SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3366.

SZENTIVÁNYI ANDRÁS IMRE

Klinikai és kísérletes angiológiai kutatások
című program

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Innovations in Aortic Repair: Addressing Long-Term Efficacy and Procedural Safety

PhD thesis

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Budapest

2025

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1 List of Abbreviations

AAA – Abdominal Aortic Aneurysm

AD – Aortic Dissection

BECS – Balloon-expandable covered stent

CFA – Common femoral artery

cTBAD – complicated type B aortic dissection

CT – Computed Tomography

CTA – Computed Tomography Angiography

EVAR – Endovascular Aortic Repair

FBEVAR – Fenestrated or Branched EVAR

IFU – Instructions for use

ICC – Intraclass correlation coefficient

IRAD – International Registry of Acute Aortic Dissection

MRA – Magnetic resonance angiography

OSSAF – open surgical suprarenal aortic fenestration

QISS MRA – quiescent-interval single-shot MRA

TAVR – Transcatheter aortic valve repair

TAAD – type A aortic dissection

TBAD – type B aortic dissection

TEVAR – thoracic endovascular aortic repair

US – Ultrasound

VASC – Vascular access site complication

VCD – Vascular closure device

2 Introduction

2.1 Historical overview of aortic aneurysms and dissections

2.1.1 Early approaches of aortic aneurysms

The pathology of aortic aneurysms has been studied since ancient times. The term “aneurysm” originates from Latin and Greek, meaning dilatation. Medically, it refers to a localized vessel wall widening exceeding 1.5 times the normal diameter, while less severe dilatations are termed "ectatic." Abdominal aortic aneurysms (AAA) are five times more common in men, (1) with rupture mortality reaching 80%. (2) In contrast, mortality in asymptomatic cases treated surgically—particularly with endovascular aneurysm repair (EVAR)—is about 1%. (3) Risk factors for AAAs over 4 cm include smoking, family history, ischemic heart disease, hypercholesterolemia, and cerebrovascular disease. (4)

The surgical management of AAA dates back more than 3,000 years and has progressed through three key milestones: ligation, open surgery, and EVAR. Aneurysms were first documented in 1550 BC in Egypt’s Ebers papyrus (5), and also appear in ancient Indian texts, in Sushruta Samhita (c. 800-600 BC) referring to aneurysms as 'granithi'. Religious dogma greatly limited the development of science, thanks to the prohibition of autopsies. The first public autopsy was performed by Herophilos in the mid-3rd century BC, who immediately articulated the pathological nature of aneurysms. (6) Galen and Antyllus further described the basis of the modern definition of aneurysm in the 2nd century AD. Galen refers to it as a pulsatile tumor that can disappear under pressure. The modern anatomical understanding began in the 16th century thanks to the increasing number of public dissections, that lead to Vesalius’ detailed work (De Humani Corporis Fabrica) who firstly published an accurate diagram and treatment of AAA in 1555.

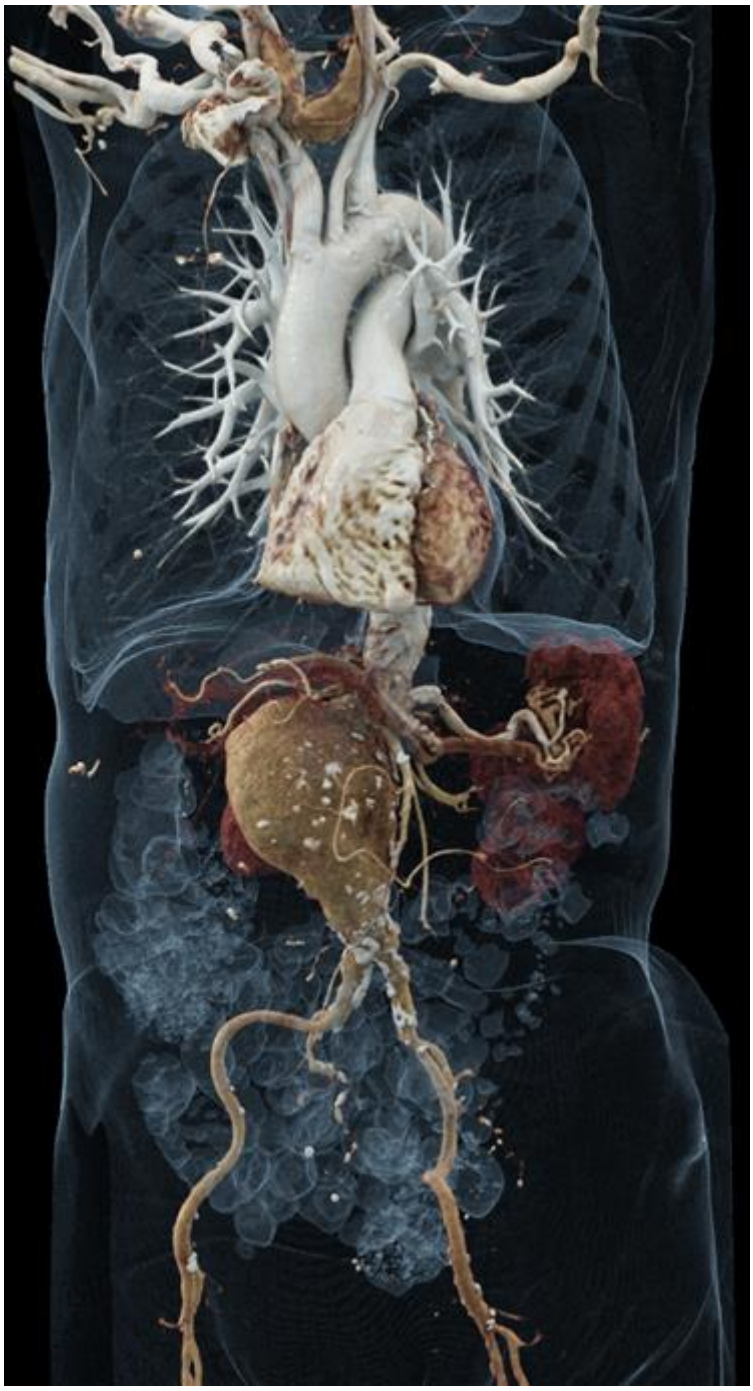


Figure 1. Representative case of an infrarenal abdominal aortic aneurysm (The image was made by Andras Szentivanyi)

2.1.2 Ligation

The earliest recorded AAA surgery was performed by Antyllus around 200 AD. (7) Following a median laparotomy, the proximal and distal neck of the aneurysm was ligated and the thrombus was removed from the aneurysm sac. It seems that a small proportion

of his patients were indeed able to survive for some time after the operation, which is remarkable by today's standards. Variations of Antyllus' aortic ligation procedure continued in the 19th century. In 1817, Cooper performed a ligation of the AAA what is becoming the modern-day's standard. The patient died four hours later, but this did not deter others from performing similar operations on aneurysms. The first successful operation was performed by Rudolf Matas. (8) The patient survived for a considerable time after the operation. The revolutionary idea of maintaining blood flow through the aorta during the operation belongs also to Matas. This became the basis for later modern operations, including open and endovascular aneurysm reconstructions.

2.1.3 Open repairs of aortic aneurysms in the modern era

An alternative intervention to ligation was to wrap the aneurysm, in an attempt to induce fibrosis and to resist radial pressure on the aneurysm sac. Wrapping of the AAA with cellophane was investigated by Pearse in 1940 and Harrison in 1943. (9, 10) The most significant intervention was performed by Nissen, who operated on Albert Einstein's AAA in 1948 and wrapped it with cellophane according to the technical possibilities of the time. (11) The aneurysm finally ruptured in 1955 and Einstein refused a second operation: "…I want to go when I want to go. It is tasteless to prolong life artificially. I have done my share; it is time to go."

The golden ages of open AAA surgery began with the development of the appropriate graft materials. Attention at this time was focused on the Americans, in particular Michael Ellis DeBakey (1908-2008) and Denton Cooley (1920-2016) surgeons, based in Houston, Texas. In the early 1950s, DeBakey and Cooley performed an astonishing amount of aortic surgery and also developed and perfected their techniques to the extreme. In 1952, a year after Dubost's first success in France, the pair performed the first thoracic aneurysm reconstruction and a year later the first aortic arch aneurysm repair. (12, 13) At that time, the risk of spinal cord ischemia during aortic surgery became apparent. First, moderate hypothermia was used, and then in 1957 Gerbode developed the extracorporal circulation, which was named "left heart bypass". In 1963 Gott extended this concept with a heparin-treated polyvinyl shunt from the ascending aorta to the descending aorta. By 1970, a centrifuge-operated left heart bypass with selective visceral perfusion was developed. In 1973, E. Stanley Crawford simplified DeBakey and Cooley's technique by inventing

sequential clamping of the aorta. By moving the clamps distally, Crawford enabled the already increasingly complex anastomoses' reperfusion and with its encouraging results introduced it into the guidelines.

2.1.4 Endovascular repair of the aortic pathologies

The foundational concept of stabilizing the vasculature by excluding the aneurysm sac from the circulation with a stent graft is attributed to Nicolai L. Volodos, a cardiovascular surgeon from Kharkov, Ukraine. His pioneering contributions and initial clinical applications were instrumental in establishing EVAR, ultimately leading to its global dominance. This innovative approach transformed aortic pathology management by offering a significantly less invasive alternative to open surgery, thereby reducing patient morbidity and mortality. Volodos and his team notably described their device as a "radial zigzag spring," a design fundamental to early stent grafts. (14) Notably, Juan C. Parodi performed the first successful EVAR for an abdominal aortic aneurysm (AAA) using a bifurcated stent graft in 1990 in Buenos Aires, Argentina, often collaborating with colleagues like Julio Palmaz on stent design. (15) Further advancements led to fenestrated and branched EVAR (FBEVAR), developed for complex aortic aneurysms to simultaneously cannulate reno-visceral branches and exclude the aneurysm sac. Similarly, thoracic endovascular aortic repair (TEVAR) provides a stent graft solution for thoracic aortic aneurysms and dissections, extending the core principles of EVAR and FBEVAR. One of the most common finding after stent grafting is an endoleak, when the excluded aneurysm sac remains perfused due to persistent blood supply, preventing its complete thrombosis. The most frequent type is type II endoleak, when the aneurysm sac is still filling retrogradely from an artery such as inferior mesenteric artery, lumbar artery, etc.

2.1.5 Early experiences with aortic dissection

Aortic dissection (AD) was first described in 1760 when King George II of England suddenly died at Kensington Palace. (16) His physician, Frank Nicholls, conducted an autopsy and identified a ruptured type A aortic dissection with fatal pericardial tamponade. He noted coagulated blood in the pericardium, a compressed heart, and a transverse tear in the aorta through which blood had leaked. This was the earliest documented case of AD. However, the terminology took time to evolve. In 1802, Swiss

surgeon Maunoir accurately named the condition “aortic dissection.” Later, in 1819, René Laennec referred to it as a “dissecting aneurysm,” a term still causing occasional confusion with thoracic aortic aneurysms today. Despite Laennec’s misnaming, his fame – mainly from inventing the stethoscope – helped spread the term. Until the arrival of aortography in the 1920s, AD could only be a postmortem diagnosis.

Figure 2. Extensive type B dissection with persistent false lumen reaching the left common iliac artery (The image was made by Andras Szentivanyi)

2.1.6 Technical approaches of aortic dissection surgeries

In 1954, the magical aortic surgery team from Houston performed the first successful resection of a dissection aneurysm. DeBakey, Cooley and Creech did not pause at a single

procedure, and 25 years later they have published a 20-year follow-up study of 527 patients. (17)

Building on their legacy, the International Registry of Acute Aortic Dissection (IRAD) was established to systematically collect and analyze data from multiple centers worldwide. IRAD has since become one of the most influential sources of clinical evidence on acute aortic dissection, significantly shaping current management protocols. In fact, 18 out of 19 major cardiovascular guidelines reference findings from IRAD studies, underlining its critical role in evidence-based care.

2.2 Vascular imaging – Is it the most important supporting actor?

Vascular imaging has always been a cornerstone of cardiovascular medicine, providing important information that helps with diagnosis and treatment as well. Over the years, major improvements in imaging technology have played a crucial role in the early detection and treatment of vascular diseases, especially acute syndromes. These advances have not only made diagnoses more accurate but have also helped reduce the morbidity and mortality rates. The ability to visualize and evaluate the blood vessels more clearly has changed how physicians treat complex conditions, allowing for more urgent and more precise treatments. As we continue to move forward in cardiovascular medicine, imaging will remain an essential tool in modern healthcare.

2.2.1 Ultrasonography

The period of the 1940s and 1950s was a crucial time for the development of diagnostic ultrasound (US). This period saw parallel, foundational research efforts in several countries, with key contributions originating from the United States, Sweden, and Scotland. From these collective advancements, Ian Donald's seminal 1958 publication, "Investigation of Abdominal Masses by Pulsed Ultrasound," emerged as a cornerstone of modern diagnostic imaging, fundamentally shaping the field. By the 1960s, Doppler ultrasound provided clinicians with structural and functional images of blood vessels, and in the 1980s, color flow Doppler enabled visualization of blood flow direction. The Multi-Centre Aneurysm Study demonstrated that ultrasound screening reduced mortality from ruptured AAAs by 42% over four years up to 2002 that facilitated the recommendation

for population screening for AAA with US in all men over 65 years of age. (18) Ultrasound screening has led to an overall increase in hospital admissions for asymptomatic aneurysms.

Duplex US is the primary non-invasive imaging method for suspected vascular access site complications (VASC), effectively locating and quantifying stenoses, measuring flow and detecting thrombotic occlusions. However, US diagnostic quality is highly examiner-dependent, offers no angiographic map for therapy guidance. Despite these limitations, US remains a cost-effective tool for VASC maturation assessment, surveillance, and complication detection.

2.2.2 Computed Tomography

Alongside the diagnostic capabilities of ultrasound imaging, computed tomography (CT) scanners became available in the early 1970s, what made AD diagnosis possible however it is used to be a post-mortem finding. As faster, higher-resolution spiral CT machines became more accessible in the 1980s, the diagnosis and treatment of AAAs and ADs were significantly refined. This led CT angiography (CTA) becoming the standard for assessing aneurysm and dissection morphology and guiding surgical planning. CTA is vital for determining treatment urgency, identifying unstable calcification, detecting aortic wall changes, and confirming rupture. These advancements, alongside surgical improvements, have drastically reduced mortality from aortic pathologies.

Nowadays, cardiovascular CT is the primary imaging method for aortic disease diagnosis, prognosis, and therapy planning. Valued for its quick acquisition, wide availability, high reproducibility, and suitability for emergency departments, it offers excellent diagnostic accuracy (100% sensitivity, 98% specificity for Acute Aortic Syndromes (19, 20)). Modern CT protocols often include double or triple rule-out scans for simultaneous assessment of the aorta, pulmonary and coronary arteries. ECG triggering is crucial to prevent motion artifacts that could distort measurements or mimic dissections. A standard protocol involves non-enhanced scans, contrast-enhanced CT angiography, and late scans to detect issues like contrast leakage (e.g.: endoleak associated with stent grafts) or inflammation. Additionally, radiation caution is important, especially for young females undergoing CT for chronic aortic disease monitoring.

CTA is a valuable, less invasive, and often more cost-effective alternative to Digital Substraction Angiography (DSA) for evaluating vascular access and VASC. It reliably detects significant stenosis or occlusion, correlating well with DSA and effectively assesses the entire vascular tree but lacking the capability for immediate therapy.

2.2.3 Magnetic Resonance Imaging

A significant advantage of Magnetic Resonance Imaging (MRI) is that it obviates the need for ionizing radiation and iodinated contrast agents (when using 3D contrast MRI), making it an ideal choice for young patients, women (including during pregnancy). Despite its many benefits, MRI's utility in the acute setting is limited due to lower availability, difficulties in monitoring unstable patients, and longer acquisition times compared to other rapid imaging modalities.

For detailed imaging of the aortic root, cine steady-state free precession (SSFP) sequences or ECG-gated angio-MRI are employed, while non-gated sequences suffice for other aortic segments. Recent advancements, particularly 4D flow sequences, have revolutionized the evaluation of complex intravascular flows. (21) These sequences allow for the assessment of intricate flow parameters like wall shear stress, pulse wave velocity, and kinetic energy, or even flow quantification at various levels in a single acquisition, proving incredibly useful in conditions like aortic dissection (AD) or congenital heart diseases. Recent advances include quiescent-interval single-shot (QISS) MR angiography, a promising non-contrast technique for assessing aorto-iliac disease. (22)

2.3 Clinical background of aortic interventions

Aortic pathologies, particularly aneurysms and dissections, represent a major clinical challenge in vascular surgery. These conditions are often asymptomatic for extended periods, yet they can lead to life-threatening complications in the event of rupture or progressive dissection. Early diagnosis and timely intervention are therefore critical to improving patient survival.

Over the past decades, the management of aortic disease has evolved significantly. While open surgical procedures remain the basis of treatment, endovascular techniques have gained increasing prominence due to the minimally invasive nature, offering a safer

alternative for many patients. However, these novel approaches also present new complications, such as the risk of air embolism during endograft implantation and access-related injuries due to the use of large-bore devices. Many of our patients, however, are seen in our outpatient clinic following previous open aortic surgeries, such as open surgical suprarenal aortic fenestration (OSSAF), procedures that would now be managed endovascularly. Data on this patient group is limited, but it is crucial that we examine their outcomes as part of our efforts to improve care.

2.4 Background to the saline flush trial

Stroke is a feared complication of TEVAR, with reported rates ranging from 2% to 8%. (23, 24) The primary mechanisms leading to stroke during TEVAR include debris embolization from the aortic wall, which occurs due to catheterization and device manipulation across the aortic arch, and air embolization. (25, 26) Air embolization is a significant concern during TEVAR and other endovascular procedures involving the aortic arch. (27) The source of the air emboli is the stent graft delivery system, where air bubbles become trapped between the folds of the stent graft. This graft is loaded into a large delivery catheter at the factory under dry conditions in ambient air, and these air bubbles are released when the graft is deployed. (28, 29)

To mitigate the risk of air embolization from endovascular devices, delivery systems are designed with ports for saline flushing before insertion to displace air. However, it is common belief that standard volume flushing with normal saline might result in incomplete deairing of the delivery system. Several approaches have been tested to achieve more thorough deairing and thereby reduce the rate of air embolism. These methods include using normal saline volumes supplemented with carbon dioxide or perfluorocarbon lavage. (28-32)

In clinical practice, a common approach is to flush 120 ml of saline through the delivery system to reduce the volume of ambient air in the sheath. This volume is approximately four times the amount prescribed in the device's instructions for use (IFU) and aligns with findings from previous studies. (33, 34) The rationale behind this increased volume is to

ensure a more complete displacement of air, which is critical in reducing the risk of cerebral air embolism during the procedure.

Various studies have examined the efficacy of different flushing techniques. For instance, abdominal EVAR is frequently used as a model to evaluate these techniques due to its similarities to TEVAR. (28, 31, 35) Researchers have explored the impact of different flushing protocols on the incidence of air embolism, including the use of carbon dioxide and perfluorocarbon as flushing agents. These studies have shown that alternative flushing methods can enhance the removal of air bubbles from the delivery system, potentially reducing the risk of stroke and other complications associated with air embolization.

Despite these advancements, the challenge of completely deairing the delivery system persists. Incomplete deairing can still result in the introduction of air emboli during stent graft deployment. Therefore, ongoing research and development are focused on improving the design of delivery systems and flushing protocols to ensure the highest level of safety for patients undergoing TEVAR and other endovascular procedures. The goal is to achieve a balance between effective air removal and practical application in the clinical setting, minimizing the risk of embolic events and enhancing patient outcomes.

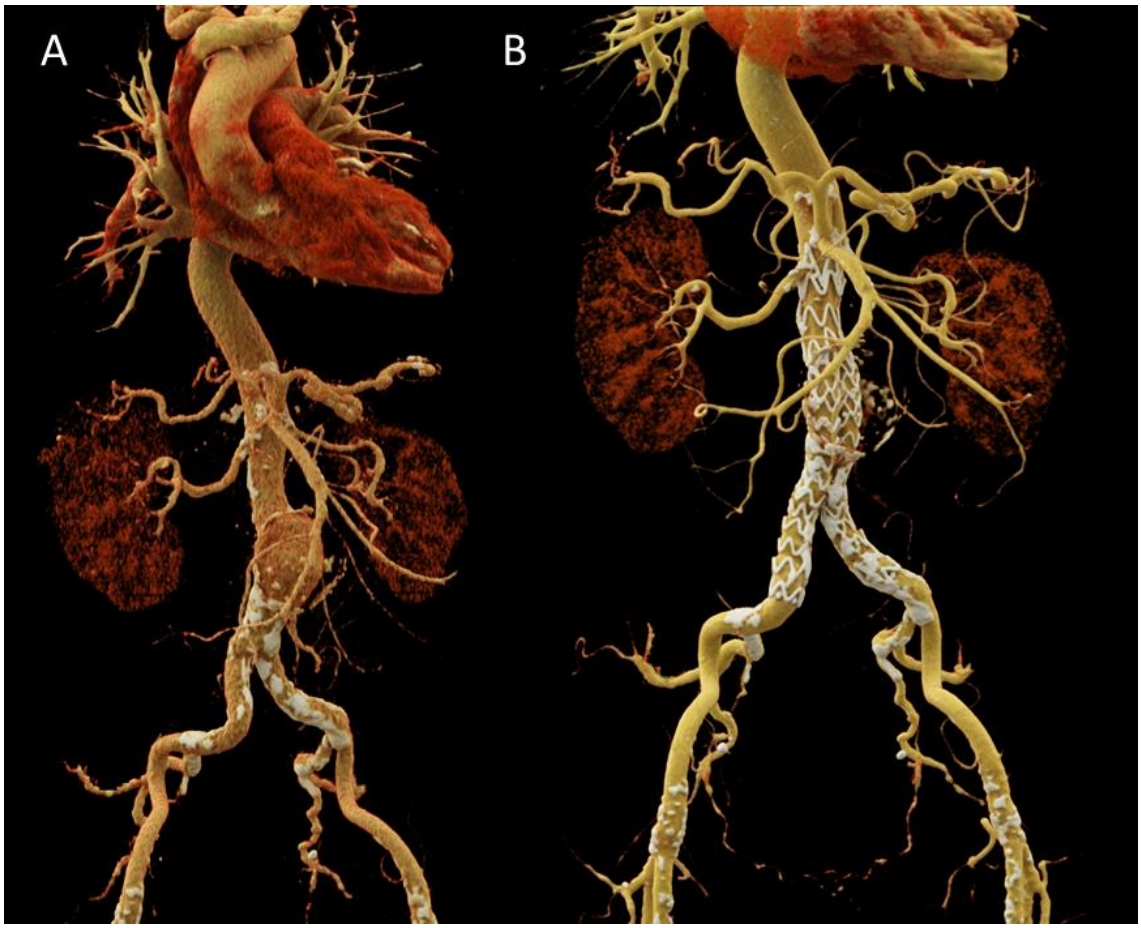


Figure 3. Abdominal aortic aneurysm treated with a Terumo Treo graft (A: preoperative CT scan, B: post EVAR CT scan) (The image was made by Andras Szentivanyi)

2.5 Introduction of surgical refenestration study

Although the treatment of acute type B aortic dissection (TBAD) has undergone significant changes over the past decades, the fundamental principle remains the same: addressing malperfusion and preventing adverse remodeling of the aorta. TEVAR is recommended by guidelines as the first-choice treatment for complicated TBAD (cTBAD). (18, 36-38) However, there is still a lack of consensus regarding the optimal treatment approach for TBAD, suggesting that we may not fully understand the natural history of the underlying disease.

With the advent of TEVAR, (18, 36, 37) open surgical techniques such as extra-anatomical bypass grafting, aortic bypass grafting, and surgical fenestration of the intimal membrane have largely been abandoned. These techniques are now generally considered

last-resort options for patients who are not suitable candidates for endovascular repair. One such open surgical technique, open surgical suprarenal aortic fenestration (OSSAF), was used to prevent and resolve reno-visceral and/or lower limb malperfusion, a serious complication occurring in about 30-40 % of cases. (39, 40) Before TEVAR became the standard of care, some centers preferred OSSAF for treating visceral malperfusion associated with TBAD. This procedure theoretically minimized the risk of spinal cord ischemia by preserving the flow of the intercostal arteries. However, its highly invasive nature led to significant perioperative morbidity and mortality, rendering it mostly obsolete in modern TBAD treatment. Nonetheless, it remains recommended in specific guidelines for selected cases where TEVAR is not feasible. (38)

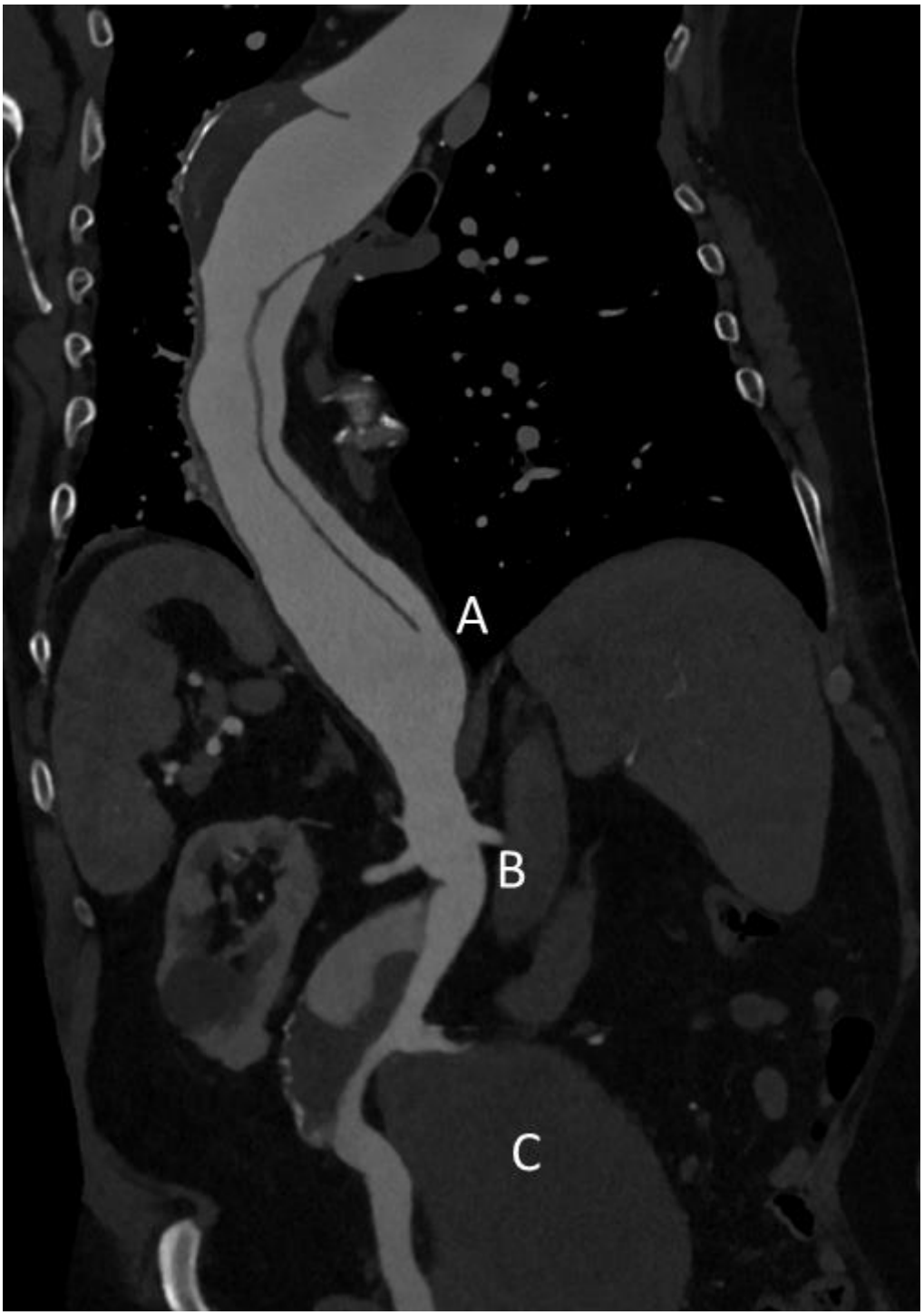


Figure 4. Control CT image of a patient after OSSAF surgery for type B aortic dissection (A: level of the end of the intimal flap, B: level of renal arteries and the end of the refenestration, C: post-dissection aneurysm in right common iliac artery) (The image was made by Andras Szentivanyi)

As a pioneering center in open surgical repair for TBAD, we continue to treat a notable number of patients who underwent OSSAF as far back as twenty years ago. At the time of these procedures urgent TEVAR was not available due to reimbursement and device availability issues. In the last 15 years, situation with TEVAR improved vastly, opening the way for urgent and emergent cases, leading to a sharp decrease in open surgery (OS) in TBAD. (41, 42) Previously, we reported our seven-year outcomes of treating TBAD with OSSAF. (43) The insights gained from studying the long-term survival of such repairs can enhance our understanding of the evolution of TBAD.

By delving into the historical data and outcomes of OSSAF, we can better comprehend the progression of TBAD and the effectiveness of various treatment modalities. This retrospective analysis not only sheds light on the viability of OSSAF as a treatment option but also contributes to the broader knowledge base regarding TBAD management. Understanding the late outcomes of OSSAF is crucial for informing future treatment strategies and improving patient care for those with this complex and potentially life-threatening condition. Previously we reported our 7-year outcome of treating TBAD with OSSAF. (43) The knowledge gathered regarding the late survivals of such repair might help better understand the evolution of TBAD.

2.6 Background of covered stenting in CFA study

Endovascular interventions that require a large-bore puncture are most commonly performed using the common femoral artery (CFA) for access. (44) Proper closure of the access site at the end of the procedure is crucial to ensure patient safety and procedure success. Vascular closure devices (VCDs) are employed to seal the arterial puncture site, and they have demonstrated greater efficacy compared to manual compression. (45) In recent years, advancements in reducing the diameter of delivery systems and increasing operator experience have led to a significant reduction in the incidence of vascular access site complications (VASC). (46) However, despite these improvements, complications related to femoral access remain among the most frequent adverse events in interventional laboratories. The reported incidence of these complications can be as high as 20% following procedures such as transcatheter aortic valve repair (TAVR) and EVAR. (47, 48)

The most common vascular access site complications associated with femoral access include bleeding, stenosis, and occlusion. (49) These issues arise due to vessel injury, incomplete closure, or dissection of the vessel wall. Although VASC is associated with increased morbidity and mortality, there is no standardized treatment protocol, leading to a reliance on the operator's experience and preference, the severity of the complication, and the availability of local resources. Treatment options vary and include open surgical repair as well as several endovascular techniques, such as prolonged balloon dilatation and stenting with covered or uncovered self-expandable and balloon-expandable stents.

Among these options, the implantation of balloon-expandable covered stents (BECS) has been increasingly used. Traditionally, the use of balloon-expandable stents in flexible vessel segments like the CFA has been avoided due to concerns about stent kinking, fracture, and subsequent arterial occlusion. (50-52) Despite these concerns, covered stent implantation has shown promising results in managing femoral access complications. (49, 53) However, long-term data on the efficacy and safety of these stents remain limited. (50) As the medical community continues to gather more evidence, the potential for BECS to become a standard treatment option for femoral access site complications looks promising, though further research is needed to confirm these initial positive outcomes.

3 Objectives

3.1 Saline flush trial

The primary objective of this single-center, randomized trial was to compare two saline flushing protocols — standard (1x IFU) and increased volume (4x IFU) — in the context of standard EVAR. Specifically, we aimed to evaluate the efficacy of these flushing techniques in reducing the amount of air present in the aneurysm sac, as assessed through pre-discharge CT scans.

3.2 Surgical refenestration trial

This retrospective cohort study aimed to evaluate the long-term outcomes of OSSAF and examine the patterns of adverse remodeling in the repaired aorta.

3.3 Covered stenting in CFA study

In this multi-centric retrospective cohort study the aim was to assess the safety and efficacy of balloon-expandable covered stent implantation of CFA vascular-access related complications associated with a large-bore puncture.

4 Methods

All of these studies were conducted in accordance with the Declaration of Helsinki and approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (94/2021; 30/2024; 213/2021). Saline flush trial followed the CONSORT reporting guideline (54) and the other cohort studies adhered to the STROBE guideline. (55)

Institutional picture archiving and communication system, hospital information system and the national healthcare database were used to collect pre-, intra- and postprocedural data.

4.1 Saline flush trial methodology

4.1.1 Settings and participants

This study enrolled consecutive patients underwent standard EVAR for AAA in our tertiary center between June 11, 2021, and April 11, 2022. Eligibility required suitability for three EVAR devices (Cook Zenith Alpha Abdominal, Terumo Treo, Anaconda), considering anatomical requirements, age over 18, and informed consent. Exclusion criteria included compromised landing zones needing FBEVAR, endoanchors or additional graft components. All procedures were conducted by an experienced team in a hybrid operating room with a GE Discovery IGS 730 system. (56-59) The scrub nurse handled contrast media injector de-airing as per the IFU. Aspiration and flushing were done as recommended for each injection, using a 20 ml syringe for saline flushing. For the Anaconda graft, the lavage volume was 30 ml or 120 ml, while for the other grafts, it was 20 ml or 80 ml. A 3-way stopcock was kept closed and opened only when flushing syringes were connected. The delivery system tip was elevated by 45° during flushing, and the graft rested horizontally on the operating table. The remaining steps followed standard EVAR protocol, with all devices being flushed per IFU.

4.1.2 Data sources and randomization

Pre-discharge CTA was performed for all patients on the same CT scanner, following institutional protocol. The scans were processed using IntelliSpace Portal software (Version 9.0.4, Philips Healthcare, The Netherlands) to measure the volume of trapped

air within the aneurysm sac. Initially, volume rendering was performed, after which the software automatically detected and measured the air volume using a Hounsfield Unit-based algorithm. Volume clipping was applied using 3D and 2D images to exclude unwanted areas, such as extracorporeal air or air in the lungs and in the gastrointestinal system. The remaining air volume within the aneurysm sac was recorded. A single blinded reader (SB), unaware of the stent graft type or flushing volume, carried out this semi-automated measurement. For five randomly selected cases, the measurement was repeated, and test-retest repeatability was evaluated using the intraclass correlation coefficient (ICC).

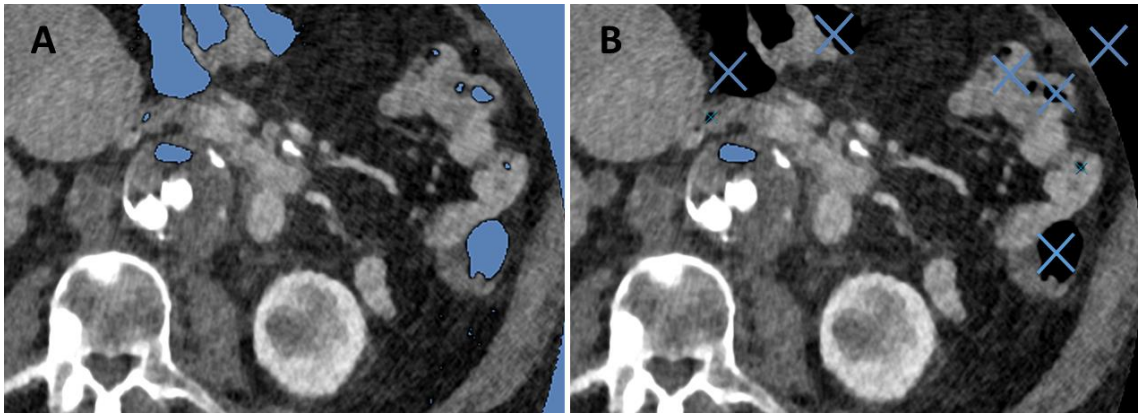


Figure 5. Evaluation of remained air in the aneurysm sac (Panel A: density-based automatic segmentation highlighting the air volume (blue), Panel B: Manual exclusion of air volumes outside the aneurysm sac (indicated by blue 'X' marks)) (The image was made by Andras Szentivanyi)

Patients were enrolled into 2 groups: Group A: saline volume according to the IFU and Group B: flushing with quadrupled volume per the IFU. Block randomization was performed on an equal basis, using sealed envelopes stating group and type of graft (Group A-Treo, Group B-Treo, Group A-Anaconda, Group B-Anaconda, Group A-Zenith Alpha, Group B- Zenith Alpha). Half of the cases were randomized to Group A and the other to Group B and within a single graft type, number of Group A and B were divided equally (Figure 6).

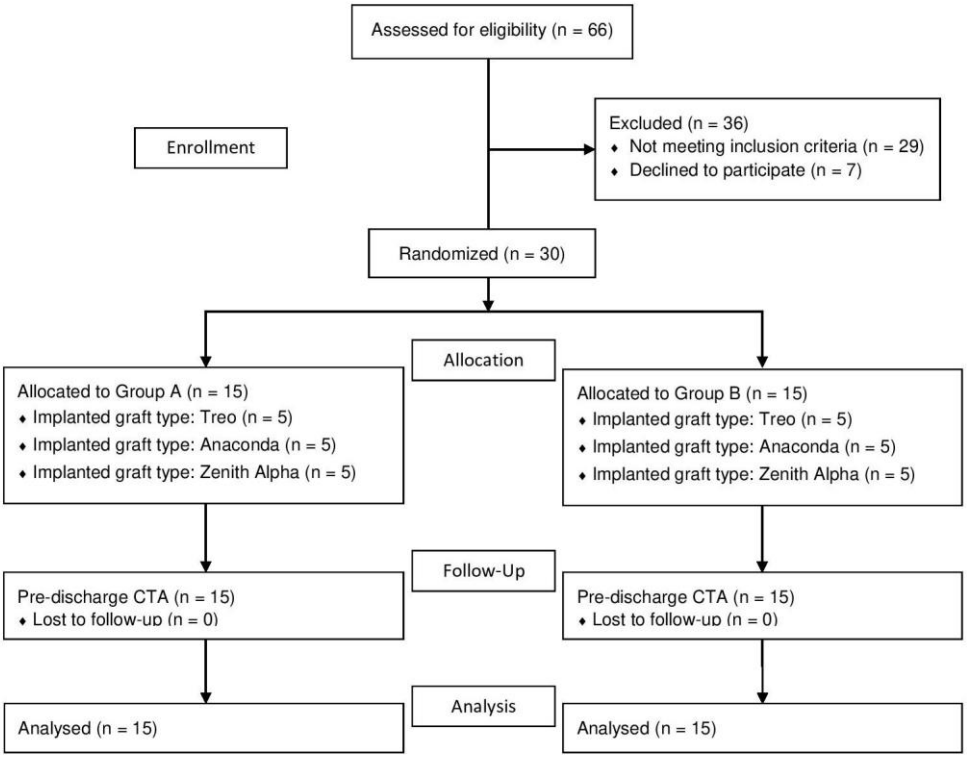


Figure 6. Flow chart of saline flush study (Figure was made by András Szentiványi)

4.2 Surgical refenestration study methodology

4.2.1 Data Collection and preoperative patient management

All 58 patients were enrolled into the study who were presented with cTBAD and treated with OSSAF, from January 1996 to November 2013.

Heart rate and blood pressure were regulated with intravenous drugs targeting 60 bpm and 100–120 mm Hg systolic blood pressure. Pain was treated with minor and/or major analgesics.

4.2.2 Definitions

TBAD was considered complicated if rupture, malperfusion, intractable pain, refractory hypertension or rapid expansion of the aortic diameter was proven, in accordance with current guidelines. Patients with high-risk features were also included in the complicated category. (18, 36-38) Clinical success was defined as the absence of major adverse events (such as in-hospital mortality, myocardial infarction, cerebrovascular events, or dialysis),

(60) aortic-related death, or significant life-altering complications (e.g., permanent dialysis, paraplegia). Aortic diameter was measured on MRI or CTA scans, with the thoracic aortic diameter defined as the largest diameter of the proximal descending aorta (zones 3-5) and the visceral aortic diameter defined as the largest diameter of the aorta at zones 6-8. (37) An in-hospital second surgery was considered as an early reoperation.

4.2.3 Open surgical suprarenal aortic fenestration

Under general anesthesia and without utilizing left heart bypass, the operation was conducted by positioning the patients in a right oblique supine posture. Patients were approached through a left thoraco-abdominal incision initially to access the descending aorta, which was then prepared for clamping and opening from the lower thoracic zones to the bifurcation. Before supraceliac clamping for proximal aortic control, Heparin (100 IU/kg) was administered intravenously. Subsequently a posterolateral incision along the aorta was made without damaging the intercostal or lumbar arteries. The dissected intima was resected from the aorta and from the orifices of the involved visceral branches (celiac artery, superior mesenteric artery, and/or renal arteries). Any thrombus in the false lumen (FL) at this level was also eliminated. The remaining intimal membrane was then sutured in place, leaving behind a proximal and distal dual-lumen aorta with a single-lumen visceral aortic segment. The aortotomy was sealed with a running suture.

4.2.4 Follow-up

Follow-up visits were scheduled at 1, 3, 6, and 12 months post-surgery, and annually thereafter. Post-procedural assessment included physical examination, clinical data collection, and follow-up imaging with CTA or MRA. In most cases, the cause of death was determined by autopsy or based on data from the national database.

4.3 Covered stenting in CFA study

4.3.1 Patient management

All patients who underwent BECS for a CFA VASC at the participating major tertiary cardiovascular centers – Heart and Vascular Center of Semmelweis University, Division of Invasive Cardiology of University of Szeged, and Gottsegen National Cardiovascular Center – between January 2020 and May 2023 were enrolled. Demographic data,

cardiovascular risk factors, anatomical, procedural and postoperative data were collected retrospectively. The clinical status of all patients was initially assessed in the hospital, with follow-up evaluations scheduled at 6 or 12 months and annually thereafter, according to hospital protocol. For patients unable to attend in-person visits, clinical data were gathered via telephone interviews, focusing on new claudication and other adverse events such as myocardial infarction, stroke, respiratory failure, renal failure, or death. Each follow-up visit included a clinical examination to assess symptoms like rest pain, walking distance, and ulceration, along with a duplex ultrasound to check the patency of the covered stent and identify significant restenosis (Peak Systolic Velocity Ratio > 2.5). (61)

4.3.2 Data Analysis and Clinical Endpoints

The primary outcome was clinical success, defined as lack of restenosis, freedom from target lesion reintervention or amputation, freedom from newly onset claudication or VASC-related mortality at two years. The secondary outcome was overall and VASC-related mortality, renal failure, myocardial infarction, stroke, respiratory failure and technical success. Technical success was defined as successful restoration of blood flow after BECS implantation without significant extravasation, with no complications needing surgical conversion or reintervention within 30 days. We analyzed the severity of VASC using the Vascular and access-related complications criteria of Valve Academic Research Consortium 3 (VARC-3). (62) Early and midterm outcome was measured up to and from 30 days after the surgery. CFA calcification was evaluated on pre-operative CTA scans or on follow-up ultrasound scans if CTA was not available.

4.4 Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median [interquartile range (IQR)], while categorical data are reported as numbers and percentages [n(%)]. Normality for continuous parameters was assessed using the Shapiro-Wilk test. Group comparisons for continuous variables utilized unpaired t-tests for normally distributed data or Mann-Whitney U tests for non-normally distributed data, whereas categorical variables were compared using Pearson’s chi-squared tests. Kruskal-Wallis rank sum tests were also employed for inter-group differences.

Long-term outcomes, including all-cause survival, aortic-related survival, and reoperation estimates, were assessed using Kaplan–Meier survival curves. Paired T-tests compared average thoracic and visceral aortic diameters on baseline and follow-up scans. Univariate linear regression analysis was performed to evaluate determinants, with variables having a p-value <.10 entered into multivariate linear regression to identify independent predictors. A two-sided p-value <.05 was consistently considered statistically significant. Sample size calculations, based on an expected trapped air frequency of 85% in Group A and 35% in Group B (at .05 significance and 80% power), determined a need for 14 patients per group, leading to the inclusion of 15 patients per arm to account for potential dropouts. Statistical analyses and graphical illustrations were performed using either StataCorp LLC Stata (College Station, TX, USA, version 18) or SPSS Statistics 28 software (IBM, Armonk, NY, USA).

5 Results

5.1 Result of saline flush study

5.1.1 Descriptive data

A total of 66 patients were prospectively enrolled into the trial between 10/06/2021 and 30/06/2022. 7 of them declined to participate, 29 more patients were excluded due to the use of endoanchors (n=3), additional graft component implantation besides the main body, ipsilateral limb and the contralateral limb (n=20), complex aortic intervention like fenestrated or branched EVAR (n=5) or the surgeons' disagreement with all three graft types (n=1). 30 patients were randomized in the study and all study participants underwent a successful EVAR procedure, an uneventful postoperative period and a pre-discharge CTA.

Table 1. Baseline demographics of saline flush trial

	Group A (1 x IFU); n=15	**Group B (4 x IFU); n=15**	**p value**
Age - y	71.8 ± 7.4	70.6 ± 6.3	.49
Sex (Male)	13 (87)	13 (87)	1.0
Body Mass Index - kg/m^2	27.5 ± 5.9	26.2 ± 3.7	.069
Smoking	7 (47)	7 (47)	1.0
Hypertension	11 (73)	13 (87)	.36
Diabetes	3 (20)	1 (7)	.28
Hypercholesterolemia	4 (27)	5 (33)	.69
CKD 3-5	1 (7)	0 (0)	.31
History of stroke	2 (13)	0 (0)	.14
Malignancy	4 (27)	5 (33)	.69
COPD	2 (13)	3 (20)	.62
Heart failure	3 (20)	4 (27)	.67

IFU = Instruction for use; CKD = Chronic Kidney Disease; COPD = Chronic Obstructive Pulmonary Disease, Data are presented as n (%) or mean ± standard deviation.

Table 2. Anatomical factors and baseline characteristics for 30 patients with endovascular aneurysm repair (EVAR). Flush volume equals or quadruples by the recommended volume in the instruction for use (IFU) of the specific device.

	Group A (1 x IFU); n=15	**Group B (4 x IFU); n=15**	**p value**
Anatomical factors			
Mean aneurysm size (mm)	61.5 ± 13.4	60.6 ± 8.1	.66
Mean lumen size of aneurysm (mm)	43.8 ± 10.2	43.5 ± 15.3	.085
Medical treatment			
Antiplatelet	12 (80)	10 (67)	.41
Anticoagulant	3 (20)	2 (13)	.62
Statin	11 (73)	7 (47)	.20
Antihypertensive	10 (67)	12 (80)	.41
Procedural data			
Volume of trapped air (mm3)	**103.5 ± 210.4**	**175.5 ± 175.0**	**.04**
Presence of trapped air	**7 (47)**	**13 (87)**	**.02**
Air Kerma (mGy)	711.5 ± 836.6	454.1 ± 415.6	.66
Length of Stay (day)	3.7 ± 1.0	4.1 ± 4.0	.31
Days until CTA (day)	3.5 ± .74	4.8 ± 3.8	.40
Volume of trapped air for graft types			
Treo (mm^3)	56.3 ± 92.1	62.6 ± 69.5	.74
Anaconda (mm^3)	183.1 ± 338.6	328.8 ± 217.1	.25
Zenith Alpha (mm^3)	71.1 ± 140.8	241.8 ± 135.2	.17

CTA = Computed tomography angiography. Data are presented as n (%) or mean ± standard deviation. P values <.05 were considered significant and are shown in bold.

Half of the patients were treated with a quadruple-volume flushed graft with an equal distribution among the three devices. There were no significant differences neither in age, sex ratio, demographical risk factors, premedication, medical history or in aneurysm characteristics between Group A and B (Table 1 and Table 2). Table 2 summarizes the morphological and procedural data and results of postoperative trapped gas analysis in

both groups. All implantations were performed using three components: a main body, an ipsilateral limb and a contralateral limb.

5.1.2 Outcome data

The volume of trapped air was significantly lower in Group A (103.5 ± 210.4 vs 175.5 ± 175.0, p = .04) compared to Group B, which used quadruple flushing. Additionally, the presence of trapped air was significantly higher in Group B (7 (47) vs 13 (87), p = .02).

Table 3. Subgroup analysis in saline flush study, based on device type.

	Terumo Treo n=10	**Terumo Anaconda n=10**	**Cook Zenith Alpha n=10**	**P value***
Age – years	68.9 ± 6.0	73.3 ± 7.9	71.4 ± 6.3	.40
Body Mass Index - kg/m^2	27.3 ± 5.1	28.3 ± 4.0	25.0 ± 5.4	.39
Mean aneurysm size	62.1 ± 9.6	59.1 ± 3.8	62.0 ± 16.5	.69
Mean lumen size of aneurysm	49.3 ± 10.6	40.5 ± 14.6	41.1 ± 12.1	.17
Days until CTA	3.6 ± .70	3.2 ± 1.3	4.9 ± 4.8	.86
Length of Stay	3.8 ± .63	4.0 ± 1.1	4.7 ± 4.7	.41
Air kerma (mGy)	614.2 ± 895.3	460.0 ± 315.6	674.7 ± 689.8	.84
Volume of trapped air	59.4 ± 77.0	256.0 ± 279.0	103.2 ± 115.7	.16
Presence of trapped air	5 (50)	8 (80)	7 (70)	.35
Endoleak type II	6 (67)	3 (30)	7 (78)	.086

CTA = Computed tomography angiography. * p values at .05 were considered statistically significant.

Subgroup analysis based on device types showed no significant differences in air kerma (614.2 ± 895.3; 460.0 ± 315.6; 674.7 ± 689.8), trapped air volume (59.4 ± 77.0; 256.0 ± 279.0; 103.2 ± 115.7) and endoleak type II [in 6 (67%); 3 (30%); 7 (78%) patients] between the Terumo Treo, Terumo Anaconda and Cook Zenith Alpha devices, accordingly. Details are reported in Table 3. ICC demonstrated excellent repeatability (1.0).

5.1.3 Secondary outcome

There were no clinically significant complications due to air embolism. Demographical, anatomical, interventional, procedural and anamnestic factors were assessed with univariable regression analysis (Table 4), that showed Terumo Anaconda graft type as a significant variable (p= .017) on trapped air. This factor and hypertension were analyzed with multivariate linear regression and Anaconda (p= .039) was found to be an independent risk factor.

Table 4. Uni- and multivariate linear regression analysis of anatomical and interventional factors of volume of trapped air.

	Univariate				**Multivariate**			
	β	95% CI, lower-upper		p	β	95% CI, lower-upper		p
Anatomical factors								
Aneurysm diameter	1.84	-5.0	8.7	.59				
Lumen diameter	1.13	-4.7	7.0	.67				
Patent inferior mesenteric artery	-26.2	-192.6	140.1	.75				
Endoleak	-59.9	-215.6	95.9	.44				
Stent graft type								
Treo	-120.2	-269.4	29.1	.11				
Anaconda	**174.7**	**33.8**	**315.6**	**.017**	**154.8**	**21.1**	**288.5**	**.025**
Zenith Alpha	-54.5	-209.4	100.4	.48				

Bold indicates statistical significance (p < .05).

5.2 Surgical refenestration study results

5.2.1 Demographics and pre-procedural characteristics

Preoperative variables of the overall population are described in Table 5. 58 cases (54.5 ± 12.1 years, 46 male) diagnosed with cTBAD and treated by OSSAF were enrolled in this study. Initial thoracic aortic and visceral aortic diameters were 40.6 ± 10.6 mm and 29.4 ± 5.7 mm. Average time from the admission to surgery was 4 days (4.0 ± 7.7 days).

Table 5. Baseline demographics and characteristics for patients with Open Surgical Suprarenal Aortic Fenestration

Variable for index operation	**n (%) or Mean ± Standard deviation**
Demographics	
Age at surgery (year)	54.5 ± 12.1
Sex (male)	77,6
Time to surgery (day)	4.0 ± 7.7
Anatomical factors	
Thoracic aortic diameter (mm)	40.6 ± 10.6
Visceral aortic diameter (mm)	29.4 ± 5.7
Clinical characteristics	
History of MI	3 (7.0)
History of Stroke	3 (7.0)
History of Hypertension	38 (79.2)
History of COPD	1 (2.6)
Tobacco use	1 (2.6)
History of DM	5 (9.6)
History of aortic surgery	7 (13.5)
Indication of repair – complication of dissection	
Refractory hypertension	16 (30.0)
Intractable pain	29 (54.9)
Limb malperfusion	13 (26.5)
Visceral malperfusion	13 (26.5)
Renal malperfusion	7 (14.3)
Diameter increase	8 (16.3)
True lumen collapse	9 (17.6)

Abbreviations: MI-Myocardial Infarction, COPD-Chronic Obstructive Pulmonary Disease, DM-Diabetes mellitus

5.2.2 In-hospital and long-term follow-up

Perioperative and long-term follow-up data are summarized in Table 6 and Table 7, respectively. A significant in-hospital mortality of 15 (27%) was found with a 9.5 ± 5.2 days average hospital length of stay. A common postoperative complication was acute kidney injury (20%) and consequently perioperative dialysis (18%), however none of them ended in permanent dialysis. In 3 cases (4%) transient spinal cord ischemia was recorded, without becoming a permanent complication. At an average follow-up of 8.6 ± 7.3 years, approximately two thirds of the cases were clinically successful (64%). There were 42 deaths (74%) of which 15 (26%) were aortic related.

Table 6. Perioperative details of open surgical suprarenal aortic fenestration

Variable	**n (%) or Mean ± Standard deviation**
ICU stay (day)	5.2 ± 3.9
Length of stay (day)	9.5 ± 5.2
30-day mortality	14 (27.3)
Perioperative Stroke	1 (2.1)
Perioperative Spinal Cord Ischemia	3 (4.4)
Perioperative Acute Kidney Injury	10 (20.0)
Perioperative Dialysis	8 (17.8)
Permanent Dialysis	0 (0.0)
Perioperative Myocardial Infarction	1 (2.1)
In-hospital Reoperation	6 (10.3)
Gastrointestinal failure – Open Surgery	4 (6.9)
Bleeding – Open surgery	1 (2.2)
Renal failure – Endovascular stenting	1 (2.2)

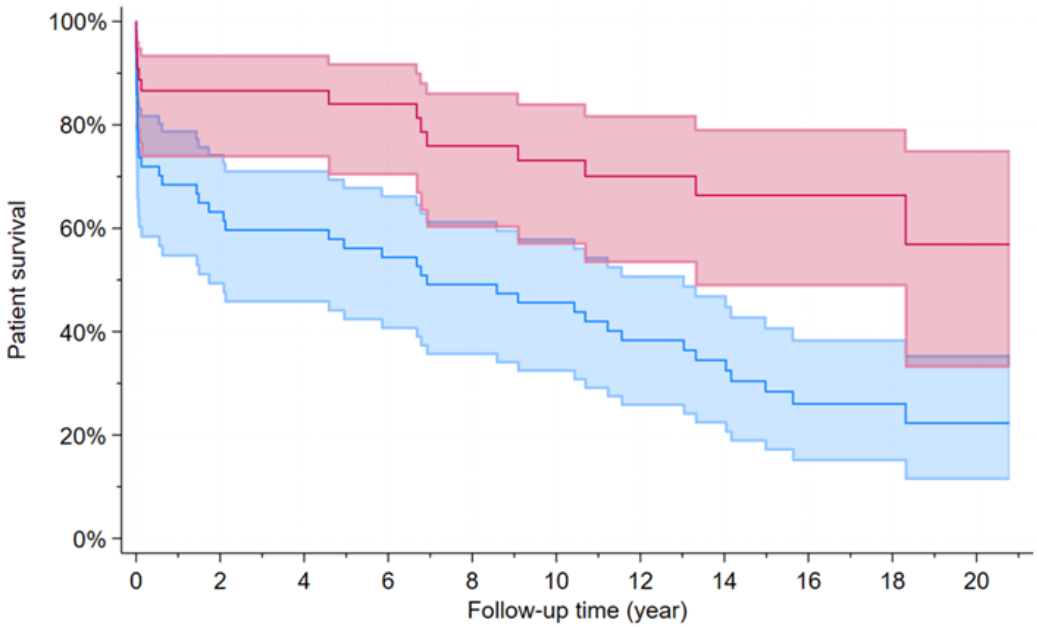
Abbreviation: ICU = intensive care unit

Table 7. Long-term follow-up characteristics of open surgical suprarenal aortic fenestration

Variable	n (%) or Mean ± Standard deviation
Long-term follow-up details	
Clinical success	37 (63.6)
Late Redo	11 (20.8)
Postdissection Aneurysm – Open Surgery	6 (10.3)
Debranching for Endo – Open Surgery	4 (6.9)
Postdissection aneurysm – Endovascular Repair	8 (13.8)
Overall mortality	42 (73.7)
Aortic mortality	15 (26.3)
Follow-up characteristics	
FU thoracic aortic diameter (mm)	56.7 ± 15.6
FU visceral aortic diameter (mm)	32.6 ± 10.3
Follow-up time	
Surgery to late redo surgery (year)	8.0 ± 5.2
Total follow up time (year)	8.6 ± 7.3

Abbreviation: FU-follow-up,

The 5- and 10-year survivals were 56.1% (95% confidence interval [CI], 42-68) and 45.6% (95% CI, 32-58), respectively (Figure 7.). Survival rate at 20 years was 21.6% (95% CI, 11-35). The aortic related survival at 5, 10 and 20 years were 83.8% (95% CI, 70-92), 72.9% (95% CI, 57-84) and 55.3%(95 CI, 30-75), sequentially.

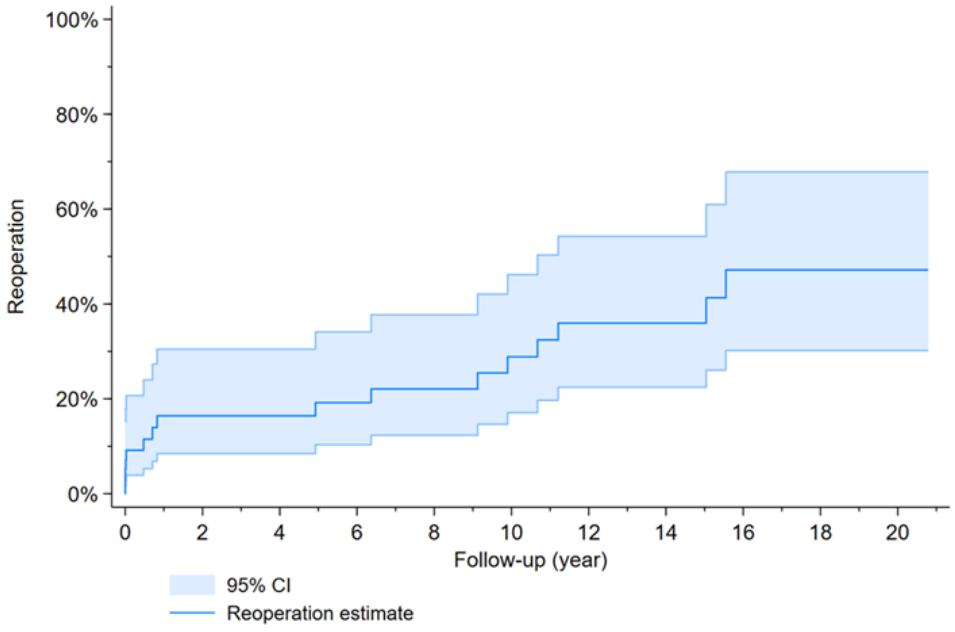


Follow-up time (year)	1	2	5	8	10	14	18
Number at risk (n)	58	39	34	28	27	20	10
All cause survival	68.4%	63.2%	56.1%	47.4%	45.6%	34.4%	26.1%
Aortic related survival	86.4%	86.4%	83.8%	75.7%	72.9%	66.3%	66.3%

Abbreviation: CI – Confidence Interval

Figure 7. All-cause survival and aortic related survival rate after Open Surgical Suprarenal Aortic Fenestration

Almost half of the patient needed reoperation at 18 years of follow-up [47% (30-68)], as it is illustrated in Figure 8. The median interval time to reoperation was 5,9 (0-13) years. Early reoperation was mainly due to abdominal complaints, (4/6) and only one endovascular in-hospital reintervention was performed (1/6). Late reoperations were basically needed due to aneurysm formation. 8 TEVARs (13.8%) were carried out, half of which were preceded by open surgical debranching. Open aortic surgery was performed in 6 cases (10.3%), mainly because progressing aortic dissection.



Follow-up time	10 days	5 years	10 years	15 years	18 years
Number at risk	44	30	22	15	7
Reoperation estimate	9.2%	19.2%	28.9%	36.0%	47.2%
(95% CI)	(3.9-20.7)	(10.3-34.1)	(17.1-46.1)	(22.5-54.3)	(30.2-67.8)

Abbreviation: CI – Confidence Interval

Figure 8. The cumulative incidence of reoperation for patients who underwent open surgical suprarenal aortic fenestration

5.2.3 Adverse remodeling of the visceral aorta

As shown in Table 8. by comparing the baseline and follow-up measurements, the increase of the thoracic aortic diameter (typically at zone 3-4) was significant (p= .0001). The visceral aortic diameter also showed a significant but more moderate increase during the follow-up (p= .028).

Regarding the comparison of the diameter increments in the two localizations, the increment measured at the thoracic aorta was significantly greater than at the level of the visceral branches where the refenestrations were performed (p= .0001).

Table 8. Baseline thoracic aortic and visceral aortic diameter compared to follow-up diameter

	Baseline measurement (mm)	**Follow-up measurement (mm)**	**p value ***	**Delta diameter (mm)**	**p value ***
Thoracic aortic diameter	42.9 ± 10.6	58.8 ± 15.8	**.0001**	15.7 ± 15.4	**.0001**
Visceral aortic diameter	29.4 ± 5.5	33.8 ± 10.7	**.028**	4.4 ± 9.3	

Delta diameter: Difference of follow-up measurements and baseline measurements. Average follow-up CT time is 11.9 ± 5.7 years. * p values at 0,05 were considered statistically significant

5.3 Results of covered stenting in CFA study

Between January 2020 and May 2023, 23 patients (mean age 74.2 ± 8.6 years, 13 females) with VASC underwent endovascular treatment with BECS. According to the ASA score, the patient group was relatively high-risk, with 15 patients (65.2%) classified as ASA 3-4. Symptomatic peripheral artery disease was present in 8 patients (34.8%). A detailed overview of the baseline patient and anatomical characteristics can be found in Table 9.

Table 9. Baseline demographical and anatomical characteristics of patients in covered stenting in CFA study

Variable	**n (%) or Mean ± Standard deviation**
Demographics	
Sex (male)	10 (43.5)
Mean age (years)	74.2 ± 8.6
BMI (kg/m^2)	29.5 ± 6.1
Cardiovascular risk factors	
Current smoking	7 (30.4)
Hypertension	21 (91.3)
Hypercholesterolemia	15 (65.2)
Diabetes mellitus	9 (39.1)
Coronary artery disease	17 (73.9)
Symptomatic PAD	8 (34.8)
COPD	9 (39.1)
CKD III-V	10 (43.5)
Cerebrovascular history	3 (13.0)
ASA score 3-4	15 (65.2)
Malignancy	3 (13.0)
Anatomical characteristics	
CFA diameter (mm)	7.7 ± 1.1
Calcification on CFA	12 (54.3)

Abbreviations: N-number; SD-standard deviation; IQR-interquartile range; BMI-body mass index; PAD-peripheral artery disease; COPD-chronic obstructive pulmonary disease; CKD-chronic kidney disease; ASA-American Society of Anaesthesiologists; CFA-common femoral artery

In 14 patients (60.9%), the primary intervention was TAVR (Table 10). Vascular closure devices (VCDs) were utilized in a total of 20 procedures (83.3%). Regarding VASC, bleeding complications were the most common indication for BECS implantation, accounting for 66.7% of cases. Based on the VARC-3 criteria for vascular and access-related complications, major complications occurred in 17 cases (73.9%), while the

remaining patients experienced minor complications. Blood transfusions were administered to 14 patients (58.3%), with a median of 2 (0-2) units per patient.

Table 10. Baseline procedural characteristics of patients in BECS study

Variable	**n (%) or Mean ± Standard deviation or median (IQR)**
Primary procedure	
TAVR	14 (60.9)
EVAR	2 (8.7)
Peripheral intervention	7 (30.4)
Vascular closure device	
Proglide	12 (60.0)
Angioseal	7 (35.0)
Manta	1 (5.0)
Cause of BECS implantation	
Bleeding	16 (69.6)
Pseudoaneurysm	5 (21.7)
Dissection	2 (8.7)
BECS's details	
Stent length (mm)	37(27-47)
Stent diameter (mm)	8(7-8)
More than one stent	5 (21.7)
Overdilatation, %	10.5 ± 9.0
BECS's location	
Left CFA	9 (20.8)
Right CFA	19 (79.2)

Abbreviations**:** TAVR-Transcatheter aortic valve repair; EVAR-Endovascular aortic repair; BECS-balloon-expandable covered stent; CFA-common femoral artery.

Regardless of the treatment center, a Begraft Peripheral covered stent (Bentley Innomed GmbH, Hechingen, Germany) was used in all procedures. Nineteen patients (79.2%) received a single BECS, while five patients (20.8%) required more than one covered stent

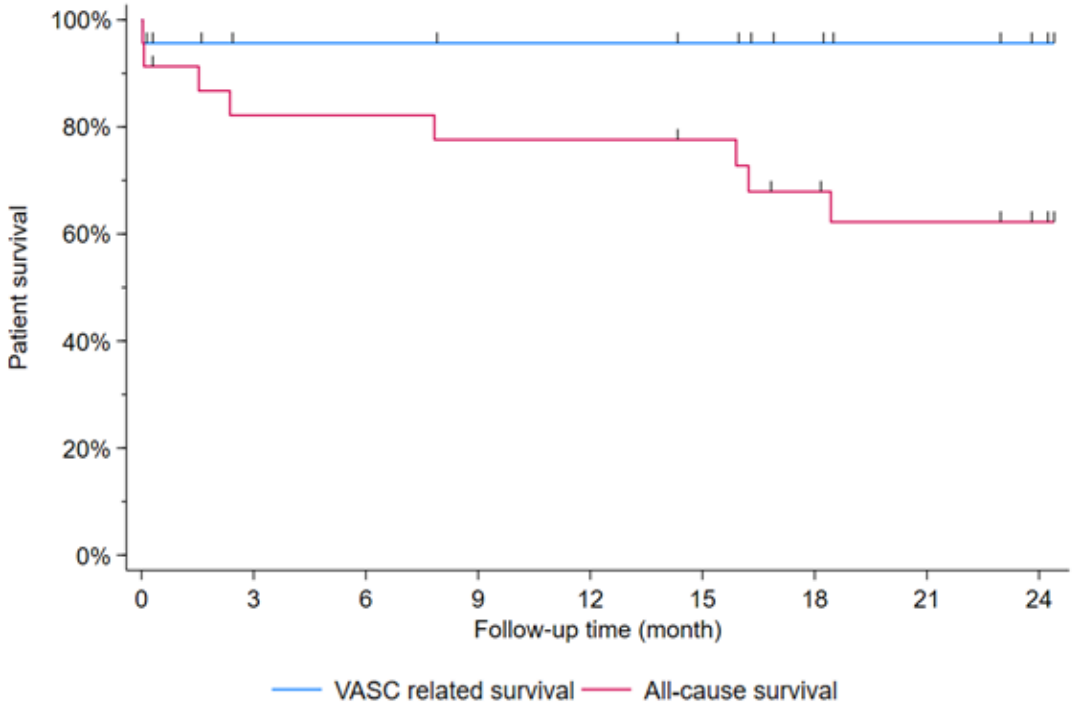
for adequate coverage. Overdilatation of the covered stents was performed in 12 patients (52.2%). Detailed additional outcome parameters are provided in Table 11.

Table 11. Outcome parameters in covered stenting in CFA study

Variable	**n (%) or Mean ± Standard deviation or median (IQR)**
Early outcome at 30 days	
VARC-3 vascular and access-related complications	
Minor	6 (26.1)
Major	17 (73.9)
Technical success rate	21 (91.3)
Transfusion (unit)	2 [0-2]
ICU stay (days)	2.0 ± 1.2
Hospital stay (days)	9.4 ± 7.0
Renal failure	0 (0)
Myocardial infarction	2 (8.7)
Stroke	1 (4.2)
Respiratory failure	2 (8.7)
Overall mortality	2 (8.9)
VASC related mortality	1 (4.2)
Clinical success	21 (90.5)
Midterm outcome	
Follow-up time (months)	18.0 ± 11.4
Stent fracture	2 (8.7)
Restenosis	0 (0)
Amputation	0 (0)
Newly onset claudication	1 (4.2)
VASC-related mortality	2 (8.9)
Overall mortality	9 (37.5)

Abbreviations: VARC-3 = valve academic research consortium-3; RBC = red blood cell; ICU = intensive care unit; VASC = vascular access site complication.

Technical success was achieved in 21 patients (91.3%). The only in-hospital death occurred due to recurrent bleeding at the femoral access site on the first postoperative day. The mean follow-up duration was 18.0 ± 11.4 months. Among the 23 patients included, 9 (37.5%) died during the follow-up period. Two patients died within 30 days post-discharge, one of whom had a VASC-related death. An additional 7 deaths (30.4%) were recorded at midterm, none of which were VASC-related. The estimated freedom from all-cause mortality was 85.4%, 77.2%, and 65.7% at 1, 12, and 24 months, respectively. VASC-related survival was 96.4% (Figure 9). Stroke occurred in 1 patient (4.2%), while respiratory failure and myocardial infarction were each observed in 2 patients (8.3%) during the follow-up period.

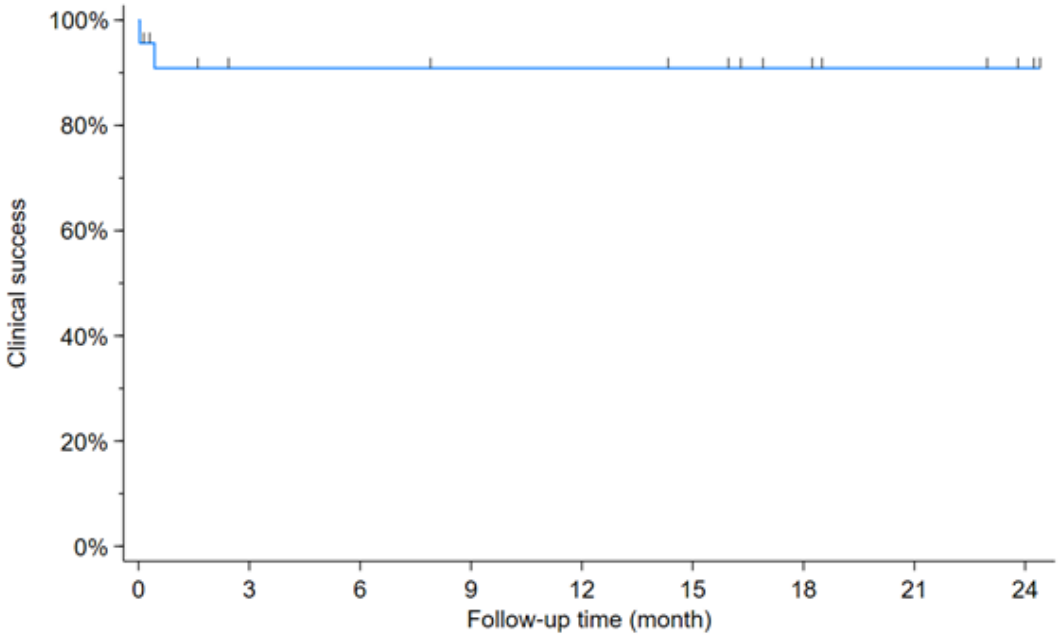


	6 months	12 months	18 months	24 months
Number at Risk	18	17	13	9
VASC related survival	95.5% (71.8-99.4)	95.5% (71.8-99.4)	95.5% (71.8-99.4)	95.5% (71.8-99.4)
All-cause survival	82.0% (58.9-92.8)	77.4% (54.0-89.9)	62.2% (38.2-79.1)	62.2% (38.2-79.1)

Figure 9. Kaplan-Meier estimates of VASC related and all-cause survival

Duplex ultrasound follow-up identified stent fractures in two patients (8.3%) without significant restenosis. One patient (4.3%) experienced covered stent occlusion, which

occurred within two weeks. Kaplan–Meier estimates revealed a freedom from stent graft occlusion in the common femoral artery (CFA) of 95.7% at 1, 12, and 24 months. A new onset of mild claudication was reported by 1 patient (4.2%) after two and a half years, although no intervention was needed. Clinical success throughout the entire study period was 90.5%, with two adverse events occurring within the first two weeks (a VASC-related death and BECS occlusion) (Figure 10).



	6 months	12 months	18 months	24 months
Number at Risk	17	16	12	8
Clinical success	90.5% (67.0-97.5)	90.5% (67.0-97.5)	90.5% (67.0-97.5)	90.5% (67.0-97.5)

Figure 10. Clinical success of covered stent implantation after vascular access-related complication

In the study population only 1 patient had to undergo a reintervention, who had a covered stent occlusion, which was treated by open surgery. According to the Kaplan–Meier estimates the freedom from target limb revascularization was 95.7% after one and two years as well.

6 Discussion

6.1 Overall synthesis of findings

This thesis presents a comprehensive exploration of key advancements and challenges in aortic intervention, focusing on both open surgical and endovascular techniques. The three studies presented above contribute to a deeper understanding of strategies aimed at improving patient outcomes in complex aortic pathologies. At first, contrary to prior theories suggesting that increased saline flush volume would more effectively reduce residual air during EVAR, our randomized controlled trial demonstrated a significant reduction in residual air within the delivery system in case of normal flushing volume. This observation not only challenged the previous theory but also highlighted the critical importance of strict adherence to the device's IFU to ensure procedural safety. Secondly, the twenty-year results of open surgical suprarenal aortic fenestration for complicated type B aortic dissection highlighted the long-term durability and efficacy of this open surgical approach, providing crucial insights into the natural history and management of these challenging cases. Finally, the evaluation of midterm outcomes following BECS implantation for femoral access site complications demonstrated the feasibility and effectiveness of this minimally invasive technique. However, given the variability in outcomes observed, further studies are warranted to refine patient selection criteria and standardize procedural techniques. Due to the potential for crucial complications associated with this procedure, experienced physicians are recommended to perform it. Taken together, these studies describe the ongoing evolution of aortic surgery, from refining established open techniques to optimizing contemporary endovascular procedures. These studies collectively highlight our ongoing efforts to improve patient safety and achieve better long-term results in the treatment of complex aortic diseases.

6.2 Discussion of individual studies

6.2.1 Saline flush study

Stroke is a common complication of TEVAR. While device manipulation over the aortic arch may lead to embolization from dislodged thrombus or debris, a significant number of emboli are believed to be gaseous, resulting from air bubbles trapped in the delivery

system. This was confirmed by Bismuth et al. in 2011, who found that transcranial Doppler during zone 0-2 TEVAR identified the highest rate of embolic events during device deployment, not wire manipulation. (25)

To study air embolism rates, EVAR is increasingly used as a model because:

1. Its delivery systems are almost identical to those of TEVAR,

2. Air bubbles on the prosthesis surface can be trapped in the aneurysm sac between the ventral surface of the graft and the dorsal surface of the aneurysm sac/thrombus in the sac. It can be easily detected on the first follow-up CT (63, 64).

3. EVAR is performed more often than TEVAR. (31, 35)

Trapped air in the aneurysm sac after EVAR shares the same cause as stroke during TEVAR, making EVAR a suitable model to assess the effectiveness of delivery system deairing.

Various research groups have aimed reducing residual air after aortic interventions several times in the last few years. In 2016, Kölbel et al (30) administered CO2 into the delivery system prior to standard saline flush. They found this method effective and safe, but lacked the control group. In the same year, Rohlffs et al (28) conducted the first in vitro study, and published that saline lavage with CO2 supplementation can result in less remained air in the delivery system. Her images visualized clearly that trapped air remains between the folds of the stent graft material. Three years later, this research group reported another in vitro trial demonstrating decreased trapped air after perfluorocarbon flush. The detected air bubbles were located at the tip of the delivery system. The result was primarily observed as large bubbles at the tip of the sheath. (29) One year prior, Saleptsis et al. (35) were the first to describe the correlation between a larger perfused lumen diameter and the presence of residual air after EVAR. The study also investigated different types of grafts, finding that EVAR had a higher risk of air presence compared to FEVAR or BEVAR. This aligns with the findings of Eleshra et al. (31), who reported a retrospective analysis of the differences in gas presence in the aneurysm sac post-EVAR. The introduction of additional CO2 flushing into the protocol led to a reduced incidence of trapped air in EVARs and a decreased volume of air on control CTA scans.

Anatomical predictors, such as perfused lumen diameter and aneurysm size, were associated with the presence of higher residual gas. In 2019, Rylski et al. (33) determined in an in vitro study that a 120 ml saline flush, compared to a 40 ml saline flush, significantly reduced the residual air in the delivery system of a TEVAR. Two years later, a 120 ml flush of 0.9% heparinized saline was found to minimize neurological events after TEVAR in a retrospective study by Branzan et al. (34). Our study investigates air embolism in EVAR, and our findings has potential influence on clinical practice, particularly on TEVAR, but it should be approached with caution.

Our randomized controlled trial is the first to compare different volumes of saline flush in an aortic prosthesis delivery system. Our results suggest that larger saline flush volumes do not reduce trapped air, contrary to expectations. This supports the idea that following device instructions may lower complication rates.

Despite using a 3-way stopcock to prevent ambient air intake, the most likely cause of increased air was multiple syringe changes. Manual flushing, unlike injectors, did not maintain constant pressure.

A significant difference in trapped air volumes was observed across three devices, with the Terumo Anaconda graft showing higher volumes, likely due to the larger caliber of its delivery system, thus larger lavage volume and unique flush port design. Rohlffs et al. demonstrated that additional flush ports may reduce trapped air, warranting further design investigation. The Anaconda's metal core, which consists of a single wire shaped like a spring, may also contribute to the higher air volumes, as it differs in morphology from the other two devices.

In comparison of graft types, the Treo graft showed minimal difference between groups, while the Anaconda and Zenith Alpha grafts showed a noticeable, although non-significant, difference. These differences may be due to the sterilization methods, with Treo undergoing gamma radiation and the others using ethylene oxide (EtO). After EtO sterilization, the EtO/gas ratio is below 250 ppm (65), and gamma radiation uses no additional gas. Therefore, the trapped air composition is nearly identical to ambient air, making any theoretical differences in water solubility unlikely to affect the air detected on CT. However this likely does not affect trapped air composition, future studies could explore the impact of sterilization methods on trapped air.

Some studies (26, 28-30) have raised similar questions about reducing air by novel flushing methods, but they administered carbon dioxide (CO2). According to the IFU, saline lavage is mandatory, so in these studies, the solution was applied to the flushing port after CO2 lavage. Two techniques were used to reduce intravascular air, making a direct comparison with our study inappropriate. Eleshra et al. (31) compared gas and saline flushing, finding that extra gas flush resulted in fewer trapped air bubbles. Their results stand on the better penetration of CO2 due to constant pressure during flushing, without the need for reconnections to the flushing port. Recently, Cook Medical introduced the Zenith Alpha 2 (ZTA2) device, which officially accommodates CO_2 flushing as part of its approved protocol, aiming to further minimize intravascular air embolism. This highlights the real need for both further investigations in the field of deairing procedures and the growing industry trend toward integrating CO_2 flushing into standard practice.

6.2.2 Surgical refenestration study

The landscape of complicated Type B aortic dissection treatment has undergone a significant transformation in recent decades. The shift from invasive surgical techniques, to the less invasive endovascular interventions has been profound. While OSSAF, performed primarily in the early 2000s, adhered with guidelines of that era, its indications have evolved. Today, it serves as a viable option for patients deemed poor candidates for endovascular interventions, OS is usually limited to bypass grafting a vessel that is malperfused. (38)

OSSAF's theoretical advantage lies in its potential to address malperfusion by resecting the intimal membrane at the level of the visceral arteries, while preserving the intercostal and lumbal arteries. This approach aims to minimize the risk of spinal cord ischemia, a complication reported to occur in 4-7% of cases. Notably, in our cohort, approximately only one-third of patients presented without symptoms of malperfusion. A multidisciplinary team, carefully considering available resources, team expertise, and high-risk radiological features, made treatment decisions.

Our experience with OSSAF for cTBAD has pointed several key insights. Firstly, the early outcomes, particularly operative mortality, represent a significant drawback compared to TEVAR. Meta-analyses of TEVAR cases in cTBAD have reported in-

hospital mortality rates ranging from 3% to 13% (66-69), while operative mortality for open surgeries in TBAD has exhibited a broader range, from 5% to 34% (39, 60, 70, 71), likely influenced by the heterogeneity of open surgical strategies. Our observed operative mortality rate of 26.8% aligns with these reported figures.

Although TEVAR has risen to become the current gold standard for cTBAD treatment, long-term data from single-device trials remains limited. In a recent publication detailing 5-year outcomes of TEVAR, all-cause mortality, aortic-related mortality, and reintervention rates were found to be comparable to our results, with 65%, 83%, and 14%, respectively. (72) An outstanding study comparing 266 complicated and 176 uncomplicated TBAD cases revealed 5- and 10-year survival rates of 63% and 48% for cTBAD patients treated with open surgery, (71) which is also in line with our findings of 56% and 46% survival rates in our complicated TBAD cohort.

In 2023, Lau et al. (60) published their long-term results on open surgery for cTBAD in 75 patients, reporting similar long-term survival rates to ours, with 66% at 5 years and 47% at 10 years. However, they reported an exceptionally low operative mortality rate of 5%, likely attributable to their high-volume center's expertise and advancements in operative anesthesia, surgical technique, and perioperative care, as evidenced by Coselli et al.'s publication (73) of a 7.5% operative mortality in 3309 thoracoabdominal open repairs. When TEVAR is not a feasible option, open surgery can be a reasonable alternative, but surely in high-volume centers.

In 2010, Trimarchi et al. (74) published the longest follow-up study to date after OSSAF, with a 22% in-hospital mortality rate. Their long-term results were encouraging, with approximately 70% and 57% estimated survival rates at 5 and 10 years, respectively. This study was the first to suggest that the refenestrated visceral segment might exhibit reduced dilation compared to the ectatic thoracoabdominal aorta, a finding consistent with the phenomenon observed in the STABILISE concept (75), as the reno-visceral segment is less dilated.

We accurately examined all available baseline and follow-up scans to assess thoracic and visceral aortic diameter increments. Our analysis found a significant increase in thoracic aortic diameter (p=.001), while the increment of the visceral segment was not significant, being one-third of the thoracic aortic diameter increment (4.4 ± 9.3 mm vs. 15.7 ± 15.4

mm). This protection against late dilation could be attributed to the absence of the intimal membrane or the presence of periaortic scar tissue formation. Consequently, we believe our relatively high reoperation rate is primarily due to the treatment of post-dissection thoracic aortic aneurysms, rather than our surgical technique. Importantly, OSSAF preserved intercostal arteries, resulting in no cases of permanent paraplegia.

Endovascular surgical fenestration of the dissected aorta, as investigated by Norton et al. (76) in 2019, leads to similar long-term survival results (49% at 10 years) but lower operative and early mortality rates (8% and 72%) and reintervention rates compared to our OSSAF experience. On the other hand, reintervention rates were similar to our results at 5 and 10 years (freedom from reintervention: 21% and 31% respectively).

6.2.3 Covered stenting in CFA

Femoral vascular access site complications pose a significant risk in endovascular procedures using large-bore devices. (77-79) While open surgery in these acute cases remains a traditional and highly successful treatment, its 30-day mortality and morbidity rates, up to 14%, necessitate exploring less invasive alternatives. (80) This study evaluated balloon-expandable covered stents for treating CFA VASCs, aiming to reduce risks associated with open surgical groin exposure.

In our cohort of 23 patients, technical success with BECS was 91.3%. We observed one in-hospital death from recurrent bleeding, two 30-day deaths (one VASC-related), and seven midterm deaths (none VASC-related). Freedom from all-cause mortality was 91.1% at 1 month, 77.4% at 12 months, and 62.2% at 24 months. Clinical success was 90.5%.

BECS offers advantages over surgery: local anesthesia reduced surgical burden, shorter mobilization, and shorter hospital stays. Our technical success rate (91.3%) aligns with surgical outcomes and similar studies (91-93%). (49, 81) Our CFA occlusion rate of 4.3% is comparable to other research (5.6-6.2%). (50, 51) Stent fractures did not lead to restenosis, consistent with prior studies. (82-84)

Our study's female predominance, despite male dominance in atherosclerosis, mirrors other findings. (46, 48, 50, 53) This likely reflects females' tortuous vasculature and

smaller vessel diameters, increasing VASC risk. (85, 86) Major complications, classified by VARC-3, were 73.9%, higher than any other similar studies as they published 50-56.8%, (48, 49) but Sedaghat et al. (50) reported even lower rates (28.2%).

Despite conventional contraindications due to CFA bending and torsion, that can result in BECS kinking, fracture and occlusion, BECS could be considered, in our frail, elderly patient population where bending forces are less impactful. (46, 53) Percutaneous VASC management requires multidisciplinary decisions and close follow-up. The high-risk patient cohort and observed complication rates necessitate further study prior to the liberal application of BECS.

Preventing VASCs is crucial. Preoperative planning should include physical examination, duplex ultrasound, and CT scans to detect peripheral arterial disease. CFA calcification and undiagnosed PAD increase complication risks. Our cohort had high rates of CFA calcification (52.4%) and PAD (34.8%), likely contributing to complications. Ultrasound-guided puncture is also vital for prevention. (87, 88)

Compared to the publication of Benic et al. (89), who reported a 100% patency rate at 6 months and a similar rate (~95%) at one year, their study observed no VASC-related mortality or stent fractures. Their focus on TAVR patients may have allowed them to analyze a more favorable cohort than ours, which included individuals with diffuse vascular disease. While they acknowledged the limitations of their small cohort and emphasized the need for randomized trials, their promising results support the use of BECSs for VASC treatment, but it also underscores the need of caution in use and the necessity of further investigations.

7 Conclusions

This thesis provides a comprehensive investigation into the advancements and challenges in both open surgical and endovascular aortic interventions. Through three distinct studies, various strategies have been analyzed to enhance patient outcomes in complex aortic pathologies.

Our randomized controlled trial on air embolism during endovascular aortic repair demonstrated that adhering to the IFU, rather than increasing saline flush volume, may be more effective in minimizing air embolism. Furthermore, differences between endografts suggest that the design of the delivery system and of the stent graft itself plays a crucial role in optimizing deairing, highlighting the importance of device engineering in procedural outcomes.

In our long-term analysis of open surgical suprarenal aortic fenestration for cTBAD, we found that while perioperative mortality remained high, long-term survival was acceptable. Interestingly, resection of the intimal membrane may help mitigate local aortic diameter increase, though global remodeling remains a concern. These findings have valuable insights into the role of open surgery in selected patients and provide long-term follow up data.

Lastly, our evaluation of balloon-expandable covered stents for femoral access site complications demonstrated technical feasibility and an acceptable success rate but also revealed a concerning mortality risk. Given these findings, BECS implantation in this setting should be approached with caution and ideally be investigated further in the context of clinical trials to establish standardized protocols and ensure patient safety.

Collectively, these studies illustrate the ongoing evolution of aortic surgery, from refining established open techniques to optimizing contemporary endovascular approaches. While technological advancements continue to expand treatment options, our findings emphasize the critical importance of meticulous procedural execution, adherence to device-specific protocols, and ongoing research to refine patient selection criteria. Moving forward, rigorous evaluation of emerging techniques and standardization of best practices are essential in improving both immediate and long-term outcomes in aortic interventions.

8 Summary

This thesis comprises three studies addressing critical aspects of aortic intervention, covering both open surgical and endovascular techniques, with the overarching goal of improving patient outcomes in complex aortic pathologies.

The first study, an RCT, investigated the impact of saline flush volume on air embolism during EVAR. Contrary to current theories, the study demonstrated that following the device-specific IFU, rather than increasing saline flush volume, significantly improved deairing efficacy. This finding underscores the importance of strict procedural technique and highlights the influence of endograft design on deairing efficacy.

The second study examined the long-term outcomes of OSSAF for cTBAD. Over a 20-year period, the study revealed high perioperative mortality associated with OSSAF. However, it also demonstrated acceptable long-term survival rates and a unique protective effect against visceral aortic dilation. This suggests that while OSSAF remains a viable option for certain patients, careful patient selection and procedural expertise are crucial to mitigate risks and optimize outcomes.

The third study evaluated the feasibility and safety of BECS for treating complications at the CFA vascular access site. This retrospective analysis demonstrated high technical success rates with BECS. However, it also revealed significant mortality risks, particularly in the short- and mid-term. This highlights the need for cautious application of BECS and emphasizes the importance of rigorous patient selection, standardized procedural techniques, and thorough post-procedural monitoring. Furthermore, this study strongly suggests that until more data is available, this treatment should be performed in the context of clinical trials.

Collectively, these studies contribute to a deeper understanding of the evolving landscape of aortic surgery. They highlight the ongoing effort to refine both established open techniques and contemporary endovascular procedures. While each study addresses distinct clinical scenarios, they are unified by the common goal of improving patient safety and achieving better long-term outcomes in the treatment of complex aortic diseases. They also highlight the necessity of meticulous technique, device specific protocols, and ongoing research to optimize patient care.

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10 Bibliography of the candidate's publications

10.1 Original articles with relevance to the current thesis

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10.2 Other publications of the candidate

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11 Acknowledgements

I would like to express my sincere gratitude to everyone who supported me throughout the process of writing this dissertation. First and foremost, I am deeply indebted to my mentor and supervisor, **Csaba Csobay-Novák**, for his unwavering guidance, expertise, and patience. His insightful feedback and encouragement were invaluable in shaping this research and ensuring its successful completion. I am truly grateful for his mentorship and the opportunities he provided.

I would also like to extend my thanks to **Professor Béla Merkely**, Director of the Heart and Vascular Center of Semmelweis University, and **Balázs Nemes**, Head of the Department of Interventional Radiology, and **Professor Zoltan Szeberin**, Deputy head of the Department of Vascular and Endovascular Surgery, for their support and for providing me with the resources and environment necessary to conduct this research.

Special thanks are due to **Sarolta Borzsák**, whose PhD work laid the groundwork for my own studies. Her practical insights and willingness to share her knowledge were instrumental in my own learning and development, since my medical student years. I am grateful for her guidance in navigating the practical aspects of this research.

I am also indebted to **András Süvegh**, who embarked on this journey with me. Our shared experience and mutual motivation were crucial in maintaining our focus and driving us to achieve our best.

I deeply appreciate the dedication of my **radiologist colleagues**, as well as the invaluable contributions of the **assistants** and **radiographers** who worked alongside us.

Finally, I would like to express my deepest gratitude to my family! Especially to my wife, **Juli** and **my parents** unwavering love, support, and understanding sustained me throughout these challenging years. Their belief in me and their constant encouragement have been a source of strength and inspiration.

This dissertation would not have been possible without the collective support and guidance of these individuals. I am truly grateful for their contributions.

NYILATKOZAT EREDETISÉGRŐL ÉS SZERZŐI JOGRÓL

a PhD disszertáció elkészítésére vonatkozó szabályok betartásáról

Alulírott Dr. Szentiványi András Imre jelen nyilatkozat aláírásával kijelentem, hogy az "Innovations in Aortic Repair: Addressing Long-Term Efficacy and Procedural Safety" című PhD értekezésem önálló munkám, a dolgozat készítése során betartottam a szerzői jogról szóló 1999. évi LXXVI tv. vonatkozó rendelkezéseit, a már megjelent vagy közlés alatt álló közlemény(ek)ből felhasznált ábra/szöveg nem sérti a kiadó vagy más jogi vagy természetes személy jogait.

Jelen nyilatkozat aláírásával tudomásul veszem, hogy amennyiben igazolható, hogy a dolgozatban nem saját eredményeimet használtam fel vagy a dolgozattal kapcsolatban szerzői jog megsértése merül fel, a Semmelweis Egyetem megtagadja PhD dolgozatom befogadását, velem szemben fegyelmi eljárást indít, illetve visszavonja a már odaítélt PhD fokozatot.

A dolgozat befogadásának megtagadása és a fegyelmi eljárás indítása nem érinti a szerzői jogsértés miatti egyéb (polgári jogi, szabálysértési jogi, büntetőjogi) jogkövetkezményeket.

Tudomásul veszem, hogy a PhD értekezés nyilvánosan elérhető formában feltöltésre kerül az Országos Doktori Tanács honlapjára.

Budapest, ……

aláírás