Aus der Klinik für Gefäß- und Endovaskularchirurgie

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Die endovaskuläre Versorgung der Pathologien der Aorta abdominalis bei Patienten mit einer schmalen Aortenbifurkation

Dissertation

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For my parents who helped me everytime

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Zusammenfassung

Das Ziel der Studie war die Evaluation des Patientenoutcomes nach endovaskulärer Therapie von Aortenpathologien mit einer sehr schmalen Aortenbifurkation (AB) mittels AFX Stentgraft (AFXsg) (Endologix, Irvine, CA, USA). Der schmale Durchmesser der AB gehört zu den anatomischen Limitationen der endovaskulären Therapien. Der AFXsg ist ein „unibody" Stentgraft der direkt auf der AB sitzt und somit nicht die Passage von zwei Schenkeln im distalen infrarenalen Aortenabschnitt benötigt. Ein Durchmesser der AB ≤18 mm ist ein limitierender Faktor für konventionelle moduläre Endoprothesen und ist mit einem erhöhten Risiko für Schenkelobstruktionen/-verschlüsse assoziiert.

Für die klinisch-retrospektive Datenanalyse wurden medizinische Akten von 35 Patienten mit einem Durchschnittsalter von 78.3 +/- 7.2 Jahren ausgewertet, die aufgrund eines abdominalen Aortenaneurysmas (AAA) (48.6 %) und /oder eines penetrierenden Aortenulcus (PAU) (51.4%) bei schmaler AB (≤ 18mm) zwischen Januar 2013 und Mai 2020 in vier zertifizierten deutschen Aortenzentren behandelt wurden. Alle Patienten wurden mit dem AFXsg versorgt. Die Überlebensraten, Freiheit von Endoleaks (EL), Freiheit von Obstruktionen/Verschlüssen der Beckenachse und Reinterventionen waren die primären Endpunkte.

Der durchschnittliche Durchmesser der AB betrug 15.8 +/- 2.2 mm. Während des durchschnittlichen Follow-up-Zeitraums von 20.4 +/- 22.8 Monaten wurden keine Todesfälle registriert, die im kausalen Zusammenhang mit der Implantation des AFXsg stehen könnten. Es wurden keine Konversion auf ein offenes Operationsverfahren durchgeführt und die technische Erfolgsquote lag bei 100%. Während des initialen 30-tägigen Follow-up-Zeitraums wurden zwei Endoleaks Typ II beobachtet. Ein Endoleak Typ III trat 54 Monate nach AFXsg Implantation auf, sowie eine Stenose der Arteria iliaca communis (CIA) am vierten postoperativen Monat bei dem gleichen Patienten. Das durchschnittliche Patientenüberleben betrug 95 +/- 5%, die Freiheit von AFXsg Schenkelverschlüssen betrug 94 +/- 5%, die Freiheit von EL Typ II betrug 94 +/- 4 % und die Freiheit von EL Typ III lag bei 83 +/- 15% am Ende der Follow-up Zeitraums.

Der AFXsg liefert gute Ergebnisse bei der Therapie von Aortenpathologien mit sehr schmalen AB ohne dabei höhere Okklusionsraten der Prothesenschenkel in der kurz- und langfristigen Nachbeobachtung zu generieren. Das Outcome von Patienten mit PAU ist dem der Patienten mit AAA überlegen. Es sind Studien mit längerer Überwachungszeit und größerer Patientenkohorten erforderlich, um die Haltbarkeit des AFXsg und die Nachhaltigkeit der Therapie sowie die damit verbundenen Komplikationen valide zu bewerten.

Abstract

The goal of this project was the evaluation of morphologic and anatomic changes and durability after endovascular aortic aneurysm repair (EVAR) of infrarenal aortic lesions with very narrow aortic bifurcations treated with AFX (Endologix, Irvine, CA, USA) stent graft. One of the anatomical limitations for endovascular repair is the diameter of the aortic bifurcation. A distal aortic diameter under 18 mm is considered as a limiting factor for modular devices with increased risk of obstructions of the limbs. The advantage of the AFX system is its preservation of the aortic bifurcation. The risk of obstruction is reduced due to the absence of limb competition in the distal infrarenal aorta.

The data was analyzed from retrospectively collected medical records of 35 patients with a mean age 78.3 +/- 7.2 years who were treated for abdominal aortic aneurysm (AAA) (48.6 %) and/or penetrating aortic ulcers (PAU) (51.4 %) with narrow aortic bifurcation (≤ 18mm) between January 2013 and May 2020 at four vascular surgery centers in Germany. Patient survival, freedom from endoleak (EL), limb occlusion (LO), re-intervention rates and changes of vascular sac diameter were evaluated as primary objectives of the study.

The project focused on very narrow bifurcation aortic bifurcations with an average diameter of 15.8 +/- 2.2 mm. No procedure-related deaths were registered during the mean follow-up time of 20.4 +/- 22.8 months. No conversions to open repair were performed and technical success was 100%. Two type II ELs were observed within 30-day follow-up. The same patient of the AAA group suffered from common iliac artery stenosis after four months of AFX implantation and type III EL at 54 months occurred, both of these complications were treated with endovascular re-interventions. By means of Kaplan-Meier estimator, overall patient survival of 95 *+/- 5% (AAA: 100%; PAU: 89 +/- 10%)* was calculated; freedom from limb occlusion reached 94 *+/- 5*% (AAA: 91 *+/- 9%; PAU*: 100%). At the end of the follow-up period, freedom from type II EL achieved 94 *+/- 4*% (AAA: 88 *+/- 8%*; PAU: 100%) and freedom from type III EL was 83 *+/- 15*% (AAA: 80 *+/- 18%;* PAU: 100%*)*.

In these cases of narrow aortic bifurcations, the AFX stent graft is considered as suitable and provides promising early- and long-term results in patient outcome. The incidence of endoleaks and limb occlusions/ stenoses showed promising results, but a longer follow-up time is required to observe the durability of the AFX stent graft. The overall short- and long-term procedure-related patient outcomes are encouraging, though the PAU patient group provided superior outcomes in comparison with AAA patients.

Abbreviations

AAA	abdominal aortic aneurysm
AAC	abdominal aortic calcification
AB	Aortenbifurkation
ABI	ankle brachial index
ACC	American College of Cardiology Foundation
ACE	angiotensin converting enzyme
AFXsg	AFX stent graft
AHA	American Heart Association
AKI	acute kidney injury
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
AT1R	angiotensin type 1 receptor
CAD	coronary artery disease
CEUS	contrast-enhanced ultrasound
CIA	common iliac artery
COPD	chronic obstructive pulmonary disease
CFA	common femoral artery
CT	computed tomography
CTA	computed tomography angiogram
DGG	Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin, Gesellschaft für operative,endovaskuläre und präventive Gefäßmedizin
DREAM	Dutch Randomized Endovascular Aneurysm Management
DRG	Diagnosis Related Goups
EC	endothelial cells
ECM	extracellular matrix
EIA	external iliac artery
EL	endoleak
ePTFE	expanded polytetrafluoroethylene
EVAR	endovascular aortic repair (or endovascular aneurysm repair)
ESC	European Society of Cardiology
ESVS	European Society of Vascular Surgery

EUROSTAR	European collaborators on stent graft techniques for abdominal aortic aneurysm repair
FDA	Food and Drug Abdministration
Fr	French
HDL	high density lipoprotein
HIV	human immunodeficiency virus
ICU	intensive care unit
IFN	interferon
IFU	instructions for use
IL	interleukin
LO	limb occlusion
max	maximum
MCP	monocyte chemoattractant protein
min	minimum
miRNA	microRNA
mm	millimeter
MMP	matrix metalloproteilases
µm	micrometer
nrAAA	non-ruptured abdominal aortic aneurysm
OR	open repair
OVER	Open Versus Endovascular Repair
PAU	penetrating aortic ulcer
PAD	peripheral artery disease
PAOD	peripheral arterial occlusive disease
PCI	percutaneous coronary intervention
rAAA	ruptured abdominal aortic aneurysm
TGF	transforming growth factor
TNF	tumour necrosis factor
US	ultrasonography
VELA	the AFX2 Endovascular AAA system proximal extension
vSMC	vascular smooth muscle cells

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1. Introduction

1.1 Abdominal aortic aneurysm

1.1.1 Definitions

The most common definition of an abdominal aortic aneurysm (AAA) is related to the diameter of the abdominal aorta: an AAA is defined as a dilatation of the anteroposterior diameter of the aorta over 30 mm, which usually exceeds two standard deviations above the mean aortic diameter, considering the gender-specific normal values (1,2). The standard aortic diameter varies according to patient age, gender, and body habitus. However, the average diameter of an adult human aorta is 20 mm; 95% of the adult population have aortic diameters ≤30 mm (3). AAAs are classified into suprarenal and infrarenal aneurysms. The majority of AAAs is characterized by infrarenal localization, proximal to the aortic bifurcation (3).
Another less frequently occurring aortic pathology is acute aortic syndrome of the infrarenal aorta. According to current reviews, aortic dissection, intramural hematoma, and penetrating aortic ulcers are included in the definition of "acute aortic syndrome" (4). However, differences exist in the clinical symptoms, etiopathogenesis, and therapy approaches for each (4). In 1986, Stanson et al. defined a penetrating aortic ulcer (PAU) as an "atherosclerotic lesion with ulceration in the aortic intima and media with rupture of the elastic lamina" (5).

1.1.2 Epidemiology

The prevalence of AAAs depends on demographic factors such as advanced age, male sex, and smoking history and ranges from 4% to 8% in population-based screening studies, affecting mainly males (6). However, AAAs found during screening are generally small (29 to 49 mm in diameter); those measuring over 55 mm are registered in only 0.4%–0.6% of the screened population (7). Generally, the incidence of small aneurysms ranges from 1.3% for men aged 45 to 54 and up to 12.5% for men between 75 and 84 (2). The incidence for women of comparable ages ranges between 0% and 5.2% (2). Because of the sharply rising incidence of AAA in individuals over 60 years, the future prevalence of AAA could increase significantly in association with the aging population (7). The annual incidence of new diagnosed AAAs is

approximately 0.4% to 0.67% in Western countries; this resembles 2.5 to 6.5 aneurysms per 1,000 person-years (8).

According to the data from the diagnosis-related groups (DRG) statistics of the Federal Statistical Office (*Statistisches Bundesamt*) for the years 2005–2014, approximately 3% (1%–7%) of the population over the age of 50 are affected by AAAs in Germany (9). AAAs often remain clinically inapparent until they rupture (9). However, they have an intrahospital mortality of about 40% (9). The overall lethality of a ruptured AAA (rAAA) is probably significantly higher due to preclinically deceased patients (approx. 60%–80%) (9).

Current literature lacks incidence data on PAUs of the infrarenal aorta, although rates of 2.3%–7.6% in symptomatic patients with an acute aortic syndrome were described (10). The majority of acute aortic syndromes relates to aortic dissections with a reported incidence of 2.6–3.5 per 100,000 person-years (11); 70% of them are in the ascending aorta, 20% in the descending aorta, and 7% in the aortic arch (11). In contrast to the thoracic aorta, the abdominal aorta is less frequently affected by PAUs (incidence of 1%–5%) (11). Interventional treatment of PAUs accounts for approximately 3.5% of all aortic surgical repairs (4).

1.1.3 Risk factors and pathophysiology

According to high-volume clinical trials such as the TromsØ study, male sex, advanced age, smoking, arterial hypertonia, high levels of serum total cholesterol, and low HDL cholesterol are significantly associated with increased risk of developing an AAA (8). A meta-analysis by Elkaliooubie demonstrated that patients with AAA have comparable risk profiles to those with coronary artery disease (13). As reported by the DRG statistics of the Federal Statistical Office, the most frequently documented comorbidities in AAA patients are “arterial hypertension (69%), coronary heart disease (33%), other cardiac diseases (32%), peripheral arterial disease (32%), and renal insufficiency (20%) (9). Coincidence with cerebrovascular diseases is reported at 7% and with malignant diseases at 3% “(9).

In the relevant literature, patients with PAU are predominantly male with comorbid conditions including hypertonus, chronic kidney disease, coronary artery disease, and peripheral arterial disease (4). Patients with PAU are typically older than patients with acute aortic dissection and frequently have concomitant AAA (12). The natural history of acute aortic syndrome is spontaneous rupture with 15% probability, and mortality varies from 17% to 28% (11).

Diabetes is the only cardiovascular risk factor with a negative correlation with aneurysm growth. Proteolysis, leading to the destruction of structural connective tissue, and inflammation are the pathological mechanisms of the origin of AAA (6,8,14). In AAA, diabetes mellitus is obvious to have a protective effect (14). The protecting aspect of diabetes is relevant not only to the genesis of AAA but also to reducing its progression (14). According to the Laplace law, a thicker aortic wall lowers the wall tension, which is considered to cause the progression of aneurysmal growth (14). From a molecular biological viewpoint, the progression of glycation end products, characteristic of diabetes, causes conjoin of collagen fibers (14). In vitro, this increases their function as an inhibitor of proteolysis and the secretion of typical macrophage matrix metalloproteinases that participate in AAA formation (14).

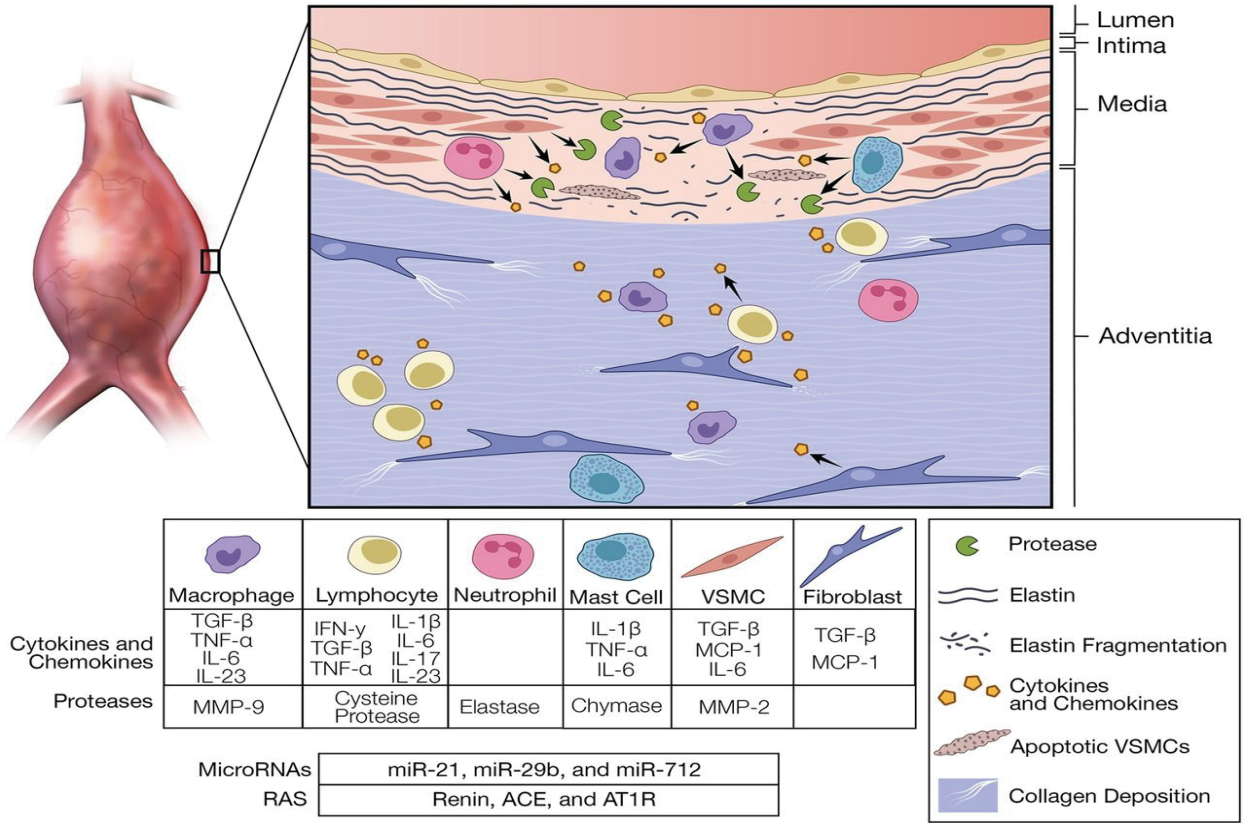
The majority of AAAs occurs in the infrarenal aortic segment and extends to the aortic bifurcation (9,15). Genetic, hemodynamic, and inflammatory factors contribute to the progression of aneurysms. AAAs usually develop a fusiform morphology, including all layers of the aortic wall. The saccular aneurysm form, which affects a single part of the aortic circumference, is less typical (15). The degeneration of aortic media as the most frequent cause of AAAs has complex biochemical pathomechanisms, such as chronic adventitial and medial inflammation, cell infiltration, degradation of collagen and elastin, and medial depletion (2,15). Aneurysm development is provoked by the destruction of vascular smooth muscle cells (vSMCs) in the aortic media and the extracellular matrix (ECM) (16). The history of the molecular mechanisms of AAA is incompletely researched. Angiogenesis in the aortic media and vascular endothelium is a relevant factor in the etiopathogenesis of AAA; furthermore, inflammatory processes play a key role (15,16). Vascular inflammation includes complex mechanisms of interaction between endothelial cells, vSMCs, the ECM, and inflammatory cells.

Inflammatory cellular elements such as macrophages are responsible for producing and activating matrix metalloproteinases (MMPs). MMPs belong to the class of proteolytic enzymes and are initially synthesized as preproenzymes and secreted in an inactive form (16). MMPs are involved in proteolytic reactions, which can amplify their proteolytic activities. Especially, MMP-9 can be considered a potential trigger of medial disruption and inflammation processes between endothelial cells (ECs) and vSMCs and can play a significant role in the degradation of the ECM. MMP-9 expression can be regulated by cytokines, especially tumor necrosis factor α (TNF-α) (16).

Chronic local infiltration of the adventitia and media with inflammatory cells (T- and B-lymphocytes and macrophages) and elastin fragmentation are important histological

characteristics of AAAs (15). Collagen types I and III are responsible for the tensile strength of the aortic media and adventitia (15,17). In early aneurysmatic stages, collagen synthesis is initially increased. In later stages, an imbalance occurs between collagen synthesis and degradation (17).

Micro-RNAs (miRNAs) have an additional function as effective intracellular regulators of inflammatory processes: miR-24 acts as an important regulator of inflammation in the aneurysmatic progression (18). MiR-29b shows an important influence on regulating the qualitative and quantitative compositions of different collagen types (18). Figure 1 shows a schematic of AAA pathogenesis.



TGF: transforming growth factor; TNF: tumor necrosis factor; IL: interleukin; MMP: matrix metalloproteinase; IFN: interferon; MCP: monocyte chemoattractant protein; miR: microRNA; ACE: angiotensin-converting enzyme; AT1R: angiotensin type 1 receptor; VSMC: vascular smooth muscle cell

Figure 1. Pathogenesis of abdominal aortic aneurysms. Inflammatory cells, including macrophages and mast cells, release various inflammatory factors such as cytokines and leukotrienes. An intraluminal thrombus may cause functional hypoxia at the luminal intima and inner media, leading to inflammation. Inflammatory cells in the thrombus also secrete proteases, for example, matrix metalloproteases (MMP)-9. Proteases (MMP-9, serine proteases, cysteine proteases) induce the destruction of structural proteins of the aortic wall and weaken the aortic lumen (2, 15). Modified according to Davis, F. M., Rateri, D. L. & Daugherty, A. Mechanisms of aortic aneurysm formation: translating preclinical studies into clinical therapies. Heart. Oct;100(19):1498-505 (2014) (16) (with kind permission from the BMJ Group, licensed, Order Number 4987830333266).

1.1.4 Diagnostic (imaging)

Ultrasound screening

Duplex ultrasound is the diagnostic method of choice for diagnosing and monitoring AAAs in asymptomatic patients (19). Abdominal ultrasonography is recommended by all guidelines as a primary screening test (19). According to the European Society for Vascular Surgery (ESVS) guidelines, an ultrasound screening test (single scan) is to be performed on all men aged over 65 (evidence level 1a, recommendation level A, strong consensus) and women over 65 with a current or past smoking history (evidence level 2a, recommendation level A, strong consensus) (19). First-degree siblings of patients with AAA should also receive sonographic examination (evidence level 2c, recommendation level B, strong consensus) (19). Based on the abdominal ultrasound screening data from Walsh et al., PAUs resemble saccular aortic aneurysms (20).
No uniform international standard exists for AAA measurement using ultrasound. Three measurement methods exist: leading to leading edge, inner to inner edge, and outer to outer edge (21,22). The definition of the process is based on the caliper placement in relation to the maximum aortic diameter in ultrasound (22). The leading to leading edge method is defined as measuring from the aortic adventitia to the media (for example, from the outer anterior aortic wall to the inner posterior wall, demonstrated in Figure 2) (21). The inner to inner edge method is characterized as measuring from intima to intima (inner anterior aortic wall to inner posterior wall), while the outer to outer edge measurement is determined as caliper placement from adventitia to adventitia. Depending on the measurement method, a difference of up to 3 mm may occur (21).

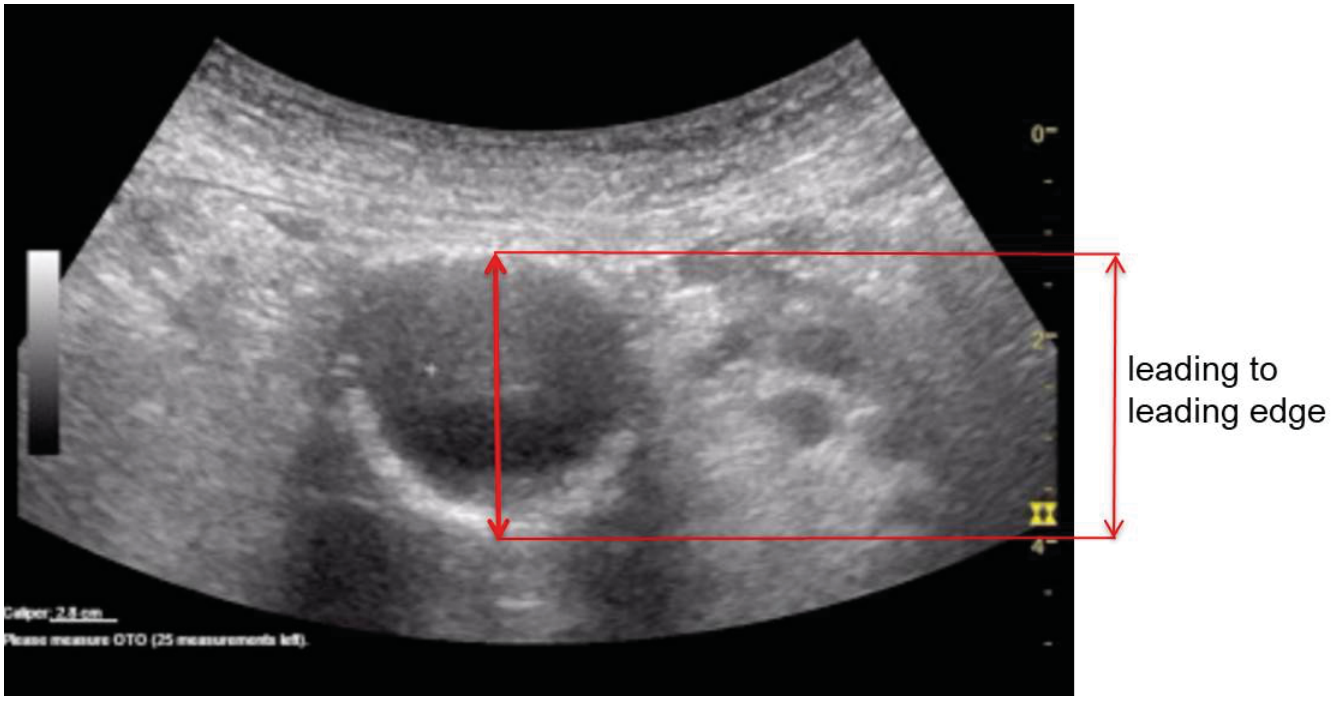


Figure 2. Leading to leading edge measurement method for aneurysm diameter. This demonstrates the procedure for measuring the maximum aortic diameter with the leading to leading edge method. Calipers are positioned on the outer layer of the anterior aortic wall and the inner layer of the posterior wall. Modified according to Borgbjerg, J. et al., Superior reproducibility of the leading to leading edge and the inner to inner edge methods in the ultrasound assessment of maximum abdominal aortic diameter. Eur J Vasc Endovasc Surg; 55:206-2012 (2018) (22) (with kind permission from Saunders, licensed, Order Number 5123220146836).

The German Society for Vascular Surgery (*Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin Gesellschaft für operative, endovaskuläre und preventive Gefäßmedizin*, DGG) issued the leading to leading edge method as a recommendation due to its superior reproducibility (23). It is important to perform the measurement perpendicular to the axis of the aorta since purely axial measurements can be imprecise (22). A standardized measurement procedure is relevant for evaluating and treating aortic pathologies. According to the current DGG guidelines, the aorta must be measured at its largest diameter anterior-posterior and orthogonal to the transverse plane. The topographic relationship to the renal arteries and involvement of iliac vessels must be evaluated (23).

CEUS (contrast-enhanced ultrasound)

Due to its availability, reproducibility, and economy, ultrasound (US) is typically used as a first-line imaging method for fast and sufficient evaluation of aortic anatomy (24). The introduction of contrast agents has extended ultrasonography use to a wide spectrum of organs and conditions. Contrast-enhanced US (CEUS) is already clinically established for diagnosing

endoleaks. US contrast agents comprise microbubbles from a phospholipid shell containing gas, measuring less than 8 μm in diameter (24).

These microbubbles are smaller than erythrocytes but larger than the diameter of the capillaries. With active intravasation or hemorrhage, microbubbles are visually represented outside the vascular lumen (25). Life-threatening allergies to microbubbles occur in fewer than 0.002% of cases (25). Microbubbles are metabolized in the liver, and the gas is exhaled, so they can be applied safely in patients with renal insufficiency, unlike the CT contrast agent (24).

Computed tomography

Sequential computed tomography angiography (CTA) supplies relevant data on AAAs and adjacent anatomical structures, including venous and renal anomalies and especially retroaortic left renal veins (26). CTA is considered a verifiable imaging tool for the diagnostics and surveillance of AAAs and implements all the important anatomical characteristics for planning the treatment of aortic pathologies (26). After confirmation of the diagnosis, it is important to perform imaging of the complete aorta with an appropriate technique, such as CTA, to determine all the possible aortic pathologies (26). During the planning phase of endovascular aneurysm repair (EVAR), the CTA measurements should be conducted by a competent vascular surgeon, with a second assessment by a skilled operator in case of inconclusive or dubious results after the first evaluation of imaging (1). Figure 3 demonstrates a typical CT image of an AAA.

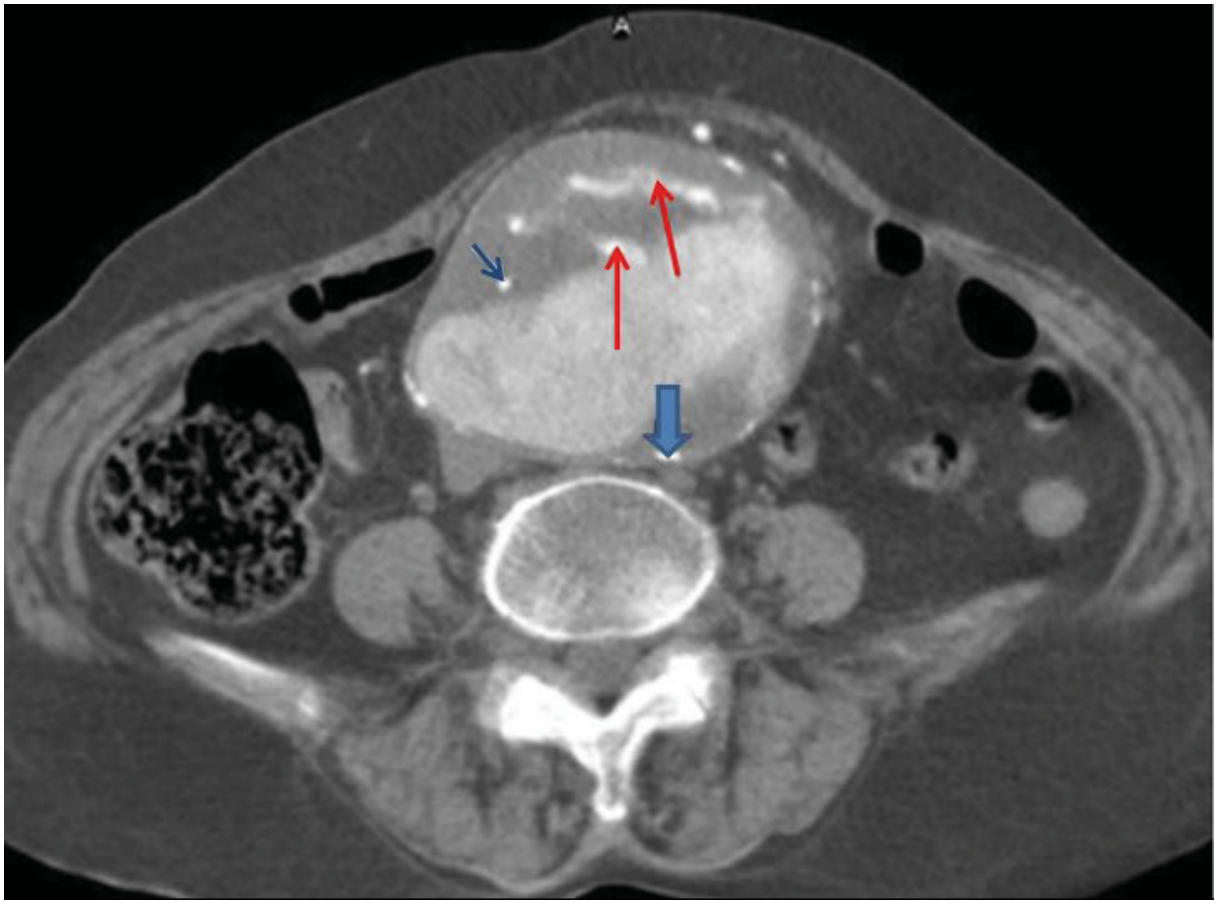


Figure 3. Computed tomography angiography scan of female patient with typical risk factors and symptomatic abdominal aortic aneurysm. The long red arrows represent the extravasation of contrast medium into the intraluminal thrombus. Calcified plaques in the circumference of the aneurysmatic wall are marked as a thick blue arrow. Tiny, calcified structures in the intraluminal thrombus are highlighted as a short blue arrow. Modified according to Taheri, S.M. et al., Multidetector computed tomography findings of abdominal aortic aneurysm and its complications: a pictorial review. Emergency Radiology.20, pp. 443-51 (2013) (27) (with kind permission from Springer, licensed, Order Number 0000-0003-4096-0690).

Due to the similar clinical manifestation of all forms of acute aortic syndrome, they must be radiologically differentiated (13,28). Focal involvement with adjoining hematoma detected below the frequently calcified intima are typical CTA features of PAUs (28). The ulcer is often accompanied by thickening of the aortic wall. CT angiography can demonstrate complex intra- and extraluminal pathological conditions (28). According to Mayo Clinic classification, three radiological features of PAUs include the following criteria: crater of the ulcer with localization in the aortic wall, subadventitional pseudoaneurysm, or transmural rupture with extra-aortic hematoma (13).

Several factors should be considered to select the post-EVAR surveillance modality. US is less sensitive than CTA for detecting and visualizing the flow outside the stent graft. CTA has limitations, such as requiring ionizing radiation and an iodinated contrast medium (25). CTA with a maximum of three phases acting has limitations in verifying dynamic phenomena such

as endoleaks. CEUS has advantages for detecting and identifying the type of endoleak, which is essential for therapy planning (24).

1.1.5 Treatment

Conservative treatment

After the establishment of standardized screening programs, abdominal aortic aneurysms are detected more frequently at an early stage of the disease (1). Conservative treatment is recommended for asymptomatic abdominal aortic aneurysms with diameters measuring under 50 mm (1). Consensus exists in all vascular surgical guidelines that the rupture risk of small asymptomatic AAAs (diameter from 30 to 39 mm) is negligible and that these aneurysms do not require surgical treatment but should be closely monitored (23).

Patients with aneurysm diameters exceeding 45 mm need careful evaluation, adjustment of risk factors (especially therapy for arterial hypertension), and close follow-up intervals of 3–6 months due to their risk of AAA progression (1,23). For patients with aneurysm diameters below 45 mm and without further aneurysm risk factors, follow-up controls with a time interval of 12 months are advised (1).

According to the current guidelines, an abdominal aortic diameter exceeding 30 mm in patients with PAUs should be recommended for elective treatment by reason of higher rupture rates and increased mortality compared with AAAs (29).

Open surgical repair

According to the ESVS guidelines, in cases of symptomatic AAAs, EVAR is preferred due to lower procedural mortality in symptomatic cases than with open surgery (evidence level 2c, recommendation level B) (19). Nevertheless, the patient preference should be considered (19). In accordance with the guidelines of the American Association for Vascular Surgery on AAA therapy, open and endovascular treatment of AAAs have proven equivalent over time, with similar rates of overall survival and aneurysm-related morbidity and mortality (30). For patients with a life expectancy exceeding 2 years and a good risk constellation, open repair (OR) and endovascular procedures (EVAR) are equally recommended (19).

Despite the lower procedural mortality of EVAR, this advantage is not maintained over time, so the choice of the operative procedure is individual and patient-oriented. EVAR should only be used on anatomically suitable patients, and it should be ensured that the required follow-up examinations can be performed (1). OR is appropriate for patients who are well-predisposed for surgical care but cannot maintain the long-term monitoring required for EVAR (evidence level C) (26). Figure 4 presents the relevant operational steps of OR of suprarenal AAA.

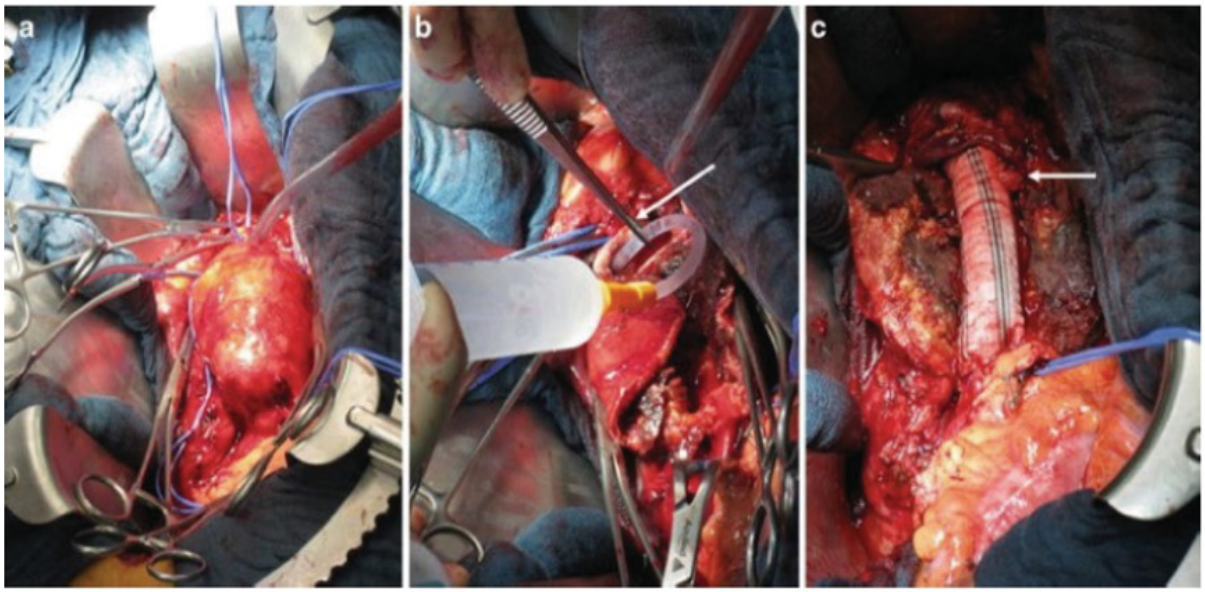


Figure 4. Open repair of suprarenal aortic aneurysm with reinsertion of left renal artery. This image represents the complex procedure of open repair (OR) of a suprarenal aortic aneurysm. This operative treatment is technically more demanding than OR of infrarenal aneurysms due to the high risk of renal ischemia. Critical steps of the operation are summarized in this image. **A)** Preparation of the aorta before clamping. The left renal vein crosses the aorta and is provided with vessel loops. **B)** After clamping and opening the aneurysm sac, cold perfusion of the renal artery is performed for intraoperative organ protection. **C)** Operative situs after implantation of aortic prosthesis and reinsertion of left renal artery. Modified according to Debus, E.M. et al., Aneurysmen der infrarenalen Aorta: Klinik, Diagnostik einschließlich Screening und Therapieindikationen, Springer Link, Operative und interventionelle Gefäßmedizin, pp.1-17 (2017) (39) (with kind permission from Springer, licensed, Order Number 0000-0003-4096-0690).

Two surgical techniques exist for OR access: the midline transperitoneal and retroperitoneal approaches. A standard, midline transperitoneal approach is most frequently used in aneurysm surgery (31). The retroperitoneal approach demonstrates the following advantages: the duodenum does not need to be adhesiolysed from the aorta, and the left renal vein is moved up the neck of the aneurysm with ventral mobilization of the kidney, simplifying the proximal control during the preparation (32). Several studies comparing the perioperative outcomes of both approaches for AAA repair stated that the retroperitoneal approach is associated with a

lower incidence of postoperative ileus, a reduced hospital stay, and improved respiratory function compared with transperitoneal procedures (29,33,34).

The comparison of perioperative mortality of OR versus EVAR remains a controversial topic. The following notable randomized trials focused on comparing the outcomes of OR with EVAR: DREAM (Dutch Randomized Endovascular Aneurysm Management), EVAR trial 1, and OVER (Open Versus Endovascular Repair) (35,36,37). These studies have offered superior early outcomes for endovascular treatment.

According to current clinical trials, open surgical treatment of PAUs is also connected with higher perioperative morbidity and mortality due to advanced patient age and multimorbidity (11). With prolonged follow-up time, the survival benefit of patients with EVAR is reduced after 1 or 2 years according to the DREAM and EVAR 1 trials, and after 5 years in the OVER study (35,36,37). The DREAM and OVER trials showed a continuously rising rate of secondary interventional procedures after a median follow-up time of approximately 6 years (35,37). The durability of stent grafts and continued follow-up examinations remain key points of EVAR.

Endovascular treatment

The first implantation of an aortic endograft in a human was performed in 1987 by Volodos and his team in Kharkov (Ukraine) in a patient with common iliac artery stenosis (38). EVAR provides an alternative concept of the therapy in high-risk patients because it reduces the morbidity and mortality related with expanded retroperitoneal dissection and prolonged aortic cross-clamping (40). In comparison to OR, EVAR reduces perioperative mortality, morbidity, and the duration of stay in the intensive care unit (ICU). In the hospital, it reduces postoperative pain and avoids general anesthesia (9). These aspects represent huge advantages for multimorbid and older patients (9).

Relevant long-term multicentric randomized clinical trials, such as the EVAR 1, DREAM, and OVER trials, compared the data from patients with OR versus EVAR and analyzed morbidity, aneurysm-related mortality, and reintervention rates. These studies demonstrated an early perioperative mortality benefit with EVAR in comparison with OR (41,42). Furthermore, patients treated with EVAR had less blood loss and consequently less blood transfusions, and had a reduced intensive care stay compared with patients treated with OR (35,36,37,41,42). However, no long-term (>2 years) difference between these two treatment options was described for total and aneurysm-related mortality (35,36,37,42). EVAR is also recommended for patients with PAUs due to its lower mortality and reduced rate of complications in the short-

and long-term follow-up time (11). Patients can be treated with EVAR under local anesthesia, and EVAR can be used in asymptomatic patients to prevent potential complications (13).
However, the disadvantages of EVAR include low device durability and higher reintervention rates, especially during the mid- and long-term follow-up (43). In comparison with OR, EVAR is associated with higher reintervention rates: OR with 0.3% versus EVAR with a 3% reintervention rate per year (19). Every patient treated with EVAR must match specific anatomical criteria listed in the instructions for use (IFU) of the chosen device. An inability to meet these criteria leads to a reduced success rate or even a reduced choice of the procedure, leaving implantation of another stent graft, OR, and hybrid revascularization treatment as options (40).

1.2 EVAR

1.2.1 EVAR procedure

EVAR is defined as eliminating an aneurysm sac through the radiologically guided placement of an endovascular device within the native aortic lumen, including proximal and distal endograft fixation (23,51). This procedure can be performed under general anesthesia or locoregional anesthesia combined with analgosedation or even under peridural anesthesia depending on the physical and mental condition of the patient and the internal standards of clinical institutions and routines of vascular surgeons. EVAR implantation should be performed in an operating room or hybrid operating room with angiography on a radiolucent operating table. A fluoroscopy machine or C-arm must be used (51).
Originally, open arteriotomy (“cut down”) was performed as typical access for EVAR via femoral or iliac arterial exposure for stent graft introduction. A newer generation of endovascular devices with smaller access sheath sizes allows complete percutaneous access. Wound complications (infections, hematomas) and lesions of lymphatic vessels are considered typical complications of open arteriotomies. However, risk factors such as morbid obesity and high levels of calcification can lead to poor outcomes in the percutaneous access technique (23,51). The main body of the endograft requires an access vessel with a larger diameter. The side of the introduction of the main body is defined as the ipsilateral vessel and the side of the opposite limb as contralateral (52).

An angiographic flush catheter must be initially deployed via the contralateral artery with the aim of digital subtraction angiography and localization of renal arteries. The main body of the endograft must be introduced via a vascular access sheath through the ipsilateral vessel. Under fluoroscopic monitoring, the device is advanced over a previously positioned stiff guide wire until the proximal end of the stent graft is positioned below and immediately before the renal arteries (51). With a modular device, the ipsilateral limb can be deployed at this time. The next step is introducing the contralateral limb and "docking" with the main body (51,23). After positioning all the device components, distension of the proximal and distal graft attachments can be performed via a large-volume compliant balloon to prevent incomplete expansion of the endograft. Finally, the procedure must be completed via angiography. In case of kinking or stenosis of the limbs, a correction must be performed immediately.
Although EVAR is established as the first-line treatment of abdominal aortic pathologies, it still risks procedure-related complications during the early- and long-term follow-up time.

1.2.2 Endoleaks

With a rate of 20%–25%, endoleaks (ELs) remain the most typical complication of EVAR and are defined as "blood leakage with backflow into aneurysm sac" (44). Five types of ELs occur, each with different pathogenesis and treatment options (Table 1). Depending on the time of their occurrence, ELs are divided into primary and secondary types. In a primary EL, the detection occurs intraprocedurally, presenting from the time of stent graft implantation or within 30 post-procedural days (1). ELs occurring after prior negative CTA and more than 30 days after endograft implantation are defined as secondary types. Based on the origin and localization of the leakage, ELs are classified into types I–V. Among all ELs, types I and III significantly increase the risk of aneurysm rupture after EVAR and require early interventional treatment (44) (Table 1).

Table 1. Classification of endoleaks. Classification of endoleak (EL) following endovascular treatment for abdominal aortic aneurysm (AAA). ELs are subgrouped into five different types depending on the location and nature. Modified according to Moll, F.L. et al., Management of abdominal aortic aneurysms clinical practice guidelines of the European Society for Vascular Surgery, J Vasc Endovasc Surg, 2011. 4, p.1-58 (1)

Endoleak type	Definition

I	inadequate circumferential proximal or distal seal (attachment site leak) -Ia: proximal attachment site of stent graft -Ib: distal attachment site of stent graft -Ic: common iliac artery
II	aneurysm sac filling from aortic collaterals -IIa: single patent branch (simple) -IIb: two or more patent branches (complex)
III	endoleak secondary to structural defect of endograft -IIIa: junctional leak or modular disconnect -IIIb: stent fabric disturbance (holes)
IV	porosity of stent graft wall <30 days after placement
V (endotension)	continued increase of intrasac tension following EVAR without endoleak origin on delayed contrast CTA

EL: endoleak; AAA: abdominal aortic aneurysm; EVAR: endovascular aneurysm repair; CTA: computed tomography angiography

1.2.3 Narrow aortic bifurcations

One of the anatomical limitations for EVAR is the diameter of the aortic bifurcation. A distal abdominal aortic diameter of <20 mm (according to some authors ≤18 mm) defines a narrow aortic bifurcation (5). According to the current guidelines, a minimum bifurcation diameter of 20 mm is required for treatment with standard commercial bifurcated endografts (1). Narrow aortic bifurcations are considered a limiting factor for modular devices with an increased risk of limb obstruction (1). PAUs are also frequently associated with the following challenging anatomical structures: narrow aortic bifurcation and limited length of the infrarenal aorta (11). PAUs frequently represent the following limiting features for standard endovascular devices: a short infrarenal aorta, narrow aortic lumen, and especially narrow aortic bifurcation (11).

EVAR can be particularly challenging in patients with narrow aortic bifurcations (45). Aortic dissections, disruptions, thromboses, and iliac stent graft occlusions are considered potential complications in patients with narrower distal aortas. Limb occlusions are the most frequent adverse events. According to the current literature, the incidence of limb occlusions varies between 3.2% and 7.2% in endovascular treatment of aortic aneurysms with narrow bifurcations (46). This phenomenon can be explained by limb kinking due to the narrow distal anatomy of the aorta, which is usually accompanied by severe calcification. Space limitations do not allow the complete expansion of the limb components; this leads to limb competition, kinking of one or both iliac limbs, and higher occlusion rates (47).

Most currently available stent grafts are not approved for stenting of aortic pathologies with narrow bifurcations. Narrow distal aortas, often encountered in patients with PAUs and

concomitant aortoiliac occlusions, are often treated with aortomonoiliac stent grafts and femoral crossover bypasses. Groin wound healing disorders, graft infections, and thromboses are considered possible complications of this procedure (48). Open surgical repair was the therapy of choice for infrarenal PAUs (49). In recent years, stent graft implantation as a minimally invasive procedure has also gained acceptance for PAUs, especially for older and multimorbid patients (4). Current literature lacks incidence data on infrarenal aortic segments and endograft durability in these cases.

In aortic pathologies with narrow bifurcations, most commercially available endografts comprising a main body and two docking limbs require adjunctive intraoperative procedures. The performance of intraprocedural intraoperative maneuvers increases additional cost, risk, and time factors. The other possible solution in treating aortic pathologies with narrow bifurcations is implanting an AFX endovascular system (Endologix, Irvine, CA, USA) as an unibody device (50).

1.2.4 Endovascular stent grafts

Endovascular devices include three components: a delivery system for endograft deployment, a self-expanding metallic endograft framework, and graft fabric (50,51). While the metallic endograft framework provides vascular attachment, the fabric enables aneurysm exclusion and new blood flow regulation (52). Sufficient distal and proximal landing zones are essential for sealing the endograft to the aorta (51). The variety of endovascular devices enables adaptation to different aortic anatomies (51).

Currently, different subtypes of endovascular stent grafts are available. According to their construction, endografts are classified as completely modular devices (graft body with unilateral limb extension, combined with contralateral docking limb), unibody self-expanding devices (fixation on the aortic bifurcation), and aorto-mono-iliac endografts (requiring completion with crossover bypass) (51). According to their fixation, aortic endografts are subdivided into those with infrarenal (for example, Gore Excluder (W.L. Gore & Associates, Flagstaff, AZ, USA), AneuRX (Medtronic Inc., Minneapolis, MN, USA), and suprarenal fixation (Cook Zenith (Cook Inc., Bloomington, IN, USA)) (52). AFX devices as unibody grafts have fixation and sealing with both landing zones. AFX offers anatomical fixation to bifurcations, while other devices mainly use the infrarenal neck as a fixation zone. This feature reduces the possibility of device migration and improves the safety of AFX systems (52,53).

Before the approval of the Endologix Powerlink (Endologix, Irvine, CA, USA) device, the Cook Zenith (Cook Inc., Bloomington, Ind., USA) stent was the only graft suitable for treating 32-mm proximal aortic necks, which was accepted by the Food and Drug Administration (FDA) (54).

Medtronic (Minneapolis, MN) currently manufactures two devices for treating abdominal aortic aneurysms (52,54). The AneuRX stent graft system (Medtronic Inc., Minneapolis, MN, USA) is the device with the smallest delivery system, suitable for a 26-mm aortic neck. This system features an integrated sheath and provides no active fixation (54). The Talent abdominal stent graft system (Medtronic Vascular, Santa Rosa, CA, USA) is also produced by Medtronic and is currently a unique device approved for stenting infrarenal aneurysms with necks shorter than 10 mm. This system does not provide active fixation with proximal hooks; however, it includes a suprarenal uncovered stent (54).

The Gore Excluder endograft (W.L. Gore & Associates, Flagstaff, AZ, USA) is introduced through percutaneous sheaths without incorporating sheaths in the delivery system (52). This feature allows the stent graft to develop flexibility, especially with problematic iliofemoral access (54). Using the Gore Excluder device, a two-piece repair of an AAA is more frequently successful due to the diversity of diameters and the length of the main body and ipsilateral limb (52,54). The different structures of frequently used endovascular stent grafts are demonstrated in Figure 5.

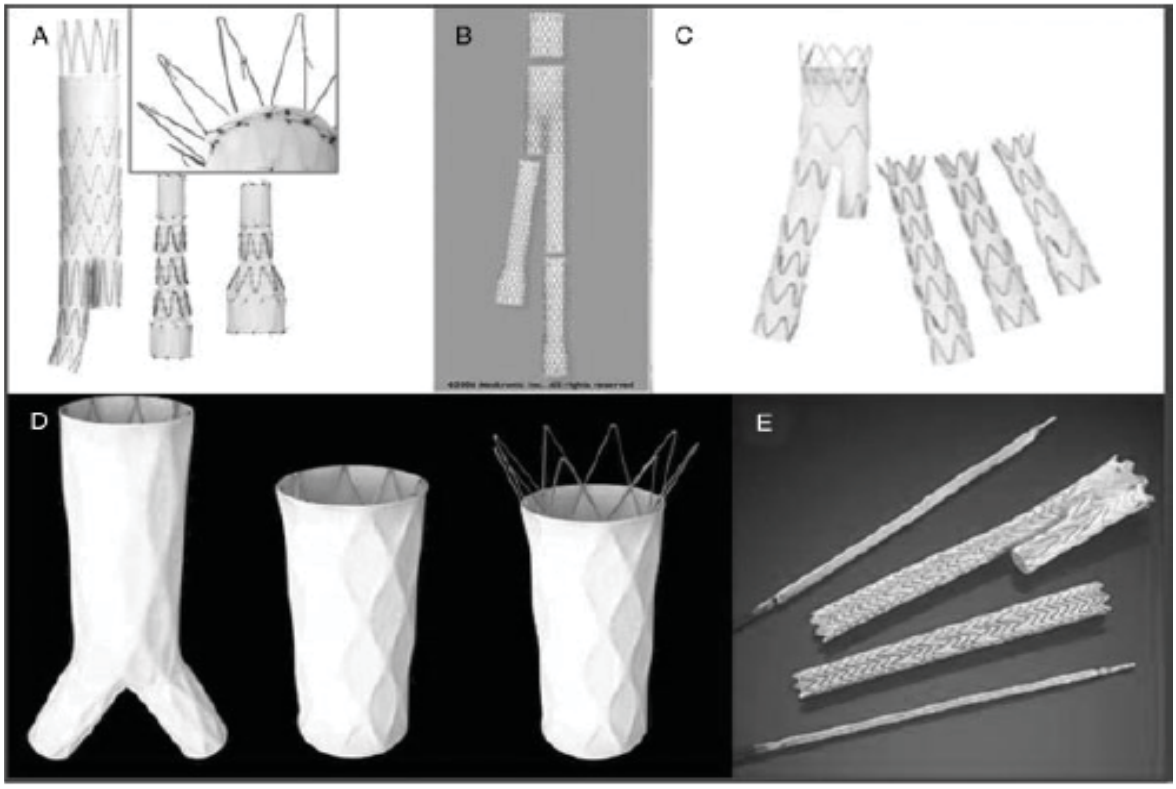


Figure 5. Common Food and Drug Administration approved endovascular devices for treating abdominal aortic pathologies. This figure displays different endovascular stent grafts: modular devices (A–C and E) and unibody stent graft (D). **A)** Zenith Alpha Abdominal (Cook Inc., Bloomington, IN, USA); **B)** AneuRX (Medtronic, Minneapolis, MN, USA); **C)** Talent (Medtronic Vascular, Santa Rosa, CA, USA); **D)** AFX (Endologix, Irvine, CA, USA); **E)** Excluder (W.L. Gore & Associates, Flagstaff, AZ, USA). From Jackson, B.M. et al., Devices used for endovascular aneurysm repair: past, present and future, 2009. Seminars in interventional Radiology. 1, p. 39-43 (with kind permission from Thieme, (54) licensed, order number 501626299)

1.2.5 AFX stent graft

Special characteristics of AFX stent graft

The Endologix Powerlink device (Endologix, Irvine, CA, USA) has been available in Europe since the beginning of 1999 and was commercially approved in the USA in 2004. This device was designed as a unibody bifurcated stent graft indicated for preventing endograft migration. The endograft limb configuration resembled the native aortoiliac anatomy and reversed the bifurcation anatomy; this feature improved the device safety and demonstrated a low risk of endograft limb occlusions in multiple clinical trials (55). The Endologix AFX2 endovascular system enacts the second generation of the Endologix endograft system and uses innovative

STRATA high-density expanded polytetrafluoroethylene (ePTFE) graft material (56). The AFX stent graft (AFXsg)has been commercially available since 2011.

The AFX system includes two components: the delivery catheter system (AFX 2 introducer) and implantable stent graft. The AFXsg is a unibody endograft comprising a main bifurcated body (self-expanding cage) formed with iliac legs from a single wire (cobalt-chromium alloy) (50). The stent graft cover is produced from low porosity expanded polytetrafluoroethylene (ePTFE). Implantation of distal iliac extensions or proximal aortic extension (the AFX2 endovascular AAA system proximal extension (VELA)) can also be performed (50). VELA provides sealing and additionally reduces the risk of migration of the stent graft (50). The main body is regularly produced with standard diameters from 22 to 28 mm; the iliac limbs have regular sizes from 13 to 20 mm (57). The typical structure of the AFXsg is demonstrated in Figure 6.

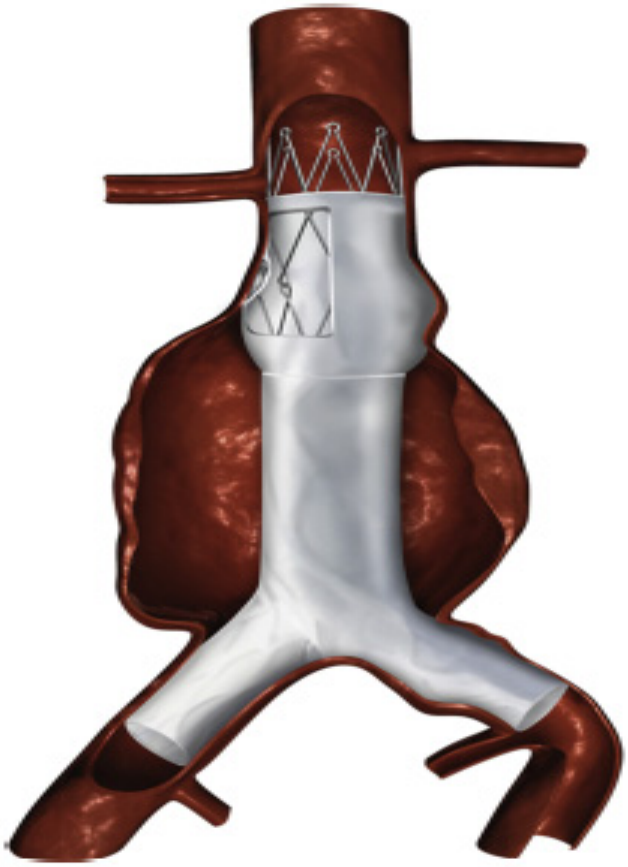


Figure 6. The AFX (Endologix, Irvine, CA, USA) stent graft. The AFX skeleton comprises a cobalt-chromium alloy in a self-expanding unibody. Exterior to the stent, the fabric comprises a multilayer ePTFE (expanded polytetrafluoroethylene) material. The stent is adhered only to the proximal and distal ends at the proximal aortic extension, allowing the ePTFE to move autonomously and adjust to different surfaces, providing sufficient sealing of the aneurysm sac (38). This is the unique feature of this endograft. From

Welborn, M.B. et al., Clinical outcome of an extended proximal seal zone with the AFX endovascular aortic aneurysm system, J Vasc Surg. 60(4): p.876-83 (55) (with kind permission from Elsevier, licensed, order number 4987700797191)

The AFXsg sits on the aortic bifurcation and is the only unibody device using anatomical fixation for device stabilization (58,59). The design, known as ActiveSeal, allows the comfortable STRATA material to move independently of the stent and accomodate varied shapes of the proximal neck and aortic bifurcation (50). This endograft provides relining of the aorta and common iliac arteries, and the risk of obstruction or occlusion is minimized (50). The endograft acts as a pillar and allows the use of a proximal, larger diameter tube endograft for sealing in the aortic neck (60). This feature is relevant when treating individuals with pathologies such as PAUs of the infrarenal aorta, which are in most cases combined with a narrow or normal aortic bifurcation (60).

Instructions for use (IFU) of AFXsg

The proximal aortic anatomy was often discussed as the main criterion for the technical success and durability of EVAR. Conversely, the distal anatomical parameters were less clearly defined, although they can be considered potential pitfalls of this procedure (50). Currently, a narrow aortoiliac bifurcation is considered a relative contraindication for a patient's eligibility for EVAR (60). Regarding AFX endografts, no minimum cutoff exists for the aortic bifurcation. According to the IFU, "the appropriate patient selection includes an adequate iliac/femoral artery access congruent with delivery systems (diameter 6.5 mm), an adequate proximal aortic neck seal zone ≥18 to ≤32 mm diameter, ≥15 mm distal fixation length and ≤60° angle to the aneurysm sac, and adequate common iliac artery seal zones (≥10 to ≤23 mm diameter, ≥15 mm length, ≤90° angle to the aortic bifurcation)" (57,60). The key anatomical elements of successful aneurysm exclusion also include freedom from thrombus and calcification at the aortic seal zones (26,61). Failure to meet these anatomical criteria is associated with a reduced success rate. In these cases, more invasive procedures are recommended (open repair or hybrid procedure with or without extra-anatomical reconstruction such as a crossover femoro-femoral bypass) (62). Figure 7 presents an example of successful treatment of PAU with an AFXsg with CT imaging before and after the procedure.

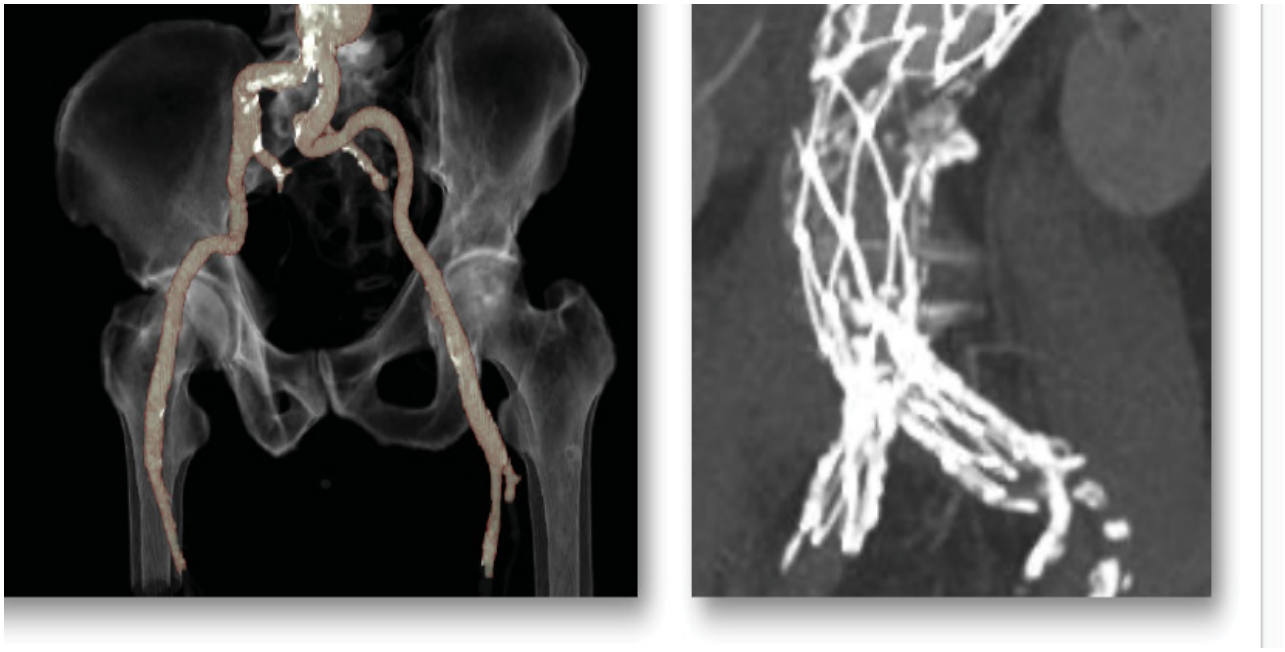


Figure 7. Penetrating aortic ulcer before and after endovascular treatment with AFX stent graft. A) Three-dimensional volume imaging of penetrating aortic ulcer (PAU**).** This illustration represents an infrarenal PAU with calcification and narrow aortic bifurcation before endovascular treatment. **B)** Coronal multiplanar reformation 3 years after implantation of AFX stent graft. The main body of the device was placed directly onto the aortic bifurcation. The proximal extension (VELA) seals the infrarenal segment. No endoleaks, limb occlusions/stenoses, or endograft migration were observed during 3 years follow-up time. Modified according to Wagenhäuser, M.U. et al., Use of AFX stent graft in patients with extremely narrow aortic bifurcation – a multicenter retrospective study, Int j Vasc Med,2021 Oct4; 2021:7439173. doi: 10.1155/2021/7439173 (63) (with kind permission from Hindawi, Creative Commons Attribution License (CC BY 4.0)).

1.3Aim of the study

Endovascular treatment of aortic pathologies with narrow bifurcation remains a controversial subject. A distal aortic diameter under 20 mm is the limiting factor for modular devices with an increased risk of limb obstruction. The unibody design of the AFXsg with its fixation on the aortic bifurcation is believed to benefit the treatment of abdominal aortic aneurysms and PAUs with narrow bifurcations.

The current study's overarching aim was to evaluate patients with narrow infrarenal aortic pathologies treated with AFXsgs, particularly focusing on stenoses, occlusions, and EL rates for patients with AAA and PAU in the short- and long-term follow-up period. The trial focused on analyzing the intraoperative, perioperative, and postoperative results for both patient groups. Demographic, anatomical, and procedural parameters, freedom from reinterventions, stenoses/limb occlusions, and ELs and aortic diameter shrinkage in the follow-up time were retrospectively analyzed regarding the differences between AAA and PAU patients.

The primary objective of this study was to investigate the technical success of the AFXsg in narrow bifurcations, and the primary endpoint was freedom from limb occlusions/stenoses. The secondary endpoints were freedom from type I and III ELs, freedom from late rupture, and a stable or decreased aneurysm sac diameter.

2. Materials and methods

2.1 Study design

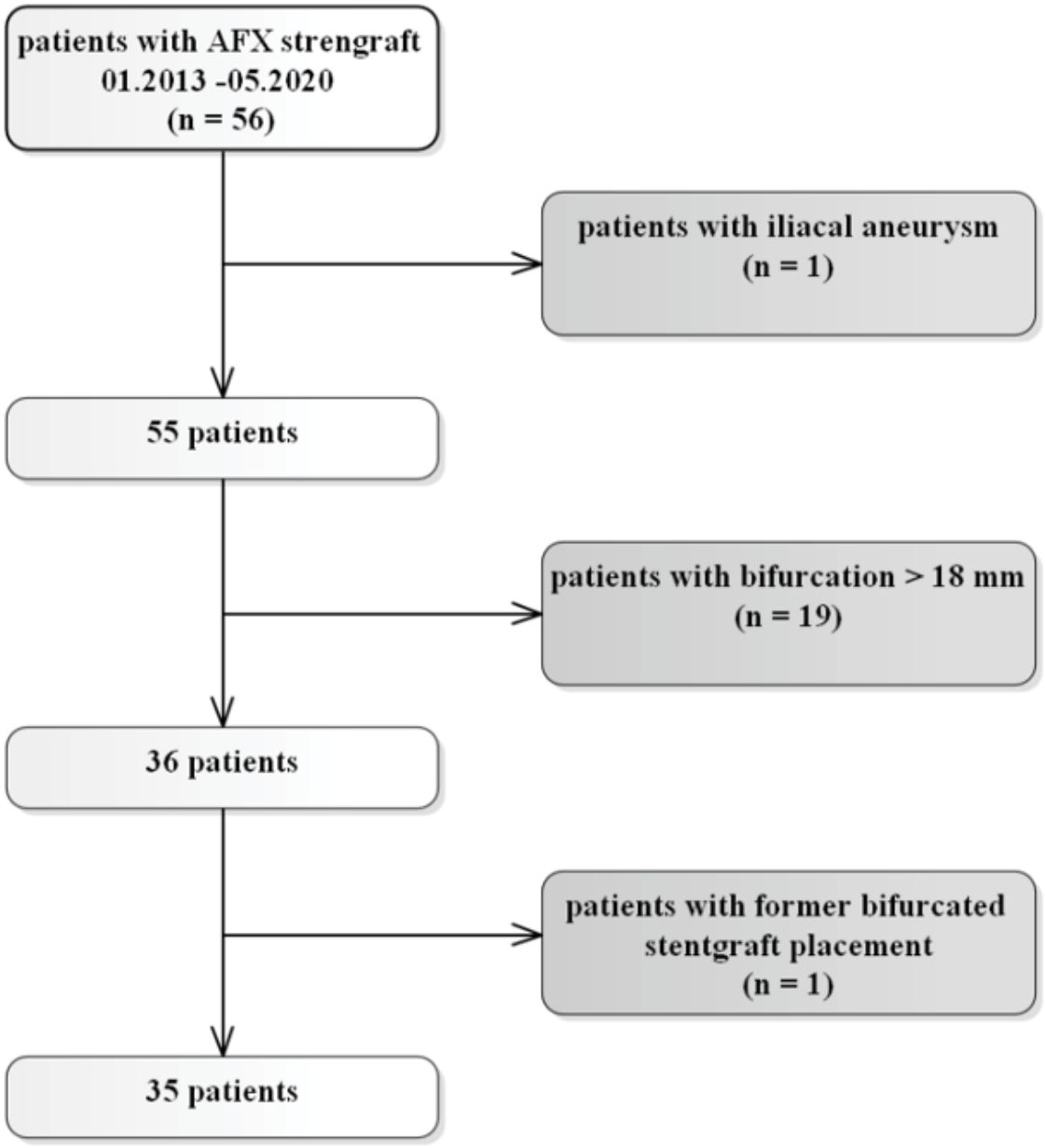
This clinical trial is a retrospective multicenter study conducted according to the principles of the Declaration of Helsinki, good clinical practice, and the appliable guidelines, regulations, and facts. University Hospital in Düsseldorf and three other centers participated in the recruitment: University Hospital of Muenster, St. Marien Hospital in Bonn, and Hubertus Protestant Hospital in Berlin. The study was approved by the Ethics Committee of the University of Düsseldorf and adhered to the principles of the Declaration of Helsinki (Study Nr: 6117R, Register ID: 201705).

2.2 Patient data

University Hospital in Düsseldorf and three more centers were enrolled: University Hospital of Muenster, St. Marien Hospital in Bonn, and Hubertus Protestant Hospital in Berlin. The inclusion criteria in the study were patients with aortic pathologies (AAAs and/or PAUs), which were electively treated from January 2013 to May 2020 with AFXsgs (Endologix, Irvine, CA, USA), aortic bifurcation diameter ≤18 mm, and patient age over 18 years. Sixteen patients (45.7%) treated before September 2016 received AFX1 stent grafts. In September 2016, the AFX2 stent graft was launched in Germany. Nineteen study patients operated on after September 2016 (54.3%) were treated with AFX2 stent grafts. The conventional definition of a narrow aortic bifurcation is generally considered as 18 or 20 mm (12). For this project, the threshold was defined as 18 mm to assess the outcomes with more complex, challenging aortas. The following parameters were retrospectively examined: demographic parameters, anatomical dimensions of the infrarenal aorta and iliac vessels, comorbidities, medication, duration of the operation, adjunctive procedures, intensive care period, the total length of hospital stay, 30-day mortality and morbidity, long-term morbidity, and complications.

During the total study period, 1,062 EVAR procedures were cumulatively performed in the participating hospitals: 56 patients underwent EVAR with AFXsg in the above-mentioned hospitals during the study period, and 35 patients were finally enrolled in the study. The algorithm for selecting the patients for the trial is demonstrated in Figure 8. One patient with

an iliac aneurysm was excluded due to the lack of aortic pathology, and 19 patients with aortic bifurcations >18 mm were also excluded from the study.



n: number

Figure 8. Selection of patients for the study. The exclusion criteria of the study were non-aortic aneurysms and patients with aortic bifurcation >18 mm. One patient with a former bifurcated stent graft mismatched the inclusion criteria because, with this status, measurement of the native aortic bifurcation is impossible.

The documentation of parameters included smoking history; cardiac, renal, and pulmonary status; hyperlipidemia; hypertension; diabetes mellitus; concomitant aneurysms; prior interventions; and peripheral artery disease. These data were collected retrospectively using standardized questionnaires designed specifically for the current project.

The primary endpoints of the study were defined as freedom from limb stenoses/occlusions and freedom from ELs. Secondary endpoints were defined as the necessity for reinterventions, procedure-related mortality, and adverse events (e.g., cardiological events and stroke). Clinical success was defined as complication-free stent graft deployment with sufficient angiographic sealing of the AAA or PAU with free perfusion of limbs by true aortic lumen, without aneurysm-related death, type I or III ELs, device thrombosis, aneurysm -related complications, or conversion to open repair. The early morbidity was assessed using the Dindo-Clavien (represented in Table 2) classification (64).

Table 2. Dindo-Clavien classification of postoperative complications. The Dindo-Clavien classification is a standardized, reproducible system for registering surgical complications. It comprises seven grades. The severity of surgical complications is graded according to the type of therapy needed for complication management. Modified according to Dindo, D. et al. Classification of surgical complications: a new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg, 2004. 240(2): p. 205-13 (64) (with kind permission from Wolters Kluwer, licensed, Order Number 4992080363557).

Grade	Definition
I	Any deviations from normal postoperative course without the need for any treatment (Allowed regimes are antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy.)
II	Requiring pharmacological treatment
III	Requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention without general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication requiring intensive care management
IVa	Single-organ dysfunction (including renal replacement therapy)
IVb	Multiorgan dysfunction
V	Death of patient

The follow-up protocol included physical examination, CEUS, or CTA at 30 days, 1 year, and then yearly thereafter. All data were retrospectively collected in a dedicated database, including demographic data, perioperative risk factors, medication, clinical and diagnostic preoperative assessments, intraoperative findings, and early (30 days) and long-term follow-up results, focusing on limb occlusions and hemodynamically relevant stenosis. The measured outcomes were separated into technical success and early (first 30 postoperative days) and long-term (after 30 postoperative days) results. Early outcomes comprised mortality, morbidity, and freedom from ELs. Long-term outcomes included survival, freedom from ELs, limb occlusions/stenoses and secondary reinterventions, symptom recurrence, and stent graft durability.

2.3 Practice of AFXsg implantation

Seventeen French (Fr) introducer systems can be positioned via either iliac artery. As with every EVAR, the less calcified and less tortuous iliac artery is preferred for delivery catheter access, allowing easier manipulation for introducing the main body (50). The access vessel diameter should be congruent with the endovascular access technique and the dimensions of the endograft delivery systems (51). Significantly calcified, occlusive, tortuous, or partially thrombosed arteries may interfere with the EVAR placement and may increase the risk of embolization and occlusion (50,51). The freedom from kinking of at the minimum one internal iliac artery should be preserved to prevent the risk of pelvic ischemia (50,57).

The deployment of AFXsg as a unibody device requires using guidewire systems deployed across the bifurcation from the contralateral side with the endograft, which is directly introduced from the other side (50,51). The contralateral limb will be guided into position by retraction of the wire introduced from the contralateral side, so the graft rides the aortic bifurcation (51).

Extreme proximal neck angulation, a short proximal aortic neck seal zone, and abnormal calcification and/or plaque are the anatomical features leading to insufficient exclusion of the aneurysm with an AFXsg (57,59). According to the recommendations of Endologix, endovascular surgeons should arrange the maximum overlap of stent graft components, especially in cases of large or long aneurysms. In cases of inadequate overlap through a two-part configuration, positioning of a third (bridging stent graft) should be performed (53,57,59). As per the revised IFU for an AFXsg, a minimum component overlap of at least 30 to 40 mm is recommended (55,57).

According to the IFU of the AFXsg, the following parameters should be evaluated in selecting devices when planning stent graft implantation: “angulation of the infrarenal aortic neck and iliac arteries, anatomy of the aortic neck, infrarenal aortic diameter, aneurysm diameter and aortic tortuosity, length from the most caudal renal artery to the aortic bifurcation, diameter of the aortic bifurcation, length from the aortic bifurcation to the distal seal zone, diameter of the external and common iliac arteries” (57). The algorithm for deploying the AFXsg is demonstrated in Figure 9.

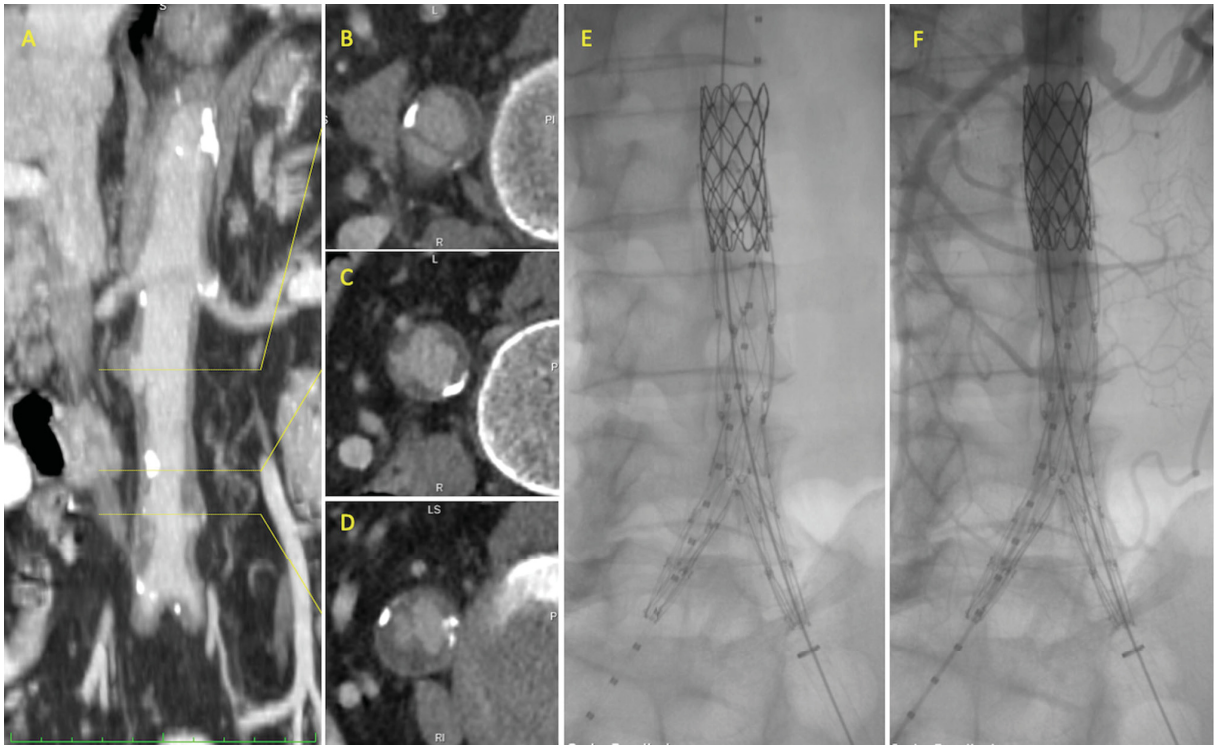


Figure 9. Deployment of the AFX2 (Endologix, Irvine, CA, USA) stent graft. Demonstration of preoperative CTA: **A)** infrarenal acute aortic syndrome, **B)** infrarenal aortic dissection, **C)** intramural hematoma, **D)** penetrating infrarenal abdominal aortic ulcer, **E)** intraoperative angiogram after deployment of AFX system with additional proximal extension. **F)** after contrast medium application (11)**.** Modified according to Pecoraro et al., Endovascular treatment of spontaneous and isolated infrarenal acute aortic syndrome with unibody aortic stent-grafts, World J Surg. 44, pp. 4267-4274 (2020) (11) (with kind permission from Springer, licensed, *Creative Commons Attribution 4.0 International* (*CC*-BY-4.0)).

2.4 Statistical analysis

The data were statistically analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Ill.). A repeated measures ANOVA was used to analyze changes in the mean score at different points in time; p-values of <0.05 were considered statistically significant. Furthermore, a Kaplan-Meier analysis was performed to assess the freedom from reinterventions, mortality, and freedom from limb occlusion. Kaplan-Meier estimations are graphically presented as mean ± standard deviation. The log rank test was performed to compare differences between PAU and AAA patient groups. All continuous variables are presented as mean ± standard error or relative frequencies with percentages. According to the Kolmogorov-Smirnov normality test, the Student`s t-test or Mann-Whitney U-test were used to compare differences between AAA and PAU patients for relevant morphological and procedural parameters and short- and long-term outcomes. Aycan Workstation OsiriX MD Version 10.0 was used for measuring angulation-adjusted aortic dimensions.

3. Results

3.1 Patient population

From January 2013 to May 2020, 35 patients characterized by narrow aortic bifurcation with a mean age of 73.8 ± 7.2 years were treated with AFXsgs. Within the study cohort, 17 (48.6%) patients suffered from AAA and 18 (51.4%) from PAU, while two (5.7%) patients presented with a combination of both aortic pathologies. For one patient (2.9%), an EVAR with AFX was performed due to an EL type Ib with a causal connection to an insufficient landing zone after tube stent graft implantation (Medtronic, Dublin, Ireland) for PAU treatment. The demographic data and American Society of Anesthesiologists (ASA) classification of the study patients, concomitant diseases, and risk factors are summarized in Table 3.

Table 3. Patient demographics and comorbidities. The table demonstrates patient baseline characteristics for the AAA and PAU groups and the total study cohort. Data are presented as frequency distribution with percentages or mean ± standard deviation (SD) (n = 35). Of note is the higher proportion of patients with ASA IV classification and patients with prior interventions in the AAA group. Modified according to Wagenhäuser, M.U. et al., Use of AFX stent graft in patients with extremely narrow aortic bifurcation – a multicenter retrospective study, Int J Vasc Med. 2021 Oct4; 2021: 7439173.doi: 10.1155/2021/7439173 (63) (with kind permission from Hindawi, licensed, Creative Common Attribution License (CC BY 4.0)).

	AAA (n = 17)		**PAU (n = 18)**		**Total (n = 35)**	
Target	frequency distribution / mean	percentage (%) / standard deviation	frequency distribution / mean	percentage (%) / standard deviation	frequency distribution / mean	percentage (%) / standard deviation
gender m:f	13:4	76.5:23.5	14:4	77.8:22.2	27:8	77.1:22.9
ASA classification	II: 4/17 III: 7/17 IV: 6/17	II: 23.6 III: 41.1 IV: 35.3	II: 6/18 III: 10/18 IV: 2/18	II: 33.3 III:55.6 IV:11.1	II: 10/35 III: 17/35 IV: 8/35	II: 28.6 III: 48.6 IV: 22.8
age (years)	71.2	6.6	75.8	7.6	73.8	7.2
PAOD	8/17	47.1	2/18	11.1	10/35	28.6
prior interventions (CAD or PAOD)	5/17	29.4	3/18	16.7	8/35	22.8
type 2 diabetes	5/17	29.4	0/18	0	5/35	14.3
smoking history	8/17	47.1	3/18	16.7	11/35	31.4
hypertension	17/17	100	16/18	88.9	33/35	94.3

hypercholesterinemia	17/17	100	14/18	77.8	31/35	88.6
CAD	5/17	29.4	6/18	33.3	11/35	31.4
CKD (serum creatinine value >1.5 mg/dl)	3/17	17.6	5/18	27.8	8/35	22.8
COPD	6/17	35.3	4/18	22.2	10/35	28.6

AAA: abdominal aortic aneurysm; PAU: penetrating aortic ulcer; m: male; f: female; ASA: American Society of Anesthesiologists; PAOD: peripheral arterial occlusive disease; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; mg/dL: milligrams per deciliter; n: number

The mean maximum aortic diameter before the AFX device implantation procedure was 44.0 ± 11.4 mm. The mean aortic bifurcation diameter was 15.8 ± 2.2 mm (range 11–18 mm). The preoperative measurements and anatomical characteristics, including all the aforementioned aortic pathologies, are summarized in Table 4. The anatomical parameters were comparably distributed between PAU and AAA with exceptions for the maximal aortic diameter (p = 0.000), maximal infrarenal aortic neck diameter (p = 0.001), and infrarenal aortic neck length (p = 0.019).

Table 4. Preoperative artery dimensions. The table demonstrates the preoperative anatomical characteristics of the study patients. The data were derived from angulation-adjusted measurements and are presented as mean ± standard deviation with minimum–maximum range (n = 35). Modified according to Wagenhäuser, M.U. et al., Use of AFX stent graft in patients with extremely narrow aortic bifurcation – a multicenter retrospective study, Int J Vasc Med. 2021 Oct4; 2021: 7439173.doi: 10.1155/2021/7439173 (63) (with kind permission from Hindawi, licensed, Creative Common Attribution License (CC BY 4.0)).

	AAA (n = 17)		**PAU (n = 18)**			**Total (n = 35)**	
Target	**mean ± standard deviation**	**min–max range**	**mean ± standard deviation**	**min–max range**	**p-value**	**mean ± standard deviation**	**min–max range**
maximal aortic diameter (mm)	51.6 ± 9.5	34–72	36.1 ± 6.8	23–72	*p = 0.000	44.0 ± 11.4	23–72
aortic bifurcation diameter (mm)	16.2 ± 2.12	12–18	15.9 ± 2.2	11–18	p = 0.50	15.8 ± 2.2	11–18
max CIA left diameter (mm)	12.8 ± 2.00	8–15	11.8 ± 2.1	7–17	p = 0.60	11.9 ± 2.2	7–17
min CIA left diameter(mm)	9.8 ± 1.5	7–12	10.6 ± 1.9	6–13	p = 0.14	10.1 ± 2.5	6–13
max CIA right diameter (mm)	12.9 ± 2.3	10–20	12.4 ± 2.7	8–21	p = 0.87	12.7 ± 2.5	8–21
min CIA right diameter(mm)	9.6 ± 1.4	8–12	10.7 ± 2.1	6–15	p = 0.44	10.4 ± 1.9	6–15
CIA length right (mm)	50.1 ± 16.0	24–76	53.8 ± 15.3	31–80	p = 0.88	51.9 ± 16.0	24–80

CIA length left (mm)	50.8 ± 14.1	29–83	53.3 ± 15.3	26–80	p = 0.61	52.1 ± 14.6	26–83
max EIA left diameter (mm)	8.3 ± 1.6	7–10	7.7 ± 1.2	5.5–10	p = 0.18	8.0 ± 1.9	5.5–10
min EIA left diameter(mm)	7.9 ± 1.9	5.5–10	7.6 ± 2.3	3–9	p = 0.06	7.8 ± 1.8	3–10
max EIA right diameter (mm)	9.2 ± 1.5	7–10	8.8 ± 1.8	5–10	p = 0.63	9.0 ± 1.6	5–10
min EIA left diameter (mm)	8.2 ± 2.3	3–10	7.9 ± 1.9	4.5–9	p = 0.62	8.1 ± 2.2	3–10
max infrarenal aortic "neck" diameter (mm)	28.4 ± 10.8	17–61	20.9 ± 2.8	17–26	*p = 0.001	24.8 ± 8.2	17– 61
infrarenal neck length (mm)	36.2 ± 16.8	10–68	38.4 ± 17.8	15–80	*p = 0.02	38.2 ± 24.2	10–80

AAA: abdominal aortic aneurysm; PAU: penetrating aortic ulcer; CIA: common iliac artery; EIA: external iliac artery; mm: millimeter; n: number; max: maximum; min: minimum

Significant intraluminal thrombi occurred in 19 patients (54.3%), and 15 patients (42.9%) had kinking of the iliac arteries. The abdominal aortic calcification (AAC) score was used to evaluate the progression of the calcific lesions of the aortic bifurcation, and the AAC grading is presented in Table 5. The AAC scores for the study patients were as follows: grade 0: 1 (2.9%), grade 1: 20 (57.1%), grade 2: 12 (23.3%), grade 3: 2 (5.7%).

Table 5. Abdominal aortic calcification (AAC) score. Grading of the classification was measured at the walls of abdominal aorta adjoining to vertebrae L1–L4 modified according to Honkanen, E. et al., Abdominal aortic calcification in dialysis patients: results of the CORD study, Nephro Dial Transplant, 2008. 23: p. 4009-4015 (65) (with kind permission from Oxford University Press, licensed, Creative Common Attribution License (CC BY 4.0)).

Grading	Definition
0	no calcification in front of the vertebra
1	small calcific deposit filling less than 1/3 of aortic circumference
2	calcification of 1/3–2/3 of aortic wall
3	calcification of 2/3 of aortic wall or more

Considering antiplatelet and anticoagulation treatment, information was collected for 33 patients. There were 18 patients (51.4%) who were treated with single antiplatelet therapy. Of these, 17 patients were treated with aspirin, and one patient (2.9%) was treated with clopidogrel; eight patients (22.9%) were received dual antiplatelet therapy; seven patients (20%) received oral anticoagulation; four of them had a combined treatment with aspirin.

3.2. Procedural parameters

Thirty-two (91.4%) AFXsg implantations were performed under general anesthesia; three (8.6%) patients underwent the procedure under regional anesthesia. A surgical cut-down for artery exposure was used for 19 (54.3%) operations, while percutaneous access was performed for the remaining 16 (45.7%) stent graft implantations. The overall mean procedure time was registered as 114.8 ± 39.9 min (range 52–223 min) with a mean fluoroscopy time of 19.9 ± 9.9 min (range 3.8–40 min). The intraoperative technical data are presented in Table 6. Significant differences were found for all three intraoperative technical parameters between AAA and PAU patients. Patients with PAU required significantly shorter procedure times (p = 0.029), significantly reduced fluoroscopy time (p = 0.001), and lower contrast media volume (p = 0.014).

Table 6. Intraoperative technical data. Data were extracted from operative reports and are presented as mean ± standard deviation with minimum to maximum range. All registered perioperative technical parameters were shorter/less for patients with penetrating aortic ulcers compared with patients in the abdominal aortic aneurysm group. Modified according to Wagenhäuser, M.U. et al., Use of AFX stent graft in patients with extremely narrow aortic bifurcation – a multicenter retrospective study, Int J Vasc Med. 2021 Oct4; 2021: 7439173.doi: 10.1155/2021/7439173 (63) (with kind permission from Hindawi, licensed, Creative Common Attribution License (CC BY 4.0)).

	AAA (n = 17)		**PAU (n = 18)**			**Total (n = 35)**	
Target	**mean ± standard deviation**	**min–max range**	**mean ± standard deviation**	**min–max range**	**p-value**	**mean ± standard deviation**	**min–max range**
operation time (min)	127.0 ± 43.9	75–223	103.3 ± 35.2	54–171	*p = 0.029	114.8 ± 39.9	54–223
fluoroscopy time (min)	24.2 ± 7.8	9.5–40.0	13.5 ± 7.6	3.8–35.3	*p = 0.001	19.9 ± 9.9	3.8–40.0
contrast volume (ml)	43.9 ± 27.1	13–120	22.4 ± 14.5	15–70	*p = 0.014	33.3 ± 22.5	13–120

AAA: abdominal aortic aneurysm; PAU: penetrating aortic ulcer; min = minute; ml = milliliter; n: number

The mean component overlap was 48.3 ± 11.5 mm (AAA: 48.3 ± 11.5 mm; PAU: 48.5 ± 11.1 mm) with no significant differences for either group (p = 0.654). Based on changes in the IFU of the AFXsg, the mean component overlap zone augmented in the course of the study period from 46.3 ± 11.1 mm in 2013 to 51.8 ± 7.4 mm in 2019. Twelve AFXsg implantations were performed without using the VELA proximal aortic extension (AAA: 4; PAU:8).

No perioprocedural mortality, endograft thrombosis, intraoperative conversion to OR, AFXsg migration, or ELs based on postoperative angiograms were registered. Additional operative procedures (summarized in Table 7) were performed on four patients (11.6%). These procedures contained endarterectomy of the common femoral artery (CFA) in two cases (5.8%; one PAU and one AAA patient), iliac relining with bare metal stent (BMS) implantation in one PAU patient (2.9%), and balloon angioplasty of the external iliac artery (EIA) and common iliac artery (CIA) in one AAA patient (2.9%).

Table 7. Common intraoperative adjunctive procedures. Four study patients required additional intraoperative procedures. Data are presented as absolute frequency with percentages (%). Modified according to Wagenhäuser, M.U. et al., Use of AFX stent graft in patients with extremely narrow aortic bifurcation – a multicenter retrospective study, Int J Vasc Med, 2021. Oct4; 2021:7439173 (63) (with kind permission from Hindawi, licensed, Creative Commons Attribution License (CC BY 4.0)).

Additional procedure	Number	Percentage (%)
endarterectomy of CFA	2	5.8
iliac relining (stent)	1	2.9
angioplasty of EIA and CIA	1	2.9

CFA = common femoral artery, CIA = common iliac artery, EIA = external iliac artery

3.3 30 days – outcome

The mean length of intensive care unit stay was 0.9 ± 0.9 days (AAA: 1.1 ± 0.9 days; PAU: 0.8 ± 0.4 days, p = 0.807), and the mean length of in-hospital stay was 8.2 ± 4.2 days (AAA: 8.7 ± 3.6 days; PAU: 7.5 ± 3.4 days, p = 0.613); 31 patients (88.6%) were discharged home while one geriatric patient (2.9%) was transferred from hospital to short-term care. Another three patients (8.7%) were either transferred to the nephrology or cardiology department due to an acute kidney injury (AKI) or an acute coronary syndrome (ACS).

During the short-term 30-day follow-up, no deaths, reinterventions, access-related pseudoaneurysms, or other AFXsg-associated complications (such as ELs, stent graft

thrombosis, or limb occlusions) were observed. The early morbidity was summarized according to the Dindo-Clavien classification (64) and is presented in Table 8.

Table 8. Postoperative complications in the study patients, classified according to Dindo-Clavien (64). The above-mentioned Dindo-Clavien classification is a standardized form for systematization of postoperative surgical complications. By grade ≥ IIIa, an intervention is required, and grade V means the death of a patient. The types of early postoperative complications of the study patients are represented with absolute frequency with percentages (%).

Complication	n (%)	
grade I	2 (5.8%)	small endoleak type IIa without therapy
grade II	4 (11.6%)	urinary infection with acute kidney injury grade I, tachyarrhythmia, bilateral pneumonia, gout attack
grade IIIa	2 (5.8%)	acute coronary syndrome
grade IIIb		
grade IVa		
grade IVb		
grade V	1 (2.9%)	acute kidney injury grade III leading to hemodialysis, respiratory insufficiency
major, ≥ IIIb	1 (2.9%)	
total	8 (23.2%)	

n: number

One patient with PAU (2.9%) reported intravenous heroin abuse and HIV infection in his medical history. In the first postoperative week, this patient suffered an AKI due to contrast medium exposure, which required hemodialysis. Furthermore, this patient developed consecutive respiratory decompensation with acute lung injury in the following postoperative weeks. The weaning time was prolonged, percutaneous dilatation tracheostomy was performed, and the patient was transferred to a specialized weaning hospital. Another two AAA patients (5.8%) suffered acute myocardial infarctions (ACS), which were treated with percutaneous coronary intervention (PCI). Cardiac arrhythmia (atrial fibrillation) manifested in only one patient (2.9%), who was successfully converted to sinus rhythm with antiarrhythmics.

The first imaging follow-up examination was performed for 33 patients (94.3%) of the study cohort within the first 30 days post-surgery (excluded: patient with AKI and one patient with ACS). Twenty patients (60.6%) received a CTA scan, while 13 patients (39.4%) had a CEUS control. In these examinations, two AAA patients (5.8%) with type II ELs were observed. They were treated conservatively and showed neither diameter progress nor stent device migration nor limb occlusion/stenosis during the entire follow-up time.

During the hospital stay, all study patients received thrombosis prophylaxis with low-molecular-weight heparin; 29 patients (82.8%) were treated with anticoagulation with aspirin and 9 patients (25.7%) with clopidogrel or other antiplatelets. After discharge, patients pretreated with marcumar continued to be readmitted for marcumar after completion of wound healing.

3.4 Long-term follow-up

The mean long-term follow-up time was 20.4 ± 22.8 months (AAA: 23.6 ± 21.6 months; PAU: 18.5 ± 15.4 months, p = 0.135). Notably, a reduction in the mean maximum aortic diameter was observed compared to the baseline (44 ± 11.4 mm versus 40.7 ± 9.9 mm) at 15.5 ± 12.8 months follow-up time (AAA: 51.6 ± 9.5 mm versus 48.7 ± 7.7 mm at 17.0 ± 15.8 months follow-up; PAU 36.1 ± 6.8 mm versus 33.8 ± 7.8 mm at 13.6 ± 10.6 months follow-up).

Endoleaks in the long-term follow-up

Besides the two type II ELs registered within 30 days after the AFXsg implantation, no additional type II ELs occurred. Overall freedom from type II ELs was 91% (68%–98%) at the end of the follow-up time (Figure 10A). No type I ELs were registered.

One new type III EL (2.9%) was experienced in the trial. The aforementioned AAA patient presented with a type III EL at a 4-year follow-up after bilateral limb stenosis. The patient was treated with two cuff implants (diameter: 28 mm; length: 70 and 82 mm, Medtronic, Dublin, Ireland) into the AFXsg. Initial technical success on completion of an angiogram was confirmed by CTA scans and CEUS during further follow-up imaging and examinations. The patient remained free from ELs. Therefore, freedom from type III ELs was 100% after 3 years and 83% (27%–97%) at the end of the follow-up time (Figure 10B).

Stenotic complications in the long-term follow-up

One AAA patient experienced limb stenosis (2.9%). This patient suffered from a peripheral arterial occlusive disease (PAOD), and his baseline AAA diameter was 72 mm. The patient complained of intermittent claudication due to bilateral limb stenosis of the CIAs at 4 months follow-up. The patient received bilateral BMS implantation in the CIAs and simultaneous

transluminal angioplasty (PTA) of the right popliteal artery as an additional procedure. This treatment was successful. At the end of the follow-up period, overall freedom from occlusive/stenositic complications of the limbs was 94% (67%–99%; Figure 10C).

During the long-term follow-up time, one death (2.9%, PAU patient) was registered in the second follow-up month caused by an acute chronic kidney injury with hospital-acquired pneumonia. Patient survival was 95% at the end of the follow-up time (Figure 10D). No aortic ruptures or stent device migrations occurred in the study cohort, while limb occlusions and ELs were observed only in the AAA group. Nevertheless, the study did not detect a significant difference between AAA and PAU patients considering relevant long-term patient outcomes (63).

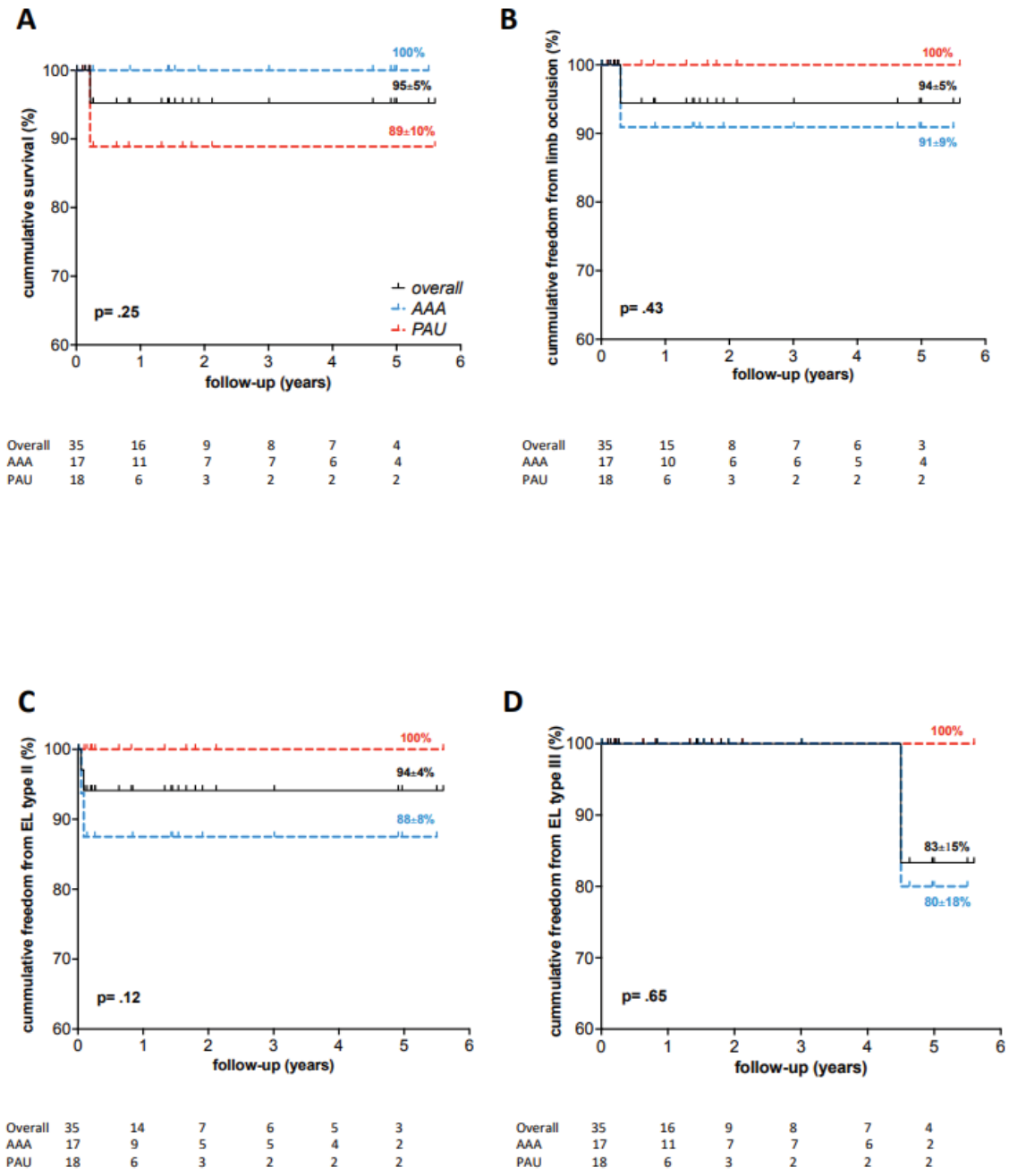


Figure 10. Kaplan-Meier estimator for patient survival. Patient survival **A)** freedom from endoleak (EL) (B) was estimated using the Kaplan-Meier estimator (A), freedom from type II EL **B**), type III **C)** and limb occlusion **D)**. Patient survival at the end of the follow-up after 5.6 years was 95% ± 5%, freedom from type II EL was 91% ± 6%, type III EL was 83%± 15%, and limb occlusion was 94.1%± 5% (n = 35). Modified according to Wagenhäuser, M.U. et al., Use of AFX stent graft in patients with extremely narrow aortic bifurcation – a multicenter retrospective study, Int J Vasc Med. 2021 Oct4; 2021: 7439173.doi: 10.1155/2021/7439173 (63) (with kind permission from Hindawi, licensed, Creative Common Attribution License (CC BY 4.0)).

4. Discussion

Endovascular repair of AAAs substantially reduces intraoperative mortality, morbidity, and hospital stay duration. These topics represent a consistent perioperative advantage, especially for more morbid and older patients (66). However, device durability and reintervention rates are frequently discussed as disadvantages of EVAR, especially in the long-term follow-up. Moreover, every patient should match specific anatomical criteria listed in the IFU of each endograft (61).

The proportion of patients with aortic pathologies that do not have favorable anatomical characteristics compatible with the IFU of the commercially available modular endovascular device is estimated as approximately 20% (62). The diameter of the aortic bifurcation is included in these anatomical limitations for EVAR. A distal aortic diameter under 18 mm is a limiting factor for modular devices with an increased risk of limb obstructions (62).

AFXsg is an unique device which is anatomically fixed at the aortic bifurcation (63). This stent graft has a completely different structure with a long and small main body, which sits on the native aortic bifurcation, whereas in traditional aortobiiliac stent grafts, the bifurcation of the device is higher, and the two limbs must pass parallel to the aortic bifurcation (43). This feature is critical when treating individuals with pathologies such as PAUs of the infrarenal aorta, frequently combined with narrow/normal aortic bifurcations (50).

Some reference clinical trials focused on the advantages of the AFXsg versus modular devices; other authors published concerning the treatment of AAAs with narrow bifurcations using different endovascular devices. At the beginning of the current project, no published clinical data were available on the durability of AFXsgs in patients with narrow aortic bifurcations. Thus, this study remains the first clinical trial especially focused on patients undergoing treatment with AFXsgs for AAAs or PAUs with extremely narrow aortic bifurcations with a mean aortic bifurcation diameter of <18 mm (63).

Veraldi et al. retrospectively collected data from 195 patients with abdominal aortic aneurysms treated with Excluder/C3 Gore endoprostheses in two high-volume Italian centers between 2005 and 2017 (61). There were 141 patients with regular aortic bifurcations and 54 patients with narrow aortic bifurcations (<18 mm) (61). Technical success and procedural time were considered primary outcomes. Secondary outcomes included perioperative complications, long-term device-related complications, and reintervention rates (61).

Troisi et al. prospectively analyzed data from 817 patients with AAAs treated between July 2007 and August 2014 with Endurant stent grafts (66); 87 patients had narrow aortic

bifurcations ≤20 mm, and 730 had standard aortic bifurcations (65). Early and estimated 3-year outcomes were evaluated in these patients regarding mortality, freedom from stent graft-related reinterventions, and freedom from graft occlusions (66).

Strajina et al. reviewed data from 1,070 patients treated with heterogenous endovascular devices between 2000 and 2011; among them, 112 patients had narrow aortic bifurcations <18 mm (67). This study focused on freedom from ELs, stenoses/limb occlusions, and the rate of reinterventions (67).

Kouvelos et al. performed a retrospective analysis of data from 10 elective AAA patients treated from March to December 2014 with the AFXsg compared with a matched group of 20 patients with the Excluder stent graft implantation (53). The endpoints of the trial contained technical success and freedom from secondary reintervention and ELs, and aneurysm-related mortality (53).

Welborn et al. (2014) published a retrospective, multicenter, single-arm, observational study performed on 108 patients with intact and ruptured AAAs treated with AFXsgs with observation times exceeding 25 months; the focus was on ELs, limb occlusions, and performance of aneurysm-related secondary procedures (55).

Skibba et al. performed a retrospective study on 701 patients who underwent primary EVAR using Endologix Powerlink (2006–2011) and AFX (2011–2014) endografts; they analyzed the durability of these stent grafts focusing on type IIIa ELs during that period (70).

Melas et al. analyzed 21 patients with AAAs and abnormal aortic necks treated with AFXsgs with active proximal sealing (from April 2013 to July 2014) (59). Aneurysm exclusion and type Ia ELs served as primary outcomes; secondary outcomes included mortality, morbidity, stent graft migration, and other device-related complications (59).

The demographic data and data on risk factors and comorbidities of the study patients are comparable with data from other clinical studies (53,55,66,67). Compared with the data from the reference studies, the prevalence of female patients in the trial was relatively higher than in other study populations. This phenomenon can be explained by the high proportion of patients with PAUs. According to the current literature, the proportion of male patients treated for PAUs varies from 33% (Brinster et al.) to 73% (Eggenbrecht et al.) (68,12). One possible explanation for a high proportion of patients with PAU in the study is that increasingly multimorbid patients were assigned to major vascular surgery centers for endovascular therapy.

One of the most relevant registries of patients with AAA treated endovascularly is EUROSTAR. In 2007, Leurs et al. published the results for 1,190 patients from 62 European centers who participated in the EUROSTAR (EUROpean collaborators on Stentgraft

Techniques for Abdominal Aortic Aneurysm Repair) registry (69). In the EUROSTAR registry, 90.5% of the patients were male, 23.7% had a smoking history, 51.4% suffered from hypertension, and 34.1% had chronic pulmonary disease (69). The number of male patients in the EUROSTAR registry also reflects that mainly male patients suffer from abdominal aortic aneurysms (69). In patients with PAUs, gender-specific prevalence is variable; this could be confirmed by the current project. The prevalence of other risk factors in the trial is consistent with the EUROSTAR registry.

The patient cohort of the current study is characterized by a high proportion of multimorbid patients (71.4% of the study patients were ASA III or IV classified) (63). A possible explanation for this phenomenon is the assignment of increasingly multimorbid patients to major vascular surgery centers for endovascular treatment by referring physicians.

The age and sex of the patients were equally distributed in the PAU and AAA groups. Noticeable was the increased proportion of multimorbid patients (ASA IV-classified patients) in the AAA group (35.3%) versus 10.8% in the PAU group (63). The distribution of risk factors such as hypertension, hypercholesterinemia, and coronary artery disease was comparable in the PAU and AAA groups. Based on the detailed risk factors, it is assumed that AAA patients were more multimorbid than the PAU group. Factors such as PAOD and prior reinterventions were more frequently represented in the AAA patient group (*PAOD*: AAA – 47.5% versus PAU – 11.1%; *prior reinterventions*: AAA – 29.4% versus PAU – 16.7%) (63). These factors may provide a basis for potentially difficult iliac access in AAA patients.

Based on preoperative artery dimensions, significant differences were observed in the maximal aortic diameters between the AAA and the PAU group ($p = 0.000$) (63). This is consistent with the definitions of both aortic pathologies. The other parameters with significant differences were maximal infrarenal aortic neck diameter ($p = 0.001$) and infrarenal neck length ($p = 0.019$) (63). The aneurysm neck morphology is an important parameter of the applicability of EVAR. The proximal AAA neck is determined as the length of a normal caliber aorta between a more inferior situated renal artery and the beginning of the aneurysm sac (51). Thrombus, calcification grade, and proximal neck diameter are relevant determinants affecting endograft fixation and should be carefully evaluated preoperatively (51).

The PAU patients had an average infrarenal aortic neck diameter of 20.9 ± 2.8 mm; meanwhile, the AAA patient had an average neck diameter of 28.4 ± 10.8 mm (63). Thus, this may lead to the conclusion that the endovascular treatment of the AAA study patients involved more challenging anatomy for AFXsg implantation.

This hypothesis can be confirmed by analyzing procedure-related technical data. Procedural parameters such as operation and fluoroscopy times and contrast medium volume are important clinical and economic factors and can affect patient outcomes. The average operation time in the current study was 114.8 minutes, with significant differences for PAU and AAA patients p = 0.029). The mean procedure duration for AAA patients was 127.0 ± 43.9 minutes; meanwhile, the mean procedure time for PAU patients was 103.3 ± 35.2 minutes (63). The significantly lower operative procedure time for the PAU group can be explained by simpler and more suitable access vessels with lower angulation grades. Furthermore, PAU patients had fewer previous vascular interventions and operations in their history.

Due to the multimorbidity of study patients, the procedure duration is significant. At this point, EVAR shows clear advantages over open aortic repair. For example, in the DREAM study, 135 minutes were required for EVAR, while the average surgery time for open aortic repair was 151 minutes (36). On average, endovascular therapy can be performed in a shorter time than open surgery of the aortic aneurysm. However, the advantage is observed less in the slightly shorter operation time and more in the lower invasiveness of the endovascular method, which is reflected in the number of registered complications but also in the shorter hospital stay (42). In the clinical trial of Kouvelos et al., an average AFXsg implantation time of 97.5 min was recorded, while Welborn et al. took an average of 151 minutes to perform this procedure (53,55). The patients in the AFX group in the trial of Kouvelos et al. had favorable anatomical features compared with the current study: only 10% of the patients in the trial of Kouvelos had intraluminal thrombi, and 20% of them had AAC scores of 3, while in the current project, 54.3% of the patients had intraluminal thrombi and 29% measured an AAC score of 3. These factors can extend the procedure time. While only non-ruptured AAAs were included in the current study, Wellborn`s project also treated ruptured aneurysms (4.6% rAAA). This may be a possible explanation for a prolonged operative time in this trial.

In the clinical studies on the treatment of aortic aneurysms with narrow aortic bifurcations, the average procedure time was lower as in the current study: Veraldi et al. registered 88 minutes and Troisi et al. 86.9 minutes (61,66). A possible explanation is the narrower diameter of aortic bifurcation (15.8 mm) compared with 17.1 mm in the narrow bifurcation group in the study of Veraldi and 18.5 mm in the study of Troisi (61,66). Narrow aortic bifurcation is a particular challenge for endovascular surgeons and is associated with different pitfalls (high-grade calcification of bifurcation). Additionally, higher surgery duration in the earliest study patients can be explained by an initial lack of experience with the AFXsg.

With an average fluoroscopy time of 19.9 minutes, the results of the current project are significantly below those in the studies of Troisi et al. (24.4 minutes), Strajina et al. (25 minutes), and Welborn et al. (25 minutes) (66,67,55). The PAU patient study group required significantly shorter fluoroscopy time than AAA patients ($p = 0.001$) (63). This observation corresponds to the more challenging anatomy of the AAA group (significantly larger maximal aortic diameter of AAA patients), higher rate of PAOD, and previous reinterventions, which were registered more frequently in the AAA patients.

These anatomical characteristics also explain the significantly lower contrast volume in PAU patients versus AAA patients ($p = 0.014$). Meanwhile, the study patients required a much smaller dose of contrast medium (33.3 ml) compared with the other studies (63). In 20% of patients with chronic renal disease, a lower volume of contrast medium is relevant for preventing acute renal failure. For the AFXsg implantation, the average contrast medium volume in the study of Kouvelos et al. was 62.5 ml and in the study of Welborn et al. – 100 ml (53,55).

These discrepancies appear reasonable because all procedures (AAA and PAU) were performed only electively in the current project, where parameters such as procedure duration, fluoroscopy time, and contrast medium volume were simpler to control than in emergency situations (ruptured AAA) (63). The bifurcated design of the AFXsg makes cannulation of the contralateral iliac artery unnecessary. This leads to a reduction of nephrotoxic contrast medium use and fluoroscopy time (58).

Silingardi et al. published a comparative clinical trial focused on fluoroscopy time, amount of iodine contrast medium during elective unibody, and modular EVAR implantations. Since unibody stent grafts do not require gate cannulation, unibody devices require significantly less contrast medium and radiation exposure than modular devices (58). These promising results could be confirmed in the current trial, especially in the PAU patient group. Patients with preexisting nephropathies are at high risk of AKI after the application of iodinated contrast medium. Thus, reducing the contrast medium can benefit the postoperative outcome.

According to the relevant clinical studies, endovascular treatment of aortic pathologies with narrow bifurcations is associated with higher rates of additional intraoperative procedures (53,55,61,66,67). In the AAA and PAU groups, additional procedures were performed in 11.6% of patients (iliac relining with stent, angioplasty of EIA and CIA, and thromboendarterectomy of CFA) (63). In the study of Troisi et al., 20.6% of patients in the narrow bifurcation group received additional procedures (chimney technique in 13.8%, proximal active fixation in 3.4%, proximal aortic cuff in 2.3%, and hypogastric embolization in 1.1% (66). No significant

differences were found in the rate of additional procedures between the groups with narrow and standard aortic bifurcation, according to Troisi (66). In the trial of Strajina et al., implantation of kissing stents with balloon-expandable stents was performed in 21 patients (21%) with histories of recoiling after angioplasty, extremely narrow aortic diameter, or severe calcification (67). It is notable that in the study of Strajina et al., EVAR was performed with heterogeneous devices, so this could be a possible explanation for the higher rate of additional procedures (67). Frequently performed adjunctive procedures in patients with narrow bifurcations include high-pressure kissing balloon angioplasty and stent reinforcement of the iliac limbs (50). Intraprocedural concomitant maneuvers increase factors such as additional costs, time, and risk of periprocedural injuries with subsequent reinterventions. Even the consecutive risk of aortic rupture is elevated and could trigger the development of ELs (50). The use of unibody stent grafts can decrease the need for adjunctive ballooning and stenting, improve safety, and preserve the natural aortic bifurcation. These benefits can explain the lower rate of concomitant procedures performed in AAA and PAU patients compared with studies with bifurcated stent devices (50).

In both patient groups of the current study, sufficient postoperative results could be confirmed. In the AAA and PAU patients, 100% technical success was achieved. No graft thrombosis, conversions, stent migrations, or aneurysm-related deaths were observed during the perioperative period (63). The authors of reference studies also recorded maximum technical success. Troisi et al. described 99.4% technical success in their study (66). Type I ELs occurred in two patients. In one patient with a narrow aortic bifurcation, a massive peripheral embolization was detected and treated with a fibrinolytic drug (66). Veraldi et al. also described a technical success rate of 100% (61). In two cases, a balloon-expandable stent was implanted due to persistent kinking/stenosis (in the group of patients with a narrow aortic bifurcation) (61). In the study of Strajina et al., technical success was also observed in all patients; no conversions or disruptions of an aortic bifurcation were described (67). These data reinforce that EVAR is associated with high periprocedural success for modular and unibody devices.

Hospital and ICU stays are important qualitative and economic markers. The mean duration of the ICU stay of the study patients was 0.9 days. The average hospital stay was 8.2 days for both patient groups in the study (63). No significant differences in length of ICU stay ($p = 0.807$) and hospital stay ($p = 0.613$) were observed between the PAU and AAA patients (63). Due to the potential advantages of EVAR, such as reduced operative time, operative trauma, postoperative pain, and blood loss, the duration of ICU stay could be significantly reduced (42). In the DREAM study, patients were treated for open surgical therapy in the intensive care unit

for significantly longer than after endovascular therapy (3 days vs. 0.7 days on average) (43). The duration of the ICU stay in the DREAM trial is congruent with the data from the current study and reaffirms the advantages of EVAR in this point.

According to the current literature, EVAR is correlated with lower 30-day mortality and morbidity, shorter hospital stay, and reduction of complications, albeit more late interventions are related to the stent graft in comparison with OR (55,70). In clinical trials, AFX endografts show a low rate of complications such as EL type I, even in an atypical aortic anatomy after 30 days of follow-up (55, 59, 67, 70). Therefore, a 30-day follow-up was included in the current project as a relevant time point for patient examination and imaging.

In the AAA and PAU groups, no stent graft-associated complications, reinterventions, or mortality were recorded in the first 30 days. Els type II occurred in two AAA patients (5.8%), who remained asymptomatic and did not require secondary interventions (63). Kouvelos et al. analyzed the results for 10 patients treated with AFXsgs versus 20 patients treated with Gore Excluder endografts (53). In the AFX group, 20% of complications were observed during the postoperative period. One case of iliac thrombosis on the second postoperative day was treated by thrombectomy and iliac relining, and one patient with limb ischemia underwent an embolectomy on the fifth postoperative day (53). Both cases related to patients with severe peripheral obstructive artery disease and high-grade iliac tortuosity. In the current project, the proportion of patients with iliac kinking was 42.9% (63).

Studies focusing on AFXsgs demonstrated 30-day outcomes comparable with those of the current project. In the clinical trial of Welborn et al., no mortality and no stent graft-associated complications were registered in the patient group with intact aneurysms (55). Two reinterventions (1.9%) were performed in the first 30 days: the first reintervention could be explained by an inadequate overlap between the extension and the main body, and the other was caused by a type III EL (55). A similar incidence of complications in early outcomes was described in the study of Melas et al. (59). One patient developed a type II EL; however, he remained asymptomatic throughout the follow-up time (59).

In the aforementioned studies, aortic bifurcations of all calibers were observed. The next focus relates to studies on endovascular treatment of aortic aneurysms with narrow bifurcations. De Bruijn et al. collected the data from five patients with small bifurcations and/or large aortic necks (43). This patient group was treated with AFXsgs topped with Valiant Captivia endografts (Medtronic); no graft-related complications were registered as early outcomes (43). In the study of Troisi et al., no differences were found in 30-day mortality, aneurysm-related mortality, or major morbidity between the patient groups. The 30-day success rate of the group

with narrow bifurcations was 97.8%. The 30-day mortality rate was 1.7%. Two deaths occurred in the group of patients with narrow bifurcations; one of them was aneurysm-related (66).

In the trial of Veraldi et al., 9.5% of the narrow bifurcation group (five patients) had postoperative complications during the first 30 postoperative days: one groin hematoma (conservative treatment), one postoperative heart failure, and three bleedings from the iliac artery. No ELs, graft infections, kinking, or thrombosis occurred within the first 30 postoperative days in this study (61).

Based on these results, it can be assumed that the AFXsg is safe in the early postoperative period in PAU and AAA patients. Compared with data from studies focused on AFXsgs, the PAU and AAA groups of the current project had lower rates of major adverse events in the 30 days follow-up time (63). This appears reasonable as all patients enrolled in the study were treated on a planned basis, so the rate of complications, which has a causal relationship with shock, blood loss, and thromboembolic events, is significantly lower.

Type II ELs remain the most frequent complications in the first postoperative weeks in most reference studies. The pathomechanism of a type II EL is retrograde blood flow into the aneurysm via collaterals (for example, inferior mesenteric artery or lumbar arteries as one collateral artery in case of type Ia EL, and two or more collateral arteries in case of type IIb EL) (71). There is neither direct contact with the stent graft nor with the high-pressure aortic system. Type II ELs are mainly associated with a benign course and prognosis of spontaneous regression; an observative therapeutic approach with regular controls is justified in most cases (72).

Current guidelines recommend intervention in patients with type II ELs only in cases when the sac diameter exceeds 10 mm (risk factor for sac expansion) (73). The following interventional options are available: transarterial or translumbar embolization of collaterals via coiling (stainless steel/platinum coils) or agents (N-butyl cyanoacrylate) as well as direct puncture of the aneurysm sac with perfusion and coil application (74). Most type II ELs resolve spontaneously, and the 1-year postoperative prevalence ranges from 1% to 10% (74). However, evidence exists that persistent type II ELs are associated with increased risk of the following complications: sac enlargements, aneurysm rupture, reinterventions, and conversions to OR (19). The results from the EUROSTAR registry suggest that type II ELs are associated with progredient aneurysmal growth and reintervention but not with rupture or conversion to OR (75). The current study showed no correlation between type II ELs and adverse outcomes.

Lo et al. retrospectively analyzed 2,367 patients who underwent EVAR from 2003 to 2014 (Powerlink and Endurant stent grafts), focusing on the potential predictors of persistent type II

ELs including baseline demographics, comorbidities, and operative parameters (76). In this study, the patient group that developed ELs was on average older than the group of patients without ELs, less likely to have had high creatinine levels (>1.8), and less likely to have chronic obstructive pulmonary disease (COPD). This correlation with COPD can be explained by an increased blood viscosity in COPD patients leading to increased thrombus formation in atherosclerotic arteries (76). In both patient groups of the study, the two patients with type II ELs did not match the above-mentioned risk profile.

No anatomical differences were found between the patient groups with and without ELs in the study of Lo et al., while other clinical trials demonstrated an increase in the risk of ELs with a larger aneurysm diameter (76). While the coverage of the hypogastric artery and stent graft configuration had no association with the persistent type II EL, the hypogastric coil embolization was associated with a higher rate of persistent type II EL, according to the study of Lo et al. (76).

Long-term outcomes addressed the outcomes from postoperative day 30 onward. In the study with a mean follow-up time of 20.4 months, one multimorbid patient with PAU (ASA IV classified) died of pulmonary complications and acute and chronic kidney failure after the second postoperative month. This was the only deceased patient (2.9%) registered in the trial, and his death was neither connected to the procedure nor aneurysm-related (63).

The single case (2.9%) of limb stenosis during the long-term follow-up related to one AAA patient with a preoperatively diagnosed peripheral artery disease (PAD; bilateral ABI (ankle brachial index) of 0.4), who suffered from stenosis in the limbs (postoperative intermittent claudication, right > left) 4 months after the AFXsg implantation. He was treated by placement of BMSs in both CIAs with an additional PTA of the right popliteal artery. Four years after this treatment, a CTA incidentally showed a type III EL with aortic diameter growth up to 90 mm. Two cuffs were implanted proximal to the AFXsg. The intraoperative angiography showed no occlusions or ELs (63).

During the long-term follow-up time, no stent graft migrations were observed (63). Compared to unibody devices, stent grafts without active fixation (Aneu Rx or Talent) have a higher risk of migration and development of type 1a ELs (77). The use of the active seal method (for improving the distal seal and device patency) in combination with longer (20 mm) distal iliac limbs can guarantee the avoidance of distal limb extensions and stent migration (58).

Several current trials offered promising clinical results, with limb occlusion/ stenoses rates under 2% (53,55,70). The unibody design of the AFXsg with its fixation on the native aortic bifurcation provides a sufficient iliac covering (53). Other clinical studies approve low limb

occlusion rates, although the current project was the only study that focused on aortic bifurcation of <18 mm. Melas et al. and Welborn et al. described no limb occlusions (55,59). Skibba et al. observed 701 patients after endovascular treatment with Endologix Powerlink and AFXsgs during an 8-year period and registered only three cases requiring interventions (0.4%) (70). In the study of Troisi et al., the patient group with narrow aortic bifurcations (medium follow-up time 16.3 months) had 85.5% freedom from device-related reinterventions; 96.9% freedom from limb thrombosis was achieved in the patient group with narrow bifurcations. Four conversions to open repair were performed (66). Veraldi et al. observed their patients for 40 months (62). During that long-term follow-up, a device-associated complication rate of 38.3% was registered. Type I ELs occurred in two patients (3.7%), type II ELs with aneurysm sac enlargement in 22.2%, and no sac enlargement in 9.3% (61).

In the AAA group of the current project, one patient (2.9%) had an indication for a reintervention due to a type III EL (reintervention with implantation of two Medtronic cuffs in the AFX stent graft without complications). This patient remained asymptomatic during the whole follow-up period (63). A possible explanation of this adverse event is component drift between the main body and proximal extension (VELA).

Skibba et al. reported a 2.4% rate of type IIIa ELs in 17 patients treated with AFXsgs (70). Welborn et al. observed a similar incidence (2.3%) in 108 patients (55). At the beginning of 2013, a revised IFU recommending a minimum component overlap of not less than 30 to 40 mm was published, and this was implemented in the current project (mean overlap zone in the current project was 54.5 mm) (55,57). Skibba et al. observed no type III ELs in patients treated within the revised IFU (70). Welborn et al. registered an incidence of type II ELs in only 6.7% of patients over 12 months, while Melas et al. reported only one EL in 21 patients treated with an AFXsg (55,59).

Based on the long-term follow-up results, an AFXsg can be considered an effective method of treating patients with narrow aortic bifurcations, offering satisfying early- and long-term patient outcomes. A limitation of the trial is the lack of rigid follow-up protocol as a result of the retrospective and multicentric study design (63). Furthermore, the single-armed design prevented general comparisons with outcomes of other stent grafts for similar pathologies; thus, a comparison was performed with current clinical trials focusing on treating aortic pathologies with AFXsg and treating aortic pathologies with narrow bifurcation with other stent devices. In summary, similar outcomes were achieved in the PAU and AAA groups compared to other endovascular devices used for similar pathologies with wider aortic bifurcation diameters (63).

Limb occlusions and stenoses are considered typical complications in treating aortic pathologies with narrow aortic bifurcations. Endovascular therapy can lead to occlusion of the arteria iliaca communis interna or externa. One reason for this could be the formation of an intraluminal thrombus in the stent graft (50). In-stent thrombosis can be treated with a thromboendarterectomy and/or an angioplasty. Another reason for limb occlusions can be limb stenosis due to kinking of the stent graft. Endovascular devices can more frequently induce limb stenoses and occlusion than bifurcated surgical grafts (30,42). The narrow anatomy of a distal aorta can provoke the occurrence of graft limb stenoses/occlusions. With an incidence of 0%–7.2%, limb occlusions are the most frequent cause of reinterventions and secondary operative procedures after EVAR (63,78). Severe calcification induces high intraluminal radial forces and may induce limb occlusion following EVAR (50). Additionally, tortuosity and significant angulation of iliac arteries are considered notable risk factors (79). From a pathophysiological viewpoint, a narrow distal aorta with significant calcification can provoke significant differences in iliac limb diameters, inducing limb occlusions (50).

Inaba et al. retrospectively reviewed 227 patients with AAA who underwent EVAR between 2007 and 2017 (78). The applied stent grafts were Endurant (Medtronic, Santa Rosa, CA, USA), AFX (Endologix, Irvine, CA, USA), Gore Excluder (Gore & Associates, Flagstaff, AZ, USA), and Zenith (Cook Inc., Bloomington, IN, USA). Inaba et al. analyzed the preoperative risk factors and anatomical features of the patients with endograft limb obstructions after EVAR (78). The incidence of endograft limb occlusions was 0%–7.2% in their study. The incidence of limb occlusions in the EVAR trial 1 was approximately 4% (36,78). Tortuosity, calcification, significant angulation of iliac arteries, and landing in the external iliac artery were regarded as risk factors for limb occlusions (78). A narrow distal aorta was also considered a risk factor. In the study of Inaba et al., the medial time from EVAR to occlusion was 2.8 months, and the rate of occlusions was 4.0% (78). In that study, a young age and narrow distal aorta were associated with a significantly high incidence of limb occlusions (78). In the case of occlusion, significant discrepances in each limb were found at the terminal aorta (78). Severe calcification results in high intra-aortic radial forces, which may cause limb stenosis after stent graft deployment (63,78). A large difference between limb diameters is often a result of a narrow distal aorta with severe calcification (61,66). Of note, the difference in the iliac artery diameters in the current project (CIA right vs. left: 12.7 ± 2.5 vs. 11.9 ± 2.2 mm) was comparable with the diameters reported in other trials, suggesting valid comparability regarding this parameter (61,66). With a narrow distal aorta, a kissing balloon technique or additional stent graft implantation should be performed in case of relevant discrepancy between the limb diameters (78).

According to the EVAR trial 1, most limb occlusions and stenoses can be diagnosed within the first 2 months after endovascular treatment and approximately all within the first year after EVAR (36,42). This correlates with the result of the current project: in the AAA group, one patient (2.9%) suffered bilateral limb stenosis at the 4th month of follow-up and was successfully treated with a bilateral BMS implantation in both CIAs (63).

The EUROSTAR registry (over 6,700 patients) reported a 3.2% rate of limb occlusions (75). According to multicentric studies focusing on a single device (device-specific post-market studies), the rate of limb stenoses of the Nellix endograft (Endologix, Irvine, CA, USA) was 5%, the Gore Excluder (Gore & Associates, Flagstaff, AZ, USA) 1.3%, and the Endurant (Medtronic, Santa Rosa, CA, USA) 2.0% (75,80,81,82,83). In these clinical trials, there was no differentiation between standard and narrow bifurcation. In the projects focusing on narrow aortic bifurcation, the rate of limb occlusions for the Endurant device was 2.3% (Troisi et al.) and for the Gore Excluder 3.8% (Veraldi et al.) (61,66).

Based on these reports, the AFX device provides comparable, if not superior, results to those of other clinical trials, even in narrower aortic bifurcations. Thus, the use of AFXsg in patients with narrow aortic bifurcations does not increase the rate of limb stenoses/occlusions. A limitation of the current study is a smaller number of patients compared to the above-mentioned studies, which can be explained by the selection criteria for inclusion in the clinical trial (63).

Beyond limb occlusions, ELs remain frequently observed complications of endovascular treatment. Despite the rapid development of endovascular techniques, ELs remain the most frequently reported complication following EVAR for AAA and PAU (44,63). Depending on the time of manifestation, ELs are subdivided into two groups: primary ELs, which occur intraprocedurally or in the perioperative time up to 30 days after surgery, and secondary ELs, which manifest in the further course after the first 30 postoperative days after prior negative imaging (44).

Primary ELs occurred in 5.8% of the study patients. These were exclusively type II ELs, caused by retrograde blood flow via lumbar arteries or the inferior mesenteric artery in the aneurysm sac. None of these patients required a reintervention. Similar data on the occurrence of primary ELs are represented in the cited literature. In a review of a total of 19,804 patients with endovascular therapy for abdominal aortic aneurysm, Drury et al. described a primary EL rate of 17.5%. In 80% of cases, this was a type II EL (83).

As a reaction to the word “endoleak,” one may first assume that the endovascular therapy has failed once an EL is diagnosed. However, current clinical studies demonstrate that a type II EL is not correlated with an increased rupture rate and consequently does not equate to the failure

of endovascular therapy (61,67). These statements on type II ELs match provided no enlargement of the aneurysm sac has occurred. In a meta-analysis of 2,617 patients, Gelfand et al. also reported a spontaneous occlusion rate of primary type II ELs of up to 58% in the first year (84). It is suggested that a postoperatively diagnosed type II EL should only be initially controlled and treated conservatively. If the diameter of the aneurysm sac expands by more than 5 mm or if a type II EL is still present 12 months after surgery, an intervention is recommended (44,74). The following interventional options are available: transarterial or translumbar embolization of collaterals via coiling (stainless steel/platinum coils) or agents (N-butyl-cyanoacrylate) as well as direct puncture of the aneurysm sac with perfusion and coil application (74).

In both patient groups of the current project, the two observed cases of type II ELs (AAA patients) regressed spontaneously in the first year of follow-up, so no reinterventions were required. In the further course, no other abnormalities occurred in these patients (63). A relatively low risk of type II ELs in patients treated with AFXsgs can be explained by the following phenomenon: the fabric covering the AFXsg is fixed only via its extremities and has the freedom to expand under the blood flow. Consequently, it has a low rate of type II ELs due to expansion of the stent cover fabric, probably minimizing retrograde blood flow from the lumbar arteries (58).

In the case of a persisting EL, the aneurysm wall is continuously exposed to the systemic blood pressure. Enlargement of the aortic diameter and, finally, rupture of the aneurysm can be expected. In this case, the EL should be sufficiently treated to prevent aortic rupture (44). Type I and III ELs represent an urgent indication for reintervention (44).

No type I ELs were observed in either patient group (63). A type I EL occurs due to inadequate sealing of the stent graft in the aneurysm neck (44). For example, sealing is not guaranteed in the case of a strong angulation of the aorta or calcified plaque in this area. Changes that developed over the years, such as dilation of the aorta, could also result from inadequate sealing of the stent graft (50). The stent graft should be carefully secured in the aneurysm neck to prevent type I ELs. Further stabilization can be achieved by a suprarenal fixation of the stent graft. Type I ELs do not usually resolve spontaneously (74). Early reinterventions in the case of type I ELs are recommended as soon as possible (85).

As the therapy of choice for type Ia ELs, balloon angioplasty of the proximal attachment site is recommended to remodel the stent graft; this procedure helps to achieve an adequate seal (44). If angioplasty remains unsuccessful, treatment with balloon-expandable BMSs can be performed (stenting over the affected attachment site). Type Ib ELs are generally simpler to

manage than Ia with numerous available iliac extender limbs, covered stents, and BMSs for covering EL defects (86).

One study patient with AAA (2.9%) experienced a secondary type III EL during long-term follow-up. This patient underwent a reintervention with implantation of a cuff in the AFXsg without complications. The following CTAs and duplex controls of this patient demonstrated stable results with no signs of an EL. The cause of the type IIIa EL, in this case, was a possible borderline anatomy due to a previous reintervention (stenting of both CIAs due to stenosis 4 months after AFX device implantation) (63).

Type III ELs can occur in cases of faulty connection of modules of the stent graft (41,42). These complications must be treated similarly to type I ELs to remove the systemic blood pressure from the wall of the aneurysm sac. Careful preoperative diagnostics are essential for optimal stent graft fitting to prevent secondary ELs (44,74). The risk of a rapid progredience of the aneurysm dimension requires urgent reintervention (74). Endovascular repair of a type III EL can be performed by deploying a new bifurcated stent graft over the defect area, including angioplasty to optimize the seal (86).

The study patient (AAA group) with a type III EL was successfully treated by implanting two additional cuffs proximal to the endograft. In this case, sufficient sealing was achieved, and the patient had a good result with no EL and secondary reintervention in the long-term follow-up (63). Still longer monitoring time over 5 years is lacking for further evaluation of this procedure.

Of note, no type IIIb ELs were observed in the study patients. It is worth mentioning at this point that the texture of the ePTFE fabric with its low porosity can increase the risk of type IIIb Els (58). However, this feature provides excellent adaptability of the AFX device to different endoluminal surfaces (58).

In the study of Veraldi et al., two type I–III ELs (3.7%) occurred in the group of patients with narrow aortic bifurcation (61). Eleven type II ELs with no aneurysm enlargement (22.2%) and five type II ELs with an aneurysm growth (9.3%) were described in this patient group (61). Notably, in the current project, 100% freedom from type III ELs was observed after the same follow-up period (63). Furthermore, the mean aortic bifurcation diameter was 1.5 mm narrower (63). Welborn et al. observed type Ia ELs in two patients (2.35%) and five type II ELs (5.7%) over a mean follow-up of 9 ± 6 months. None of the 5 type II ELs needed a reintervention, and no aneurysm sac was enlarged (55).

In the PAU and AAA groups of the study, the revised IFU for the AFXsg of 2018 was considered; this recommended a minimum graft component overlap of at the minimum 30 to 40 mm (63). Thus, the mean overlap in the present study was 48.7 mm (63,57). A short overlap

with a proximal extension can induce modular disconnection with a high risk of a columnar EL (58).

The vascular surgeons considered the class I recall of July 2018 on all AFXsgs for AAA due to increased risk of type IIIa ELs (63). The ultimately revised IFU-advised maximization of the overlap between the main unibody and proximal endoprosthesis component of the device (VELA) aimed to eliminate disconnection and prevent type III ELs (57). An escalation in the mean component overlap was observed throughout the entire study period (63). In patients treated before July 2018, the mean component overlap between the main body and proximal extension was 44.8 ± 8.0 mm; in patients treated after July 2018, this overlap measured 50.9 ± 14.1 mm (63).

While type I and III ELs necessitate reintervention and repair, the clinical significance of type II ELs remains controversial (44,74). The majority of type II ELs resolves spontaneously, and the 1-year postoperative prevalence ranges from 1% to 10% (19). However, evidence exists that persistent type II ELs are associated with an increased risk of the following complications: sac enlargements, aneurysm rupture, rate of reintervention, and conversions to OR (19). In the PAU and AAA groups of the study, no correlations were observed between type II ELs and adverse outcomes (63). The results from the EUROSTAR registry suggest that type II ELs are associated with progredient aneurysmal growth and reintervention but not with rupture or conversion to open repair (75).

The PAU and AAA patients presented similar outcomes in the frequency of type II ELs compared with reference trials, which used AFXsgs for endovascular treatment of similar anatomical constellations with wider aortic bifurcation diameters (63). The relatively low rate of type II ELs in both groups can be explained based on the fabric of the device, which can expand under the blood flow. This feature can potentially reduce retrograde lumbar blood flow and minimize the risk of type II ELs (58). Notably, the trial data suggest that the risk of type II ELs during the follow-up time may be higher in AAA than PAU patients (63).

In contrast to open surgical treatment of aortic aneurysms, secondary interventions are frequently necessary after endovascular therapy (1). In the DREAM trial, 9 months postoperatively, reintervention was three times more frequent in endovascular patients than in open surgery patients (35). In the patients of the EVAR trial 1, the reintervention rate 4 years postoperatively was 20% after stent graft implantation compared to 6% after open surgery (36). Type I and III ELs, thrombosis or stenosis of the stent graft, and persisting type II ELs can be considered typical indications for secondary reinterventions (50).

Troisi et al. published similar conclusions in their retrospective study with the Medtronic Endurant device, with 92.9% freedom from reinterventions in the patient group with narrow aortic bifurcations (≤20 mm) (66). In their multicenter experience with the Gore Excluder device, Veraldi et al. reported safe and effective results at early and long-term follow-up (24.6% reinterventions in the patient group with narrow bifurcations of <18 mm during 70 months of follow-up) (61).

Strajina et al. (2015) reported their experience with bifurcated devices in patients with narrow aortic bifurcations (67). Despite the described frequent performance of adjunctive co-procedures, effective long-term results with 84% freedom from reinterventions could be achieved. Moreover, this study was performed with heterogenous stent grafts of old and new generations (67).

In both patient groups of the current project, one patient suffered bilateral limb stenosis of CIAs at 4 months follow-up and was successfully treated with bilateral BMS implantation (63). The same patient presented with a type III EL at a 4-year follow-up and was treated with cuff implantation into the AFX stent graft. Thus, both reintervention cases refer to a single patient. The number of patients with reinterventions (in both patient groups) is mainly lower than in the reference studies. The AFX device also provides good results concerning this point in the long-term follow-up. A limitation of the study is the small study group, which further limits the conclusiveness of this case.

The most challenging aspects in treating acute aortic syndrome, and especially PAUs, are the lack of suitable and approved endografts and the use of standard aortic stent devices outside the IFU. In the endovascular treatment of PAUs, limb occlusions and persistent ELs remain the most frequent indications for reinterventions (11).

In terms of treating PAUs in patients with narrow bifurcations, different endovascular therapy options were reported. A tube stent graft can only be used in patients without involvement of iliac arteries and is associated with high rate of device migration (because of deprivation of distal fixation) (11). Kissing stent grafts can induce shape changes in the distal aorta and can provoke occlusions/stenoses (11). The special features of the AFXsg allow its use even for treating PAUs with narrow bifurcation diameters and short distances from renal arteries to aortic bifurcations.

In the current trial, patients with PAUs demonstrated excellent results in the short- and long-term follow-up period with 0% rates of secondary interventions, 0% observed ELs, and 0% limb occlusions (63). Thus, the treatment of PAUs with narrow aortic bifurcations with the AFXsg can be considered safe and effective within the long-term follow-up time. The better

outcomes of the PAU patients can be explained by more suitable anatomical conditions and the lower preoperative morbidity status of this group. Limitations of the current trial were the low number of included patients and lack of rigid follow-up protocol as a result of the retrospective study design and recruitment of patients from different hospitals with different internal standards (63).

Conclusions

The current project provides important results regarding endovascular treatment of aortic pathologies with extremely narrow aortic bifurcations under 18 mm. Narrow aortic bifurcation remains challenging and is considered a potential anatomical risk of endograft occlusions or stenoses. This study presents clinical outcomes, focusing on perioperative morbidity and mortality and freedom from ELs, stenoses, and reinterventions in the long-term follow-up. Although a larger patient cohort should have been observed over a longer period, the study offers a promising approach for therapy of these challenging aortas. Endovascular treatment of extremely narrow aortic bifurcations using an AFXsg according to the IFU is regarded as safe and effective and provides satisfying early- and long-term outcomes at extremely narrow aortic bifurcation diameters. Further evaluation is needed to demonstrate whether these outcomes are maintained in a follow-up period exceeding 5 years. Specifically, the results may be superior in patients with PAUs compared with patients in the AAA group.

According to the current literature, EVAR is associated with lower 30-day mortality and morbidity, shorter hospital stay, and reduced rate of periprocedural complications, albeit there are more secondary reinterventions compared with open surgical repair. This underlines the importance of patient participation in follow-up examinations at regular intervals.

A relatively small patient cohort is the main limitation of the study. A longer follow-up period with more patients is required to evaluate the durability of the AFXsg and long-term clinical results. An international multicentric study would be a possible useful extension of this trial.

5.References

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8. Supplements

Supplementary Table 1. Overview of the cited studies (AAA, abdominal aortic aneurysm)

The 30-day and long-term outcomes of relevant clinical trials (patients with abdominal aortic aneurysms) are represented with information about the endovascular devices and distributions of narrow and standard aortic bifurcations. The rates of complications are registered as percentages.

Author	Stent graft used	Number of patients	30-day outcomes	Follow-up time (months)	EL by NB	LO by NB	Reinterventions by NB
Troisi (66)	Endurant (Medtronic)	SB*: 730 NB*: 87	TS*: 97.8% M*: 1.7% EL*: n/d LO*: 1.5% C*: n/d	16.3 (1–73)	n/d	2.3%	2.3%
Veraldi (61)	Excluder/C3 (Gore)	SB: 141 NB: 54	TS: 100% M: 0% EL: 0% LO: 0% C: 9.5%	40 ± 30.2 (1–130)	I & III: 3.7% II: 31.5%	3.8%	24.6%
Strajina (67)	Zenith (Cook) AneuRX (Medtronic) Excluder (Gore) AFX (Endologix)	SB:0 NB:112	TS:100% M: 1.8% EL: I: 2% II:23% LO: 2% C: 10.7%	35 (1–134)	I & III: 5.4%	6.3%	17%
Kouvelos (53)	AFX (Endologix) Excluder (Gore)	SB: n/d NB: n/d	TS:100% M: 0% EL: 0% LO: 20% C: –	23 (18–26)	II: 10%	n/d	n/d
Welborn (55)	AFX (Endologix)	SB: n/d NB: n/d	TS:100% M:1.85% EL: 0.9% LO: 0% C: 4.6%	11 ± 5	I: 1.9% II: 16.7% III: 0.9%	n/d	n/d
Skibba (70)	AFX Powerlink (Endologix)	SB: n/d NB: n/d	TS: n/d M: n/d EL: n/d LO: n/d C: n/d	12.1 (6–22)	Ia: 0.6% Ib: 1.2% IIIa: 2.42% IIIb: 0.3%	0.4%	n/d
Melas (59)	AFX (Endologix)	SB: n/d NB: n/d	TS: 90% M: 0% EL: 4.8% LO: 0% C: 9.6%	10 (2–15)	0%	n/d	n/d
Own results (63)	**AFX I and II (Endologix)**	**SB: 0 NB: 35**	**TS:100% M: 0% EL: 5.8% LO: 0% C: 23.2%**	**20.4 (1.2–67.2)**	**III: 2.9%**	**Stenosis 2.9% LO 0%**	**5.8%**

SB: standard aortic bifurcation; NB: narrow aortic bifurcation (definition: <18 mm, except Troisi et al.: ≤20 mm); AA: aortic aneurysm; PAU: penetrating aortic ulcer; TS: technical success; M: mortality; EL: endoleak; LO: limb occlusion; C: other complications; n/d: no data

Supplementary Table 2. Overview of the cited studies (PAU: penetrating aortic ulcer)

The 30-day and long-term outcomes of relevant clinical trials (patients with abdominal aortic aneurysms) are represented with information about the endovascular devices and distributions of narrow and standard aortic bifurcations. The rates of complications are registered as percentages.

Author	Stent graft used	Number of patients	30-day outcomes	Follow-up time (months)	EL	LO	Reinterventions
Gifford et al. (88)	Excluder (Gore) Zenith (Cook) AneuRX (Medtronic) (n/d) Endologix	93	TS:97% M:0% EL: LO: C: –	40.4 (3–108)	-	-	13 (14%)
Georgiadis et al. (87)	Excluder (Gore) Powerlink (Endologix) Talent (Medtronic) Endurant (Medtronic)	19	TS:100% M: 5.3% EL: 10.6% LO:0 C: 0	33 (8–51.5)	Ib: 5.3%	10.6%	86.4% freedom from reinterventions at 12 months, 71.6% freedom from reinterventions at 36 months)
Taher et al. (89)	AFX (Endologix) Endurant (Medtronic)	12	TS: 100% M: 8.3% EL: 8.3% LO:0 C: 8.3%	24.5 (12–59)	I: 1.8%	0	1(8.3%)
Hyhlin-Durr et al. (90)	Excluder (Gore) Talent/Valiant AneuRX (Medtronic) Zenith (Cook)	20	TS: 100% M: 10% EL: 20% LO:0 C:-	23 (0.4–104)	I: 5%	0	10%
Own results (63)	**AFX (Endologix)**	**35 / 18 PAUs**	**TS:100% M: 0% EL:0% LO:0% C: 11.1%**	**20.4 (1.2–67.2)**	**0**	**0**	**0**

SB: standard aortic bifurcation; NB: narrow aortic bifurcation (definition: <18 mm); AA: aortic aneurysm; PAU: penetrating aortic ulcer; TS: technical success; M: mortality; EL: endoleak; LO: limb occlusion; C: other complications

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