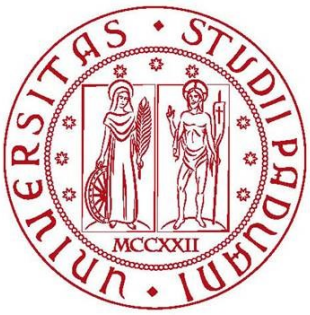

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TESI DI LAUREA

Geometrical determinants of target vessel instability in fenestrated endovascular aortic repair

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CONTENTS

ABSTRACT

Objective: The goal of this study is to evaluate the impact of geometrical factors on target vessel instability in fenestrated endovascular aortic repair (FEVAR) for thoracoabdominal (TAAA), juxtarenal (AJR) and pararenal (APR) aortic aneurysm.

Methods: This was a retrospective study including patients who underwent FEVAR from 2014 to 2021 at the Operating Unit of Vascular and Endovascular Surgery in Padova. All geometrical values derived from the first post-operative multiplanar computed tomography angiogram reconstruction and the subsequent angio-CT during follow-up. Every bridging stent placed in a target vessel was considered for the analyses.

Bridging stent length and diameter, stent conformation and graft misalignment were considered as geometrical factors. Bridging stent length was categorized into three components: protrusion length (PL) into the main endograft lumen, bridging length (BL) between the graft fenestration and the origin of the target vessel, and sealing length (SL) of apposition into the target vessel. Stent conformation was evaluated with the flare ratio, intended as ratio between the maximum and minimum bridging stent diameter. Horizontal misalignment was measured as the angle between the midpoint of endograft fenestration and the axial cut of the target vessel ostium. Vertical misalignment was measured as the distance between the fenestration midpoint and the target vessel origin midpoint.

The primary endpoint was freedom from target vessel instability, defined as any branch-related death, occlusion, rupture, or any reintervention for stenosis, endoleak or disconnection.

Time-dependent outcomes were estimated with Kaplan-Meier curves and Cox proportional hazard models were used to identify the predictors of target vessel instability.

Results: This study included 46 patients, 34 (74%) with juxta or pararenal aortic aneurysm and 11 (26%) with thoracoabdominal aortic aneurysm. One patient had a chronic dissection.

Overall, 147 target arteries were incorporated through a bridging stent.

Freedom from target vessel instability was 87% at 42 months (95% confidence interval [CI] 80-94). Primary patency was 98% (95% CI 96-100) and freedom from endoleak was 85% (95% CI 76-93). PL (hazard ratio [HR] 1.08, 95% CI 0.22-5.28; *p*=0.923), SL (HR 0.95, 95% CI 0.87-1.03; *p*=0.238), and flare ratio (HR 4.66, 95% CI 0.57-37.7; *p*=0.149) were not associated with target vessel instability.

In the multivariate analysis, a BL longer than 5 mm (HR 4.98, 95% CI 1.13-21.85; *p*=0.033) resulted significantly associated with instability. Patients with a BL of 5 mm or more had a significantly greater degree of horizontal misalignment (21 ± 12° vs 9 ± 13°; *p*=0.011).

Conclusions: This study demonstrated that the distance between the fenestration and the target vessels' origin (BL) is an important geometrical factor determining target vessel instability, especially greater than 5 mm. Sizing and planning of FEVAR should be performed to maintain this distance < 5 mm. Fenestrations with a BL of > 5 mm increase the risk of type Ic or IIIc endoleak and secondary interventions.

The use of inner or outer branches instead of fenestrations may be considered in cases with anticipated excessive distance between the endograft and the target vessel. A more frequent follow-up may be appropriate in case of fenestration-target vessel distance > 5 mm.

RIASSUNTO

Obiettivo: L'obiettivo dello studio è stato quello di valutare l'influenza dei fattori geometrici sull'instabilità dei vasi bersaglio, in pazienti sottoposti ad impianto di endoprotesi fenestrata per via endovascolare (FEVAR) per aneurismi toraco-addominali, juxtarenali e pararenali.

Metodi: Lo studio retrospettivo ha incluso i pazienti sottoposti a FEVAR dal 2014 al 2021 presso l'Unità Operativa di Chirurgia Vascolare ed Endovascolare dell'Azienda Ospedaliera di Padova. L'analisi geometrica è stata svolta grazie alle angio-TC pre- e post-operatorie nel follow-up. Tutti gli stent a ponte posizionati a livello dei singoli vasi bersaglio sono stati presi in considerazione per le analisi.
I fattori geometrici considerati sono stati la lunghezza e il diametro dei singoli stent a ponte, la loro conformazione e il loro disallineamento rispetto all'endoprotesi. La lunghezza di ogni singolo stent, inoltre, è stata suddivisa in tre componenti: il *protrusion length* (PL) ossia l'estensione dello stent nel lume dell'endoprotesi, il *bridging length* (BL) ossia l'estensione tra la finestra e l'origine del vaso target, e il *sealing length* (SL) ossia l'estensione dello stent adeso alla parete del vaso bersaglio. La conformazione degli stent è stata valutata con il *flare ratio*, calcolato come rapporto tra il diametro massimo e minimo di ogni stent.
L'*Horizontal misalignment* (disallineamento orizzontale) è stato misurato come l'angolo tra il punto medio della finestra e il punto medio dell'asse passante per l'origine del vaso target. Il *Vertical misalignment* (disallineamento verticale) è stato invece misurato come distanza lungo l'asse centrale aortico tra il punto medio della finestra e il punto medio dell'origine del vaso target.
L'endopoint primario è stato quello di non riscontrare instabilità dei vasi bersaglio, intesa come morte correlata, occlusione, rottura, reintervento per stenosi, endoleak o disconnessione.
L'outcome tempo-dipendente è stato stimato con le curve di Kaplan-Meier, mentre modelli di rischio proporzionale di Cox sono stati utilizzati per identificare i determinanti dell'instabilità dei vasi bersaglio.

Risultati: Lo studio ha incluso 46 pazienti; di questi 34 (74%) presentavano un aneurisma aortico juxta o pararenale e 11 (26%) un aneurisma toraco-addominale. Un paziente ha presentato una dissezione cronica. I vasi bersaglio incorporati con stent a ponte sono stati 147.

La *freedom from target vessel instability* è stata dell'87% a 42 mesi (95% intervallo di confidenza [CI] 80-94). La pervietà primaria è stata del 98% (95% CI 96-100) e la *freedom from endoleak* dell'85% (95% CI 76-93). Il PL (rischio relativo [HR] 1.08, 95% CI 0.22-5.28; *p*=0.923), il SL (HR 0.95, 95% CI 0.87-1.03; *p*=0.238), e il flare ratio (HR 4.66, 95% CI 0.57-37.7; *p*=0.149) non sono stati associati ad instabilità dei vasi target.

All'analisi multivariata un BL ≥ 5 mm (HR 4.98, 95% CI 1.13-21.85; *p*=0.033) è risultato essere significativamente associato all'instabilità. Nei pazienti con un BL ≥ 5 mm è stato inoltre registrato un più alto e significativo grado di disallineamento orizzontale (21 ± 12° vs 9 ± 13°; *p*=0.011).

Conclusioni: Questo studio ha dimostrato che la distanza tra la finestra dell'endoprotesi aortica e l'origine del vaso target è un importante fattore geometrico determinante instabilità dei vasi bersaglio, specialmente quando il BL supera i 5 mm. Gli impianti con un BL > 5 mm hanno in particolare rilevato un aumento del rischio di endoleak di tipo Ic o IIIc e di reintervento.

La pianificazione e l'attuazione della FEVAR dovrebbero, per questo, essere eseguite mantenendo il bridging length < 5 mm.

In caso di BL > 5 mm sarebbe appropriato eseguire un follow-up più rigoroso o meglio ancora, considerare l'uso di branches al posto delle fenestrazioni.

KEYWORDS

Abdominal aortic aneurysm; Fenestrated endovascular aortic repair; Geometrical factors; Target vessel instability; Bridging stent; Computed tomography angiograms.

INTRODUCTION

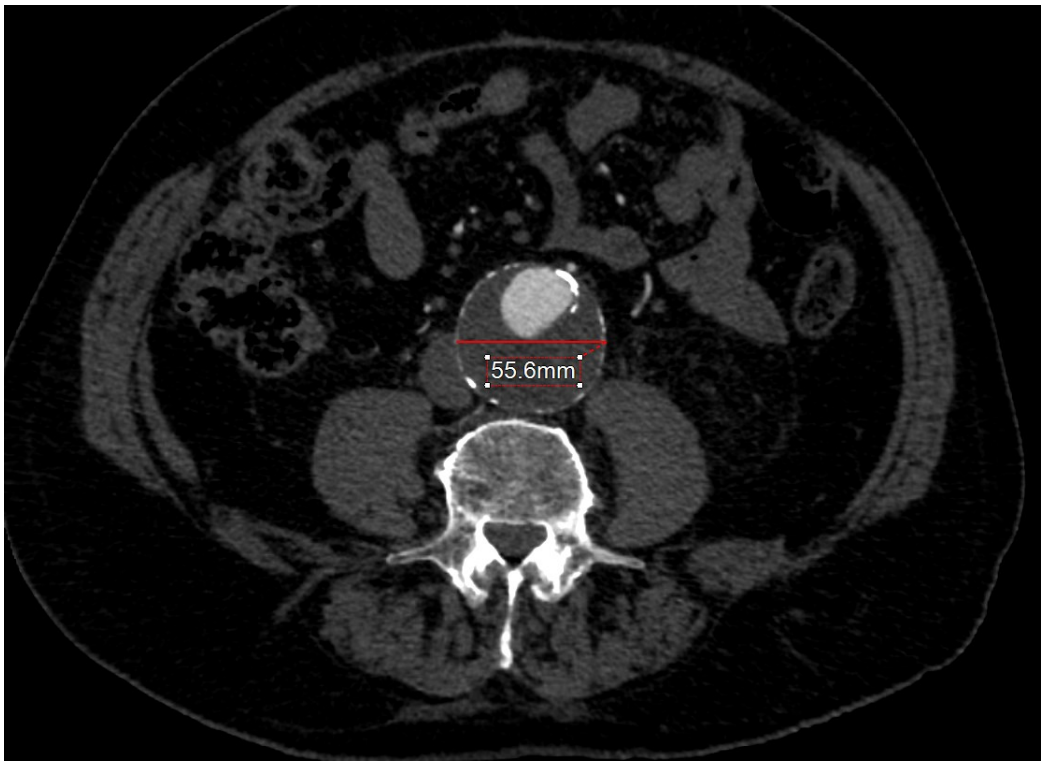
Abdominal aortic aneurysm

Definition and classification

The current definition of abdominal aortic aneurysm (AAA) refers to the measure of the abdominal aorta diameter. The AAA is defined as an antero-posterior or transverse diameter dilatation ≥ 3 cm; this value is the upper limit of two standard deviations of the mean diameter in both sexes[1] (Fig 1).

A recent study reports diameters in terms of mean and ninety-fifth percentile of the thoracic and abdominal aorta measured by nuclear magnetic resonance for both sexes and for each age[2]. The average diameter of the sub-renal abdominal aorta misures 1.49 cm (95th percentile: 1.77 cm) in women younger than 30 years old and 1.76 (95th percentile: 2.18 cm) in women older than 70; in males under 30 years old it measures 1.67 cm (95th percentile: 1.92 cm), while in those over 70 it reaches 2.12 cm.

Fig 1. Angio-CT of abdominal aortic aneurysm with a maximum diameter of 55.6 mm



Aortic aneurysm involves all three layers of the arterial wall (the inner endothelial layer, the middle muscular tonaca and the adventitia), unlike the other pathologies such as aortic dissection, IMH (aortic intramural hematoma), PAU (penetrating aortic ulcer) and pseudo-aneurysm.

The aorta originates from the left ventricle of the heart, runs along the thoracic cavity, and continues into the abdominal cavity. It's the artery with the greatest flow rate of the body: a ruptured abdominal aortic aneurysm can cause life-threatening bleeding.

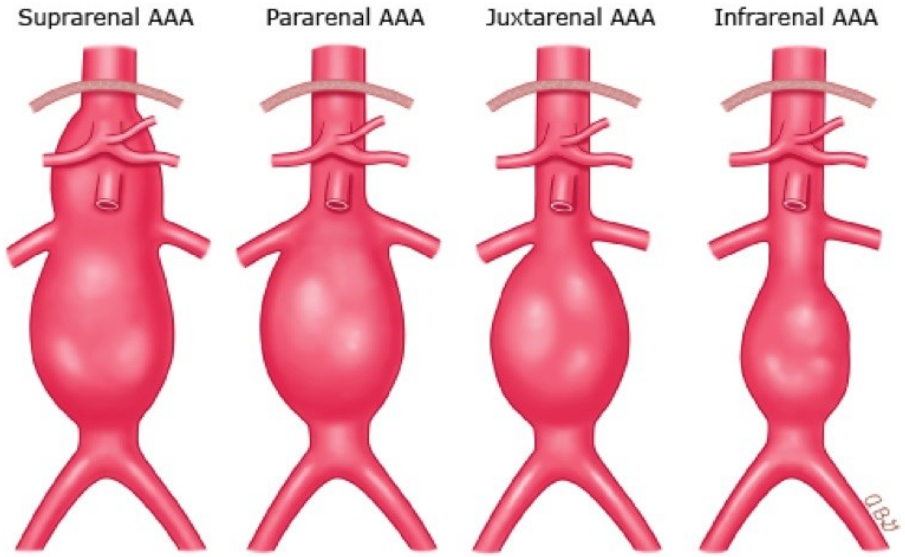
The approach to an abdominal aortic aneurysm can be very different; programmed monitoring may be sufficient, but in case of rupture emergency surgery will be needed.

An aneurysmal pathology can extend to the supra-renal aortic tract or involve the aortic carrefour and iliac arteries. A common iliac artery aneurysm has a diameter ≥ 2 cm. Involvement of the iliac artery can significantly alter the endovascular aortic repair, and some ancillary procedures may be required to ensure therapeutic success.

Different types of abdominal aortic aneurysm can be detected, based on their location (Fig 2). An infrarenal AAA has a regular caliber aorta segment (proximal collar) of at least 10 mm between the renal arteries and its cranial portion; a juxtarenal aneurysm extends to the renal arteries, with a regular aorta caliber above it; a pararenal AAA extends to the renal arteries including their origins. A suprarenal AAA involves the renal arteries and extends above them, with possible intra-aneurysmal origin of the celiac tripod (CT) and superior mesenteric artery (SMA).

The topographic criteria become relevant when taking decisions on the therapeutic strategies to adopt.

Fig 2. Topographic classification of aortic abdominal aneurysm



Epidemiology

The epidemiology of aneurysmal pathology has changed profoundly over the past 20 years. The incidence of AAA has significantly reduced, probably in response to a better control of cardiovascular risk factors such as the reduction of smoking and better control of hypertension[3]. There has been a 20 to 50% reduction in hospitalizations and surgeries for AAA in both Europe and America in the last 20-30 years[4]. The prevalence of AAA is estimated between 8.43 and 2422 per 100.000 in the whole population varying according to age and geographical area[5]. Prevalence is three times higher in men[5] (the prevalence rate of men ranges from 4 to 9% in developed countries), and the peak of incidence among men is of 70 years old. It is a disease that affects mainly the elder population. The current prevalence in men over 65 years old is 1.5% in the Swedish Screening Programme[6], 1.3% in the UK National Screening Programme[7], and 3.3% in a Danish screening study performed in men aged 65 to 74 years[8]. In Italy, AAA affects over 84.000 people with approximately 27.000 new cases diagnosed each year[9].

The frequency is much higher in smokers (8:1) and the risk decreases with smoking cessation[10].

It is 2 to 4 times more common to find AAA in patients with first-degree relatives having the same disease.

A reduced risk of AAA is associated with female sex and non-caucasian people[11].

The rupture of the AAA occurs in 1-3% of men aged 65 or more, and mortality from rupture is between 70 and 95%. Rupture of AAA is the 15th cause of death in the United States, and it is the 10th leading cause of death in men over 65 years old[12]. The death rate is around 5:100.000 inhabitants and has been declining since the late 1990s.

Pathogenesis

The AAA is caused by a degenerative process mainly of atherosclerotic type, which involves all layers of the aortic wall.

The natural history of the AAA is characterized by a progressive growth that doesn't seem to have changed in the past 25 years[13]. The growth rate is highly variable, and the situation can remain stationary even for years. Various studies report that an AAA of 3-5 cm can grow between 0.2 and 0.6 cm each year; for an AAA of about 3.0 cm of diameter the average growth does not exceed 0.2 cm every year, while an AAA of about 5.0 cm of diameter can increase of 0.4 cm every year with a rupture rate of about 0.64:100 person every year[14-15]. However, the dimensions do not represent the only parameter to be taken into consideration for surgical treatment. The high growth rate, the presence of blisters and/or parietal thrombi, sack-like morphology are also factors that increase the risk of aneurysm rupture[9].

Uncommonly, syphilis and localized bacterial or fungal infection, typically due to sepsis or infective endocarditis, weaken the arterial wall and cause infected (mycotic) aneurysms. *Staphylococcus aureus* is the first cause of mycotic aneurysms, followed by *Salmonella*.

This pathology is not an isolated phenomenon, but it is studied in the framework of vascular diseases with critical aspects. Among these, the need for early

diagnosis avoids complications. The rupture represents the most dramatic event, while peripheral embolization and complete thrombosis are rare.

Risk factors

Several things can play a role in the development of an abdominal aortic aneurysm.

Since January 2016, numerous reviews and clinical studies concerning risk factors for AAA have been published.

The meta-analysis by Kobeissi et al. including 28.162 cases of AAA and 5.440.588 controls, showed that hypertension was associated with a higher risk of developing an abdominal aortic aneurysm; the relative risk was 1.4 for every additional 20 mmHg in systolic blood pressure and 2.8 for every 10 mmHg in diastolic blood pressure[16].

Altobelli et al. conduced a systematic review and meta-analysis of the observational studies that considered the following risk factors: sex, smoking habit, arterial hypertension, familiar history of AAA, diabetes, ischemic heart disease[17]. This study has shown that all the factors analyzed can be considered as risk factors for the development of an AAA; among these, smoking and male sex are the most significant. Smoking is the strongest risk factor for aortic aneurysms. The carcinogenic substances contained in cigarette smoke can weaken the walls of the aorta, increasing the risk of aortic aneurysm and aneurysm rupture. It has been known for many years that smoking is strictly related to the diameter of the aorta: in smokers the diameter of the aorta is greater than in non- smokers. Aune et al. have shown that the relative risk of developing AAA is 1.87 for smokers of 10 cigarettes/day and 0.45 for subjects who have stopped smoking for at least 10 years[18]. Therefore, the amount and time of exposure to cigarette smoke affect the chances of developing an aortic aneurysm.

Multiple cohort studies have also highlighted that dyslipidemia, the metabolic syndrome, chronic kidney failure, albuminuria, obesity, and abdominal circumference can be considered as risk factors for AAA[19-20-21-22-23].

Another analysis on 155.731 people revealed that the prevalence of chronic obstructive pulmonary disease (COPD) almost doubles in subjects with AAA than in those without AAA[24].

Having a family history of abdominal aortic aneurysms increases the risk of having this condition (in 15 to 25% of cases)[17]. Having an aneurysm in another large blood vessel, such as in the artery behind the knee (popliteal aneurysm) or in the chest aorta (thoracic aortic aneurysm) might increase the risk of an abdominal aortic aneurysm.

Control of risk factors, especially of smoking, and treatment of some of them are indicated to reduce the risk of developing an aneurysm of the abdominal aorta.

From the data of Kaluza et al. on a Swedish population of more than 80.000 people, it emerges that a diet with anti-inflammatory characteristics has a protective role against the development of AAA[25].

Clinical aspects and diagnosis

Most abdominal aortic aneurysms are asymptomatic. An aneurysm may be found by X-rays, computed tomography scan, or magnetic resonance imaging (MRI) performed for a different reason. When an aneurysm remains asymptomatic, it may be called "silent killer" because it may rupture before being diagnosed.

The symptomatology, if present, often derives from the compression of adjacent structures. Pain is the most common symptom of an abdominal aortic aneurysm. The pain may be located in the abdomen, in the chest, lower back, or groin area. The pain may be severe or mild. Sudden severe pain in the abdomen or lower back may mean that the aneurysm is rupturing. This is a life-threatening medical emergency. Abdominal aortic aneurysms may also cause a pulsing sensation in the abdomen, depending on its size and patient habits. The probability of a patient with a pulsatile palpable mass having an aneurysm > 3 cm is about 40% (positive predictive value). A systolic bruit may be audible over the aneurysm[9].

In case of AAA rupture, most patients die before reaching a medical facility. Patients who do not die immediately present with abdominal or back pain,

hypotension, and tachycardia. They may have a history of recent upper abdominal trauma, often minimal, or isometric straining (ie, lifting of a heavy object). Even patients who reach the hospital alive have a mortality rate of about 50%.

Distal embolization of thrombus or atheromatous material may dislodge and block arteries of the lower extremities, kidneys, and bowel. Patients typically present with sudden unilateral extremity pain and often pallor and loss of pulses.

Uncommonly, large AAAs cause disseminated intravascular coagulation, perhaps because large areas of abnormal endothelial surface trigger rapid thrombosis and consumption of coagulation factors.

The diagnosis of AAA is very important since it allows the recognition of a condition burdened by notable fatalities, and subsequent monitoring and early treatment. However, the diagnosis is often difficult because in most cases subjects are asymptomatic and the typical clinical signs are affected by varying sensitivity. The small portion of patients presenting with pain related to aortic aneurysm, are usually in a situation of greater severity which requires fast diagnosis to make therapeutic decisions.

The fundamental sign is deep abdominal palpation of the pulsating mass in the epigastric region, which can be felt in both symptomatic and asymptomatic patients with risk factors. It represents a safe method, not associated with the risk of rupture, but burdened by considerable variations in sensitivity[26]. In small aneurysms (between 3 and 3.9 cm of diameter) the sensitivity is unsatisfactory (< 30%), as well as in subjects with elevated abdominal circumference. The low diagnostic accuracy, in these cases, is related to the deep retroperitoneal position of the abdominal aorta. Sensitivity increases up to 80% in larger aneurysms and in subjects with low abdominal circumference dimensions.

The only effective way to make an early diagnosis is to identify the population at risk and screen them with abdominal ultrasound. The American Societies of Vascular Surgery and Vascular Medicine recommend performing ultrasound color-Doppler of the abdominal aorta in all men aged between 60 and 85, all women between 60 and 85 presenting cardiovascular risk factors, men and women over 50 who have a family history of AAA. The ultrasound examination is the best

method to screen the AAA due to its high sensitivity (95%) and specificity (close to 100%). Accuracy of the examination in the measurement of antero-posterior and transverse aneurysm diameters can be affected by obesity and high degree of meteorism; for this reason, it is important for the patient to undergo the examination on an empty stomach and after any anti-meteoric intake. Equally important is the correct technique of performing the exam to reduce the operator-dependent variability.

The study of the abdominal aorta with computed tomography (CT) method finalizes the ultrasound investigation; it provides a much more accurate assessment of the AAA morphology required for decisions on surgical repair. The guidelines of the American College of Cardiology Foundation / American Heart Association (ACC foundation/AHA) suggest ultrasound and/or computed tomography monitoring and provides operational indications on the management of the diagnosis of iuxta-renal or sub-renal aortic aneurysm[27].

Surgical treatment

After a careful specialist evaluation of the surgical risk for patients, we can choose between traditional surgery (open aneurysmectomy) or endovascular intervention (EVAR).

The indication for elective treatment of AAAs is based on the aortic diameter. Fusiform abdominal aortic aneurysms of caliber less than 4 cm have a negligible risk of breakage and do not deserve surgical treatment; instead, there is the indication to intervene with classic or endovascular surgery in case of fusiform aneurysms of caliber > 5.5 cm in subjects without severe comorbidities, or in saccular-type aneurysms. There has been much discussion about the indications for aneurysms with diameter between 4 and 5.5 cm[28-29].

The indication should be personalized, considering patients' operative risk and suitability for open or endovascular treatment.

The recommendations included in the SICVE 2021 Guidelines state as follows[30]: in the case of a fusiform abdominal aortic aneurysm with a diameter greater than or equal to 5.5 cm it is indicated the election repair intervention; in the case of

fusiform AAA with diameter between 5 cm and 5.4 cm, the repair intervention could be indicated for subgroups of patients at increased risk of rupture, with surgical risk acceptable. The repair intervention in election of an AAA could be indicated in case it is observed a caliber's rapid growth (greater than 1 cm every year) even if the diameter does not reach the 5 cm. In case of a saccular aortic aneurysm, the elective surgical repair could be also indicated with diameters of less than 5 cm. With symptomatic (or suspected) AAA, an urgent assessment must be performed by the vascular surgeon.

Surgical treatment: vascular or endovascular aortic repair

In case of AAA, the surgical approach can be open surgical repair or endovascular repair.

Traditionally, the surgery to treat a sub-renal aneurysm is performed under general anesthesia and lasts about 2-3 hours. It involves laparotomic access into the abdominal cavity, resulting in isolation of the aortic aneurysm. After being clamped below the renal plane, the aneurysmal sac is opened, it is emptied, and a synthetic tubular prosthesis is sewn at the level of the aneurysmal collar of healthy aorta (aorto-bisiliar, aorto-bifemoral dacron or PTFE graft).

Endovascular surgery involves two small surgical cuts in the groins from where an internal prosthesis (endoprosthesis) is inserted using X-rays. This endograft excludes the aneurysm from the bloodstream. This surgery is usually performed under local anesthesia and sedation (drug-induced).

To make a correct therapeutic choice, we must read the scientific evidence on immediate and remote outcomes of the open or endovascular technique derived from literature.

Endovascular aortic repair represents a therapeutic advancement and a viable alternative to traditional open surgery. It is currently the most used treatment for the repair of AAAs in the United States. Today it has a described clinical and technical outcome equal to or better than open surgery[31]. The procedure has a shorter operative time, less intra-operative bleeding and need for transfusion,

lower peri-operative morbidity and mortality, and reduced hospital and intensive care unit admission time. However, the immediate economic benefits along with faster patient recovery time, are counterbalanced by the need for costly diagnostic follow-up for the rest of life, recommended after endovascular aortic repair[32]. Furthermore, endovascular treatment has been shown to reduce the rate of mortality and complications in the first month after the procedure compared with traditional surgery. Subsequent analyses of these longer-term randomized trials have demonstrated a substantial benefit in terms of mortality related aneurysm up to four years. The difference in overall survival, however, does not persist beyond the first two years of the post-operative[33].

Endovascular repair outcomes are highly dependent on appropriate patient and material selection, training of medical staff, and the number of procedures performed by the hospital center. This technique requires a careful assessment of the anatomical picture of subject, the perioperative risk which includes the general clinical status, the comorbidities and anesthetic risk, and last but not least, the patient's preference.

The most recent meta-analyzes[34] confirm what had already emerged from randomized trials[35-36-29-37-38] and large international registers. The endovascular treatment allows to lower the premature mortality rate from 3.27% to 1.16%. For this reason, patients considered to be at higher surgical risk can be operated on. However, the initial advantage of the endovascular method tends to gradually reduce and overlap the rate of open surgery 3 years after surgery; then it remains up during the next 10 years. Endovascular surgery also reduces the major post-operative complications, especially the cardiac, renal and respiratory ones.

Various preoperative imaging techniques can be used during the preoperative process in patients with surgical indication for AAA. The Echo-Color Doppler represents the diagnostic technique of first level for screening and diagnosis of aneurysmal pathology; it allows for an accurate assessment of the abdominal aorta in the juxta and subrenal portion, a good visualization of the iliac arteries and a study of the morphology of the aneurysm (characteristics of the parietal thrombus, presence of blister problem, wall thickening in presence of

inflammatory aneurysm). However, in the patient candidated for surgery, Echo-Color Doppler alone is not sufficient to determine a good therapeutic planning, especially for the difficulties in studying the suprarenal aorta and the iliac axes. Therefore, it is necessary to use second level radiological imaging[39].

The angio-CT is universally considered the choice for the preoperative planning of the patient candidated for surgical treatment. The processing of the acquired images allows to evaluate the anatomy of the aorta and to choose the most suitable treatment and the type of endoprosthesis to be used[40]. The angio-CT also allows the evaluation of the thoracic aorta and vascular accesses. The disadvantages of the method are represented by use of ionizing radiation and iodized contrast. In diabetic patients and in subjects with chronic kidney failure, the examination could worsen the kidney function.

Angio-RM represents a valid alternative study; however, it has some disadvantages limiting its use. With MR angiography, the calcifications of the vessels can't be seen, the acquisition times are longer and the costs higher.

Fenestrated endovascular aortic repair (FEVAR)

Currently endovascular aortic repair with fenestrated endografts (FEVAR) represents a good treatment option for juxtarenal aortic aneurysms (AJR), pararenal aortic aneurysms (APR) and thoracoabdominal aortic aneurysms (TAAA). Several studies[41-42-43-44-45] reported excellent outcomes of FEVAR in terms of safety, technical success, patency rates of target vessels, and freedom from aneurysm-related death.

Endovascular treatment of AAA is defined as the imaging-guided placement of a stent-graft (endoprosthesis) within the native abdominal aorta, ensuring attachment of the device to the proximal and distal wall of the aneurysm.

The endovascular procedure usually is performed under regional or general anesthesia. The European Collaborators on Stent Graft Techniques for AAA Repair indicate that patients benefit from locoregional anesthesia and suggest that this technique should be used more often to increase the peri-operator advantages[46].

A recent revision of selected studies showed that the patients with worse clinical conditions under local anesthetic needed less cardiovascular support both during and after surgery, less time spent in intensive care and hospital, and a lower post-operative mortality and morbidity rate[30].

Once the patient is anesthetized, peripheral vascular access is performed at the femoral arteries. From here all devices necessary for the success of the intervention will be inserted.

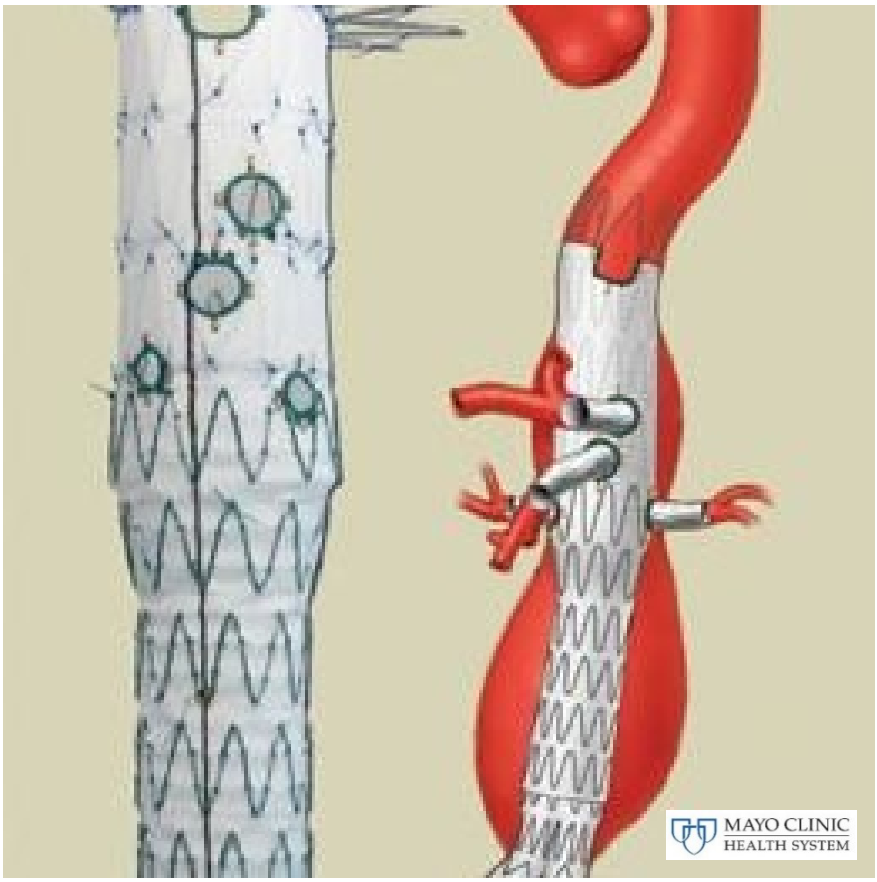
The fenestrated endoprosthesis is mounted on 18-22 Fr introducer and brought into place thanks to image acquisition by the X-ray emitting C-arc.

The endoprosthesis have three components consisting of a delivery system for introduction and placement, a self-expanding metallic stent with a high radial force that acts as a support for the endoprosthesis and allows the anchorage to the vessel, and a prosthetic tissue that excludes the aneurysm and forms a new conduit for blood flow.

The endovascular method success requires proximal and distal landing zones suitable for stable anchorage and to completely seal the endoprosthesis to the vascular wall. Different devices have different fixation systems to the vascular wall.

Custom-made fenestrated endoprosthesis are made specifically for a patient, based on his or her anatomy and on the relationship between blood vessels. Depending on the extent of the aneurysm, the endoprosthesis will have windows matching the origin of the renal arteries, superior mesenteric artery, and/or celiac tripod. Based on the number of windows, it will be called a bifenestrated, tri- or quadri-fenestrated endoprosthesis (Fig 3).

Fig 3. Custom-made quadri-fenestrated endoprosthesis imagine taken from *https://www.mayoclinic.org/medical-professionals/cardiovascular-diseases/news/endovascular-repair-of-complex-aortic-aneurysms/mac-20429867*



The following paragraph will illustrate a standard procedure for placement of a fenestrated endoprosthesis for supra-renal aneurysm.

An echo-guided puncture of the femoral arteries is performed, and two crossed Proglide systems are placed for access. At the same time the patient undergoes systemic heparinization. From the left access a catheter (usually a pig-tail) is placed in the supraceliac tract of the abdominal aorta. From the right access a guide with the custom-made fenestrated endoprosthesis is inserted (usually of Cook's company). The endoprosthesis is tri-fenestrated for the renal arteries and superior mesenteric artery. At this point it is important to define the orientation of the endoprosthesis according to the radio-opaque markers (Fig 4), and to partly open it in roadmap. From the left the endoprosthesis is captures and an 18-22 Fr introducer is brought in.

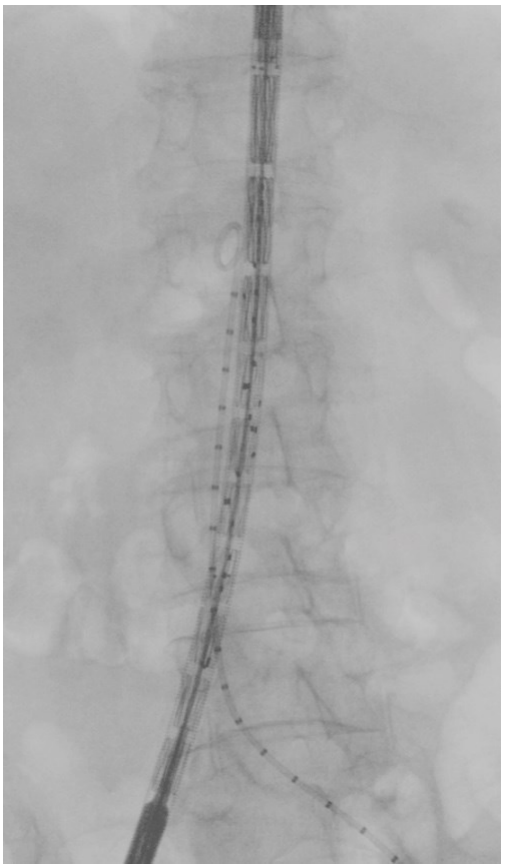


Fig 4. Intraoperative radiographic acquisition of Vascular and Endovascular Surgery Clinic of the Padova University. Notice the radio-opaque markers used to define the orientation of the endoprosthesis

Guides are now inserted into the renal arteries, superior mesenteric artery, and celiac tripod. The opening of the endoprosthesis is completed. Covered stents are inserted at the four fenestrations and opened with balloons (Fig 5-6).

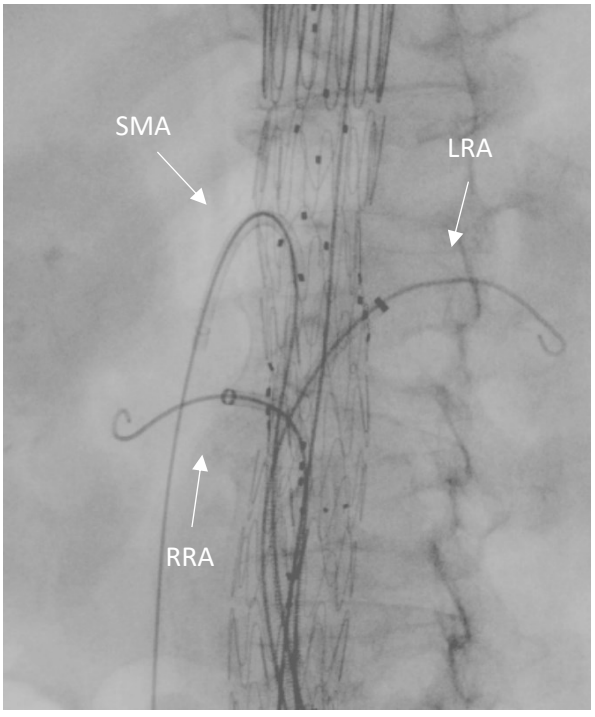


Fig 5. Intraoperative radiographic acquisition of Vascular and Endovascular Surgery Clinic of the Padova University. Placement of tri-fenestrated at the superior mesenteric artery (SMA), right (RRA) and left (LRA) renal arteries levels.

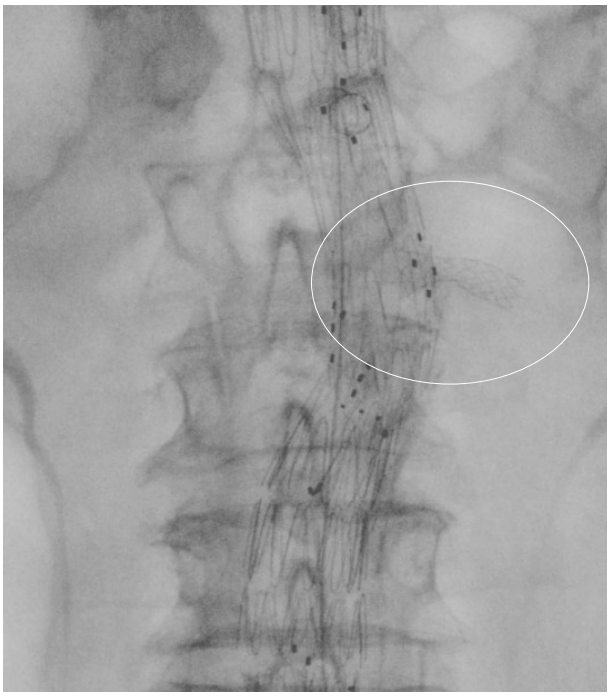
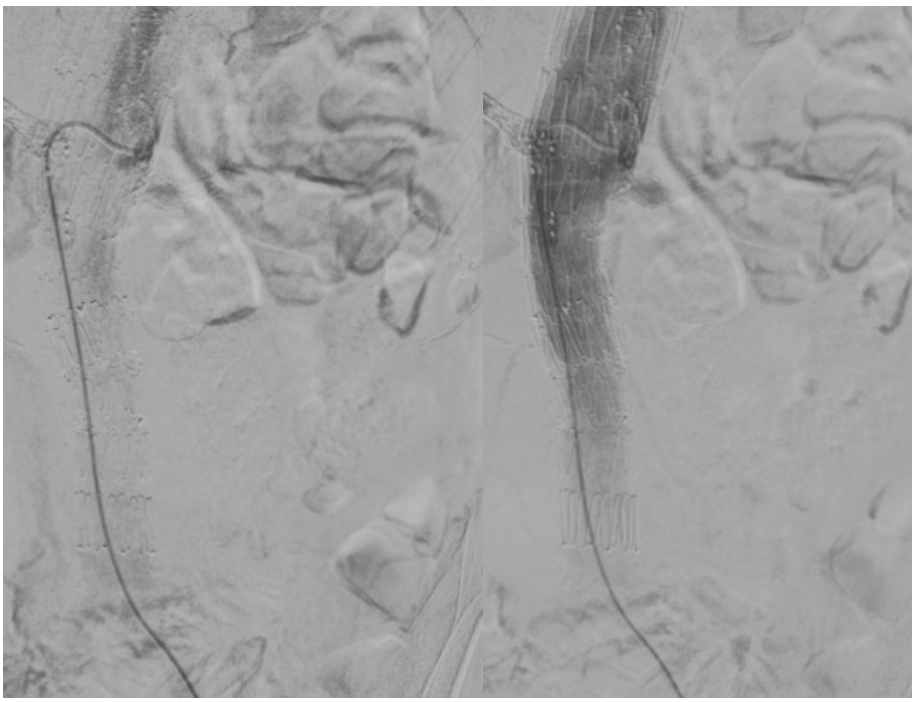


Fig 6. Intraoperative radiographic acquisition of Vascular and Endovascular Surgery Clinic of the Padova University. Covered stents are inserted at the four fenestrations and opened with balloons

At the end, an arteriographic check is performed to see if the endoprosthesis is well placed, the visceral vessels are pervious, the aneurysmal sac is excluded without endoleak of I or III type (Fig 7).

Fig 7. AGF study after implantation. This is a radiological examination performed with contrast medium to show the result post-FEVAR



The post-operative medical therapy is standardized for all patients. Every patient is subjected to dual antiplatelet therapy for 30 days (with aspirin and clopidogrel), followed by long-term single antiplatelet therapy (with aspirin). If a patient needs anticoagulant therapy for other medical reasons, this is usually continued after assessing the risk-benefit ratio of the medical therapy.

Preoperative imaging and subsequent pre-procedural planning are essential to assess the feasibility of FEVAR treatment. Imaging allows assessment of the suitability of the patient's anatomy; the degree of technical difficulty allows the selection of the most appropriate device and allows to define possible ancillary procedures to the implantation of the endoprosthesis. Imaging also can help in predicting the immediate and long-term outcome. Preoperative imaging is usually obtained with a contrast medium computes-tomography angiography with 3D volumetric reconstructions.

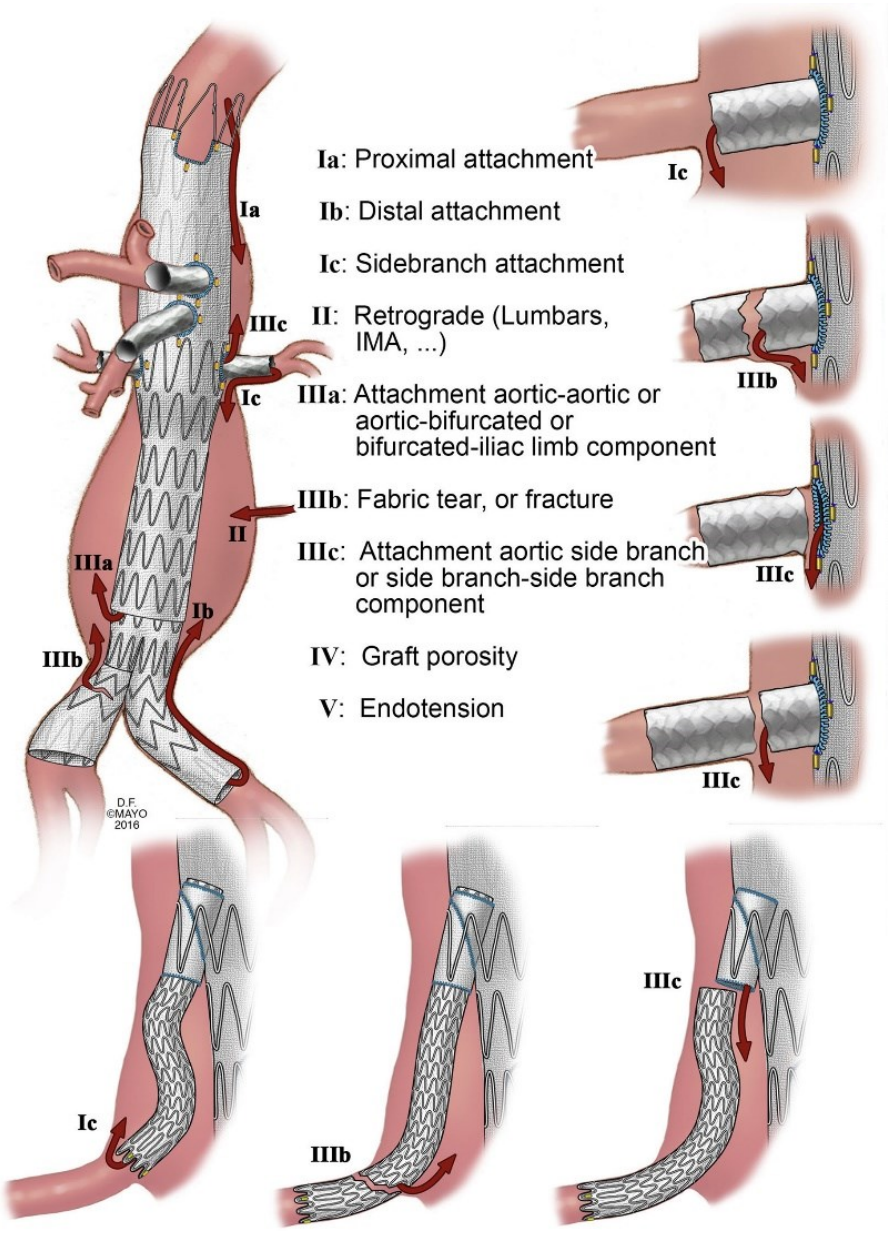
After releasing the endoprosthesis into place, a stent is inserted at each window, ensuring perfusion of collateral vessels. Depending on the length and morphology of the target vessel, two or three consecutive stents can be inserted.
All fenestrations were stented using a balloon-expandable stent graft as main bridging stent.
Some post-implantation geometric characteristics of the stent may play an important role in the target vessels-related outcomes. We considered the protrusion into the aorta, the length of sealing into the target vessel, and the morphology of the stent after flaring. However, the impact of the geometric conformation of the bridging stent on the mid-term outcomes of FEVAR is still unclear.
The study focuses on the appearance of possible target vessel instability, meaning every occlusion, endoleak, reintervention for stenosis, or disconnection.

The most common complication of the endovascular treatment of the aorta is the endoleak, characterized by the persistence of blood flow in the perigraft side after the procedure. The endoleak may be produced by an incomplete sealing of the

endoprosthesis or target vessels' stents to the arterial wall or derive from the aortic vascularization (from an intercostal or lumbar artery that retrogradely supplies the aneurysm excluded by the prosthesis). The flow persistence in the perigraft side increases its risk of rupture and induces the maintenance of endothelial damage also after the procedure. Endoleaks may become visible immediately after the endovascular treatment (primary endoleaks) or they may appear several months after the procedure (secondary endoleaks).

Endoleaks are classified into four categories (Fig 8). Els of I type are localized at the endograft anchorage, specifically they are divided into IA subtype (leaks at the proximal attachment), IB subtype (leaks at the distal attachment) and IC subtype (leaks at the sidebranch attachment); els of II type are due to aortic vascularization (from an intercostal or lumbar artery that retrogradely supplies the aneurysm excluded by the prosthesis); els of type III are divided in to IIIA (leaks at the attachment aortic-aortic or aortic-bifurcated of bifurcated-iliac limb component), IIIB (leaks for fabric tear or fracture of endograft) and IIIC (leaks at the attachment aortic side branch or side branch-side branch component); el of IV type happens in case of graft porosity.

Fig 8. Endoleaks classification taken from *https://www.jvascsurg.org/*



AIM OF THE SUDY

This study aimed to evaluate the impact of geometrical factors on target vessel instability in patient undergoing fenestrated endovascular aortic repair (FEVAR) for thoracoabdominal, juxtarenal and pararenal aortic aneurysm.

MATHERIALS AND METHODS

Study population

We conducted a single-center retrospective study including patients who underwent FEVAR from 2014 to 2021 at the operating unit of Vascular and Endovascular Surgery in Padova.

The study included 46 patients. Only patients with an available angiographic study performed within 30 days after surgery and a follow-up duration of more than 30 days were considered in the analysis.

Device design

All patients of the study received a specific device based on their anatomy and on the relationship between blood vessels. We used endograft based on the Cook Zenith (Cook Medical Inc, Brisbane, Australia) platform. No grafts were modified at the surgical site. In normal suprarenal aortic segments, a proximal sealing zone of at least 20 mm was selected, defined by a parallel aortic wall with no evidence of thrombus, calcium, or diameter enlargement greater than 10%.

Endoprosthesis fenestration for target vessel were either large (8 mm in diameter) or small (6 mm in diameter). In 8 cases proximal scallop was used for the superior mesenteric artery (n=6) or celiac trunk (n=2) without additional deployment of a bridging stent. A mixed branched and fenestrated design was used in 5 cases.

Catheterization and stenting of the target vessels were usually performed with femoral access. No preloaded catheters or guidewires were used. A balloon expandable stent graft was used as main bridging stent for all fenestrations.

In this study Lifestream (BARD Peripheral Vascular, Tempe, AZ, USA), Advanta V12/iCAST (Atrium Maquet Getinge, Hudson, NH), Viabahn balloon expandable stent-graft (VBX, W.L. Gore&Associates, AZ, USA) and Begraft (Bentley InnoMed, Hechingen, Germany) were used. The VBX stent has become the best option as a bridging stent since 2019. The bridging stent was usually placed to reach a standard seal length of 15 mm into the target artery and a protrusion of 3-5 mm

into the aortic graft. After deployment, the proximal edge of the stent was systematically adhered to the aortic wall using a 12x20 mm or 10x20 mm compliant balloon (Powerflex Pro PTA; Cordis, Santa Clara, California). Technical assessment of the stents of the target vessels included position, integrity, patency, and presence of endoleak. The geometrical analysis was based on the completion digital subtraction angiography and the first post-operative CTA study.

Postoperative medical therapy was the same for all patients. Every patient was subjected to dual antiplatelet therapy for 30 days (with aspirin 75-100 mg daily and clopidogrel 75 mg daily), followed by long-term single antiplatelet therapy (with aspirin). If a patient needed anticoagulant therapy due to other medical reasons, this was usually continued after assessing the risk-benefit ratio of the medical therapy.

Geometrical analysis and definitions

With the CT angiographic study post implantation, all geometric factors affecting target vessel instability can be deduced. Preoperative and postoperative measures were performed with the Aquarius iNtuition software (v 4.4.13; TeraRecon, Foster City, CA).

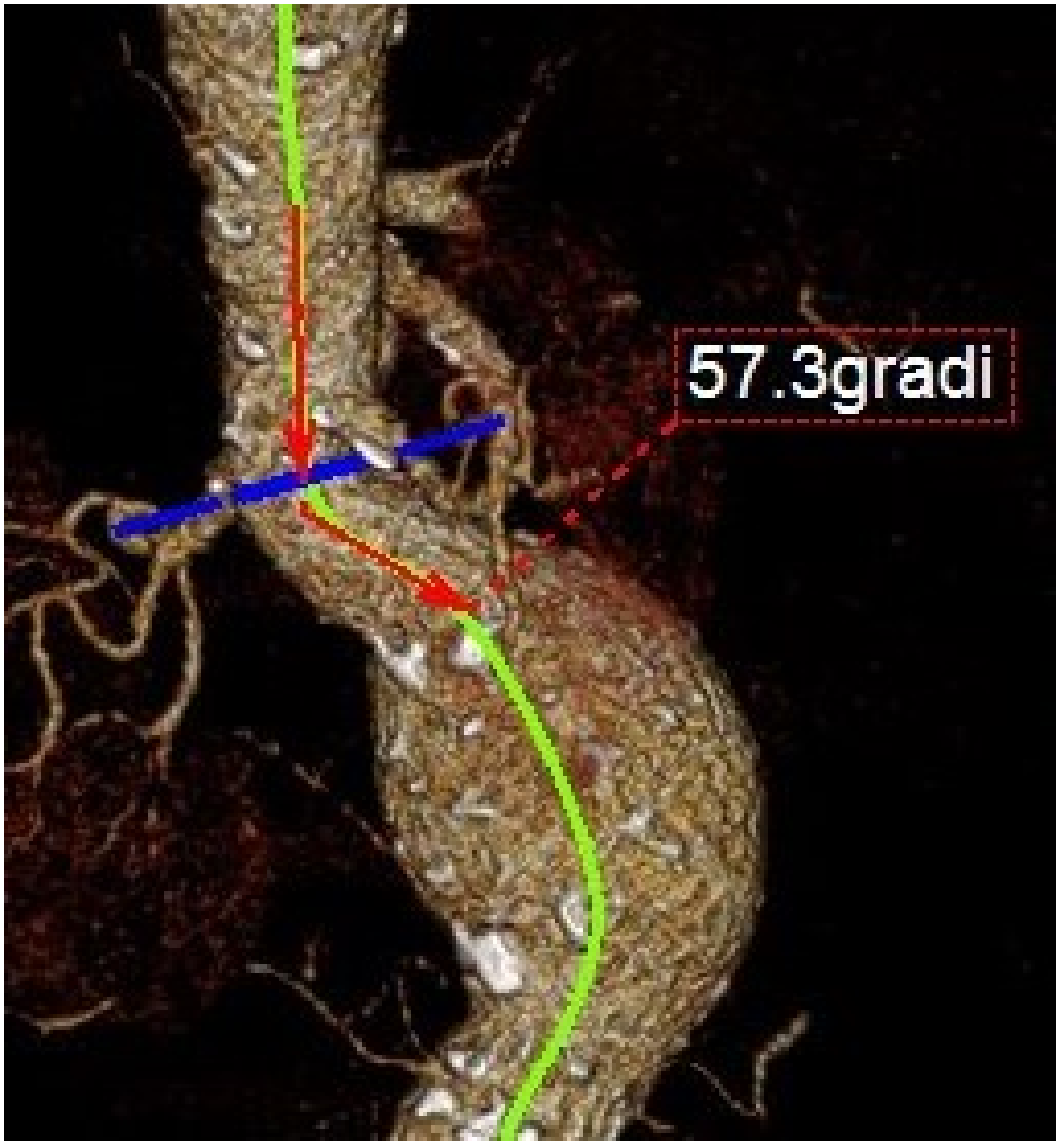
Preoperative anatomical characteristics

Preoperative anatomical characteristics included aortic angulation at the supraceliac, paravisceral, and infrarenal levels, as well as target vessels orientation.

Aortic angulation was measured using a previously reported standardized method[47-48-49-50-55]. The aortic centerline was semiautomatically generated on volume-rendered tridimensional reconstructions[48]; the three-dimensional reconstruction was then turned 360° perpendicular to the centerline at the level

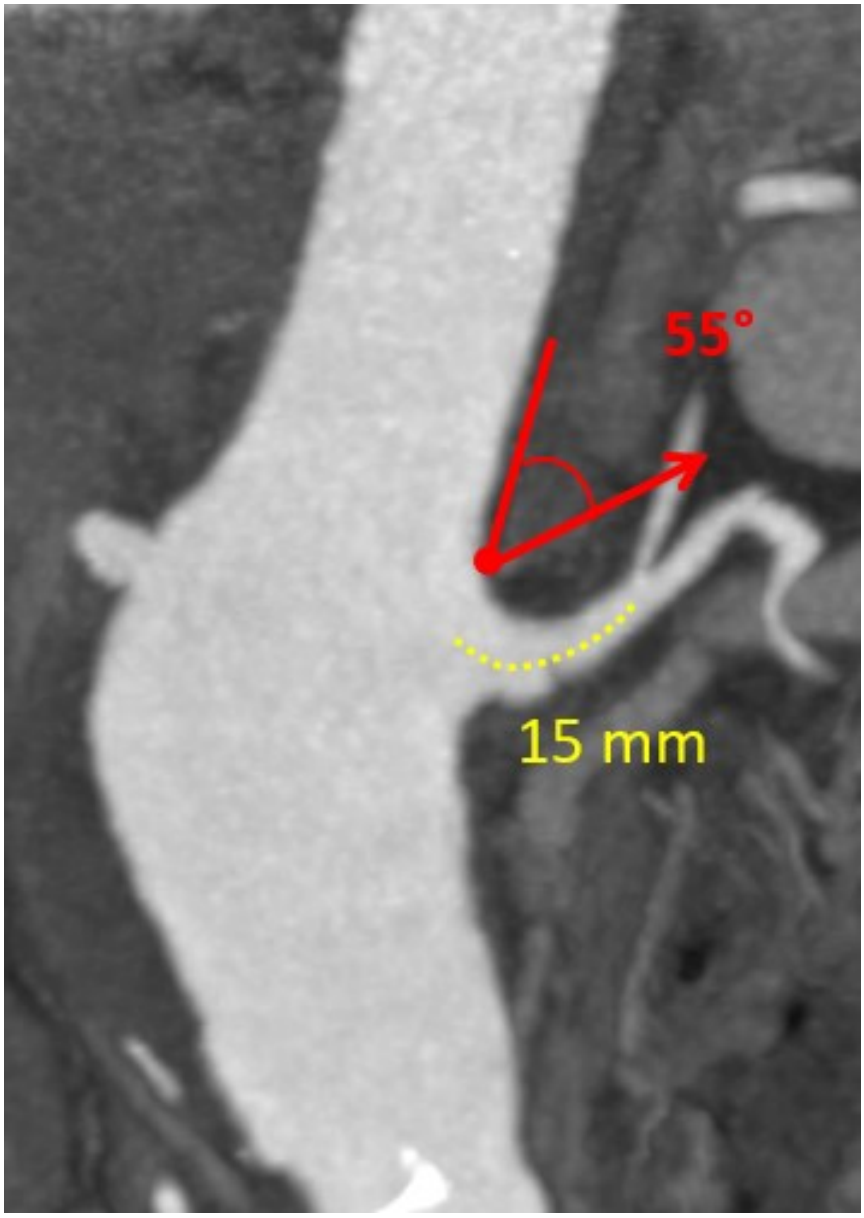
of the aortic flexion point, and the sharpest angle of the centerline was considered the real aortic angle (Fig 9).

Fig 9. Aortic angulation measured using a previously reported standardized method; *Francesco Squizzato and others, 'Effect of Aortic Angulation on the Outcomes of Fenestrated-Branched Endovascular Aortic Repair', Journal of Vascular Surgery, 74.2 (2021), 372-382.e3 <https://doi.org/10.1016/j.jvs.2021.01.027>.*



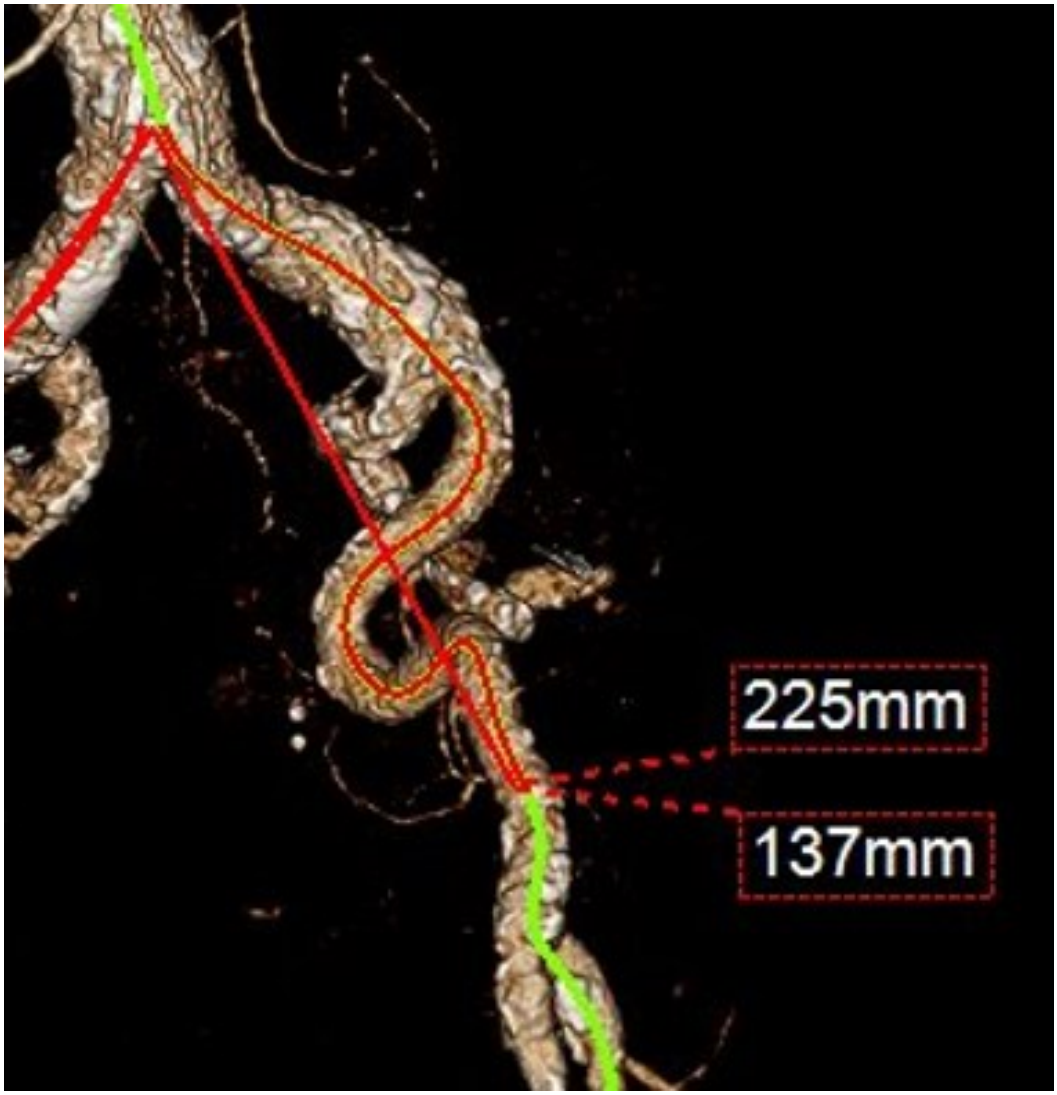
Orientation of target vessels was measured as the angle between the target vessel and the aortic centerline[51-48-52]; target vessels were categorized as upward-oriented (angle of < 60°), downwards orientated (> 120°), or straight (between 60° and 120°)[52] (Fig 10).

Fig 10. Orientation of target vessel. This is an upward-oriented target vessel



Iliac access tortuosity was measured as the right and left iliac tortuosity index, which is the ratio between the distance along the median luminal centerline between the aortic bifurcation and the common femoral artery and the straight-line distance between the same anatomical landmarks (Fig 11).

Fig 11. Iliac access tortuosity measured as the left iliac tortuosity index (225mm/137mm)



Anatomical characteristics after FEVAR

Bridging stent length and diameter, stent conformation and graft misalignment were considered as geometrical factors. Only fenestrations successfully aligned with a covered bridging stent were included in the post-implantation geometrical analysis. The geometric characteristics were assessed on the first postoperative CTA (usually performed before discharge) and included the assessment of bridging stent lengths, flare, and misalignment.

Every bridging stent length was divided into three components, after semiautomatically creation of the bridging stent centerline: the bridging stent protrusion length (PL) into the main endograft, the bridging length (BL) between the graft fenestration (identified by the radiopaque markers) and the origin of the target vessel, and the sealing length (SL) between the stent's surface and the inner side of the target vessel (Fig 12A-B).

Fig 12A. Post-implantation computed tomography angiography (CTA) geometrical analysis. The bridging stent length was categorized into three components, after the semiautomatic creation of the bridging stent centerline: protrusion length (PL, white) of the bridging stent into the main endograft, bridging length (BL, red) between the fenestration (identified by the radiopaque markers) and the origin of the target vessel, and sealing length (SL, yellow) of stent apposition to the arterial wall into the target vessel

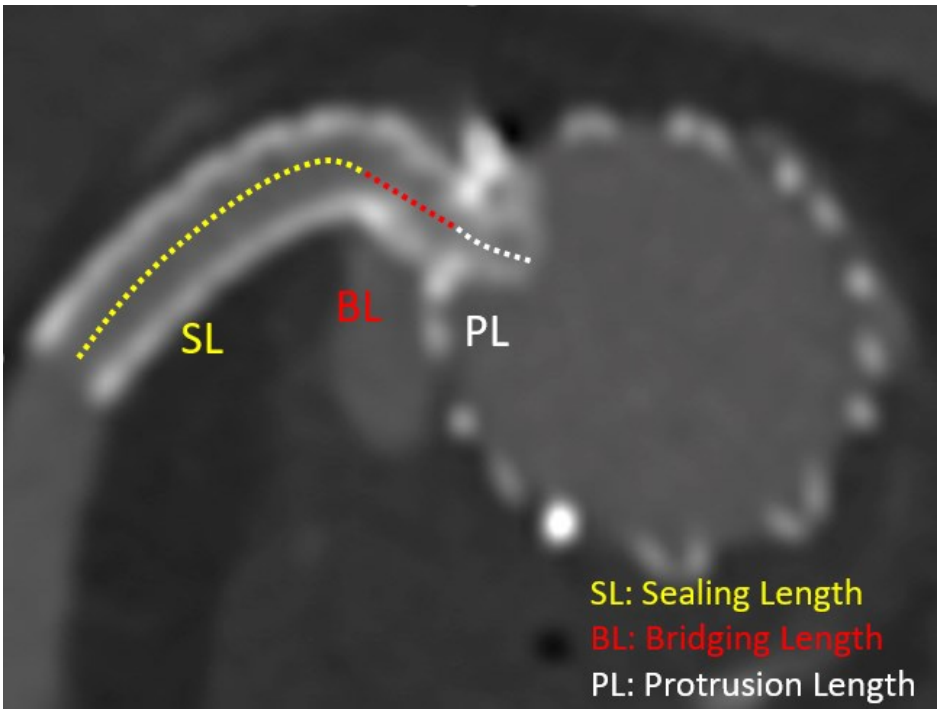
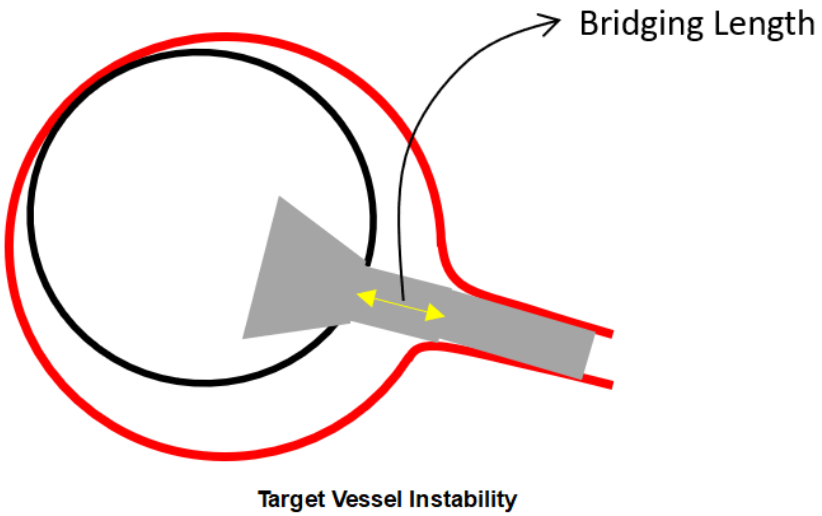
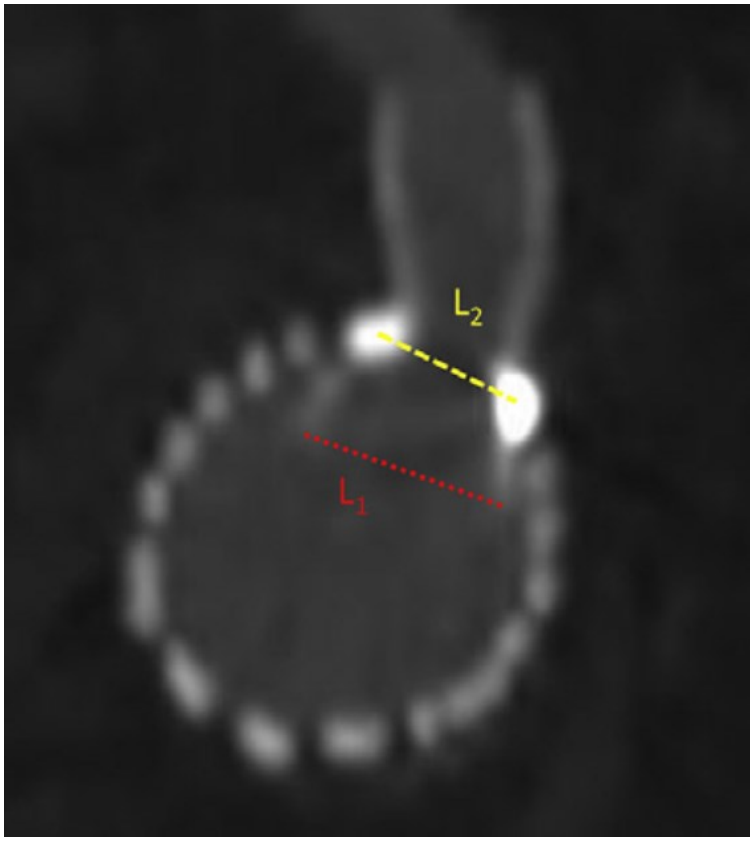


Fig 12B. Reconstruction of bridging length



The after-flare stent conformation was measured as flare ratio, that is ratio between maximum and minimum bridging stent diameter at the level of the fenestration (Fig 13).

Fig 13. Post-implantation computed tomography angiography (CTA) geometrical analysis. The flare ratio was defined as the ratio between maximum stent diameter (L1, red) and diameter at the level of the fenestration (L2, yellow)

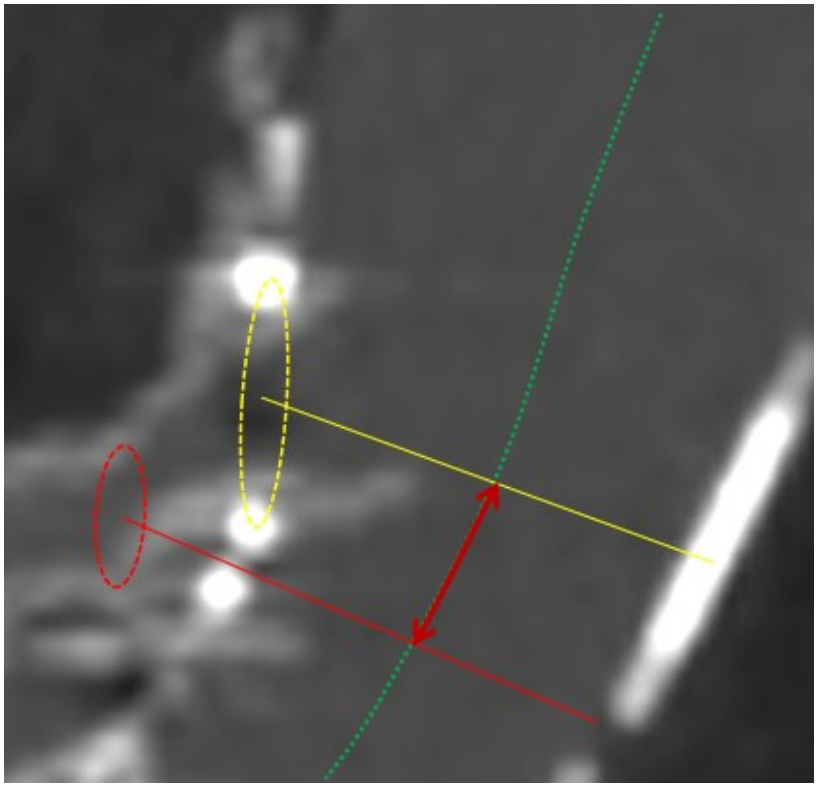


Two components of graft misalignment were analyzed, adapting the methods from Crawford et al[53].

Vertical misalignment was measured as the vertical distance between the fenestration midpoint and the target vessel origin midpoint (Fig 14).

Horizontal misalignment was measured as the angle between the midpoint of endograft fenestration and the axial cut of target vessel ostium (Fig 15).

Fig 14. The vertical misalignment was measured as the vertical distance along the aortic centerline between the midpoint of the fenestration and the midpoint of the target vessel at its origin



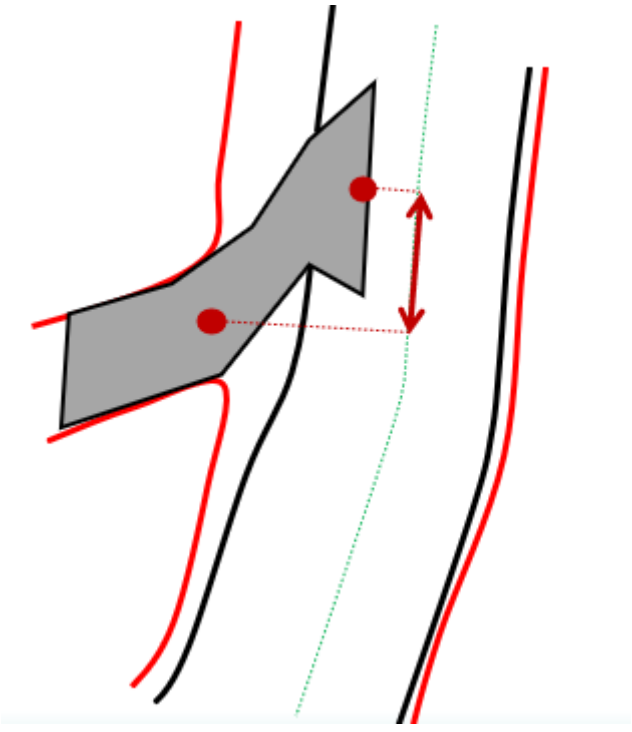
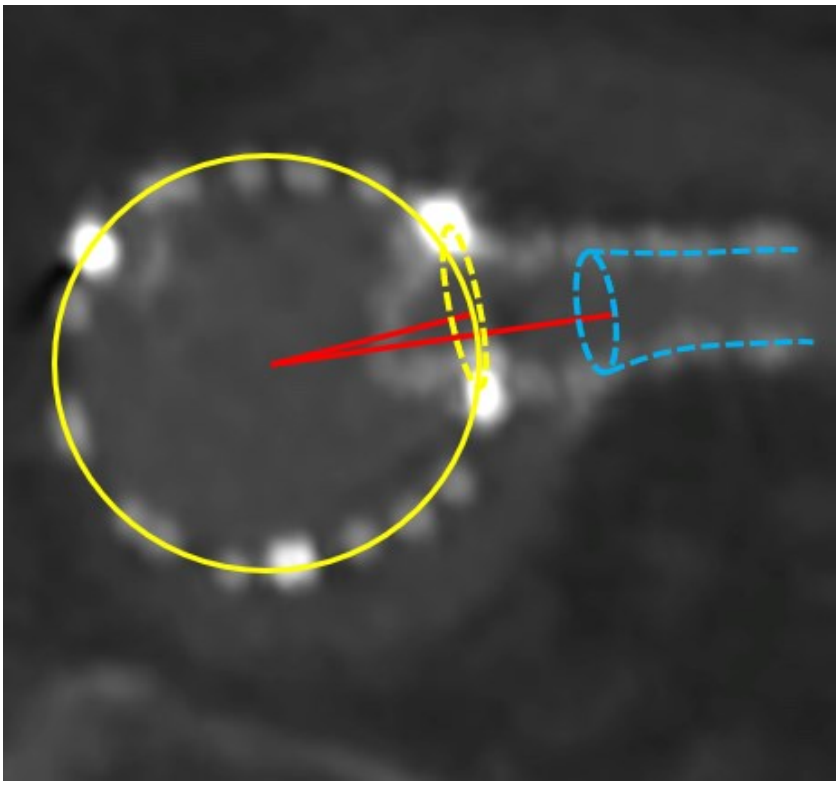
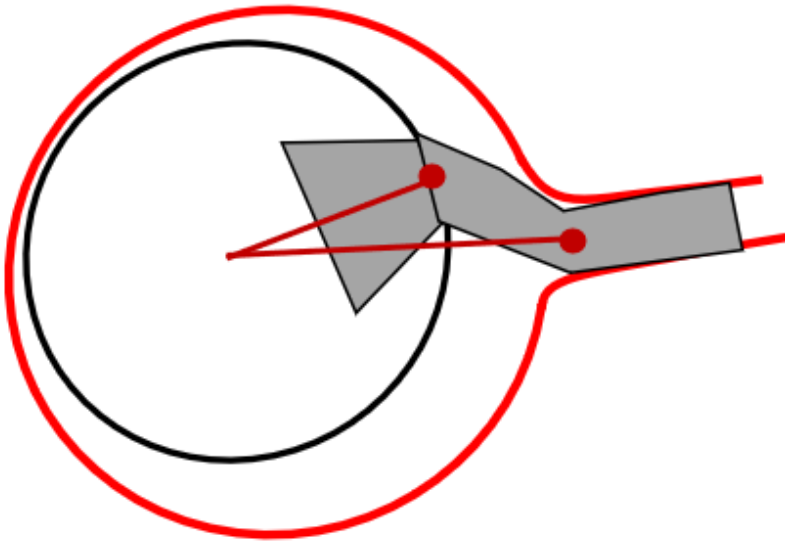


Fig 15. The horizontal misalignment was measured as the angle between the midpoint of the fenestration and the midpoint of the target vessel ostium on computed tomography angiography (CTA) axial cuts





Endpoints

The primary endpoint was freedom from target vessel instability, defined as any branch-related death, occlusion, rupture, or any reintervention for stenosis, endoleak or disconnection[54].

Secondary endpoints were freedom from target vessel endoleak and primary patency, this last defined as uninterrupted patency from the index procedure until the occlusion or any stent reintervention for stenosis.

Statistical analysis

In this study, categorical variables were reported as number and percentage, and continuous variables as mean ± standard deviation. Kaplan-Meier estimates were used to report time-dependent outcomes. Univariate and multivariate Cox proportional hazards models were performed to identify clinical, procedural, and anatomical factors associated with target vessel instability. The initial multivariate model included covariates with $p<0.2$ at univariate; a backward stepwise selection was performed and the most parsimonious multivariable model with inclusion of significant factors and confounders was considered as the final model. A penalized likelihood method based on Firth's regression[55] was adopted to account for the limited number of events. The unit of the analysis for target vessel instability was the single target vessel; to account for within-subject correlation, a shared frailty model was used. This method introduces a random effect variable that describes the conditional risk of target vessel instability (the frailty term) for each patient. In this way, each target vessel is assumed to be conditionally independent with respect to the shared frailty[56]. The association between BL and misalignment was assessed by a univariate linear regression. To assess for linearity of the relationship between continuous variables (ie. BL, target artery diameter) and the HR of the target vessel instability, a penalized spline smooth function was used without prespecified knots. This was tested for nonlinearity and, if a significant nonlinear function was confirmed, a receiver operating characteristics analysis was performed to determine the best cutoff, using target vessel instability as outcome variable. The cutoff value on the receiver operating characteristic curve

maximizing the sum of sensitivity and specificity (which is equivalent to the Youden's index[57]) was considered the optimal cutoff. Statistical significance was defined with p-value < 0.05. The R 4.0.4 software (R foundation for statistical computing, Vienna, Austria) was used for the analyses.

RESULTS

Patient cohort

There were 46 patients with JRAA/PRAA (n = 34 [76%]), extent I-III (n = 6 [13%]) or extent IV (n = 5 [11%]) TAAAs, with 147 target arteries successfully incorporated through a fenestration (mean of 3.4 ± 0.7 fenestrations per patient).

Number of patients	***46***
Number of target vessels	***147***

The mean age was 74 ± 6 years and 89% of patients were male. Most patients had an atherosclerotic aneurysm (n = 44 [98%]); one patient (2%) had a chronic dissection.

The mean maximum aneurysm diameter was 56 ± 13 mm. The other anatomical characteristics regarding aortic angulation, diameter, and orientation of the target vessels, together with demographics and risk factors of the cohort are described in Table I.

Table I. Demographics, clinical and anatomic characteristics of the 46 patients (147 target vessels) treated with fenestrated endovascular aneurysm repair (FEVAR)

Variable	Mean ± SD or No. (%)
Demographics	
Age, years	73.2 ± 6.6
Age > 80 years	5 (10.8)
Male sex	42 (91.3)
Risk factors	
Hypertension	35 (76.6)
Diabetes	7 (15.2)
Hypercholesterolemia	26 (56.5)

CAD	26 (56.5)
COPT	12 (26.0)
CKD	14 (30.4)
PAD	5 (10.8)
Prior TIA/stroke	3 (6.52)
Prior laparotomy	16 (34.7)
Prior aortic surgery	12 (26.0)
SVS/AAVS comorbidity score	0.9 ± 0.5
Anatomical data	
Aneurysm maximum diameter (mm)	55.6 ± 15.1
Anatomic aneurysm classification	
Pararenal	10 (21.7)
Juxtarenal	24 (52.2)
Thoracoabdominal	11 (23.9)
Extent I-III	6 (13.0)
Extent IV	5 (10.8)
Chronic dissection	1 (2.17)
Celiac artery	**n = 22**
Diameter (mm)	7.5 ± 1.5
Cranial orientation > 30°	1 (4.5)
Caudal orientation > 30°	13 (59.0)
Superior mesenteric artery	**n = 38**
Diameter (mm)	7.97 ± 1.4
Cranial orientation > 30°	0 (0)
Caudal orientation > 30°	17 (44.7)
Right renal artery	**n = 45**
Diameter (mm)	6.29 ± 1.46
Cranial orientation > 30°	0 (0)
Caudal orientation > 30°	18 (39.1)
Left renal artery	**n = 42**
Diameter (mm)	6.46 ± 1.4

Cranial orientation > 30°	2 (4.7)
Caudal orientation > 30°	16 (38.0)

CAD, Coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronica kidney disease; PAD, peripheral arterial disease; SD, standard deviation; SVS/AAVS, Society for Vascular Surgery/American Association for Vascular Surgery; TIA, transient ischemic attack.

Procedural data and early outcomes

A patient-specific endograft was used in all cases. Endograft design was 2 fenestrations and 1 scallop in 6 (13%) cases, 3 fenestrations in 13 (28%) cases, 3 fenestrations and 1 scallop in 2 (4%) cases, 4 fenestrations in 21 (46%) cases, and a branched plus fenestrated device in 5 cases (11%).

The bridging stent was a Gore VBX in 57% of target vessels; other types of stents were used in 43% of patients. Fourteen target vessels (9.5%) received an additional covered (n = 9 [6.1%]) or bare metal (n = 5 [3.6%]) stent as reinforcement. There were no perioperative deaths.

The overall major adverse event rate was 21%; specific early complication rates are described in Table II.

Table II. Procedural data and early outcomes of the 46 patients treated with fenestrated endovascular aneurysm repair (FEVAR)

Variable	Mean ± SD or No. (%)
Procedural data	
Endograft design	
2 fenestrations + 1 scallop	6 (13.0)
3 fenestrations + 1 scallop	2 (4.3)
3 fenestrations	13 (28.3)
4 fenestrations	21 (45.6)
Fenestrations + branches	5 (10.8)
No. of stented fenestrations for patient	3.4 ± 0.7

Type of main bridging stent	
Lifestream, Bard	38 (25.8)
VBX, Gore	84 (57.1)
Advanta, Atrium	20 (13.6)
BeGraft, Bentley	5 (3.4)
Mean bridging stent diameter (mm)	7.4 ± 1.3
Mean bridging stent length (mm)	32.5 ± 5.5
Adjunctive covered stent	9 (6.1)
Adjunctive BMS	5 (3.4)
Early outcomes	
Length of hospitalization (days)	5 ± 10
Death	0 (0)
Any MAE	10 (21.1)
EBL > 1000 mL	3 (6.5)
Spinal cord injury	3 (6.5)
Stroke/TIA	0 (0)
Myocardial infarction	2 (4.3)
Acute kidney injury	2 (4.3)
Respiratory failure	2 (4.3)
GI complications	1 (2.2)

BMS, Bare metal stent; MAE, major adverse event; EBL, estimated blood loss; GI, gastrointestinale; SD, standard deviation; TIA, transient ischemica attack; VBX, Viabahn Balloon expandable stent graft.

Post implantation geometrical analysis

Overall, the mean total length of the bridging stent was 32.5 ± 6.6 mm; the PL was 6.4 ± 2.1 mm (range, 1-13 mm), the BL was 1 ± 2.1 mm (range, 0-19 mm), and the SL was 21.7 ± 5.9 mm (range, 3-33 mm). The mean bridging stent nominal diameter was 7.4 ± 1.1 mm; this was post-dilated to 8.4 ± 1.6 mm after flare of the proximal portion.

Compared with other types of stents, the VBX showed a higher post-flare diameter (8.7 ± 1.9 mm vs 8.1 ± 1.4 mm; *p*=0.021) and flare ratio (1.27 ± 0.27 vs 1.19 ± 0.23; *p*<0.001), and a shorter PL (5.7 ± 2.2 mm vs 6.9 ± 1.9 mm; *p*=0.002) (Table III).

The mean graft vertical misalignment was 0.7 ± 1.2 mm and the horizontal misalignment was 9.6 ± 13.4°, without differences between distinct types of stent. There was a linear relationship between BL and horizontal misalignment (β=1.76; *p*=0.003), and patients with a BL of 5 mm or greater had a significantly higher degree of horizontal misalignment (21 ± 12° vs 9 ± 13°; *p*=0.011). A BL of more than 5 mm was not associated with vertical misalignment (0.7 ± 1.3 mm vs 0.7 ± 1.1 mm; *p*=0.966).

Table III. General results of the post-implantation geometrical analysis, stratified by type of bridging stent

	All stent types	**New generation (VBX)**	**Other**	***p***
Bridging stent nominal diameter	7.4 ± 1.1	7.4 ± 1.1	7.4 ± 1.1	0.750
Post-flare max diameter (mm)	8.4 ± 1.6	8.7 ± 1.9	8.1 ± 1.4	0.021*
Bridging stent min diameter (mm)	6.1 ± 1.1	6.1 ± 1.1	6.1 ± 1.2	0.973
Flare ratio	1.13 ± 0.26	1.27 ± 0.27	1.19 ± 0.23	0.011*
Bridging stent nominal length (mm)				0.524
Mean ± SD	32.5 ± 5.5	32.8 ± 4.9	32.1 ± 8.1	
Range	22-38	29-39	22-38	
PL (mm)				0.002*
Mean ± SD	6.4 ± 2.1	5.7 ± 2.2	6.9 ± 1.9	
Range	1-13	1-10	2-13	
BL (mm)				0.159
Mean ± SD	1 ± 2.1	0.6 ± 1.7	1.1 ± 2.4	
Range	0-19	0-15	0-19	

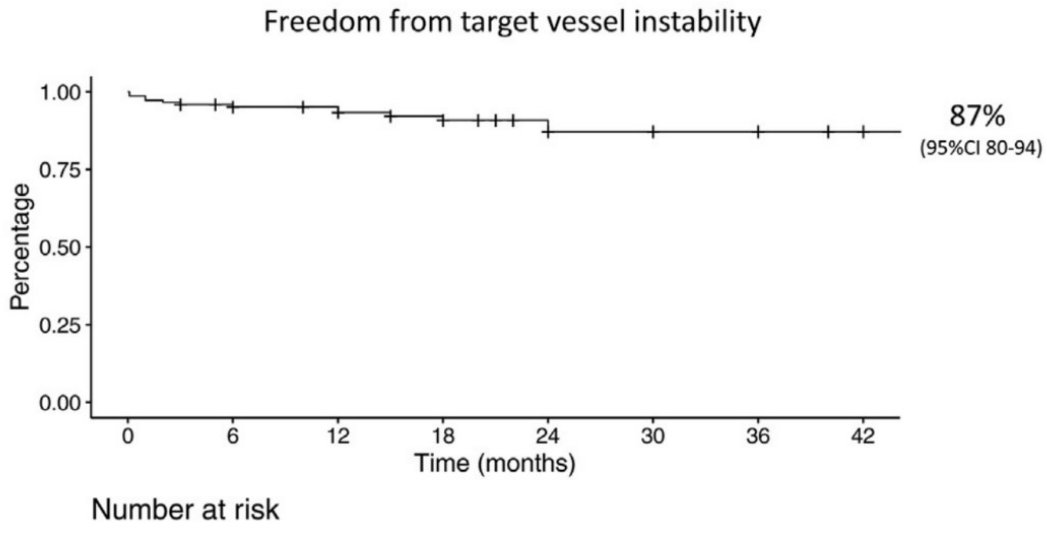
SL (mm)				0.986
Mean ± SD	21.7 ± 5.9	21.7 ± 4.5	21.7 ± 7.0	
Range	3-33	5-33	3-33	

BL, bridging length; PL, protrusion length; SD, standard deviation; SL, sealing length.
*Statistically significant.

Target vessel-related outcomes

During a 42-month period of follow-up (median 24 months), there were 13 target vessel-related complications, including 2 occlusions and 11 endoleaks (9 type IIIc owing to inadequate stent-to-aortic graft sealing, 2 type Ic). There were no cases of bridging stent fracture. No related deaths or aneurysm ruptures happened. The estimated freedom from target vessel instability was 87% (95% CI, 80-94) at 42 months (Fig 16).

Fig 16. Kaplan-Meier curve of freedom from target vessel instability for the 147 target arteries included in the analysis. The standard error is less than 10%. CI (confidence interval)



On the univariate analysis, the presence of a TAAA (HR 3.6; 95% CI 1.2-10.8; *p*=0.022) rather than a JRAA/PRAA, a smaller target artery diameter (HR 0.19; 95% CI 0.09-0.39; *p*<0.001), and renal arteries (HR 18.8; 95% CI 2.5-24.0; *p*<0.001) were significantly associated with target vessel instability, as well as a shorter PL (HR 0.72; 95% CI 0.54-0.96; *p*=0.024) and a longer BL (HR 1.49; 95% CI 1.30-1.72; *p*<0.001) (Table IV).

At multivariate analysis, a BL of 5 mm or more was confirmed as associated with less satisfactory target vessel outcomes (HR 4.98; 95% CI 1.13-21.85; *p*=0.033).

Table IV. Univariate and multivariate Cox proportional hazards (with Firth penalization) for target vessel instability during follow-up

	UNIVARIATE		**MULTIVARIATE**	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
TAAA	3.6 (1.2-10.8)	0.022*	1.04 (0.17-2.37)	0.517
Aneurysm max diameter (mm)	0.98 (0.91-1.05)	0.526	-	-
Target artery diameter (mm)	0.19 (0.09-0.39)	< 0.001*	0.20 (0.09-0.44)	< 0.001*
Renal artery	18.8 (2.5-24.0)	< 0.001*	-	-
Type of stent (VBX)	1.18 (0.38-3.65)	0.767	-	-
Flare ratio	4.66 (0.57-37.7)	0.149	-	-
PL (mm)	0.72 (0.54-0.96)	0.024*	-	-
Protrusion length < 3 mm	4.55 (1.24-16.67)	0.022*	1.08 (0.22-5.28)	0.923
BL (mm)	1.49 (1.30-1.72)	< 0.001*	-	-
Bridging length ≥ 5 mm	9.96 (2.66-37.25)	< 0.001*	4.98 (1.13-21.85)	0.033*
CL (mm)	0.95 (0.87-1.03)	0.238	-	-

BL, bridging length; PL, protrusion length; SL, sealing length; TAAA, thoracoabdominal aortic aneurysm; VBX, Viabahn balloon expandable stent graft.
*Statistically significant.

The next figure (Fig 17A-B) shows the relationship between the BL and the HR for target vessel instability, with identification of a 5 mm BL as the optimal cutoff for the prediction of target vessels complications. After performing the same analysis for target artery diameter, it was not possible to identify a specific cutoff.

Fig 17A. Penalized splines functions describing the hazard ratio (HR) of target vessel instability vs the bridging length (BL); *p*=0.029 for the nonlinear relationship.

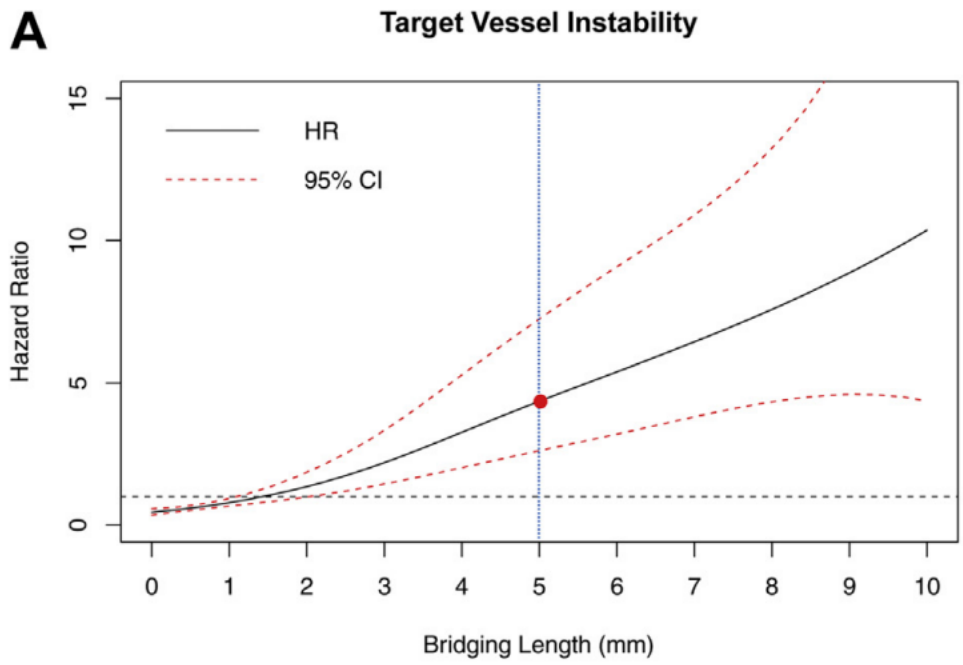
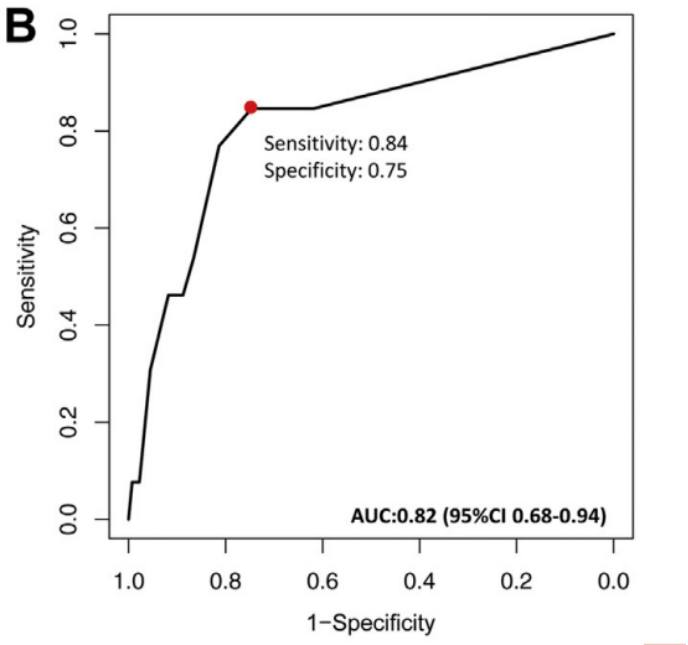


Fig 17B. Receiver operating characteristic (ROC) curve of BL in the prediction of target vessel instability after fenestrated endovascular aneurysm repair (FEVAR). The red dot indicates a 5 mm cutoff



AUC, area under the curve; CI, confidence interval

Future prospective

The study will investigate the clinical impact of misalignment between fenestration and target vessel, and the determinants of fenestration-to-target vessel misalignment after FEVAR.

If we take a closer look at the impact of horizontal misalignment on target vessel instability, we can see that there is a substantially increase in the chance of target vessel complications when horizontal misalignment is more than 15 degrees (Fig 18A-B).

Fig 18A. Impact of horizontal misalignment on target vessel instability. Penalized splines functions describing the hazard ratio (HR) of target vessel instability vs the horizontal misalignment (degrees); *p*=0.006 for the nonlinear relationship.

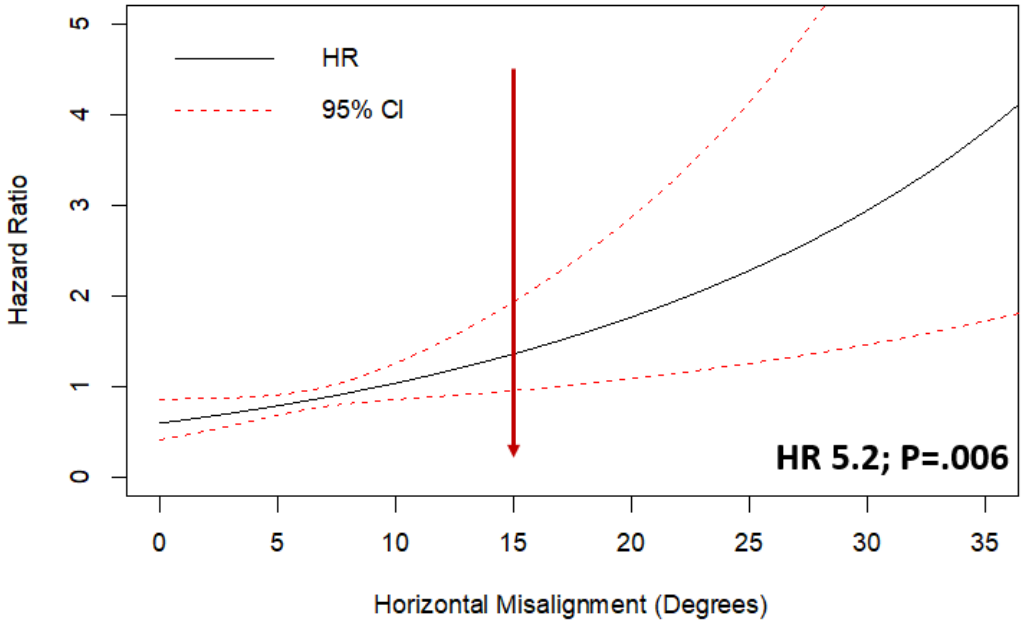
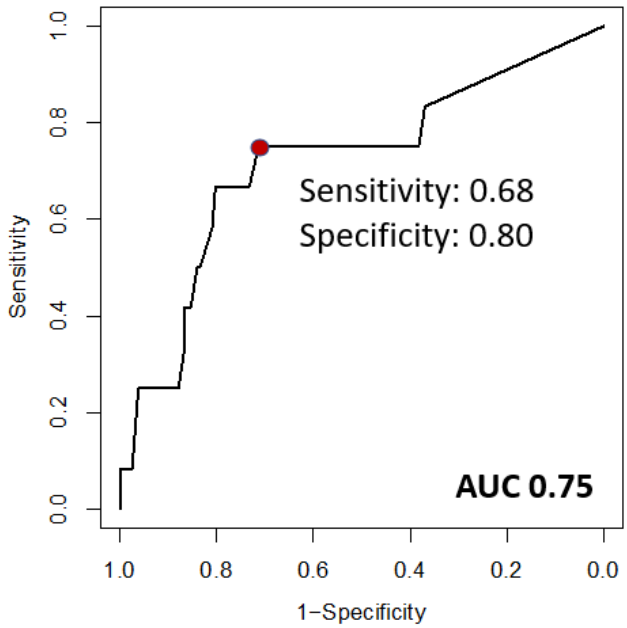


Fig 18B. Impact of horizontal misalignment on target vessel instability. Receiver operating characteristic (ROC) curve of horizontal misalignment in the prediction of target vessel instability after fenestrated endovascular aneurysm repair (FEVAR). The red dot indicates a 15 degrees cutoff.



Operator's learning curve, pararenal aortic angle, bridging distance > 5 mm, a higher profile of the device, in particular in presence of a high tortuosity of the iliac access, were significant determinants of horizontal misalignment > 15° (Table V).

Table V. Determinants of clinically significant horizontal misalignment > 15°

	UNIVARIATE		**MULTIVARIATE**	
	OR (95%CI)	***p***	**OR (95%CI)**	***p***
Operator's learning curve (quartiles)	0.96 (0.93-0.98)	<0.001*	0.96 (0.94-0.99)	0.043*
Pararenal aortic angle	1.01 (1.00-1.02)	0.024*	1.01 (1.00-1.02)	0.044*
Bridging distance ≥ 5mm	1.59 (1.14-2.12)	0.006*	1.07 (1.02-1.11)	0.003*
Endograft profile (Fr.)	1.79 (1.01-3.17)	0.046*	-	-
Iliac access tortuosity index	1.73 (1.10-2.70)	0.017*	1.55 (1.01-2.61)	0.047*
Iliac access tortuosity + Endograft profile	6.35 (4.28-9.41)	0.022*	7.55 (4.55-10.11)	0.016*

*Statistically significant.

DISCUSSION

The main challenges of FEVAR involve the occurrence of target vessel related complications, like occlusions or endoleaks[58-59].
Up to 25% of patients may require secondary interventions during follow-up.

To ensure lasting results, certain procedural and technical elements must be ideally executed. The fenestration should be perfectly aligned with the target vessel, and the bridging stent should provide a high fixation to the main endograft, a good resistance to compression, kink, or fracture, and should achieve a sufficient sealing into the target vessel.

This study investigated the impact of post-implantation geometric characteristics on the clinical outcomes of FEVAR. The main result was to define BL (the gap distance between the aortic main graft and the origin of the target vessel) as a significant determinant of target vessel instability during follow-up. This was especially seen when a BL is greater than 5 mm.

A reasonable explain for this result is that the bridging stent is subject to chronic mechanical stress, derived from the respiratory movements and the cardiac cycle. This stress produces continuous friction between the aortic endograft and the stent bridging, and between the stent bridging and the target vessel wall[60]. The presence of a long BL increases the space of movement between different fenestration components, increasing the risk of target vessel complications due to materials fatigue, disconnection, or compression. Furthermore, a greater distance between the fenestration and the target vessel implies that is more difficult to attain a good alignment of the fenestration.

The negative effect of BL on fenestration's orientation was supported by the linear relationship between BL and horizontal misalignment. An excessive BL of more than 5 mm was significantly associated with a higher degree of horizontal misplacement (Table VI).

Table VI. The negative effect of BL on fenestration's orientation was supported by the linear relationship between BL and horizontal misalignment

	BL < 5 mm	**BL ≥ 5mm**	***p***
Horizontal misalignment (degrees)	9 ± 13	21 ± 12	0.01
Vertical misalignment (mm)	0.7 ± 1.1	0.7 ± 1.3	0.96

Operator's learning curve, aortic angulation, iliac access tortuosity, and bridging distance ≥ 5 mm are associated with worsened horizontal alignment.
The use of devices with smaller and adaptable features may help improving fenestration-to-target vessel alignment in tortuous anatomies.

Factors that may contribute to misalignment include also the method of graft insertion: a long gap between endograft and target vessel increases the parallax under fluoroscopy and may also exacerbate the physiological displacement of the target vessel ostium produced by the introduction of stiff endovascular devices[61]. Although the study results show that PL is a possible determinant of horizontal misalignment, it should be kept in mind that other factors may also contribute to endotransplant misalignment, such as the operator learning curve, the aneurysm type (TAAA vs JRAA/PRAA) and aortic tortuosity. Similarly, vertical misalignment may depend on many variables; calcifications or plaques in the aortic wall can distort the final main endograft morphology.

Other determinants of the final outcome of FEVAR may be the shortening or elongation of the endograft during deployment, the mechanical properties of the bridging stent, and overall anatomy changes once the constraining wires and the stiff guidewires are removed. Although these intraoperative variables are largely unpredictable, it can sometimes be useful during the endovascular planning to adjust for an abrupt takeoff angle of aortic side branches, designing a slight vertical displacement of the fenestration in relation to the target vessel origin, to better follow the direction of the native vessel.

A peculiarity of the bridging stents used in FEVAR is that the anchorage between the stent and the main aortic graft is provided by two mechanisms: the presence of an adequate PL and the postdilatation of the proximal edge of the stent (flare). These mechanisms help to avoid the most frequent causes of complications in FEVAR (disconnections and junctional leaks). At the univariate analysis of the study, a shorter PL was associated with a higher chance of target vessel complications, in particular when PL is less than 3 mm (p=0.022; Table IV). Although this finding was not confirmed after the multivariate analysis, this result is in line with the common practice to aim at 3 to 5 mm of bridging stent protrusion into the aortic endograft[62].

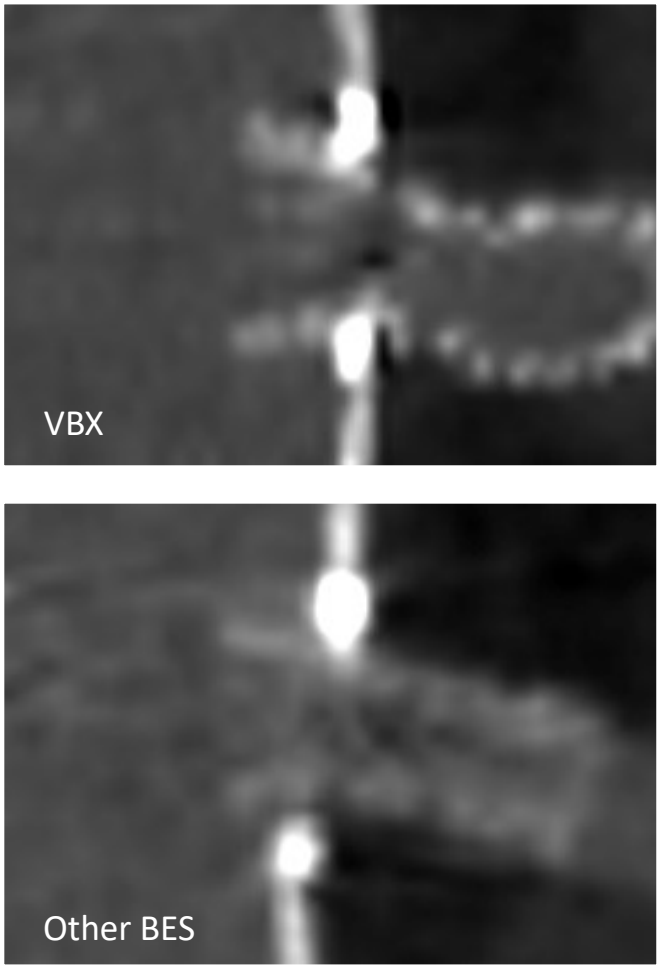
The role of the post-flare stent conformation is more difficult to assess because it depends on both the operative technique and the type of bridging stent. Regarding the bridging stent, satisfactory results have been traditionally described with the use of the iCAST/ Advanta[63-64]; more recently, the VBX Gore[65] and the Bentley BeGraft[66] have been used with promising results. However, none of the currently available stents is specifically approved for FEVAR, and there is no evidence supporting the use of a specific type. According to the study's results, the VBX stent showed a higher flare capability, intended as the possibility to selectively postdilate the stent at a greater diameter only in its proximal segment (p=0.011; Table III).

The peculiar structure of the VBX stent consisting of independent stainless-steel rings is responsible for this feature (Fig 19). Although this may be theoretically advantageous in FEVAR for increasing the attachment of the bridging stent to the main graft, preventing type III endoleaks and disconnections, the stent type was not found to be associated with midterm outcomes (p=0.767), neither was the flare ratio (p=0.149). It is worth mentioning that in this experience a standardized flaring technique was systematically used for all cases independently from the type of stent, based on the post-dilatation with a compliant 10-12 mm diameter balloon. This process allows a proper dilatation of the proximal portion of the stent

protruding into the aortic graft, without exerting an excessive pressure on the fenestration.

Studies with a longer follow-up and larger patients' cohorts are still needed to further assess the role of the stent type and post-flare conformation on clinical outcomes, and to make more definitive conclusions.

Fig 19. From the multiplanar computed tomography angiography (CTA) reconstruction of the post-flare conformation of two different types of bridging stents, we can see the different conformation between VBX stent and the other ones.



Small size target arteries were associated with a higher risk of instability both at the univariate and multivariate analysis (HR 0.20; $p<0.001$). In the clinical practice, the problem of small target vessel diameters basically affects the renal arteries.

Unfortunately, no specific cutoff diameter associated with worse outcomes could be found. A patient-specific decision should be made, weighing the benefits of a small target vessel incorporation (ie, preservation of renal function) against the risks of intraoperative complications (longer operating time, excessive contrast, and radiation exposure due to difficult cannulation and stenting, target vessel rupture) and late failures related to the small artery size. In this experience, renal artery stenting was systematically planned for renal arteries greater than 5 mm.
In case of a 4-5 mm diameter, renal artery bridging can still be performed, but with more technical difficulties; in these cases, a few suggestions can be used to optimize the final stent conformation. In the patients of the study with a 4-5 mm diameter of the renal artery a bridging stent with a 6 mm nominal diameter was used. This was gently inflated at the level of the target vessel until the target vessel's diameter, just to adapt it to the arterial wall and avoiding excessive overdilatation, and then it was postdilated just in its proximal part, to adapt it to the diameter of the fenestration (usually 6 mm). Proximal flaring was then performed as usual. After bridging stent deployment, intravascular ultrasound examination was used to check for the stent apposition at the level of the target vessel, and post-ballooning was eventually performed with an adequate size balloon if needed. A self-expanding bare metal stent was sometimes used to smoothen the transition between the bridging stent and the native artery.
In case of renal arteries that are less than 4 mm in diameter, the risks of both intraoperative complications and late occlusion may discourage renal artery incorporation. In any case, preoperative renal sequential scintigraphy may be helpful to guide endovascular planning for elective procedures, avoiding the incorporation of small renal arteries with evidence of poor preoperative renal perfusion.

Overall, the results of this study expand the current knowledge of the geometric and anatomical characteristics that may impact on the outcomes of FEVAR, and that should be considered during FEVAR planning and endograft deployment. Target vessel-related complications may be favored by unfavorable anatomical features (ie, excessive aortic angulation and tortuosity[67-68], severe kink or

implantation angle of the target vessel[69-70]. The presence of a large distance between the fenestration and the target vessel represents an additional issue that needs to be addressed.

A reasonable strategy is to try to keep the BL as short as possible during the endovascular sizing and planning, using a large aortic graft to promote an almost complete attachment of the fenestration to the target vessel. This practice may not be always feasible, especially in cases of a large aneurysmal sac. The use of directional branches instead of fenestrations may be preferred in these cases, although branched repair is mainly done in cases of TAAA and the presence of a cranial orientation of the target vessel is still a problem to be addressed[69-70-45].

The use of inner branches represents a valid alternative in cases[71] with a narrow aorta as well as PRAAs.

Finally, the results of this study may be useful during the technical assessment of the bridging stent with the cone beam CT scans or intravascular ultrasound examination[72-73]. If a long BL (>5 mm) is found, reinforcement with an additional covered or bare metal stent may be considered to improve its attachment to the aortic endograft and prevent compressions or kinks[71]. Even if these strategies are reasonable, further data are necessary to validate the best approach in FEVAR cases with a long BL.

The present study had some notable limitations. The study was a single-center, retrospective study with a limited number of patients. In this clinical practice, the use of directional branches instead of fenestrations was preferred in cases of large TAAAs, in particular when the aortic diameter at the visceral level was greater than 4 cm, as reported also by other centers[63-69]. Although this is just a general approach and not a systematic rule, and case by case selection was based on the specific patient anatomy, this factor may have been a possible source of selection bias for this specific study. The low number of events may have limited the power of the statistical analysis, so a longer follow-up is necessary for more robust conclusions. Larger confirmatory studies may be useful to correlate the specific type of target vessel instability with the postoperative geometric conformation. There were significant differences in geometric conformation between the VBX

and other types of bridging stents, but a longer follow-up and a greater number of patients are necessary to further compare different types of bridging stents used in FEVAR. This study was strengthened by detailed geometric analysis and standardization of technique procedures. Also, a standardized flaring technique with the use compliant balloons was adopted for all types of stents, allowing a fair geometrical comparison. Furthermore, the use of a regression analysis based on Firth's penalization allowed to produce a reliable HR in cases of low numbers of events.

CONCLUSIONS

A preoperative study of target vessels conformation and orientation, and a postoperative geometrical analysis of bridging stents conformation demonstrated that these geometrical factors may play an important role in the target vessels-related outcomes of FEVAR.

An optimal post-implantation geometrical conformation between the bridging stent and the aortic endograft is a prerequisite for improving the midterm outcomes of FEVAR.

With this study we demonstrated that the distance between the fenestration and the target vessels' origin (BL) is an important geometrical factor determining the target vessel instability, especially if this distance exceeds 5 mm.

A BL ≥ 5 mm was significantly associated with a higher degree of horizontal misplacement, and a stronger risk of type Ic or IIIc endoleak and secondary interventions.

A more frequent follow-up may be appropriate in case of fenestration-target vessel distance > 5 mm. The use of inner or outer branches instead of fenestrations may be considered in cases with anticipated excessive distance between the endograft and the target vessel.

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