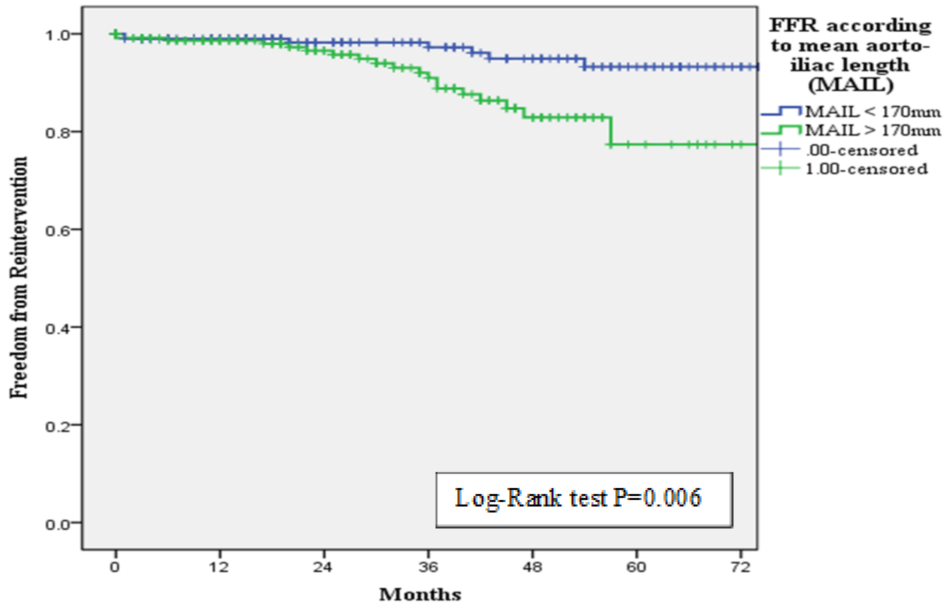

Figure 4: Mean aorto-iliac length at the cut-off value effect on freedom from reintervention.

Risk factors for Endoleak type IA (EL1A):

Aortic neck length was associated with incidence of EL1A. At student-t test, the mean aortic neck length of patients who developed endoleak during follow-up was 12.5mm compared to a mean length of 23.7mm in patients who did not present this type of complication (P=0.04).

The maximum aneurysm diameter was larger in patients who developed EL1A with a mean of 74.5mm compared to 57.2mm in patients who did not (P=0.005).

Longer IRAL was associated with a higher incidence of EL1A (P=0.045) with a mean IRAL of 136.7mm compared to 109.8mm in patients who did not develop the endoleak.

In addition, MAIL was a significant risk factor for EL1A (P=0.003) as the mean MAIL in patients who presented the endoleak was 212mm compared to 169.4mm in patients who did not.

Risk factors for Endoleak type II:

The main risk factors for EL type II were the patency of inferior mesenteric artery (P=0.03) and the number of patent lumbar arteries (P=0.047). The mean patent lumbar arteries associated with endoleak type II was 3.5 compared to 2.9.

Risk factors for Iliac Limb Occlusion (ILO):

The maximum aneurysm diameter was associated with the risk of ILO (P=0.03), as a mean diameter of 65.5mm was associated with ILO compared to a mean diameter of 57.1mm.

The analysis of the non anatomic factors showed that Statin therapy exerted a protective role against ILO (P=0.008).

Discussion:

In this retrospective, monocentric study we analyzed all consecutive patients treated for AAA by standard EVAR between 2012 and 2018. The goal of the study was to assess, based on real world data, the role of anatomic features on the behaviour of EVAR during the followup and their correlation with reintervention incidence. In our center, EVAR indication rather than open treatment is based on patient clinical characteristics and anatomical suitability as suggested by current european guidelines[4]. In the treated population more than 96% of patients presented an ASA score equal or higher than 3 which may represent a high percentage of unfit for surgery patients.

In this group, four types of commercially available endografts were used with a similar proportion between suprarenal and infrarenal fixation technology. In the majority of cases the specific IFU were observed. During the index procedure, adjunctive maneuvers were needed in about 27% of cases, mainly due to iliac limb kiniking and stenosis requiring intra-operative stenting (90% of cases). This could be related to our approach for treating iliac limb kinking and stenosis preventively in order to avoid ILO[29]. Other studies reported similar incidence of intraoperative adjunctive maneuvers associated with standard EVAR ranging between 26% and 29.2% and thus, underlining the need for particular attention to details in order to prevent complications [30-32].

The perioperative mortality was 1.4% with no case of aneurysm related mortality. This incidence is similar to results reported by Paravastu et al.[18] in a Cochrane systematic review and other studies[33]. Perioperative complications were mainly systemic accounting for about 9% of cases, composed of cardiac and pulmonary complications. Graft related perioperative complications represented by endoleaks type 1b and III and limb occlusion occurred rarely (0.6%) and were managed successfully by endovascular means.

The overall patient survival at 4 years was about 75%. Data from EVAR-1 and DREAM trials reported overall patient mortality at 4-year of 15.8% and 37% at long-term follow-up [14,15]. As mentioned before, Powel et al.[16] at the Meta Analysis of major EVAR vs open trials concluded that EVAR was characterized by lower short-term mortality but at long term this benefit was lost. Our study reports the mid-term results only as we intended to examine currently available endografts behaviour.

The FFR at 4 years in this study was 87%, which compares favourably with an 81% (at 5-year) reported by Wanken et al.[34] in their meta-analysis of long-term reintervention rates. Considering recent papers reporting new generation devices reintervention rates, similar results were found. Abdulrasak et al.[35] reported a FFR of 81% at 5-year using Cook-Zenith device, while Oliveira-Pinto et al.[36] reported a FFR of 78.6% at 4-year using Medtronic-Endurant device. The main causes for reintervention were Endoleak type I, type II and iliac limbs complications.

The total reinterventions to treat graft related complications in this study accounted for about 6% including open surgical conversion needed in 1.5% of cases, mainly due to persistent endoleak type II and I. Accordingly, a recent multicenter study assessing late open conversion of EVAR the main indication was endoleak type I and II together with graft infection [37].

The present study was focused on anatomic risk factors leading to endograft failure and the need for reintervention. Conventional anatomic risk factors were taken into consideration. In a recent paper reporting an expert opinion in a Delphi consensus process [38], authors underlined the significant risk factors as hostile aortic neck in presence of short neck (less than 10mm), neck angulation (>60°), wide neck (>28mm) and conical neck. Other studies reported maximum AAA diameter and common iliac arteries diameter as significant risk factors for reintervention [39,40]. The quality of aortic neck considering calcification and length were also reported as significant risk factors [41]. All these factors were analyzed in our study, however, the multivariate analysis confirmed a significant impact for aortic neck diameter and MAIL. This latter parameter is probably related to endograft stability and the risk of endoleak type Ib. Iliac arteries length was previously reported as a risk factor for type Ib endoleak by Mascoli et al.[28] and other papers[42]. However, we propose this single parameter as a reasonable method to express the total aortic and iliac length that endograft should cover and use for sealing.

A particular finding in this study was the role of an unusual anatomic parameter representing the infrarenal aortic length (IRAL) which was found associated with higher incidence of reintervention. This parameter was not reported in literature (to our knowledge) but could be reasonable as longer aorta is also a larger aneurysm volume and may contain more lumbar arteries. Further, the endograft main body may lose stability when longer segments need to be covered. In addition, longer prosthesis may represent a higher thrombosis risk.

Another finding of this study was the effect of patent accessory renal arteries which was found to be correlated to higher reintervention rate. The reason could be a direct type II endoleak where the accessory renal artery supplies the aneurysm sac or it can behave as the outflow for lumbar arteries contributing to maintain endoleak type II. A case-control study by Maglor et al.[43] accessing the impact of accessory renal arteries had found a correlation with persistent endoleak type II. However, in our study, the specific analysis of type II endoleak risk factors did not confirm statistical significance of patent accessory arteries.

Interestingly, statin therapy was found to have a significant protective effect with higher FFR rates. In two recent meta-analysis, statin therapy was found correlated to higher patient survival in perioperative and long-term after treatment for AAA and lower aneurysm growth rates [44,45]. Furthermore, a previous study by our group, reported endoleak type II regressione and aneurysm sac shrinkage in patients under Statin therapy[46]. In addition, the analysis of specific risk factors for iliac limb occlusion, found Statin therapy a protective factor against ILO. This finding is in accordance with the study by Choi et al[47]. with similar findings, in which authors suggested a mechanism of Statin therapy acting on endothelial cells and inhibiting stenosis at the distal edge of the stent graft. Statin therapy role in endograft patency is not well established and lacks literature data, however it represents a very interesting field for future studies.

Another observation of the current study is the association of oral anticoagulation therapy (OAT) with a higher rate of reintervention. Similar findings were reported by Lazarides et al.[48] where higher rates of any type of endoleak was observed in patients on OAT.

Specific risk factors analysis for EL1A revealed the significance of classically reported factors such as aortic neck length and maximum aneurysm diameter. The latter was reported in many studies including scores and models for EVAR complications prediction as the St George's Vascular Institute (SGVI)[40] score and Endovascular Risk Assessment Model (ERA)[49]. On the opposite, new elements were found significant risk factors for EL type 1a, which are IRAL and MAIL with hypothetical rationale but no supporting literature data.

Current study identified the AAA diameter as a risk factor for ILO, while other risk factors traditionally reported for ILO did not result significantly in this analysis. Larger aneurysms could be at risk for limb occlusion due to geometrical disposition of the endograft and the risk of a more significant sac shrinkage and subsequent graft kinking and occlusion [50,51].

Study limits

The main limitation of this study was the retrospective nature with the connected issues of uncompleted or unclear data entering statistical analysis. The other limitation is a relatively short mean follow-up as data on EVAR nowadays require a long-term outcomes analysis.

Conclusion:

As endovascular aortic repair for AAA has become the prevalent treatment especially in consideration of population aging and increasing frailty, it is essential to optimize EVAR results. This 7 years real-world study focused on the analysis of anatomic risk factors predisposing for graft-related reinterventions at mid-term. Patient survival and freedom from reintervention are satisfactory and compatible with other studies results. Aortic neck length, AAA maximum diameter, infrarenal aortic length and the mean aorto-iliac length resulted in significant risk factors for endoleak type Ia. AAA maximum diameter represented a risk factor for iliac limb occlusion while lumbar and inferior mesenteric arteries were significant risk factors for endoleak type II. Risk factors for overall freedom from reintervention were the aortic neck diameter and the mean aorto-iliac length.

As a side finding, Statin therapy demonstrated a protective effect against iliac limb occlusion and persistent type II endoleak with higher rates of FFR.

The two proposed parameters (infrarenal aortic length and mean aorto-iliac length) resulting significant factors are not described before and need further investigations.

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الحمد لله رب العالمين.

أنا ما أنا عليه الآن بفضل التوجيه والصبر وتضحيات والديّ لسنوات طويلة. هذه الرسالة مكتوبة بالحروف والكلمات الأولى التي علمتها لي عزيزتي والدتي في سن الخامسة. أهدي لها كل حبي وكل إنجازاتي. أنا حيث أنا الآن بسبب تشجيع أبي الغالي ونصيحته ، أكرس واهدي له هذه الأطروحة.

أنا ممتن لزوجتي الحبيبة، لدعمها لي باسمرار وحماسها وتفانيها من أجل عائلتنا. لأبنتي الجميلة تذهب دعواتي القلبية من أجل مستقبل جميل وسعيد.

إلى أخواتي وإخوتي الأعزاء، امتناني الكبير للحب والاهتمام اللذان تعطوني دوما ، على النصيحة والفرح اللذين لا ينتهيان.

لقد تشرفت بكوني أحد طلاب جامعة بولونيا ألما ماتر ستوديوروم ، وقد حظيت بفرصة التعلم والعمل والنمو ضمن فريق جراحة الأوعية الدموية في بولونيا. أود أن أعرب عن امتناني الخاص لـ:

الأستاذ البروفيسور ماورو غارجيولو، مشرفي ، للإلهام والإرشاد والتعليم المستمر. موقفه العلمي وتفاؤله. تصميمه على التغلب على المواقف الصعبة بالمعرفة والصبر الذي يعرف كيف يقوده في الفريق بأكمله.

الأستاذ البروفيسور الفخري أندريا ستيلا، لإيمانه بقدراتي و دعمي. أستاذ عظيم لديه أفكار ملهمة ونية ثابتة لتحفيز وتثقيف الأجيال الشابة.

الاستاذ البروفيسور جيانلوكا فاجيولي، لتعاليمه وتفانيه في العلم. قدرته الخاصة على إظهار الزوايا الخفية داخل الحقائق وبين الخطوط.

جميع زملائي من فريق جراحة الأوعية الدموية ، الذين تعلمت معهم ومنهم في هذه السنوات ، ولكن أيضًا أقمنا روابط قوية من الصداقة والاحترام المتبادل.