# INITIAL RESULTS OF COMPLEX ENDOVASCULAR INTERVENTIONS FOR THE TREATMENT OF AORTIC DISEASE IN HUNGARY

**PhD thesis**


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# 1. Introduction

Aneursyms are the vessels' irreversible focal dilatation, defined as exceeding the expected normal diameter by at least 1.5 times. Aneurysms can occur anywhere in the vascular system but can be found most commonly on the arterial side, especially on the aorta. In terms of location, abdominal (AAA), thoracic (TAA) and thoracoabdominal aortic aneurysms (TAAA) are distinguished.

Whenever the indication of repair is met, in addition to open surgical repair, more and more endovascular treatment options are available. Moreover, in patients with suitable anatomy, the management of aortic and aorto-iliac pathologies shift towards endovascular procedures as endovascular treatment possibilities evolve. During the endovascular aneurysm repair (EVAR), the aneurysm sac is excluded from the systemic circulation with the use of a stent graft.

Fenestrated and branched devices offer the possibility of applying a suprarenal proximal landing zone and thus the method can also be used in cases of juxtarenal or thoracoabdominal aneurysms. Fenestrated or branched stent grafts are devices with reinforced fenestrations or directional branches according to the visceral orifices, thus ensuring an adequate landing zone for stent graft implantation and successful aneurysm exclusion at the same time. They are limited by diameter discrepancies and highly unconventional visceral anatomy, often requiring custom-made device design. In addition, the custom made devices have the disadvantage of long manufacturing time and high cost.

In the presence of coexisting dilatation of the aorta and the iliac system, the stent graft often has to be extended toward the external iliac artery. Due to the complications following the coverage of the internal iliac arteries, current guidelines recommend the preservation of at least one internal iliac artery, which is best achieved by the implantation of an iliac branch device (IBD).

The situation in Hungary in relation to aortic and complex aortic interventions is somewhat specific, mostly because of the financial background. There was a fixed cap budget yearly to cover all aortic interventions, which led to a relatively low number of complex aortic interventions. An important step in the learning curve of complex interventions: the

endovascular treatment of juxtarenal aneurysms, requiring two fenestrations was basically skipped, as these patients received an open surgical repair with supraceliac clamping. This resulted in relatively difficult first cases.

## 2. Objectives

Several papers have been published on the outcomes and determinants of the above discussed complex aortic interventions, but no data on outcomes in Hungary have been available before. Our objective was to investigate the initial results of the application of these endovascular treatments at a tertiary vascular center in Hungary.

1. **We aimed to study the initial results of FBEVAR and IBD implantation.**
   Our objective was to investigate the short- and mid-term outcomes in patients undergoing FBEVAR and IBD deployment based on a retrospective analysis.

2. **Our purpose was to assess the risk of the introduction of these procedures into our treatment portfolio in special regard to the beforementioned individual situation in Hungary, having a significant drawback in complex endovascular interventions due to the financial background.**
   We hypothesized that our initial results would not be as good as the results obtained in established centers with substantial experience, especially since the step of endovascular treatment of juxtarenal aneurysms, requiring only two fenestrations or branches was missing from our learning curve.

## 3. Methods

### 3.1. Study design

Single center retrospective studies were performed in our tertiary vascular center to evaluate the results of complex aortic interventions including our first 20 consecutive patients treated with FBEVAR and the first 35 patients receiving IBDs. The studies were approved by the local ethics committee (Semmelweis University Regional and Institutional Committee of Science

and Research Ethics: 96/2021, 92/2021) and were performed in accordance with the Helsinki declaration. Informed consent was obtained from all patients.

## 3.2. Data collection

Demographic data, cardiovascular risk factors, anatomical data, procedural and postoperative variables were collected retrospectively. When performing complex aortic interventions, intraoperative cone beam computed tomography was used to confirm technical success whenever possible. Follow-up clinical examination and imaging were performed according to current guidelines: at 30 days, 6 months, 12 months and annually thereafter. However, in some cases the results of the previous computed tomography angiography (CTA) examinations could indicate a more frequent follow-up, in other cases, especially due to the COVID-19 pandemic, some examinations were not performed in the intended time period. In patients with severely impaired kidney function, magnetic resonance angiography (MRA) was performed instead of a CTA. In some cases, duplex ultrasound or contrast-enhanced ultrasound were additionally completed.

## 3.3. Data analysis

Terminology, end point definitions and measurement techniques were used according to the most recent reporting standards document's definitions, published by Oderich et al.. Technical success was defined if arterial access, delivery and deployment of the stent graft components, side branch cannulation and the placement of the bridging stents were all successful, and if the patency of all target vessels were preserved, furthermore there was no sign of type I or III endoleak on the 30-day follow-up CTA. A clinical success was defined as the absence of disabling clinical complications, such as aortic-related complications or permanent paraplegia, newly onset permanent need for dialysis, and disabling stroke, in addition to the criteria of technical success. Primary endpoints were major adverse events, including the composite endpoints of all-cause mortality, new-onset dialysis, paraplegia, bowel ischemia, myocardial infarction, major stroke, or respiratory failure, and in-hospital and late aortic mortality. Secondary intervention was defined as any unanticipated procedure, which was performed after the index procedure, further classified as minor if percutaneous ≤10 Fr access was obtained, and major if open surgery or large-bore (≥12 Fr) endovascular access was necessary.

Categorical variables were reported as total numbers and percentages, whereas continuous variables as means with standard deviations. Time dependent variables (like patency and survival) were reported using the Kaplan-Meier method. Statistical analyses were performed

using IBM SPSS (Armonk, NY, USA, version 27.0) and GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) and the latter was also used to visualize the data on graphs. The curves are displayed up to a value of standard error (SE) <0.10. A value of $p<0.05$ was considered statistically significant for all measurements.

# 4. Results

## 4.1. Fenestrated/branched endovascular aortic repair

In our study there were 9 pararenal aneurysms (PRA, 45%) and 11 thoracoabdominal aortic aneurysms (TAAA, 55%), latter including 4 chronic dissection cases (20%) among the initial 20 FBEVAR cases (16 men, 65±11 years). All aneurysms were degenerative, there was no Marfan syndrome patient in the observed patient population. Demographics, clinical and anatomical characteristics can be found in Table 1.

**Table 1.** Demographics, clinical and anatomical characteristics

| **Variable** | | **N (%) or mean ±SD** |
|---|---|---|
| Demographics | Male gender | 16 (80) |
| | Mean age, years | 65.5 ± 11.2 |
| | BMI, kg/m$^2$ | 27.3 ± 4.1 |
| Clinical Characteristics | Hypertension | 16 (80) |
| | Smoking | 8 (40) |
| | Hypercholesterolemia | 10 (50) |
| | Diabetes mellitus | 3 (15) |
| | Coronary heart disease | 11 (55) |
| | Chronic obstructive pulmonary disease | 7 (35) |
| | Chronic kidney disease stage III-V | 4 (20) |
| | eGFR, mL/min/1.73m$^2$ | 74.6 ± 16.9 |
| | Prior aortic repair | 10 (50) |
| | Malignant disease | 5 (25) |
| ASA status | ASA II | 1 (5) |
| | ASA III | 17 (85) |
| | ASA IV | 2 (10) |
| Anatomical characteristics | Pararenal aortic aneurysm | 9 (45) |
| | Thoracoabdominal aortic aneurysm | 11 (55) |
| | Chronic dissection | 4 (20) |
| | Average size of the aortic aneurysm, mm | 72.5 ± 17.0 |

**Abbreviations:** N = Number; SD = Standard deviation; BMI = Body mass index; ASA = American Society of Anesthesiologist's physical status classification

Procedural details are shown in Table 2. The average aortic coverage length was 346.6 ± 132.8 mm. In the majority of the cases (14/20, 70%) custom made devices were used. Overall, seventy-one renal and mesenteric vessels were incorporated with 46 fenestrations and 25 directional branches. Among the first cases, two cases (10%) were managed via transaxillary access, afterwards there was a shift to a transfemoral only approach using a 16 Fr steerable guide catheter to facilitate target artery cannulation (Heli-FX Guide 22, Medtronic plc, Ireland). All target arteries were successfully cannulated and stented resulting in a 100% per vessel technical success rate. Furthermore, no open surgical conversion was necessary. Cerebrospinal fluid drainage was performed in three patients (15%), two cases were prophylactic, one therapeutic. Lately, therapeutic only approach was being preferred. In four patients (20%), who were regarded high risk for spinal cord ischemia, perfusion branches were used. The use of two (out of six) OTS devices were off-label, one with a narrow visceral aortic segment, and one with a chronic occlusion of the celiac trunk. In the latter urgent case, the occlusion of the corresponding portal was managed using a combination of a covered stent an Amplatzer plug (Amplatzer Vascular Plug II, Abbott Laboratories, USA) after neither the antegrade, nor the retrograde recanalization attempt of the celiac trunk through the gastroduodenal arcade were successful. Six adjunctive procedures were necessary in the management of five cases (5/20, 25%): two iliac bifurcation device implantations, two left subclavian transposition/bypass (zone 2 debranching), a prophylactic internal iliac artery recanalization and a branch portal embolization. Preloaded catheters were not available and therefore were not used.

The per patient technical success rate was 65% (13/20). Technical failure was mainly caused by the need for an early reintervention (minor: 5/20, 25%, major: 1/20, 5%). There was one in-hospital death due to the unintended coverage of a common hepatic artery arising from the superior mesenteric artery. The average length of stay (LoS) in the intensive care unit (ICU) was 0.8 ± 1.2 days, the average total LoS was 5.9 ± 2.4 days.

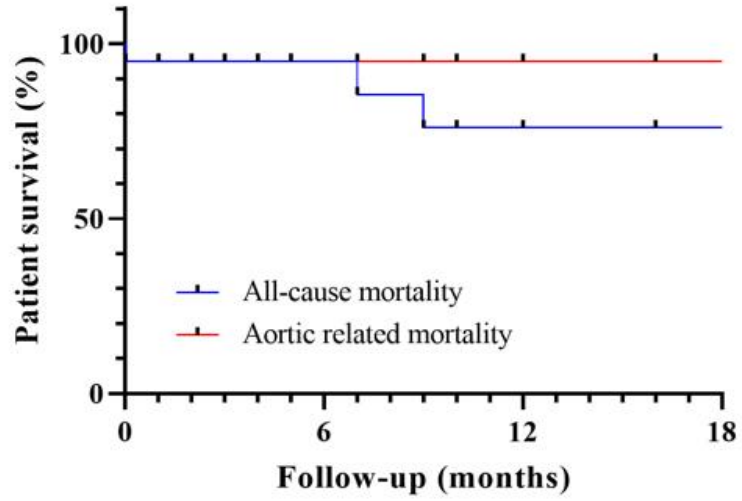
Primary clinical success rate was 45% (9/20) at an average follow-up of 14.0 ± 21.9 months. Secondary clinical success was achieved in 75% (15/20) observing the same time period. In-hospital mortality was 5% (1/20), all-cause mortality was 20% (4/20), with only one case being aortic related (5%). In that case, the above-mentioned coverage of an atypical common hepatic artery led to the patient's death. During the follow-up one celiac and three renal stent occlusions were found (4/71, 5,6%, Figure 1). In the other cases, which were not a technical success, the cause of this was type I or III endoleak and/or the need of reintervention.

Stroke, myocardial infarction, or aortic rupture were not detected. Spinal cord injury was discovered in two patients, one paraparesis occurred, and one paraplegia was found because of a spinal epidural hematoma due to a prophylactic CSFD. Three cases of new-onset permanent dialysis were observed (15%), two of them associated with renal stent occlusions.

**Table 2.** Procedural details

| **Variable** | | **N (%) or mean ±SD /[ IQR]** |
|---|---|---|
| Device design | Off-the-shelf device | 6 (30) |
| | Patient-specific device | 14 (70) |
| Proximal sealing zone | zone 2-4 | 10 (50) |
| | zone 5 | 7 (35) |
| | zone 7 | 1 (5) |
| | zone 8 | 2 (10) |
| Distal sealing zone | zone 9 | 3 (15) |
| | zone 10 | 11 (55) |
| | zone 11 | 6 (30) |
| Aortic coverage length, mm | | 346.6 ± 132.8 |
| Total incorporated vessels | | 71 |
| Incorporated vessels per patient | Total | 3.6 ± 0.9 |
| | 1 vessel | 1 (5) |
| | 2 vessels | 1 (5) |
| | 3 vessels | 5 (25) |
| | 4 vessels | 12 (60) |
| | 5 vessels | 1 (5) |
| Type of incorporation | Fenestrations | 46 (65) |
| | Directional branches | 25 (35) |
| Procedural data | Contrast volume, ml | 285.4 ± 124.0 |
| | Fluoroscopy time, min | 69 ± 39 |
| | Cumulative air kerma, Gy | 3.6 ± 2.5 |
| ICU length of stay, d | | 0.8 [0-1] |
| Total length of stay, d | | 5.9 [4-6] |
| Staged repair | | 6 (30) |
| Cerebrospinal fluid drainage | | 3 (15) |
| Temporary aneurysm sac perfusion | | 4 (20) |
| Technical success per vessel | | 71 (100) |
| Primary technical success per patient | | 13 (65) |

**Abbreviations:** N = Number; SD = Standard deviation; ICU = Intensive care unit; IQR = interquartile range

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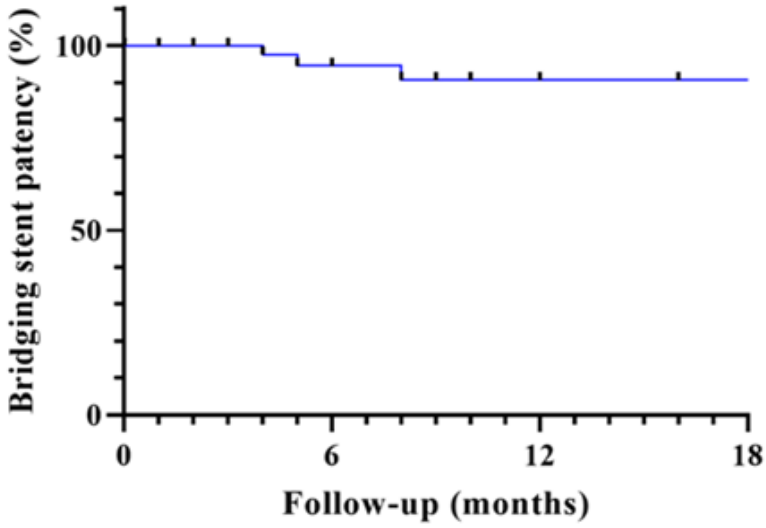
|---|---|---|---|---|
| Number at risk | 20 | 11 | 6 | 5 |
| Kaplan-Meier estimate survival rates | 1 | 0.950 | 0.760 | 0.760 |
| Standard error | 0 | 0.048 | 0.126 | 0.126 |
| Number at risk | 20 | 11 | 6 | 5 |
| Kaplan-Meier estimate survival rates | 1 | 1 | 1 | 1 |
| Standard error | 0 | 0 | 0 | 0 |




| | | | | |
|---|---|---|---|---|
| Number at risk | 70 | 29 | 17 | 13 |
| Kaplan-Meier estimate rates | 1 | 0.945 | 0.907 | 0.907 |
| Standard error | 0 | 0.024 | 0.038 | 0.051 |

**Figure 1.** Patient survival (up) and bridging stent patency (down) at an average follow-up of 14 ± 22 months.

## 4.2. Iliac branch device

In our study aiming to evaluate the midterm results of IBD implantations a total of 37 IBDs were implanted in 35 patients, between 14. December 2010 and 23. July 2021 in our tertiary vascular center. In 19 cases the primary disease was aorto-iliac aneurysm, in 11 cases isolated iliac aneurysm, in 3 cases a chronic aortic dissection and in 2 cases a Ib endoleak following an EVAR. In the 11 cases, where the indication of the IBD implantation was an isolated common iliac aneurysm, a stand-alone IBD deployment was carried out. The other patients were treated in conjunction with an EVAR. In addition to the EVAR-IBD implantation three patients also underwent a thoracic endovascular aortic repair (TEVAR) for a thoracic aortic aneurysm. The patients were mostly male (89%), the mean age was 67.9 ± 8.5 years. The patient population and aneurysm characteristics are reported in Table 3, respectively. Detailed procedural data are presented in Table 4.

Based on the instructions for use (IFU), only the Jotec E-iliac graft should be used in isolated iliac aneurysms, however in 6 cases a ZBIS Cook or a Gore IBE endograft were implanted isolated, due to proximal landing zone diameter issues. There were 14 other patients treated outside the IFU, either because they didn’t meet the anatomical requirements of the IFUs or because of aortic dissection as their primary disease. In all of these cases an aortic team decision was made to recommend IBD implantation, to which the patient consented.

**Table 3.** Baseline patient and anatomical characteristics.

| Variable | | N (%) or mean ±SD |
|---|---|---|
| Demographics | Male gender | 31 (89) |
| | Mean age, years | 67.9 ± 8.5 |
| | BMI, kg/m$^2$ | 28.5 ± 5.7 |
| Cardiovascular risk factors | Hypertension | 35 (100) |
| | Smoking | 13 (37) |
| | Hypercholesterolemia | 16 (46) |
| | Diabetes mellitus | 6 (17) |
| | Peripheral artery disease | 7 (20) |
| | Cardiac disease | 18 (51) |
| | Chronic obstructive pulmonary disease | 10 (29) |
| | Chronic kidney disease stage III-V | 11 (31) |
| | Previous aortic repair | 12 (34) |
| | Prior malignancies | 11 (31) |
| Anatomical characteristics | AAA diameter - mm | 46.9 ± 15.2 |
| | Left CIA aneurysm diameter - mm | 32.3 ± 14.1 |
| | Right CIA aneurysm diameter - mm | 35.0 ± 13.5 |

**Abbreviations:** N = Number; SD = Standard deviation; BMI = Body mass index; AAA = abdominal aortic aneurysm, CIA= common iliac artery.

None of the internal iliac arteries were lost, the per vessel technical success rate was 100%. The overall technical success rate was 88.2%, the primary clinical success was 82.4%, the assisted primary clinical success was 88.2%.

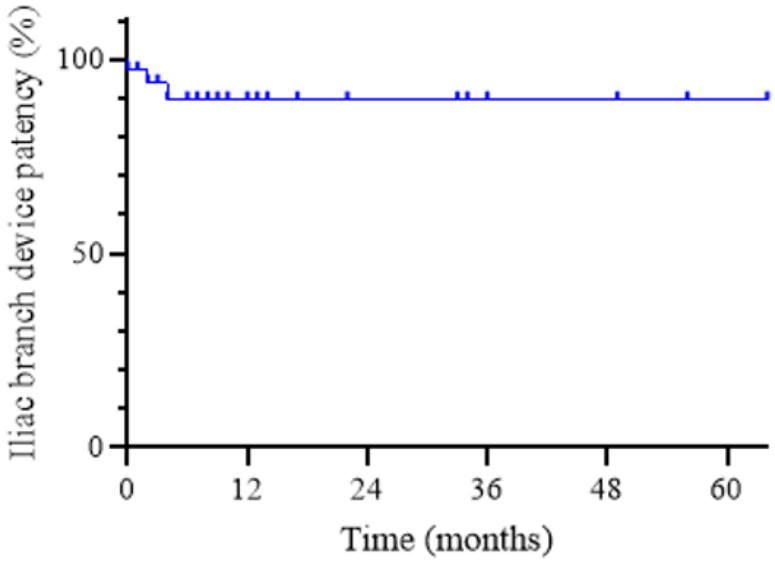
The mean length of the ICU LoS was 0.3 ± 0.5 days, the average total hospitalization duration was 4.6 ± 0.7 days. No surgical conversion was needed. The average follow-up time was 20.1 ± 26.2 months, during which one patient was lost to follow-up. No peri-operative or in-hospital death was recorded, there was no stroke, myocardial infarction, new-onset renal failure, mesenteric or spinal cord infarct, or significant buttock claudication.

Using the Kaplan-Meier estimates, freedom from IBD occlusion was 97.2%, 93.9%, 89.6% at 1, 2 and 4 months, respectively. (Figure 2.) During the follow-up, 3 iliac occlusions were detected, only the internal branch was affected. Each occlusion was left untreated.

**Table 4.** Baseline procedural characteristics.

| Variable | | N (%) or mean ±SD / [IQR] |
|---|---|---|
| Implanted devices | ZBIS Cook | 20 (54) |
| | Gore IBE | 12 (32) |
| | Jotec E-iliac | 5 (14) |
| | Isolated IBD | 11 (31) |
| | Bilateral IBD | 2 (6) |
| Procedural data | Contrast dose - ml | 139.25 ± 71.36 |
| | Fluoroscopy time - s | 2832.55 ± 1656.08 |
| | Dose area product - Gy*cm$^2$ | 294.45 ± 442.74 |
| | Hospitalization - days | 4.60 [4-5] |
| | Intensive care unit stay - days | 0.3 [0-0] |
| Complications | Type I endoleak | 1 (3) |
| | Type II endoleak | 10 (29) |
| | Type III endoleak | 2 (6) |
| | Type V endoleak | 1 (3) |

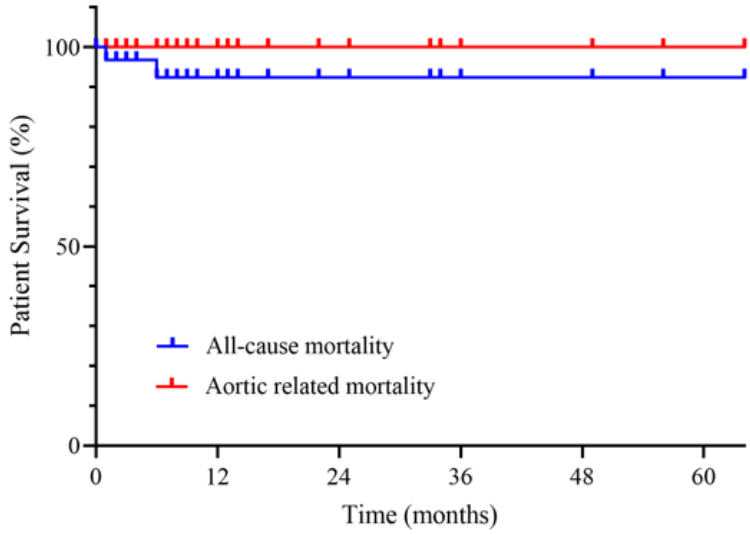
**Abbreviations:** N = Number; SD = Standard deviation; IBD = iliac branch device, IQR = interquartile range




| | | | | | | |
|---|---|---|---|---|---|---|
| Number at risk | 36 | 12 | 7 | 4 | 4 | 2 |
| Kaplan-Meier estimate rates | 0.972 | 0.896 | 0.896 | 0.896 | 0.896 | 0.896 |
| Standard error | 0.027 | 0.058 | 0.058 | 0.058 | 0.058 | 0.058 |

**Figure 2.** Kaplan-Meier estimates of iliac branch patency treated by iliac branch devices

In the observed time period, seventeen endoleaks were observed in 14 patients. One type I and type V, two type III endoleaks were detected, ten patients had type II endoleak. Five reinterventions were needed, all for endoleaks (14.7%). The need for reintervention was associated with the IBD device in 4 patients (11.8%). Two late deaths were registered, neither of them related to the aneurysm or the endovascular procedure. Both cases occurred months after the implantations, one was due to a Clostridium sepsis, the other to a gastro-intestinal bleeding. The freedom from all-cause mortality and aneurysm related mortality were 92.4% and 100%, respectively. (Figure 3.) Clinical success was not obtained in cases, where technical success was not achieved, as detailed above, in the two patients who died, and in the three patients in whom we observed growing aneurysm sacs.




| | | | | | | |
|---|---|---|---|---|---|---|
| Number at risk | 34 | 15 | 10 | 6 | 6 | 4 |
| Kaplan-Meier estimate survival rates | 1 | 1 | 1 | 1 | 1 | 1 |
| Standard error | 0 | 0 | 0 | 0 | 0 | 0 |
| Number at risk | 34 | 15 | 10 | 6 | 6 | 4 |
| Kaplan-Meier estimate survival rates | 1 | 0.924 | 0.924 | 0.924 | 0.924 | 0.924 |
| Standard error | 0 | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 |

**Figure 3.** Kaplan-Meier estimates of all-cause mortality and aortic related mortality treated by iliac branch devices

## 5. Conclusions

Based on our three studies the following statements can be made:

1. The initial outcome of the FBEVAR and IBD procedures showed high technical success with high freedom from disease-related mortality.
2. The per vessel technical success rates of the FBEVAR and IBD deployments were exceptional.
3. In spite of the special funding situation in Hungary which led to the absence of a significant proportion of the learning curve of interventions and to technically demanding initial complex endovascular cases, the outcomes of these implantations were comparable to other reported data.
4. The safe introduction of FBEVAR and IBD treatment could be a result of the few physicians performing the implantations and their previous expertise in the endovascular field.
5. PMEG can be used effectively in high-volume aortic centers in elective cases in patients with unusual anatomy or in urgent cases of complex aortic pathologies.

## 6. Bibliography of the candidate's publications

### 6.1. Publications directly related to the present thesis

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