MEDICAL UNIVERSITY OF SOFIA
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Departament of radiology

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NON-CONVENTIONAL ENDOVASCULAR METHODS FOR TREATING UNRUPTURED WIDE-NECK BIFURCATION CEREBRAL ANEURYSMS

Abstract
Of dissertation
for the awarding of scientific and educational degree of PhD

Scientific advisor:
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The dissertation consists of 142 pages with included references and contains 27 tables and 39 figures. The bibliography in the dissertation includes 229 references.

The present study was conducted with the participation of patients treated at UH “St. Ivan Rilski” Sofia.

Materials for the defense are available in the library of the Faculty of Medicine, Medical University of Sofia, and have been published on the website of the Medical University of Sofia.

Note: The numbering of the figures and tables in the thesis abstract has been adapted according to the included volume of information and is different from that in the dissertation.

The dissertation has been discussed and recommended for defense by the departmental council, held on November 23, 2023, at the Department of Radiology at the Faculty of Medicine, Medical University of Sofia.

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The public defense of the thesis will take place on April 18, 2024, at 14:00 in the auditorium of the Clinic of Neurology at the UH "Alexandrovska" in Sofia.

CONTENTS

LIST OF ABBREVIATIONS

ACA	–	anterior cerebral artery
AcomA	–	anterior communicating artery
(a)SAH	–	(aneurysmal) subarachnoid hemorrhage
AVM	–	arteriovenous malformation
CBC	–	complete blood count
CT/CTA	–	computed tomography/angiography
DFT	–	drawn filled tube
DSA	–	digital subtraction angiography
EVAL	–	ethylene vinyl alcohol copolymer
FD	–	flow-diverter
HPC	–	hydrophilic polymer coating
ICA	–	internal carotid artery
IL-1β	–	interleukin-1β
ISAT	–	International Subarachnoid Aneurysm Trial
ISUIA	–	International Study of Unruptured Intracranial Aneurysms
MCA	–	middle cerebral artery
MIP	–	maximum intensity projection
MRI/MRA	–	magnetic resonance imaging/magnetic resonance angiography
mRS	–	modified Rankin scale
MW	–	movable wire
POD	–	para-operational device
SD	–	standard deviation
SPSS	–	Statistical Package for the Social Sciences
TNF-α	–	tumor necrosis factor- alpha
TOF	–	time-of-flight
VR	–	virtual reality
WEB	–	Woven Endobridge
WEB DL	–	Woven Endobridge Double Layer
WEB SL	–	Woven Endobridge Single Layer
WEB SLS	–	Woven Endobridge Single Layer Spherical

INTRODUCTION

The term “aneurysm” originates from the Greek word “aneurýnein”, which means “dilation” or “to dilate”. Cerebral aneurysms represent a focal dilation of the intracranial arteries. Their prevalence in the general population is around 3% (Vlak et al., 2011). Cerebral aneurysms pose a significant health challenge, as the subarachnoid hemorrhage (SAH) resulting from their rupture is a condition associated with major health repercussions. Half of the patients with SAH are under the age of 55, and for one-third of them, the condition proves fatal in the first days to weeks following the initial hemorrhage. A significant portion of the survivors suffer substantial neurological or cognitive deficits. The impacts in terms of lost productive life years are comparable to those resulting from ischemic strokes (De Rooij et al., 2007; Etminan et al., 2019).

In recent years, highly specialized and more sensitive imaging diagnostic methods, such as magnetic resonance imaging (MRI), have gained widespread popularity among the population. As a result, there has been an increase in the diagnosis of incidental, unruptured cerebral aneurysms. This gives rise to many questions that have not yet found specific answers, such as: Should prophylactic occlusion of the aneurysm be performed? If yes, by which method – microsurgery or endovascular embolization? If no preventive occlusion is undertaken, should the aneurysm be monitored (how often and by which method)? Is drug treatment recommended, or lifestyle changes that can reduce the risk of rupture? (European Stroke Organization Guidelines for Management of Intracranial Aneurysms and Subarachnoid Hemorrhage). Prophylactic occlusion of the aneurysm is recommended for patients where the risk of complications associated with the potential procedure is lower than the assumed 5-year cumulative risk of rupture (Etminan et al., 2022).

After the publication of the results from the ISAT (International Subarachnoid Aneurysm Trial) and ISUIA (International Study of Unruptured Intracranial Aneurysms) studies, endovascular coiling emerged as a potential alternative to the until then established method of microvascular clipping. It progressively became the first-choice method for treating both ruptured and unruptured cerebral aneurysms (Wiebers, 2003; Molyneux et al., 2005). The endovascular method also revealed its limitations in treating a specific subtype of cerebral aneurysms, specifically those with more complex anatomy, characterized by a poorly defined neck, and those located at an arterial bifurcation. Bifurcations are the most common sites for the development of aneurysmal dilations. With bifurcation cerebral aneurysms that have a wide or ill-defined neck, typically one or both arterial branches of the bifurcation originate from the aneurysmal neck. Under these circumstances, forming a stable coil mass in the aneurysmal sac without compromising the blood flow in the adjacent vessels presents a significant challenge. Apart from the risk of thromboembolic complications related to the procedure itself, this type of aneurysms also show a much higher rate of recanalization, consequently leading to a need for retreatment. These shortcomings of endovascular treatment led to the development of new devices and techniques to address the aforementioned challenges. Such techniques include balloon-assisted coiling, stent-assisted coiling, flow-diverter stents, and intrasaccular implants. The enrichment of the interventional neuroradiology toolkit with these devices and resulting techniques has enabled the effective treatment of extremely complex aneurysms, for which the endovascular method was once deemed inapplicable. Despite this, observed results from using these contemporary methods and devices suggest they are still not adequately efficient. Their application is associated with a non-negligible rate of complications, making the treatment of wide-neck bifurcation cerebral aneurysms an ongoing, unresolved issue. The search continues for the most optimal solution to this problem (Vakharia, Munich, and Siddiqui, 2019).

AIM AND TASKS OF THE STUDY

Aim

The aim of this dissertation is to determine the application of non-conventional endovascular methods in the treatment of unruptured and wide-neck bifurcation cerebral aneurysms.

Tasks

To achieve the specified aim, we outlined the following tasks:

1 To investigate the safety and effectiveness in a group of patients with unruptured bifurcation cerebral aneurysms with wide necks, treated with an intrasaccular implant – WEB

2. To study the safety and effectiveness of permanent stent-assisted coiling in a group of patients with unruptured bifurcation cerebral aneurysms with wide necks.

3. To investigate the safety and efficacy in a group of patients with unruptured bifurcation cerebral aneurysms with wide necks, treated with “flow-diverter” stents.

4. To compare the obtained results regarding safety and effectiveness between the individual patient groups.

5. To study the influence of certain patient-related factors, such as gender, age, arterial hypertension, dyslipidemia, and smoking status, on the geometric characteristics of the aneurysms in the studied population.

6. To investigate the correlation between the geometric characteristics of the aneurysmal sac and the final outcome of the conducted endovascular treatment.

7. To study the influence of the geometric features of the arterial bifurcations, particularly the bifurcation angle, on the treatment outcome.

MATERIALS AND METHODS

Materials

The study was conducted with the participation of patients who underwent endovascular intervention at the University Hospital "Saint Ivan Rilski" – Sofia, for the period from January 2018 to December 2022. For the inclusion of patients in this study, we used the following criteria:

Inclusion criteria:

- Presence of at least one saccular cerebral aneurysm.
- Location of the aneurysmal sac at an arterial bifurcation.
- Unruptured status of the aneurysm.
- Presence of a wide aneurysmal neck, which was defined as a neck size > 4 mm and/or a dome-to-neck ratio < 2.

Exclusion criteria:

- Clinical and/or imaging data indicating a previous aneurysmal intracranial hemorrhage.
- Previous endovascular or neurosurgical intervention on another aneurysm in the same patient.
- Possibility of conducting an effective and safe endovascular intervention using conventional endovascular methods such as: non-assisted coiling, temporary stent-assisted coiling, and balloon-assisted coiling.

Based on the above criteria, it was determined that 151 patients qualified, each of whom underwent endovascular embolization of at least one unruptured bifurcation cerebral aneurysm with a wide neck, at the University Hospital "Saint Ivan Rilski" – Sofia, for the period from January 2018 to December 2022. A retrospective study of this representative sample was conducted. For the purposes of the dissertation, the patients were divided into the following three groups based on the type of endovascular method used:

Group 1, n = 41

- Comprises 41 patients, of which 10 (24,4%) are male and 31 (75,6%) are female

Group 2, n = 56

- Comprises 56 patients, of which 9 (16,1%) are male and 47 (83,9%) are female

Group 3, n = 54

● Comprises 54 patients, of which 14 (25,9%) are male and 40 (74,1%) are female.

Methods

Demographic and clinical data of the patients included in the study

For all patients included in the study, data was collected regarding gender, age, smoking status at the time of the intervention, presence of dyslipidemia, and arterial hypertension.

Preoperative preparation and assessment of the patients

Patients scheduled for endovascular embolization of an unruptured cerebral aneurysm are admitted to the hospital on a planned basis, with the intervention typically planned for the second day after admission. During the preoperative hospital stay, routine laboratory tests, chest X-rays, and consultations with specialists – interventional radiologist, neurosurgeon, neurologist, anesthesiologist, and cardiologist are conducted. Additional consultative examinations and tests are assigned as needed, depending on the specific patient. The standard laboratory tests include a complete blood count (CBC), biochemical analysis, evaluation of renal function through serum creatinine and urea, and examination of hemostasis indicators. Each patient is thoroughly informed about the disease, the different approaches to treatment, as well as the benefits and risks associated with each approach. Specialists, including neurosurgeons, neurologists, and anesthesiologists, evaluate the patient‘s somatic and neurological status as part of the preoperative preparation. The mRS score (appendix № 1) was used to assess the neurological status, which is expressed on a seven-grade progressive scale ranging from 0 to 6. After conducting a comprehensive set of clinical, laboratory, and imaging examinations, and with the patient‘s decision to proceed with an endovascular intervention, an appropriate treatment plan is developed. The final decision on how the embolization will be carried out involves a team of neurosurgeons, interventional radiologists, neurologists, and anesthesiologists. All patients participating in the study were pre-loaded with dual antiplatelet therapy orally for at least 3-5 days prior to hospitalization, consisting of Prasugrel 10 mg (1 tablet in the morning) and Aspirin 100 mg (1 tablet in the evening) due to the potential need for permanent implantation of an intraluminal device. After the completion of the intervention, depending on the chosen method, a re-evaluation and, if necessary, adjustment of the therapy was made. Patients who underwent an endovascular procedure involving the implantation of a flow-diverter stent or stent-assisted coiling continued with the dual antiplatelet therapy for a period of six months, at which point the first follow-up for these groups was scheduled. If the clinical and angiographic results are satisfactory at the first imaging follow-up after six months, patients transition to mono antiplatelet therapy with Aspirin 100 mg, taking 1 tablet in the evening for a period of twelve months. For the group of patients treated with the WEB intrasaccular device, the dual antiplatelet therapy was discontinued after the procedure, except in cases where there was a protrusion of the implant towards any of the adjoining vessels of the arterial bifurcation. In these instances, mono antiplatelet therapy with Aspirin 100 mg was prescribed for a minimum period of 10 days.

Geometric characteristics of the aneurysmal sac and adjacent vessels

Measurement of geometric characteristics, such as the size of the aneurysmal neck, the size of the aneurysmal sac, determining the dome-to-neck ratio, and the aspect ratio, were performed for all patients using the 2D images obtained during the procedure from digital subtraction angiography or data from the intra-arterial 3D rotational angiography conducted also during the procedure. The bifurcation angle measurement was made using data from the 3D rotational angiography. Its determination involved the following steps: The first step involved drawing lines along the longitudinal axis of the vessels forming the arterial bifurcation, namely the arterial bifurcation branches and the main parent vessel. These lines were positioned in the middle of the mentioned vessels. The intersection point of the three lines, located just below the aneurysmal sac, was defined as the apex of the bifurcation angle. The angle formed between the lines connecting the vessels of the arterial bifurcation and the defined apex of the bifurcation angle was considered the bifurcation angle – figures 1 and 2.

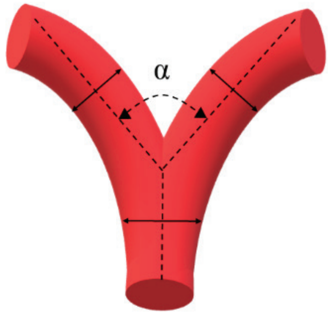


Figure 1. Determining the bifurcation angle – α

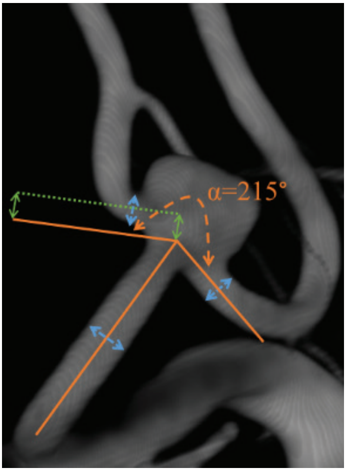


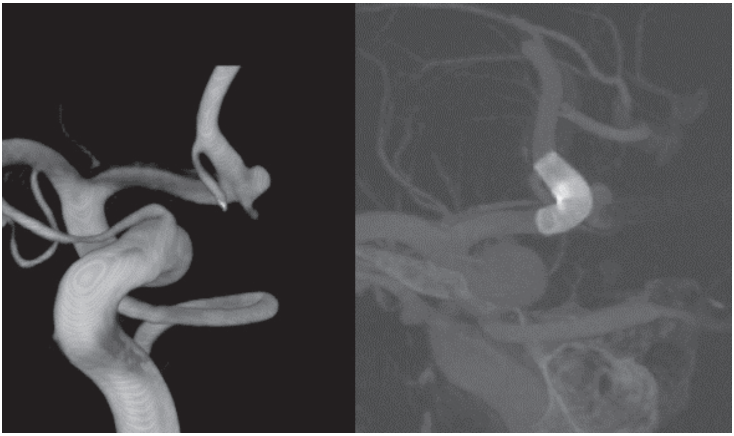
Figure 2. Example of measuring the bifurcation angle α. The blue arrows demonstrate the diameter of the vessels forming the arterial bifurcation. The continuous orange lines are positioned in the center of the vessels of the arterial bifurcation

Endovascular procedures

General considerations for all patient groups. All endovascular procedures were performed under general endotracheal anesthesia. The interventions were carried out on two biplane angiographic devices; predominantly on the „GE Inova 3131 IQ" until 2020, and subsequently on the „Philips Azurion IQ 7 Biplane". The first step of each procedure involved obtaining arterial access using the Seldinger technique. The most commonly utilized arterial access was the right common femoral artery, followed by the left common femoral artery, and the radial artery – either proximal or distal access, on the right or left respectively. The type of introducers (sheaths) used were 6, 7, and 8F with a length of 11 cm (Terumo). In cases with a more tortuous anatomy of the aorta and its branches, and when greater stability was required, longer introducers were employed, namely 60 and 90 cm, most frequently: Destination (Terumo) and Asahi Fubuki (Asahi Intecc). When arterial access was secured, an intra-arterial bolus dose of 5000 IU unfractionated heparin was administered through the introducer. The procedure then proceeded with selective catheterization and diagnostic pan-angiography of the supra-aortic vessels. The diagnostic catheters used for this purpose were 5F, and included: Judkins Right, Simmons 2, or Vertebral (Merit Medical), introduced over a hydrophilic guide wire (Terumo) measuring 0.035 inches and 260 cm in length. The next step involved navigating and delivering a guiding catheter to the target vessel through which the endovascular intervention would be performed – either the cervical or petrous segment of the internal carotid artery or the V2 segment of the vertebral artery. The most commonly used guiding system in our practice was the Chaperon 6F (Microvention). Other guiding catheters less frequently used in our practice were: Guider (Boston Scientific), Envoy (Cerenovus), and Asahi Fubuki (Asahi Intecc). The guiding catheter system was constantly infused under pressure with an iso-osmolar solution of 0.9% NaCl, to which 5 mg of nimodipine had been added. As a next step in every procedure, an intra-arterial 3D rotational angiography was performed to ensure better morphological assessment and precise measurement of the aneurysm‘s dimensions and its adjoining vessels in view of choosing appropriately sized implants. The 3D rotational angiography was conducted with an automatic injector connected to the angiograph, with parameters concerning the execution of the study, such as injection speed and the amount of contrast agent, being determined based on the target vessel and hemodynamics. Standardly, for a 3D rotational angiography of the internal carotid artery, the rotation time was 4 seconds, the flow was 4 ml per second, with a total contrast agent amount of 22 ml. For the vertebro-basilar system, the rotation time was also 4 seconds, with a flow of either 3 or 3.5 ml per second, and a total contrast agent amount of 20 ml. After selecting a working projection that clearly delineated the aneurysm neck from the adjacent arterial branches, supra-selective navigation into the intracranial circulation was performed using a set of microcatheters introduced over micro-guidewires. The most commonly used micro-guidewires had diameters of 0.010 and 0.014 inches and included the following: pORTAL (Phenox, Bochum, Germany), Synchro (Stryker Neurovascular, Fremont, California, USA), Asahi Chikai (Asahi Intecc), and Traxcess (Microvention, Aliso Viejo, California, USA). In cases of tortuous supra-aortic and intracranial arterial vessels and at the operator‘s discretion, a triaxial system, comprising a guiding catheter, distal access catheter, and microcatheter, was used. Distal access catheters included Sofia (Microvention) with sizes of 5 or 6F and lengths of 115 or 125 cm. The navigation steps and the embolization of the target aneurysm for different patient groups are described in the following sections.

Before the final completion of each procedure, control angiograms were performed in a working projection and a standard projection, without angulation, to assess the treatment‘s effect and early detection of any complications that may have arisen during the intervention itself. At the end of the procedure, hemostasis at the puncture site was achieved either through manual compression in the case of femoral access or using a TR-band (Terumo) in the case of radial access. The patient was brought out of general anesthesia in the angiography suite and transferred to the Department of Anesthesiology and Intensive Care for a post-procedural stay of at least 24 hours. Strict monitoring and assessment of the neurological and somatic status of the patient were performed multiple times throughout the early post-operative period. On the first post-procedural day, patients were transferred to the neurosurgery department, gradually mobilized. In most cases, patients were discharged on the 5th day of their hospital stay, following an assessment of their neurological and somatic status

The angiography system „Philips Azurion IQ“ is equipped with the capability to perform intravascular, flat-panel VasoCT, which enhances the visualization of endovascular implants – intraluminal and intrasaccular – as well as an assessment of their relationship to the local vascular anatomy. The procedure itself is carried out similarly to 3D rotational angiography with an automatic injector. For the intravascular VasoCT protocol, the following parameters were used: rotation time – 20 seconds, with a flow rate of 3 ml per second and a total volume of 70 ml (5 ml contrast and 65 ml physiological saline) – Figure 3.



A B

Figure 3. 3D rotational angiography and intravascular, flat-panel VasoCT in a patient with a sacciform aneurysm located in the anterior communicating artery complex. A – 3D rotational angiography before implantation, and B – VasoCT after the implantation of a „flow-diverter“ stent

Technical steps for patients in group 1 treated with the intrasaccular implant (WEB). The Woven EndoBridge (WEB, Microvention, Aliso Viejo, California, USA) is a self-expanding intrasaccular implant specifically designed for the treatment of wide-necked bifurcation cerebral aneurysms. The first-generation device, WEB DL (double layer), consists of two densely woven layers of nitinol wires and has a spherical shape. Subsequent generations, WEB SL (single layer) and WEB SLS (single layer spherical), are constructed with a single layer of nitinol wires, incorporating platinum for improved device visualization. The wires are connected at the proximal and distal ends of the implant using two radiopaque markers. WEB SL has a barrel/cylindrical shape, while WEB SLS has a spherical shape. Since the device is intended for complete intrasaccular placement without parts extending into the adjacent arteries of the aneurysm sac, there is no need for dual antiplatelet therapy. The implants are delivered with a flexible delivery wire and have an electrothermal detachment mechanism once positioned within the aneurysm sac. The sizes of the devices range from 3x2 to 11x9 for WEB SL and from 4x2.6 to 11x9.6 for WEB SLS, compatible with microcatheters with internal diameters of 0.017, 0.021, 0.027, and 0.033 inches.

In our practice, all patients were treated with WEB SL – Figure 4, with a triaxial system being most commonly used to provide access to the aneurysm sac. The most frequently used microcatheters for navigation and implant delivery were VIA 17, 21, and 27 (Microvention), with internal diameters of 0.017, 0.021, and 0.027 inches. Using a microcatheter over a microguidewire, catheterization of the aneurysm sac was performed. Once an appropriate position of the microcatheter within the aneurysm sac was determined, the microwire was removed from the microcatheter, and the latter was continuously flushed with a heparinized solution of 5000 IU in 500 ml of 0.9% NaCl. To facilitate the selection of an appropriate device size, manufacturer-developed tables were used (Appendix No. 2). For this purpose, measurements in two orthogonal planes of the following geometric characteristics of the aneurysm were necessary: aneurysmal neck, width, and height of the aneurysm sac. The next step, after selecting a specific implant for the case, is to load it into the microcatheter and deliver it into the aneurysm sac. Before the final implantation of the device, angiographies were performed to assess the position of the implant in the aneurysm and its relationship to adjacent vessels. Detachment of the implant from its delivery system is achieved through an electrothermal detachment mechanism via a handle and close monitoring under fluoroscopic control. Intravascular VasoCT, according to the described protocol, was performed at the operator‘s discretion – Figure 5.

Technical steps for patients in group 2 treated with permanent stent-assisted coiling. In the patients included in this work, two types of intravascular implants were used for stent-assisted coiling in various configurations, namely: Neuroform Atlas (Stryker Neurovascular, Fremont, California, USA) and LVIS (Microvention, Viejo, California, USA). Neuroform Atlas is a low-profile, self-expanding implant constructed from nitinol using laser technology – Figure 6.

The device has a hybrid design, combining both open and closed-cell structure. The presence of three radiopaque markers located at each end ensures visibility of the implant under X-ray. The device is compatible with microcatheters with an inner diameter of 0.0165 inches and is available in diameters ranging from 3 to 4.5 mm and lengths from 15 to

30 mm. In our practice, the delivery of the implant was most commonly achieved using the Excelsior SL-10 microcatheter (Stryker Neurovascular, Fremont, California, USA). LVIS is a self-expanding implant constructed from 16 nitinol wires with a platinum core. The implants wires are woven using the DFT (drawn filled tube) technology, which provides visibility of the implant during fluoroscopy. Four radiopaque markers are located at each end of the stent, and additional visibility is provided by two radiopaque markers running the entire length of the device. The available diameters of the implant range from 2.5 to 5.5 mm, and possible lengths range from 13 to 31 mm. The device is compatible with a microcatheter with an inner diameter of 0.021 inches, with the Headway 21 microcatheter (Microvention, Viejo, California, USA) being the most commonly used for implant delivery in the studied group of patients.

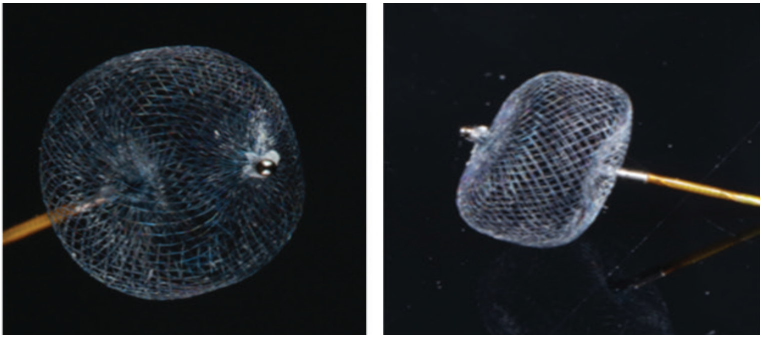


Figure 4. Macroscopic image of WEB SL device (own image)

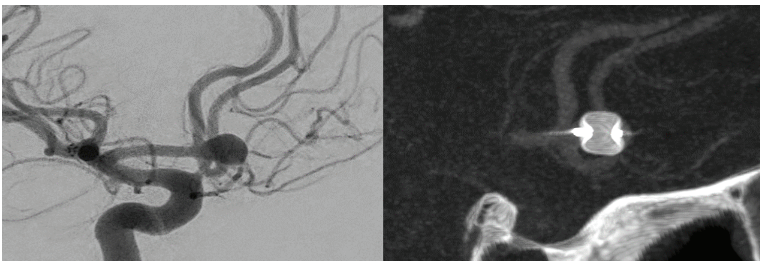


Figure 5. Saccular aneurysm of the anterior communicating artery treated with an intrasaccular implant – WEB. A – DSA in a working projection. B – Intra-arterial VasoCT after implantation of the device, demonstrating no compromise of blood flow to adjacent vessels

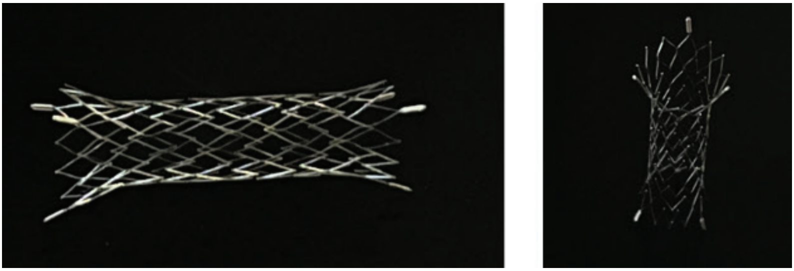


Figure 6. Macroscopic image of Neuroform Atlas stent (own image)

The first step in performing endovascular embolization through stent-assisted coiling involved the navigation and catheterization of the aneurysmal sac using a selected microcatheter for coiling, which was introduced over a microguidewire. The microcatheters commonly used for coiling included Echelon-10 (Medtronic). The delivered microcatheter was flushed with a heparinized solution under pressure, typically containing 5000 IU in 500 ml of 0.9% NaCl. Depending on the specific case, the subsequent steps involved catheterization of one or both branches of the arterial bifurcation, followed by the implantation of one or two implants. In cases of two implants, they were implanted in an X- or Y-configuration. After the delivery of the implants, coiling of the aneurysmal sac was performed until achieving maximum achievable occlusion

Technical steps for patients in group 3 treated with „flow-diverter" stent. The intraluminal devices used in this group to modulate blood flow in the aneurysmal sac were represented by the implants p48 and p48 MW and p64 and p64 MW (Phenox, Bochum, Germany). The p48 implant is composed of 48 braided nitinol wires constructed using DFT technology, with a platinum core. A variant of the device is the p48 MW (movable wide), in which the implant features a central, independently movable wire made of stainless steel that terminates with atraumatic distal nitinol tip to prevent perforation of small, distally located vessels during implant delivery. These devices are available in diameters ranging from 2 to 3 mm and lengths from 9 to 18 mm, suitable for treating vessels with diameters ranging from 1.75 to 3 mm. The implant is compatible with microcatheters with an internal diameter of 0.021 inches. The p64 device is constructed from 64 braided nitinol wires that terminate at the proximal end of the device in 8 platinum radiopaque markers, providing visibility of the implant under X-ray control – Figure 7. There are also two spiral radiopaque markers along the course of the implant, contributing to its visibility. Once delivered but not detached, the device can be fully retracted and delivered again. The detachment method of the device is mechanical. The implant is compatible with microcatheters with an internal diameter of 0.027 inches. Available diameters range from 2.5 to 5 mm, and lengths range from 9 to 30 mm. Similar to the p48 model, the device is also available in a p64 MW (movable wire) variant. The differences from the previous model include the detachment method, a design based on DFT technology, compatibility with lower-profile microcatheters with an internal diameter of 0.021 inches, and the presence of an independently movable and atraumatic tip, as in the p48 MW. Both p48 MW and p64 MW are available with an antithrombotic HPC coating (hydrophilic polymer coating). For the delivery of these implants in the studied group of patients, microcatheters Phenom 21, Phenom 27 (Medtronic, USA), and Excelsior XT-27 (Stryker Neurovascular, Fremont, California, USA) were most commonly used. In cases involving the use of „flow-diverter“ stents, the endovascular intervention consisted of superselective catheterization of the target vessel from the arterial bifurcation, with the microcatheter being flushed in a similar manner as in other patient groups, using a pressurized system of heparinized solution (5000 IU in 500 ml of 0.9% NaCl). The next step in embolization involved loading the selected implant into the microcatheter and its subsequent delivery.

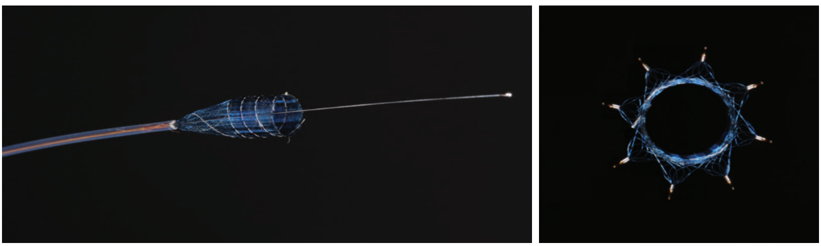


Figure 7. Macroscopic image of p64 implant (own image)

Safety Assessment

The safety profile when using the respective endovascular method in different groups of patients was determined by tracking the mRS score in the following time periods: before the procedure, in the early postoperative period, and at the first scheduled follow-up imaging examination, which occurred six calendar months after the endovascular procedure. The mRS scale is used to determine the degree of dependence or impairment in performing daily activities in patients who have experienced a stroke or neurological impairment due to another pathological condition. The scale consists of seven levels, expressed by numbers from 0 to 6, with each successive level indicating worsening of neurological status and, accordingly, a decrease in the quality of life (Appendix No.1). A neurologist and neurosurgeon participated in the assessment of overall somatic and neurological status and the determination of the mRS score. Data were collected on complications directly or indirectly related to the procedure to assess safety in the defined patient groups. Complications were categorized as follows: no complications, minor complications, moderate complications, severe complications, and lethal outcome. Minor complications were defined as procedure-related complications that do not lead to a deterioration in the quality of life and do not require additional hospitalization. Moderate complications included those that temporarily and reversibly led to a decrease in the quality of life, prolonged hospitalization, and/or necessitated additional hospitalization. Severe complications encompassed those resulting in permanent impairment of the quality of life.

Assessment of the treatment outcomes

The effect of the endovascular treatment was assessed by determining the degree of occlusion, which was monitored through diagnostic imaging studies, including digital subtraction angiography, CT angiography, and MR angiography. The computer tomography (CT) scans were performed using a 16-multidetector CT machine called „GE Brightspeed“ located in the Department of Diagnostic Imaging at UH „St. Ivan Rilski“ in Sofia. Magnetic resonance (MR) imaging was conducted using two machines, „GE Signa HDxt“ with a 1.5 T magnetic field strength and „GE Signa Architect“ with a 3 T magnetic field strength. MR imaging for assessing the treatment effect included standard sequences: DWI (Diffusion-Weighted Imaging), T1, T2, FLAIR (Fluid-Attenuated Inversion Recovery), SWI (Susceptibility-Weighted Imaging), and non-contrast 3D TOF (Time-Of-Flight) MR angiography. To ensure comparability of results across different patient groups, the degree of occlusion was classified into the following categories: total occlusion, residual aneurysm neck, and residual aneurysm. This simplified classification of occlusion status was adopted to facilitate the comparison of data from various endovascular methods, each using different occlusion scales, as well as due to differences in the nature of the imaging methods used for monitoring. Data regarding the dynamics of occlusion status observed during different follow-up imaging studies were also collected. Changes in the degree of occlusion were classified into the following categories: stable occlusion, improvement in occlusion status, and worsening in occlusion status. Stable occlusion was defined as a situation where no changes in occlusion status were observed during follow-up. Improvement in occlusion status was defined as a reduction in the size of the aneurysm, while worsening in occlusion status required an increase in the size of the aneurysm to be present. As a final outcome of the treatment in the long term, the degree of occlusion achieved at the last imaging examination was assessed for each patient group. The final degree of occlusion was divided into two categories: adequate occlusion and residual aneurysm. The term „adequate occlusion“ encompassed aneurysms where total occlusion was achieved and aneurysms that, at the end of treatment, had a residual aneurysm neck.

Statistical methods

1. Descriptive statistics – quantitative variables were summarized using mean, standard deviation (SD), minimum, and maximum values. Categorical variables were presented using absolute counts (N) and relative percentages (%).
2. One-Sample Kolmogorov-Smirnov Test – used to assess the distribution of quantitative variables.
3. Chi-square test or Fisher‘s Exact Test – employed to examine dependencies between categorical variables with two or more categories.

4. Independent-Samples t-test – used to compare two independent groups when the quantitative variable follows a normal distribution.

5. Mann-Whitney test – applied when comparing two independent groups, and the data distribution deviates from normality.

6. Wilcoxon Signed Ranks Test – used to compare two dependent groups when the data distribution is not normal.

7. One-Way Analysis of Variance (ANOVA) – for testing differences among multiple independent samples.

8. Kruskal-Wallis Test – employed for comparing more than two independent groups when the data distribution is not normal.

9. Correlation analysis – Spearman‘s rank correlation coefficient (Spearman‘s rho) was used to explore the correlation between two non-normally distributed quantitative variables.

The accepted level of significance was $\alpha = 0.05$, with statistical significance defined as $p < 0.05$. The data analysis was conducted using the specialized statistical software package SPSS (Statistical Package for the Social Sciences) version 20.0.

RESULTS AND DISCUSSION

Patient demographics and risk factors in the scope of this dissertation

Unruptured saccular intracranial aneurysms are encountered in approximately 3-5% of the adult population worldwide, regardless of geographic region or ethnic background. The probability of formation and rupture of cerebral aneurysms increases with advancing age, with the condition rarely occurring in patients under the age of twenty and most commonly affecting individuals between the ages of forty and sixty (Etminan et al., 2022). The mean age of the 151 patients included in this dissertation is 57.5 years (SD ± 11.35). After conducting a variance analysis, it was found that the mean age in the individual patient groups is comparable, with no statistically significant difference (p = 0.084) – Table 1.

Table 1. Mean age of the studied patients in the separate groups. Standard deviation, minimum, and maximum values of the indicator are presented

Group	N	Age				p
		Mean	SD	Min	Max	
Group 1	41	55,32	10,827	27	73	0,084
Group 2	56	60,11	10,934	34	81	
Group 3	54	56,44	11,824	31	76	

Cerebral aneurysms are more common in individuals of the female gender, with this association becoming particularly pronounced after the age of fifty – with up to 2.2 times higher frequency in females (Etminan et al., 2022). Similar to the data reported in the literature, our analysis regarding gender distribution found that female individuals predominate among the participants in the study (n = 118 or 78.1%), both in the overall sample and in each separate group. A chi-square test conducted did not reveal a significant difference in the gender distribution among the different groups (p = 0.412) – Table 2.

Table 2. Distribution of patients by gender in the separate groups

Gender		Group 1	Group 2	Group 3	Overall	p
Male	N	10	9	14	33	0,412
	%	24,4%	16,1%	25,9%	21,9%	
Female	N	31	47	40	118	
	%	75,6%	83,9%	74,1%	78,1%	
Total	N	41	56	54	151	
	%	100,0%	100,0%	100,0%	100,0%	

There are various hypotheses aiming to explain the higher prevalence of cerebral aneurysms in females. One of these hypotheses is associated with differences in anatomical and hemodynamic parameters between the two genders. Studies have shown that anatomical bifurcations of arteries in the Circle of Willis have different diameters and geometries in males and females, leading to varying levels of hemodynamic stress in the vessels. Females often experience greater hemodynamic stress, which may result in more significant endothelial damage and the formation of cerebral aneurysms. Another factor that may account for the higher incidence of cerebral aneurysms in females compared to males is hormonal status. Ruptured and unruptured cerebral aneurysms are more common in women, with the prevalence becoming particularly pronounced after the age of fifty and peaking in the sixth decade of life. These changes coincide with the physiological decline in estrogen levels during the perimenopausal period, suggesting a protective role of estrogen in the formation of cerebral aneurysms. This hypothesis is supported by the fact that women taking oral contraceptives or hormone replacement therapy have a lower risk of developing cerebral aneurysms. The role of estrogen is explained by its ability to inhibit certain pathogenic processes responsible for cerebral aneurysm formation, such as endothelial dysfunction, inflammation, and oxidative stress (Fréneau et al., 2022).

The pathogenetic mechanisms underlying the processes of formation, growth, and rupture of cerebral aneurysms are not fully understood. The development of intracranial aneurysms is considered a multi-step, complex process characterized by structural and functional abnormalities in the vascular wall of cerebral arteries. Factors such as arterial hypertension, tobacco smoking, dyslipidemia, and alcohol consumption play a role in this process, interacting with an individual‘s genetic predisposition for the formation of intracranial aneurysmal dilation. Arterial hypertension is a significant risk factor that contributes to both the formation and the progression to rupture of cerebral aneurysms. Clinical data on arterial hypertension were present in 143 out of 151 patients, with 108 (75.52%) having arterial hypertension. A significant association between arterial hypertension and age was identified ($p < 0.001$), with a mean age of 61 years (SD ± 9.45) in patients with arterial hypertension – as shown in Table 3. Fisher‘s exact test conducted on the overall population to analyze the distribution of patients with arterial hypertension by gender revealed no statistically significant difference between the genders ($p = 0.255$). Among individuals with arterial hypertension, 77.7% (n = 87) were female, while 67.7% (n = 21) were male.

Table 3. T-test to examine the relationship between the presence of arterial hypertension and age

Group	Arterial hypertension	N	Age				p
			Mean	SD	Min	Max	
Group 1	No	11	48,73	12,37	27,00	67,00	0,011
	Yes	29	58,24	9,03	38,00	73,00	
Group 2	No	14	49,79	11,56	34,00	69,00	< 0,001
	Yes	42	63,55	8,34	39,00	81,00	
Group 3	No	10	41,80	6,99	31,00	56,00	< 0,001
	Yes	37	60,19	10,42	34,00	76,00	
Total	No	35	47,17	11,00	27,00	69,00	< 0,001
	Yes	108	60,97	9,45	34,00	81,00	

Smoking is another risk factor strongly associated with the pathogenesis of cerebral aneurysms. In the conducted retrospective study, data on smoking status were available for 90 (59.6%) of the studied patients, of which 55.6% were non-active smokers at the time of the intervention, and 44.4% reported an active smoking status. Among active smokers, 40.3% (n = 11) were female, and 61.1% (n = 29) were male. The Fisher's exact test did not show a statistically significant association regarding smoking status between males and females ($p = 0.112$). The average age of smokers was 55.33 years (SD ± 12.14), while non-smokers had an average age of 58.84 years (SD ± 11.5). The t-test did not reveal a significant relationship between age and smoking ($p = 0.163$). Besides smoking and arterial hypertension in the complex mechanism responsible for the formation and progression of cerebral aneurysms, serum lipid levels are also believed to play a role. Histological examination of the wall of cerebral aneurysms reveals characteristic atherosclerotic changes, which are particularly pronounced in large and giant aneurysms (Savastano et al., 2018). The significance of serum lipid levels has also been studied in ruptured cerebral aneurysms. In their study, Ou et al. (2020) found significantly higher levels of LDL in patients with ruptured cerebral aneurysms compared to patients with unruptured aneurysms. For this reason, the study and monitoring of lipid status are important for patients with cerebral aneurysms. Information on lipid status was available for 62 patients, of whom 29 (46.8%) had dyslipidemia, and 33 (53.2%) did not have such a deviation. The Fisher's exact test did not show a significant difference in the presence or absence of dyslipidemia between male and female individuals ($p = 0.445$). Despite the small sample size, a significant relationship between lipid status and age was observed in the studied patient groups through a t-test ($p < 0.001$). The average age of patients with dyslipidemia was 61.8 years (SD ± 9.7), while those without dyslipidemia had an average age of 48.1 years (SD ± 12.03) – table 4.

Aneurysms – characteristics

With the advent of endovascular methods for the treatment of intracranial aneurysms, it has been established that certain geometric characteristics of the aneurysms significantly influence the final outcome of the treatment. Specifically, the localization, size of the aneurysmal neck, bifurcation angle, dome-to-neck ratio, and aspect ratio are some of the parameters that affect the level of achieved occlusion, the degree of recanalization, and assist in choosing the most suitable method and devices based on the individual morphological characteristics of the patient (Debrun et al., 1998; Kanat, Aydin, and Debrun, 1999; Brinjikji, Cloft, and Kallmes, 2009). For this reason, this study analyzes data regarding the distribution of treated aneurysms along the course of the cerebral arteries, the size of the aneurysmal neck, the height and width of the aneurysmal sac, the dome-to-neck and aspect ratios, as well as the values of the bifurcation angle.

Table 4. T-test to investigate the relationship between the presence of dyslipidemia and age

Group	Dyslipidemia	N	Age				p
			Mean	SD	Min	Max	
Group 1	No	17	51,18	12,05	27,00	70,00	0,047
	Yes	13	59,69	9,78	30,00	67,00	
Group 2	No	8	48,50	13,78	34,00	71,00	0,002
	Yes	6	71,83	4,54	65,00	77,00	
Group 3	No	8	41,13	7,83	31,00	56,00	< 0,001
	Yes	10	58,50	8,11	46,00	74,00	
Total	No	33	48,09	12,03	27,00	71,00	< 0,001
	Yes	29	61,79	9,66	30,00	77,00	

The distribution of aneurysms along the course of the cerebral arteries shows a similar pattern and tendency for certain locations to predominate over others (Nixon, Gunel, and Sumpio, 2010). Differences in this distribution are noted in specific anatomical variants within the Circle of Willis, which are associated with changes in the geometry of cerebral blood flow and, consequently, hemodynamic stress on the cerebral arteries. Aggregate data on the distribution of aneurysms – ruptured and unruptured – along the course of the cerebral arteries indicate that approximately 90% of aneurysms are located in the so-called anterior cerebral circulation, with 10% in the posterior cerebral circulation. In the anterior cerebral circulation, the highest percentage is occupied by aneurysms located on the anterior communicating complex (30-35%), followed by the internal carotid artery (30%) and its related branches, such as the posterior communicating and ophthalmic arteries. Aneurysms of the middle cerebral artery are encountered in about 22% of cases (Keedy, 2006). From the obtained results regarding the distribution of aneurysms by location in the three groups of patients in this study, it was found that the most commonly treated aneurysms are located on the middle cerebral artery (n = 93, or 61.6%), followed by the anterior communicating artery (n = 40, or 26.5%). Third in frequency are aneurysms located at the tip of the basilar artery (n = 9, or 6%), while aneurysms at the bifurcation of the internal carotid artery rank fourth (n = 6, or 4%). The least represented in terms of location in the studied population are aneurysms along the course of the anterior cerebral artery – 2% (n = 3) – Figure 8. There was no significant difference in the frequency of treated aneurysms among the individual groups, with middle cerebral artery aneurysms being the most frequently treated in each group, followed by anterior communicating artery aneurysms.

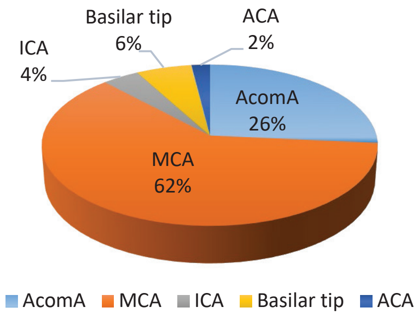


Figure 8. Summary data from the three groups of patients regarding the distribution of treated aneurysms by location

The relationship between the localization of cerebral aneurysms and gender has been well studied, with several studies reporting a prevalence of anterior cerebral artery aneurysms in male patients and a higher frequency of internal carotid artery aneurysms in female patients (Ghods, Lopes, & Chen, 2012; Fuentes, McGuire, & Amin-Hanjani, 2022; Zuurbier et al., 2022). In a retrospective analysis of patients with 682 aneurysms, Ghods, Lopes, and Chen, 2012, found that internal carotid artery aneurysms were present in 54% of female patients compared to 38% in male patients. In male patients, anterior cerebral artery aneurysms were more common, occurring in 29% of cases, compared to 15% in female patients. Similar observations were documented by Aarhus and colleagues in a study of 444 patients. Anterior cerebral artery aneurysms were more common in men, accounting for 81% (49% in women), while internal carotid artery aneurysms predominated in female patients, with a prevalence of 64%, compared to 24% in men (Aarhus, Helland, & Wester, 2009). However, in our analysis of the data, we did not find a significant relationship between gender and the localization of aneurysms ($p = 0.438$). The observed differences between the literature data and our studied patients regarding the distribution of cerebral aneurysms could be explained by the fact that the literature data include a large number of patients with an unselected sample in terms of the aneurysm rupture status and whether treatment has been performed or not. The patients examined in the present study were selected based on the strict criteria described in the ‚Materials and Methods' section, including a non-ruptured status, a wide aneurysmal neck, and arterial bifurcation location, which limits the number of studied patients and the diversity of treated aneurysms.

The included aneurysms in the dissertation have a wide neck. The calculated mean size of the aneurysmal neck in all studied patients is 4.98 mm (SD ± 2.04) – Table 5. The Mann-Whitney test did not reveal a statistically significant difference in the size of the aneurysmal neck depending on gender ($p = 0.093$). The average size of the aneurysmal neck in men from all groups is 4.53 mm (SD ± 1.77), and in women – 5.11 mm (SD ± 2.10). After analysis, average values of the aneurysmal neck are established, distributed by the location of the aneurysm: for aneurysms of the anterior communicating artery – 5.28 mm (SD ± 2.25), aneurysms of the middle cerebral artery – 4.98 mm (SD ± 1.97), aneurysms of the bifurcation of the internal carotid artery – 3.48 mm (SD ± 0.28), aneurysms at the top of the basilar artery – 4.87 mm (SD ± 2.30), and aneurysms along the course of the anterior cerebral artery – 4.23 mm (SD ± 2.08).

Regarding the observed width of the aneurysmal sac, no significant difference was found in the values between individuals of male and female gender ($p = 0.050$) – Table 6. In men from all groups, the average width of the aneurysmal sac was 5.41 mm (SD ± 2.71), while in women, it was 6.51 mm (SD ± 3.31). After analysis, data were obtained for the average values of the width of the aneurysmal sac at different locations of the cerebral aneurysms. The average values of the width of the aneurysmal sac, measured in mm, are as follows: aneurysms of the anterior communicating artery – 6.43 (SD ± 3.35); aneurysms of the middle cerebral artery – 6.34 (SD ± 2.98); aneurysms at the bifurcation of the internal carotid artery – 3.83 (SD ± 0.87); aneurysms at the top of the basilar artery – 6.94 (SD ± 5.36); and aneurysms along the course of the anterior cerebral artery – 4.77 (SD ± 2.25).

Table 5. Mann-Whitney test presenting the relationship between gender and the size of the aneurysmal neck in the studied patient groups

Group	Gender	N	Neck size (in mm)				p
			Mean	SD	Min	Max	
Group 1	Male	10	4,27	1,23	3,00	6,40	0,412
	Female	31	4,60	1,13	2,70	6,90	
Group 2	Male	9	5,79	2,36	2,70	9,30	0,927
	Female	46	6,11	2,68	2,90	14,00	
Group 3	Male	14	3,90	1,28	2,20	6,60	0,167
	Female	40	4,36	1,38	1,20	7,00	
Total	Male	33	4,53	1,77	2,20	9,30	0,093
	Female	117	5,11	2,10	1,20	14,00	

Table 6. Mann-Whitney test regarding the dependency between the width of the aneurysmal sac and gender.

Group	Gender	N	Aneurysm width (in mm)				p
			Mean	SD	Min	Max	
Group1	Male	10	5,54	1,49	3,60	8,00	0,939
	Female	31	5,39	1,45	2,30	8,00	
Group 2	Male	9	6,91	3,72	2,80	13,00	0,562
	Female	46	7,64	3,92	2,30	19,00	
Group 3	Male	14	4,36	2,29	2,50	10,70	0,039
	Female	40	6,08	3,25	1,30	14,50	
Total	Male	33	5,41	2,71	2,50	13,00	0,050
	Female	117	6,51	3,31	1,30	19,00	

The results of our study do not show a statistically significant difference in the height and width of the aneurysmal sac between men and women, with p-values of 0.258 and 0.050, respectively. The average height of the aneurysm is 5.17 mm (SD ± 2.39) in men and 6.06 mm (SD ± 3.47) in women – Table 7. After conducting the analysis, we found that the height of the aneurysm varies depending on its location. The average values of the height of the aneurysmal sac in different locations of cerebral aneurysms are as follows: aneurysms of the anterior communicating artery – 5.88 mm (SD ± 3.20); aneurysms of the middle cerebral artery – 5.82 mm (SD ± 3.08); aneurysms at the bifurcation of the internal carotid artery – 4.07 mm (SD ± 2.11); aneurysms at the top of the basilar artery – 7.56 mm (SD ± 5.33), and aneurysms along the course of the anterior cerebral artery – 5.57 mm (SD ± 4.71).

Table 7. Mann-Whitney test to examine the correlation between the height of the aneurysmal sac and gender

Group	Gender	N	Aneurysm height (in mm)				p
			Mean	SD	Min	Max	
Group 1	Male	10	5,40	1,57	3,30	8,20	0,832
	Female	31	5,26	1,61	3,00	9,90	
Group 2	Male	9	6,47	3,07	3,00	12,30	0,811
	Female	46	7,29	4,33	2,40	19,00	
Group 3	Male	14	4,18	2,08	2,20	10,30	0,252
	Female	40	5,26	3,05	1,30	14,00	
Total	Male	33	5,17	2,39	2,20	12,30	0,258
	Female	117	6,06	3,47	1,30	19,00	

The ratio between the width of the aneurysmal dome and the width of the aneurysmal neck (measured as the dome-to-neck ratio) had a mean value of 1.25 (with a standard deviation of SD ± 0.35). The ratio between the height of the aneurysmal sac and the width of the aneurysmal neck (Aspect ratio) had a mean value of 1.19 (with a standard deviation of SD ± 0.47).

The predominance of aneurysms in the female population, as well as the documented higher rupture rates, leads to the search for reasons behind these observed differences. As mentioned, disparities between genders are also observed in the localization of aneurysms. It is logical to look for differences in their geometric characteristics, as the existing literature investigating such patterns is insufficient. In their study, Krzyżewski et al., 2018, examined the relationship between the geometric characteristics of aneurysms and gender in 357 patients with ruptured and unruptured cerebral aneurysms. The research team found a statistically significant difference ($p < 0.001$) only in the dome-to-neck ratio, with individuals of the female gender having lower values. No statistically significant difference was found between gender and the size of the aneurysmal neck, the aspect ratio, the volume, and the size of the aneurysms. According to our data, this is the only study that investigates such dependencies. The results obtained in the present study correlate with those reported so far, with the difference that in our studied population, no statistically significant relationship was found between any of the studied parameters and gender (size of the neck, width and height of the aneurysmal sac, bifurcation angle, and the aspect and dome-to-neck ratios) – Tables 5, 6, 7, 8, and 9.

Table 8. Mann-Whitney test to investigate the correlation between the bifurcation angle and gender

Group	Gender	N	Bifurcation angle (in degrees)				p
			Mean	SD	Min	Max	
Group 1	Male	10	156,10	24,31	125,00	191,00	0,934
	Female	31	155,19	25,95	114,00	207,00	
Group 2	Male	9	177,22	24,57	134,00	213,00	0,733
	Female	46	182,89	44,12	95,00	276,00	
Group 3	Male	14	172,29	39,61	94,00	239,00	0,232
	Female	40	182,03	37,15	78,00	251,00	
Total	Male	33	168,73	32,09	94,00	239,00	0,419
	Female	117	175,26	39,24	78,00	276,00	

Table 9. T-test to examine the relationship between gender and Aspect ratio and Dome-to-neck ratio

Parameter	Gender	N	Mean	SD	Min	Max	p
Aspect ratio	Male	33	1,15	0,31	0,70	1,90	0,463
	Female	117	1,20	0,51	0,40	3,40	
Dome-to-neck ratio	Male	33	1,17	0,26	0,80	1,90	0,097
	Female	117	1,27	0,39	0,70	2,60	

Arterial bifurcations are a preferred site for the formation of aneurysmal dilations. The apex of an arterial bifurcation is the location subjected to the highest levels of hemodynamic stress, which leads to remodeling of the underlying vessel wall and provides the basis for processes such as atherosclerosis and aneurysm formation. It is believed that a specific morphology of the arterial bifurcation is more commonly associated with the formation of aneurysmal dilations. Larger values of the bifurcation angle are more frequently associated with the presence of cerebral aneurysms. Similar associations have been found in studies of bifurcation angles of the middle cerebral artery, internal carotid artery, and basilar artery (Tütüncü et al., 2014). Ingebrigtsen et al., 2004, investigated the geometric characteristics of arterial bifurcations involved in the formation of the Circle of Willis and found that locations with an aneurysm have a wider bifurcation angle compared to those without. Song et al., 2017, examined the bifurcation angle in middle cerebral artery aneurysms, comparing the obtained values with those of the contralateral side without an aneurysm. The authors found differences in the values, with the side containing the aneurysm having a significantly wider bifurcation angle. They defined a threshold value for the bifurcation angle of 124.8°, above which the presence of an aneurysm is more likely. Similar results regarding the association between a wider bifurcation angle in the middle cerebral artery compared to the contralateral side without an aneurysm have also been published by Baharoglu et al., 2014. The team suggests a higher threshold value for the middle cerebral artery‘s bifurcation angle – 140°, above which the formation of an aneurysm is more likely. Similar conclusions were drawn by the teams of Tütüncü et al., 2014, and Zhang et al., 2018, as they found that the basilar artery‘s bifurcation angle is significantly wider in patients with an aneurysm than in those without an aneurysmal dilatation. It has been established that normal arteries have a narrow bundle of tightly arranged collagen fibers at the location where direct collision with the strongest hemodynamic stress/turbulent blood flow occurs. This place is precisely at the apex of the bifurcation angle. From there, turbulent blood flow is distributed to the arteries forming the bifurcation. The narrower the bifurcation angle, the shorter the distance at which turbulent blood flow returns to laminar flow. When the bifurcation angle widens, the location where hemodynamic stress has the most significant impact shifts away from the zone protected by collagen fibers, the distance at which laminar flow is restored increases, and the duration of the turbulent blood flow‘s effect is prolonged. All these phenomena observed with increasing values of the bifurcation angle are associated with the formation of cerebral aneurysms (Zhang et al., 2018). The observed effects of the bifurcation angle on hemodynamic stress prompted further research on the significance of the bifurcation angle on the outcome of endovascular treatment. Gao et al., 2022, analyzed the impact of stent implantation in assisted embolization of cerebral aneurysms located at arterial bifurcations. Implanting a stent in the bifurcation‘s branch, which forms a smaller angle with the main vessel, can lead to narrowing of the bifurcation angle, displacement of hemodynamic stress, and a reduction in the force exerted by turbulent blood flow on the bifurcation apex. These changes observed after stent implantation are associated with a better final treatment outcome and a lower likelihood of revascularization.

Due to the significance of the bifurcation angle in the processes of cerebral aneurysm initiation and its effect on treatment, it is appropriate to analyze the relationship between the bifurcation angle and other parameters of the patients included in the study. In the conducted Spearman correlation analysis (Table 10), a positive correlation between age and the bifurcation angle was found, as documented in previous studies (Baharoglu et al., 2014; Tütüncü et al., 2014). In the analysis (Mann-Whitney test) for the presence of a relationship between the bifurcation angle and the gender of the studied patients, no statistically significant dependence was observed, and accordingly, no difference in the bifurcation angle between men and women ($p = 0.419$). The mean values of the bifurcation angle in men from the three groups are 168.73 degrees (SD ± 32.09), while in women, they are 175.26 degrees (SD ± 39.24). These results are consistent with previously published series where a similar relationship between the bifurcation angle and gender was not documented.

We did not find a statistically significant relationship between the bifurcation angle and the risk factors we investigated related to the processes of cerebral aneurysm formation, such as arterial hypertension, dyslipidemia, and smoking. Similar conclusions were reached by Baharoglu et al., 2014, with the exception of the significant relationship they observed between smoking and the bifurcation angle. The authors observed significantly smaller values of the bifurcation angle in smokers.

Table 10. Spearman correlation analysis expressing the relationship between age and bifurcation angle

Group	**Age – bifurcation angle**	
	R	**p**
Group 1	-0,155	0,334
Group 2	0,345	0,010
Group 3	0,280	0,040
Summary of the results	0,262	0,001

We conducted a correlation analysis to explore the relationship between the bifurcation angle and the geometric characteristics of the treated aneurysms, such as the size of the aneurysm neck, the width and height of the aneurysm sac, the dome-to-neck ratio, and the aspect ratio. The results are summarized in Table 11.

In our study, when examining the relationship between the size of the aneurysm neck and the bifurcation angle, we found a statistically significant correlation in each of the studied groups ($R = 0.374$, $p < 0.001$). Similarly, a statistically significant relationship was observed between the bifurcation angle and the width of the aneurysmal sac ($R = 0.287$, $p < 0.001$). However, we did not find a statistically significant relationship between the bifurcation angle and the dome-to-neck and aspect ratios (p = 0.769 and p = 0.788, respectively).

Similar conclusions regarding the presence of a positive correlation between the size of the bifurcation angle and the mentioned geometric characteristics were reached by Baharoglu et al., 2014, and Tütüncü et al., 2014, in their series when studying aneurysms of the middle cerebral artery and the basilar artery.

Table 11. Spearman correlation analysis with computed values of the relationship between geometric characteristics of the examined aneurysms and the bifurcation angle

Group		Neck size (in mm)	Width of the aneurysm (in mm)	Height of the aneurysm (in mm)	Dome to neck ratio	Aspect ratio
Group 1	R	0,310	0,188	0,243	-0,210	-0,031
	p	0,049	0,240	0,126	0,187	0,846
Group 2	R	0,322	0,372	0,404	0,169	0,187
	p	0,016	0,005	0,002	0,218	0,172
Group 3	R	0,433	0,258	0,263	-0,130	-0,058
	p	0,001	0,060	0,055	0,350	0,678
Total	R	0,374	0,287	0,287	0,024	0,022
	p	< 0,001	< 0,001	< 0,001	0,769	0,788

The relationship between the bifurcation angle and the respective localization of the aneurysms in the individual groups could not be investigated due to the formation of small groups and the impossibility of conducting an adequate test. Data were obtained regarding the mean values of the bifurcation angle depending on the localization of the aneurysms. For aneurysms of the anterior communicating artery, the mean value of the bifurcation angle, measured in degrees, is 180.68 (SD ± 32.58) across all groups. For aneurysms of the middle cerebral artery, it is 171.58 (SD ± 38.47). The mean value of the bifurcation angle for aneurysms located at the bifurcation of the internal carotid artery is 151.17 (SD ± 22.34). In the case of aneurysms located at the apex of the basilar artery, the average bifurcation angle is 168.22 (SD ± 53.48), and for aneurysms along the course of the anterior cerebral artery, the observed mean value of the bifurcation angle is 213.33 (SD ± 20.26) – Table 12.

Table 12. Values of the bifurcation angle based on different aneurysm locations

Group	Aneurysm Location	N	Values of the bifurcation angle			
			Mean	SD	Min	Max
Group1	AcomA	9	165,67	23,11	131,00	199,00
	MCA	26	155,23	26,35	114,00	207,00
	ICA	3	137,00	6,08	130,00	141,00
	Basilar tip	3	144,67	27,50	117,00	172,00
Group 2	AcomA	21	186,76	32,56	118,00	260,00
	MCA	29	176,83	46,77	95,00	276,00
	Basilar tip	4	187,75	52,32	135,00	259,00
	ACA	1	207,00		207,00	207,00
Group 3	AcomA	10	181,40	38,17	117,00	248,00
	MCA	37	178,95	35,87	78,00	251,00
	ICA	3	165,33	24,66	137,00	182,00
	Basilar tip	2	164,50	99,70	94,00	235,00
	ACA	2	216,50	27,58	197,00	236,00
Summary results	AcomA	40	180,68	32,58	117,00	260,00
	MCA	92	171,58	38,47	78,00	276,00
	ICA	6	151,17	22,34	130,00	182,00
	Basilar tip	9	168,22	53,48	94,00	259,00
	ACA	3	213,33	20,26	197,00	236,00

Evaluation and analysis of the obtained results regarding the safety and effectiveness of the endovascular procedure by groups

Group 1 – patients treated with WEB

The WEB device is an intrasaccular implant specifically designed to address the challenges associated with treating some of the most complex cerebral aneurysms, namely those located at arterial bifurcations with wide necks. Its application has been studied in several prospective and retrospective studies involving a large number of patients, conducted in multiple centers in the United States and Europe. The device has been investigated for the treatment of both ruptured and unruptured cerebral aneurysms, with promising results in terms of achieved levels of occlusion and safety.

In all patients from the group, the low-profile version of WEB, namely WEB SL, was used. The most frequently used size was 6 x 4 in 19.5% (8/41) of cases. Figure 9 shows the frequency distribution of the device sizes used.

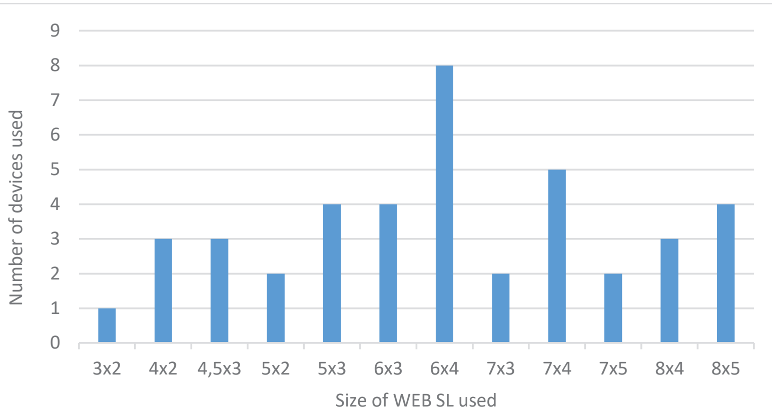


Figure 9. Frequency distribution of the intrasaccular implants used

According to the available literature, the use of WEB is characterized by high levels of technical success, ranging from 92.8% to 98.7%. Unsuccessful application of WEB is usually observed during the initial experience of operators with the device and more often with the use of the first generations, namely WEB DL, which is associated with the use of larger microcatheters (Ding et al., 2011; Klisch et al., 2011; Pierot et al., 2012; Caroff et al., 2015). Documented unsuccessful attempts are most commonly associated with technical difficulties such as challenging navigation and device delivery in tortuous anatomy, difficulties in selecting the correct device size, protrusion of the implant into the vessels forming the bifurcation, and the inability to assess its position relative to the surrounding anatomy. In our patient series, the delivery of WEB was successful in 41/44 cases (93.9%), confirming the high technical success described in the literature. Patients in whom embolization was not performed using WEB were excluded from the study. In cases of unsuccessful implantation of the device into the aneurysm, it was safely removed from cerebral circulation, and subsequently, the target aneurysms were treated using other endovascular methods such as permanent stent-assisted coiling or intraluminal flow-diverting implants. Similar to the data described in the literature, the unsuccessful attempts in our sample occurred in cases with tortuous anatomy of supra-aortic and intracranial vessels, unfavorable aneurysm morphology, and protrusion of the implant into the vessels originating from the aneurysm neck. Usually, more difficult delivery and loading of the implant were observed with larger device sizes. Consistent with the data from the literature, our unsuccessful cases occurred in our early attempts to use the device. In some of our documented technical failures, we also acknowledge the possibility of selecting the wrong device size. The introduction of newer generations like WEB SL and SLS, which utilize lower-profile delivery systems, facilitated navigation and device delivery. From our experience with using the device, we found that adapting a triaxial system protocol, consisting of a guiding catheter, a distal access catheter, and a microcatheter, was crucial for the successful procedure when using the WEB device. This system provided the necessary stability and helped overcome challenges associated with tortuous anatomy in most cases. We also found that proper device size selection was of utmost importance, which is done according to templates provided by the manufacturer, based on measurements of the geometric characteristics of the aneurysm in two orthogonal planes. For the most accurate measurements, intra-arterial 3D rotational angiography is necessary.

Data regarding the total fluoroscopy time during WEB procedures were analyzed, with the observed average value being 24.59 minutes (SD ± 13.21). Spearman correlation analysis did not find any statistically significant relationship between fluoroscopy time and the bifurcation angle ($p = 0.535$), as well as between the dome-to-neck ratios ($p = 0.388$) and aspect ratios ($p = 0.102$) with fluoroscopy time. When compared to other endovascular methods such as unassisted or stent-assisted coiling, which require more complex navigations, catheterizations of multiple arterial vessels, and the delivery of a set of implants, the procedure with WEB is simpler from a technical standpoint and consequently associated with shorter procedure times and lower radiation doses (Goyal et al., 2020). In the CLARYS and WEB-IT studies, the authors reported comparable average fluoroscopy times, specifically 27 to 30.2 minutes (Arthur et al., 2019; Spelle et al., 2022).

The safety profile of using WEB in the treatment of wide-necked bifurcation cerebral aneurysms has been investigated in various studies, including patients with both ruptured and unruptured aneurysms. The results of such studies show relatively similar safety levels with minor variations. The high safety of the method is demonstrated, for example, in the WEB-IT study, a prospective, multicenter study conducted in 21 centers in the United States and 6 in Europe, specifically investigating the safety and effectiveness of WEB in treating bifurcation cerebral aneurysms. In the study over a 1-year period, no deaths related to the procedure were observed, and the only clinically significant event that occurred was a parenchymal cerebral hemorrhage in one patient (0.7%) (Arthur et al., 2019). Another large series of patients was examined in studies such as WEBCAST, WEBCAST 2, and the French Observatory. Despite the short clinical follow-up period, the results are more or less comparable to our series, as they study mainly patients with unruptured cerebral aneurysms. Reported mortality and morbidity rates related to the procedure were low, at 0% and 1.2%, respectively (Pierot et al., 2015, 2017; Pierot, Costalat, Moret, Szikora, Klisch, Herbreteau, Holtmannspötter, Weber, A. C. Januel, et al., 2016). In the WEBCAST and WEBCAST 2 studies, there are available data on the clinical status of patients at long-term follow-up (3 years). The mortality rate related to the procedure in these studies was within the range of 1.27%, and the morbidity rate was 1.3% (Pierot, Costalat, Moret, Szikora, Klisch, Herbreteau, Holtmannspötter, Weber, A. C. Januel, et al., 2016; Pierot et al., 2017). In a study conducted in the United Kingdom by Lawson et al., 2017, safety in the application of WEB was investigated, including patients with both ruptured and unruptured aneurysms. The final assessment period for clinical status was 3 months after the procedure, with an observed mortality rate of 5% and a morbidity rate of 6%. The reported values also include complications related to the underlying condition, namely subarachnoid hemorrhage and its associated consequences. Despite the relatively good final outcome in terms of the patient‘s clinical status, as measured by the mRS scale, different complications related to the use of WEB were reported. In most cases, complications associated with the use of WEB were thromboembolic, regressed over time, and did not lead to a change in the patient‘s clinical status. Other complications encountered less frequently included intraoperative rupture, implant protrusion, and technical issues related to the premature and unintended release of the implant. Most of the described adverse events remained asymptomatic and did not require subsequent treatment.

In our study, patients did not experience thromboembolic or hemorrhagic complications related to the use of WEB. The procedure was uncomplicated in 38 out of 41 treated patients (92.7%). Complications directly related to the intervention were documented in two patients (4.9%), and they were classified as mild, consisting of subcutaneous hematoma at the puncture site, which did not require additional treatment. One patient (2.4%) experienced a fatal outcome in the postoperative period, unrelated directly to the use of the implant (pulmonary thromboembolism). The mean values of the preoperative mRS score in the group were 1.76 (SD ± 0.57). There was no observed change in the somatic and neurological status of the patients during clinical follow-up after the procedure and at six months. The mean mRS values within the early postoperative period in the group were 1.80 (SD ± 0.90), and upon assessment at the six-month mark, it was 1.68 (SD ± 0.62). When Wilcoxon‘s test was conducted, there was no statistically significant difference in the mean values of the preoperative mRS score and the mRS score calculated during the six-month follow-up ($p = 0.317$). Despite the small number of patients included in this study, the results confirm the high levels of safety associated with the use of WEB in the treatment of unruptured bifurcation aneurysms with wide necks, as described in the literature.

In most of the studies investigating the use of WEB, the scale used to assess the achieved occlusion of treated aneurysms corresponds to the one applied in our study. This scale is a three-step scale with the following categories: total occlusion, residual aneurysm neck, and residual aneurysm. For the dynamic assessment of the long-term treatment effect, a simplified three-step scale was also used, categorizing changes in the degree of occlusion as improvement, worsening, and stable occlusion. There is no unified protocol regarding the timing of angiographic follow-ups and the imaging method to be used. The most commonly used first method is digital subtraction angiography, followed by MR angiography and CT angiography. The available studies investigating the effectiveness of WEB in the treatment of wide-necked bifurcation aneurysms show promising results. The French Observatory is a prospective multicenter study that primarily includes unruptured cerebral aneurysms (81.0%) with wide necks located at arterial bifurcations. The period for evaluating the angiographic outcome of the treatment is six months. The authors report a relatively high percentage of adequate occlusion achieved through treatment, which is 79.31% (46/58). In the WEBCAST study, the assessment of treatment outcomes was conducted both post-procedure and at six months, showing significant improvement in the degree of occlusion during the study period (Pierot, Costalat, Moret, Szikora, Klisch, Herbreteau, Holtmannspötter, Weber, Januel, et al., 2016). In the post-procedure evaluation, total occlusion was observed in 9.3% (4/48), residual neck in 25% (12/48), and residual aneurysm in 66.7% (32/48) of cases. The evaluation at six months demonstrated total occlusion in 56.1% (23/41), residual neck in 29.3% (12/41), and residual aneurysm in 14.6% (6/41). Similar results were observed in the WEBCAST 2 study, where the first evaluation of treatment outcomes was performed after one year. Total occlusion was observed in 54% (27/50), residual neck in 26% (13/50), and residual aneurysm in 20% (10/50). The longest documented follow-up period for the effects of treated aneurysms with WEB is at the third year following treatment, and data have been summarized from three studies: WEBCAST, WEBCAST 2, and the French Observatory. Among the patients available for follow-up at the third year, total occlusion was observed in 50.8% (31/61), residual neck in 32.8% (20/61), and residual aneurysm in 16.4% (10/61). Adequate occlusion (total occlusion and residual aneurysmal neck) at the final follow-up was achieved in 83.61% (51/61). When assessing the dynamics during the follow-up period, 77% (47/61) of aneurysms remained unchanged in occlusion, improvement in occlusion was observed in 9.8% (6/61), and worsening in occlusion occurred in 13.1% (8/61) (Pierot et al., 2015, 2017; Pierot, Costalat, Moret, Szikora, Klisch, Herbreteau, Holtmannspötter, Weber, Januel, et al., 2016). High levels of occlusion are reported by Papagiannaki et al., 2014, and Mine et al., 2018, with a mean follow-up period of 5.3 months for Papagiannaki and 25 months for Mine. The observed levels of total occlusion for Papagiannaki and Mine are 56.9% (37/56) and 72.3% (34/47), respectively, while residual neck is documented at 35.4% (23/65) and 27.7% (13/47), respectively.

In the patients we studied, the initial assessment of the treatment effect within the group was performed during the postoperative hospital stay through MRI of the brain. A total of 38 (92.7%) out of the initial 41 patients were examined, with 28 (73.68%) showing total aneurysmal occlusion, 8 (21.05%) having a residual neck, and 2 (5.26%) displaying a residual aneurysm. The second follow-up imaging study was conducted on average 6 months after the procedure, with 36 (87.8%) of the treated patients being available for follow-up. Among these patients, 17 (47.2%) underwent conventional cerebral angiography, while 19 (52.8%) had an MRI as the method for assessing treatment outcomes. Of the patients followed up in the second assessment, 25 (69.4%) showed total aneurysm occlusion, 8 (22.2%) had a residual aneurysmal neck, and 3 (8.3%) had a residual aneurysm. The final degree of occlusion in the group was defined as adequate (total occlusion or aneurysm with a residual aneurysmal neck) in 33 out of 36 patients (91.7%), while 3 out of 36 (8.3%) of the patients available for the second angiographic follow-up showed a residual aneurysm. Despite the short follow-up period for assessing the treatment outcomes, the last follow-up showed high levels of adequate occlusion. In the literature, the longest reported follow-up period is 3 years after the procedure. The fact that the majority of aneurysms, 77.7%, remained unchanged in the degree of occlusion is indicative of the good long-term treatment effect. The limited data regarding follow-up in our sample are due to the prospective nature of data collection and processing for patients treated with the WEB device. Data collection began during the development of the dissertation, and further late follow-ups for long-term treatment effects are yet to be conducted. Regarding changes in the degree of occlusion during angiographic follow-up, 26 of the patients (74.3%) showed no dynamic changes, and the occlusion remained stable, while 4 patients (11.4%) showed improvement in the degree of occlusion, and 5 patients (14.3%) showed deterioration in the degree of occlusion. No statistically significant relationship was found between the final degree of occlusion and the location of the aneurysms in the group (p = 1.000).

Group 2 – patients treated via permanent stent-assisted coiling

Stent-assisted coiling is one of the early methods introduced in endovascular neurointerventions to address the challenges in treating complex cerebral aneurysms, particularly those with a wide neck and located at arterial bifurcations. In such cases, the bifurcation vessels are typically incorporated to varying degrees into the neck of the aneurysm, making unassisted coiling practically impossible without protrusion of the coil mass into local anatomical structures. In these situations, the technique of stent-assisted coiling becomes crucial. In stent-assisted coiling, the permanently implanted devices serve not only as a mechanical barrier to prevent herniation of the coil mass but also as a matrix upon which endothelial cells proliferate – a process that also influences the optimal therapeutic effect. There are nuances in the technical execution of stent-assisted coiling. Variations have been described regarding the number and type of implants used, as well as the configuration they assume in relation to each other. For bifurcation cerebral aneurysms, it has been observed that implanting stents in the vascular branches is associated with changes in their geometry, specifically a reduction in the bifurcation angle, and consequently, the hemodynamic stress applied to the aneurysmal sac. The choice of technique usually depends on the anatomical characteristics of the specific patient and the preferences of the operator.

In the cases included in your dissertation, permanent stent-assisted coiling was performed using two types of implants: Neuroform Atlas and LVIS EVO, applied both independently and in different configurations. In 73.2% of cases (41/56), aneurysms were treated using a single Atlas stent. For the treatment of 16.1% (9/56) of aneurysms, two Atlas stents were used, positioned in a Y-configuration. In one case, or 1.8%, both Atlas implants were placed in an X-configuration. In 7.1% (4/56) of cases, aneurysms were treated with a single LVIS stent. In one case, embolization of the aneurysm was performed using a combination of both types of devices – Atlas and LVIS – table 13. The documented average number of coils used in the procedures was 5.44 (SD ± 1.88). Due to the predominance of single-device usage in 73.2% of cases and the fact that many aneurysms were located on the middle cerebral artery, it was not possible to establish a significant trend towards the application of a specific device or configuration based on aneurysm location ($p = 0.118$) – table 14. In patients where aneurysms were treated with two implants in an X- or Y-configuration, higher average values of the bifurcation angle were observed: 224.72° (SD ± 42.94).

Table 13. Types and configurations of implants used in stent-assisted coiling

Device used	N	%
Single Atlas implant	41	73,2
Single LVIS EVO implant	4	7,1
Two Atlas implants in Y-configuration	9	16,1
Two Atlas implants in X-configuration	1	1,8
Simultaneous use of Atlas and LVIS EVO	1	1,8
Total	56	100,0

Table 14. Exact Fisher test examining the dependence between the type and configuration of the used devices and the localization of the treated aneurysms

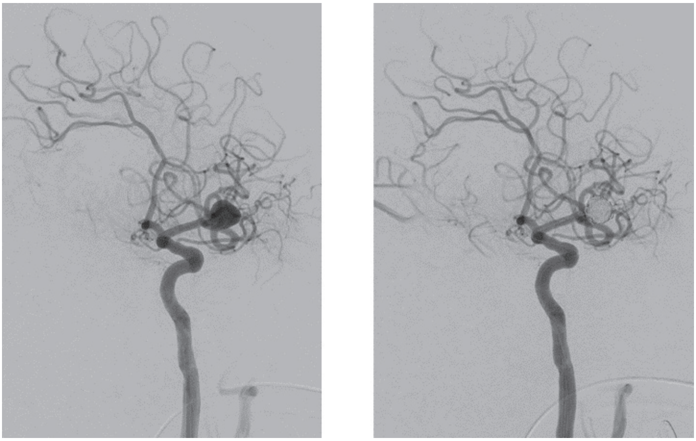
Type of device		Localization of the aneurysm				Total	p
		AcomA	MCA	Basi-lar tip	ACA		
Single Atlas	N	16	22	3	0	41	0,118
	%	76,2%	73,3%	75,0%	0,0%	73,2%	
Single LVIS EVO implant	N	0	2	1	1	4	
	%	0,0%	6,7%	25,0%	100%	7,1%	
Two Atlas implants in Y-configuration	N	3	6	0	0	9	
	%	14,3%	20,0%	0,0%	0,0%	16,1%	
Two Atlas implants in X-configuration	N	1	0	0	0	1	
	%	4,8%	0,0%	0,0%	0,0%	1,8%	
Simultaneous use of Atlas and LVIS EVO	N	1	0	0	0	1	
	%	4,8%	0,0%	0,0%	0,0%	1,8%	
Total	N	21	30	4	1	56	
	%	100%	100%	100%	100%	100%	

In none of the patients included in the group were technical difficulties observed related to the successful delivery of the implants and embolization of the target aneurysm. According to the literature, technical success in stent-assisted coiling of wide-necked bifurcation cerebral aneurysms varies between 91% and 100% (Yavuz et al., 2013; Bartolini et al., 2014; Ciccio et al., 2019; Jankowitz et al., 2019; Weinberg et al., 2020). The most common technical challenges are associated with catheterization of the vessels forming the arterial bifurcation and the proper delivery of the implants. For example, in their series of 97 patients with 100 wide-necked bifurcation cerebral aneurysms treated with X- or Y-stent-assisted coiling, Bartolini et al., 2014, reported technical problems in 9% of the treated aneurysms (9/100), leading to the following complications: 2 vessel perforations during catheterization attempts, 2 herniations of the implant in the direction of the aneurysmal sac, and 5 cases of improper implant delivery. The reported technical difficulties are associated with challenging navigation and catheterization of smaller and more angulated vessels and difficulties in assessing the proper positioning of the proximal part of the stent. Yavuz et al., 2013, reported a technical success rate of 98.5% in the treatment of 188 patients with 193 intracranial bifurcation aneurysms, with the aneurysms in the presented cohort being treated with two implants applied in a Y-configuration. The observed 3 technically unsuccessful cases were related to the inability to pass through the mesh of the first already-implanted stent to deliver the second. In these cases, the procedure was completed using stent-assisted coiling with a single stent. The presented data in both studies are related to the application of implants such as Enterprise, Neuroform, LVIS, and Solitaire. In series investigating the outcomes of using the Atlas stent, the observed technical success rate is higher, reaching up to 100% (Ciccio et al., 2019; Jankowitz et al., 2019; Maus, Weber, and Fischer, 2021). In a study conducted in the USA in 2018, examining the use of the LVIS implant for the treatment of cerebral aneurysms, mainly bifurcation aneurysms (58.9%), with wide necks (average neck size 4.2 ± 1.4 mm), the authors also reported a high technical success rate of 97.3% (149/153). The reported difficulties are associated with suboptimal implant positioning and its incomplete deployment. None of the unsuccessful attempts led to clinical or neurological consequences (Fiorella et al., 2019). Specific challenges in performing endovascular procedures are more commonly observed when two implants are required in different configurations. In these cases, it is recommended to initially catheterize the potentially more challenging arterial branch, namely the one forming a sharper angle with the main pre-bifurcation vessel or the branch with a smaller diameter. In cases where catheterization of one of the vessels forming the bifurcation is impossible or when the aneurysmal sac originates eccentrically from the bifurcation, meaning the neck is more incorporated into one branch, embolization of the aneurysm can still be successfully performed using only one implant, which protrudes gently into the aneurysm (Weinberg et al., 2020; Maus, Weber, and Fischer, 2021).

In the patient group we studied, the procedures were longer compared to other groups, with an average fluoroscopy time for the endovascular procedure of 45.75 minutes (SD ± 18.96). A correlation analysis using Spearman‘s rank correlation coefficient did not reveal a statistically significant relationship between fluoroscopy time and the bifurcation angle ($p = 0.096$), as well as between the dome-to-neck ratio ($p = 0.858$) and aspect ratio ($p = 0.457$) with fluoroscopy time.

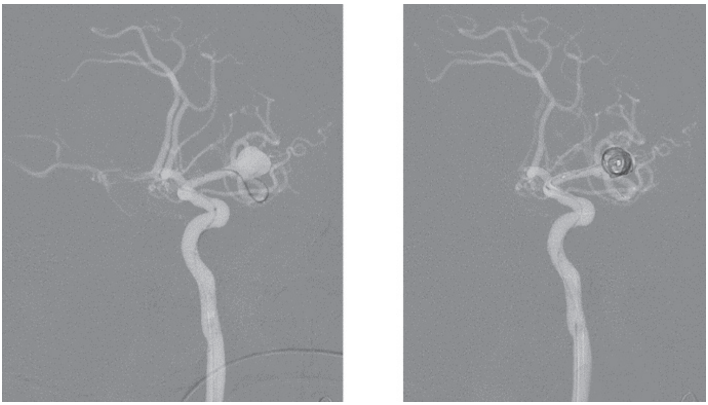
The patients we studied had an average preoperative mRS score of 1.5 (SD ± 0.69). In the early postoperative period, the average mRS score was 1.53 (SD ± 0.71). A Wilcoxon signed-rank test did not show a statistically significant difference between the preoperative mRS scores and the mRS scores calculated at the six-month follow-up after the intervention ($p = 0.180$). Procedure-related complications were observed in 5 (8.9%) of the treated patients, including three mild complications (5.4%) characterized by puncture hematoma that did not require additional treatment, and two thromboembolic complications (3.5%). One of the cases involved a patient with an aneurysm at the basilar tip. During the postoperative period, a change in the level of consciousness was observed in this patient, and a CT scan of the head confirmed a cerebral infarction in the left cerebellar hemisphere. The patient was discharged in satisfactory somatic and neurological condition with a mRS of 1. One patient developed sensory-motor aphasia of thromboembolic origin after the treatment of a large aneurysm on the left middle cerebral artery, as shown in Figures 10-13. During long-term clinical follow-up, improvement in neurological symptoms was observed in this patient, with complete resolution of the sensory component and regression of the motor component.

The specific features of performing endovascular embolization for complex cerebral aneurysms using permanent stent-assisted coiling, such as catheterization and selective navigation in distal branches, as well as the frequent implantation of at least two intraluminal devices, are associated with inherent risks of complications. Clinical data on the safety of this method are available from several studies and meta-analyses, examining the use of various types of implants for various aneurysm locations and patient characteristics. The results obtained from the MAPS study provide comparative data on the safety and angiographic outcomes of stent-assisted coiling versus non-assisted coiling. The re-



A B

Figure 10. A patient with an endovascularly embolized, saccular aneurysm at the bifurcation of the left middle cerebral artery. A – working projection before embolization, B – after embolization, through permanent stent-assisted coiling



A B

Figure 11. Technical steps of the procedure. A – selective catheterization of the lower M2 segment of the bifurcation, B – delivery of coils into the aneurysmal sac

searchers found that over a 1-year follow-up period, the two groups did not significantly differ in the total number of procedure-related adverse events, but there was a significant difference in the frequency of ischemic strokes, which were observed more frequently in the stent-assisted coiling group (8.8% vs. 2.2%, p = 0.005). The patients included in the stent-assisted coiling group had a preoperative compromised general condition, and previous cerebrovascular and cardiovascular incidents were documented in them. The combination of these factors, as well as the described variations in the protocol regarding the duration of antiplatelet therapy, could explain the observed differences in the safety of the methods (Hetts et al., 2014). A lower percentage of complications was reported by the team of Yavuz et al. in 2013, which investigated the application of two stents in bifurcation cerebral aneurysms. The authors report a cumulative complication rate of 4.8% (9/198), with one case resulting in death due to intraprocedural aneurysmal rupture (0.5%). The remaining cases are related to acute in-stent thrombosis, with reversal observed after intravenous Tirofiban administration. One case of SAH is reported, and two cases are associated with patient non-compliance and premature discontinuation of antiplatelet therapy. Permanent neurological deficits were observed in 2 patients (1.1%). Stent-assisted coiling was further investigated in a meta-analysis conducted by Cagnazzo et al. in 2019, focusing on Y-stent-assisted coiling. Complications were recorded in 8.9% (61/614) of patients, and the reported mortality related to the treatment was 1.1% (5/668). However, permanent neurological deficits were observed in only 2.4% (18/540). The most commonly observed complications were ischemic complications (6.5%, 44/594), followed by acute in-stent stenosis (2.1%, 20/577), and hemorrhagic complications (2%, 11/594). Among the implants used in the analysis, Enterprise, Neuroform, LVIS, Solitaire, and Acclino flex were utilized, with the use of Enterprise being associated with a lower complication rate compared to other implants. Safety data regarding the use of LVIS were investigated in a recent study by Fiorella et al. in 2019. Permanent neurological deficits were documented in 5.2% (8/153) of patients, and procedure-related mortality was 1.3% (2/153). The use of the Atlas implant was associated with complications, reaching up to 12.7%. In a prospective study examining the application of the Atlas stent in X- and Y-configurations, conducted by the team of Ciccio et al. in 2019, symptomatic complications were observed in 7 out of 55 patients (12.7%), distributed as follows: 4 thromboembolic complications, 1 stent occlusion, and 2 hemorrhagic complications. No reported deaths were associated with Atlas stent use.

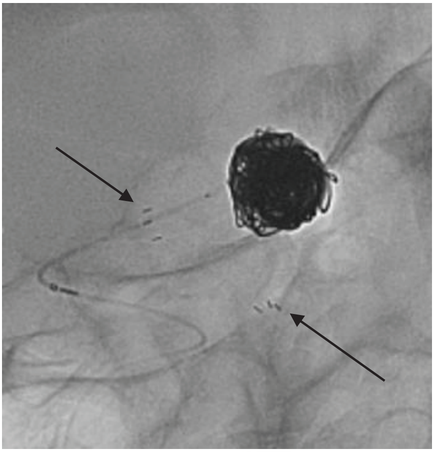


Figure 12. Fluoroscopic image demonstrating the final result. The arrows indicate the radiopaque markers on the implanted Atlas stent

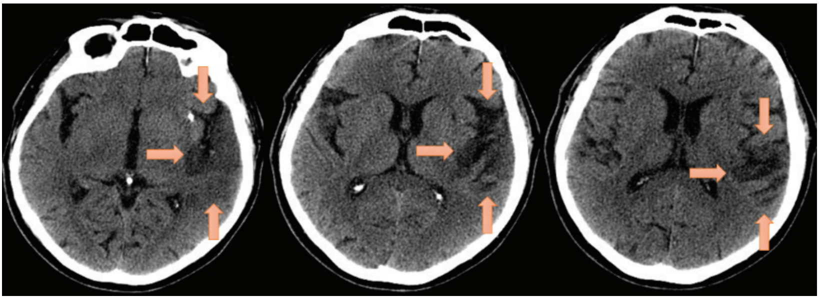


Figure 13. Non-contrast head CT after the procedure. The area between the arrows indicates the zone of ischemic cerebral infarction

A total of 38 out of the 56 patients, or 67.86%, were available for follow-up to assess the treatment‘s effects. The first follow-up imaging examination was scheduled for six calendar months after the endovascular intervention. In 31 of the patients (81.6%), the first follow-up was performed using conventional cerebral angiography, while in 6 patients (15.8%), an MRI examination was conducted, and in 1 patient (2.6%), a CT angiography was performed. The results from the early follow-up showed the following levels of occlusion: total occlusion was observed in

28 of the patients (73.68%), 5 patients (13.16%) had residual aneurysmal neck, and another 5 patients (13.16%) had residual aneurysm. The second follow-up was conducted 12 months after the therapeutic procedure, with 32 patients (84.2%) having the treatment's effect assessed through conventional cerebral angiography, and 6 patients (15.8%) undergoing a second follow-up using MRI. Total occlusion was found in 32 patients (84.21%), residual aneurysmal neck in 2 patients (5.3%), and residual aneurysm in 4 patients (10.53%) at the last available follow-up. The results obtained in this dissertation regarding aneurysm occlusion and changes in the course of radiological follow-up are consistent with those published in the literature for stent-assisted coiling. The meta-analysis conducted by Cagnazzo et al., 2019, at that time, examined the largest number of patients with bifurcation cerebral aneurysms treated with Y-stent-assisted coiling. The average follow-up period for patients was 14 months, and the authors reported high levels of achieved final occlusion at 95.4% (564/598), with reocclusion rates at 3% (20/496). The researchers observed the typical trend of improvement in occlusion levels compared to the initial follow-up examination, as is characteristic of stent-assisted coiling. The observed lower occlusion levels at the initial follow-up are believed to be due to the fact that the patient is on dual antiplatelet therapy, which hinders aneurysm sac occlusion. The improvement in occlusion levels during follow-up is thought to be related to the gradual reduction of dual antiplatelet therapy to mono-antiplatelet therapy (Piotin et al., 2010; Maldonado et al., 2011). Regarding the dynamics of the occlusion degree compared to the first and last follow-up, the following dependencies were observed: stable occlusion or no change was observed in 32 (84.2%) of patients, improvement in the degree of occlusion was observed in 4 patients (10.5%), and worsening of the occlusion level of the aneurysm was recorded in 2 patients (5.3%). Similar good results from the application of the technique in the treatment of wide-necked bifurcation cerebral aneurysms are also reported by Yavuz et al., 2013. When performing stent-assisted coiling using two implants, the authors found the following final angiographic results: total occlusion in 95.7% of patients (178/186), residual aneurysm neck in 2.2% (4/186), and residual aneurysm in 2.2% (4/186). The documented results are for a period of 6 months to 1 year after the embolization, with a tendency for improvement in the degree of occlusion during follow-up. Significant improvement in occlusion levels

is reported by Bartolini et al., 2014, from an initial total occlusion rate of 47.6% (50/105) to total occlusion in 85.8% (73/85) at the second and third follow-up examinations, respectively, at the first and third year after the endovascular intervention. The experience from these series shows that patients treated with permanent stent-assisted coiling benefit from long-term follow-up. Even if the initial angiographic results are discouraging, significant improvement in occlusion can be achieved.

Group 3 – patients treated with „flow-diverter“ stent

Intraluminal devices redirecting blood flow from an aneurysm, commonly known as „flow-diverter“ stents, have demonstrated their effectiveness in treating unruptured cerebral aneurysms, primarily located along the internal carotid artery. Evidence of high rates of occlusion and the low associated risk with the use of these implants has been presented in several multicenter prospective studies involving a large cohort of patients with aneurysms that would be technically challenging and unfeasible to treat using other conventional endovascular or neurosurgical methods (Becske et al., 2013, 2017; Hanel et al., 2020; Bonafe et al., 2022). The observed high percentage of definitively cured cerebral aneurysms with this method and documented acceptable levels of periprocedural complications have led to an expansion of the indications for the application of „flow-diverter“ technology. Of particular interest is the study of the applicability of these devices in the treatment of wide-necked bifurcation cerebral aneurysms. This interest is driven by the fact that the available endovascular methods at that time were not sufficiently effective in treating such types of lesions. The mechanical structure of „flow-diverter“ devices, composed of closely spaced mesh-like structures, achieves the therapeutic effect on the target aneurysm by reducing blood flow and creating stasis within the aneurysm sac, processes that lead to progressive thrombosis of the aneurysm. Examination of histological specimens has revealed that the implant itself serves not only as a mechanical barrier but also as a matrix upon which adjacent endothelial cells develop and proliferate (Liu et al., 2021). The described processes of interaction between the intraluminal implant and the vessels in the intracranial circulation where it is deployed raise questions about the fate of the arterial branches covered by the device in cases of aneurysms located at bifurcations. This is one of the reasons why the application of „flow-diverter“ devices in the treatment of bifurcation cerebral aneurysms should be approached with caution.

The application of implants in the treatment of bifurcation cerebral aneurysms is associated with high levels of reported technical success, ranging from 92% to 100% in the literature (Aguilar Pérez et al., 2017; Cagnazzo et al., 2019a; Limbucci et al., 2020). In most of these series, the Pipeline device was used. The use of p64 has been documented in a smaller series of patients, primarily for aneurysms located on the middle cerebral artery, and Bhogal et al. did not report cases of impossible implant delivery (Bhogal et al., 2017). Yavuz et al. describe technical problems with the delivery of the Pipeline in 8%, or 2, of the patients, with difficulties related to distal end migration of the device and inadequate coverage of the aneurysmal neck (Yavuz et al., 2014). In our series of 54 patients treated with intraluminal flow-modulating devices, we observed high levels of technical success, with successful implantation achieved in 52 cases, resulting in a technical success rate of 96.3%. The observed technical difficulties were related to the inability to adequately deliver the implant and its twisting or improper positioning immediately before its final implantation. In these cases, the implants were successfully removed from the cerebral circulation without compromising intracranial circulation. Patients in whom the implant was not successfully delivered were excluded from the study. In the majority of cases, the p64 implant was used (Table 15). The procedures involving „flow-diverter“ devices were relatively short, with average fluoroscopy times of 24.87 minutes (SD ± 11.48). There was no significant difference observed in fluoroscopy times based on the location and bifurcation angle of the aneurysm ($p = 0.514$).

Table 15. Percentage distribution of the type of device used in the group

Type of device used	N	%
p48	16	29,6
p64	38	70,4
Total	54	100,0

The endovascular procedure using a „flow-diverter" stent for wide-necked bifurcation cerebral aneurysms presents certain characteristics. Specifically, these types of lesions are located in areas rich in perforating arteries, such as the anterior communicating artery, the terminal segment of the internal carotid artery, the tip of the basilar artery, and the middle cerebral artery. Additionally, during the procedure, there is unavoidable coverage of a branch of the arterial bifurcation by the implant. These specifics raise questions about the safety of using flow-diverting stents for the treatment of aneurysms with such localization. The available comparative data from the literature regarding the safety of this method show a wide range of reported complication rates. For example, in the series by Caroff et al., the results regarding procedure-related complications are not encouraging. The authors reported the occurrence of new neurological deficits in 43% of cases, which were confirmed by small areas of diffusion restriction on MRI. Permanent neurological deficits were observed in 3 patients, or 21%, with no reported deaths (Caroff et al., 2016). On the other hand, Michelozzi and colleagues reported a better safety profile, with permanent deterioration of the condition observed in 3.2% (1/29) of treated patients (Michelozzi, Darcourt, Guenego, A. C. Januel, et al., 2019). In a single-center study of 13 patients with aneurysms located on the middle cerebral artery, primarily treated with the p64 device, Bhogal reported complications in 7.7%, with one patient experiencing an ischemic stroke with hemiparesis, which the author attributed to a post-procedural drop in blood pressure (Bhogal et al., 2017). More detailed data regarding the safety profile of „flow-diverter" implants in the treatment of bifurcation cerebral aneurysms are available from meta-analyses conducted by Cagnazzo and colleagues (Cagnazzo et al., 2017, 2019a, 2021; Limbucci et al., 2020). The authors investigated the use of these devices separately for aneurysms located on the anterior communicating artery, middle cerebral artery, and bifurcation of the internal carotid artery. In their meta-analysis of aneurysms located on the anterior communicating artery, researchers found procedure-related complications in 8.6% of cases (14/126), with thromboembolic complications being the most common at 6%, compared to hemorrhagic complications at 3% (Cagnazzo et al., 2019 In their meta-analysis for aneurysms located on the middle cerebral artery, the observed complications were higher, occurring at a frequency of 20.7%, with permanent deterioration in the condition observed in 10% of cases. Again, thromboembolic complications were the most common, followed by perianeurysmal inflammatory reactions and hemorrhagic complications (Cagnazzo et al., 2017). The meta-analysis conducted by Cagnazzo and colleagues regarding the application of implants for aneurysms at the bifurcation of the internal carotid artery included a small number of patients – 20, with 20 unruptured cerebral aneurysms. The results of the study showed a lack of early and late peri-procedural complications and no reported deaths associated with the use of these devices (Cagnazzo et al., 2021). The same group of authors conducted a comparative meta-analysis on the application of implants for aneurysms with distal locations, including aneurysms in the anterior communicating artery, middle cerebral artery, and distal segments of the anterior cerebral artery (Limbucci et al., 2020). The results of the analysis showed that procedure-related complications occurred in 12.5% of patients (63/410), with the highest frequency observed in aneurysms located in the middle cerebral artery (18% – 44/231) and the lowest in aneurysms in the anterior communicating artery (8% – 14/126). Permanent clinical status changes were associated with 5.4% of complications (29/418). Procedure-related deaths were observed in 2.2% of cases (5/374). Once again, there was a trend of thromboembolic complications being the most common (9.9%), followed by hemorrhagic complications and complications related to premature discontinuation of dual antiplatelet therapy, at 2.6% and 2.8%, respectively. In our studied patient series, the observed levels of periprocedural complications and clinical deterioration were lower than those previously documented in the literature. The procedure concluded without complications in 94.2% of cases (49/52). The mean values of the preoperative mRS score in the group were 1.07 (SD ± 0.75). When calculating the postoperative mRS score, a mean value of 1.13 (SD ± 0.95) was observed. The average mRS score at the six-month follow-up was 1.02 (SD ± 0.64). After conducting a Wilcoxon test, no statistically significant relationship was observed between the preoperative mRS score and the mRS score calculated six months after the intervention ($p = 0.988$). Complications directly related to the intervention itself were observed in 3 patients in the group (5.6%). Two of the complications (3.8%) were mild, represented by a small hematoma at the puncture site that did not require additional treatment. In one patient, a retroperitoneal hematoma was detected in the postoperative period. After active conservative treatment, the patient was discharged in a satisfactory overall condition – Figure 14. No thromboembolic or hemorrhagic complications related to the intervention were observed. In one patient, exitus occurred in the postoperative period, unrelated to the intervention itself.

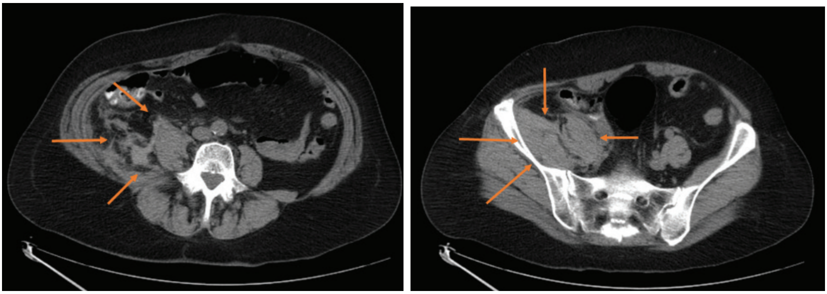


Figure 14. Post-procedural complication – retroperitoneal hematoma, demonstrated on abdominal and pelvic CT scan – axial section. The retroperitoneal hematoma that occurred post-procedure is indicated between the arrows

Out of the treated patients, 43 were available for assessment of the treatment effect. The average time for the first follow-up imaging was 7 months. In 30 of the patients (69.8%), conventional angiography was performed as the imaging method for the first follow-up, and in 13 of the patients (30.2%), MRI was used. The observed levels of occlusion at the first follow-up were as follows: total occlusion was observed in 20 (46.51%) of the patients, residual aneurysm neck in 1 (2.33%), and residual aneurysm in 22 (51.16%). The last follow-up imaging was conducted in 41 of the patients, with an average time for the follow-up of 21 months (SD ± 4). Conventional angiography was performed in 34 of the patients (82.9%), and MRI in 7 (17.1%). The analysis of the treatment effect at the last follow-up showed the following results: total occlusion in 22 of the patients (53.66%), residual aneurysm neck in 5 (12.2%), and residual aneurysm in 14 of the patients (34.15%). The final degree of occlusion in this group is as follows: adequate occlusion was achieved in 27 of the patients (65.9%), and a residual aneurysm was present in 14 (34.1%) of the participating patients. The observed dynamics in the degree of occlusion during the follow-up are as follows: stable occlusion or no change was observed in 28 of the patients (68.3%), and the remaining 13 patients (31.7%) showed an improvement in the degree of occlusion. The application of FD implants in the treatment of bifurcation cerebral aneurysms has been mainly studied in heterogeneous groups in studies primarily of retrospective nature. The documented levels of occlusion vary among different authors. In their series, Michelozzi shows high levels of total occlusion in the treated aneurysms – 82.1%, which reaches 91.7% at the last follow-up (Michelozzi, Darcourt, Guenego, Januel, et al., 2019). Similar good results and improvement in the degree of occlusion at longer-term follow-up are reported in their series by Iosif et al., 2017. In the treatment of 63 aneurysms, the authors observe 68% occlusion at 6 months, which reaches 95% at the 12-month follow-up. The most extensive data on the application of FD implants in bifurcation aneurysms with different locations have been obtained from the meta-analyses conducted by the team of Cagnazzo, examining their use (Cagnazzo et al., 2017, 2019a, 2021; Limbucci et al., 2020). When comparing the degree of occlusion in the most common bifurcation locations, the authors found that the highest degree of occlusion was achieved in aneurysms located in the anterior communicating artery. Long-term adequate occlusion was observed in 87% of aneurysms in the anterior communicating artery, and in aneurysms of the middle cerebral artery, this percentage was 80%. According to the researchers, the location of aneurysms in the middle cerebral artery is a factor associated with lower occlusion rates and a higher frequency of complications.

The change in coverage with an FD implant of an arterial branch from the bifurcation is a factor related to the observed degree of occlusion. Saleme et al. specifically studied this relationship by examining the application of FD in bifurcation aneurysms, dividing patients into two groups (Saleme et al., 2014). In one of the groups, the implant covered an arterial bifurcation branch that had a direct anastomosis with the contralateral side. This group included patients with aneurysms located at the bifurcation of the internal carotid artery or anterior communicating artery. The second group of patients had aneurysms located in the middle cerebral artery or anterior communicating artery, in cases with a hypoplastic or absent A1 segment of the contralateral anterior cerebral artery. In this group, the branch covered by the implant received indirect compensation of its blood supply through leptomeningeal anastomoses, which are differently expressed in each individual and develop at different rates. The authors found that in the first group, 78.5% of patients had stenosis or occlusion of the covered arterial branches at the sixth month, which was clinically asymptomatic. In contrast, in the second group of patients, modification of arterial branches was observed in 17.4%, and it was associated with transient but completely reversible symptoms. In the first group, total occlusion was achieved in 100% of treated aneurysms at the sixth month, while in the second group, it was achieved in 87%. At the 18-month follow-up, only 1 aneurysm from the second group did not have total occlusion, which was 2.7%. One of the theories explaining the observed low levels of occlusion in bifurcation aneurysms treated with FD implants is associated with the persistence of blood flow through the covered branch of the vascular bifurcation. In experimental studies on animals conducted by Fahed et al. in 2017, it was found that performing targeted occlusion of the coverage with an FD branch from the vascular bifurcation is associated with better levels of occlusion.

An important aspect that requires discussion is the fate of the jailed branches from an arterial bifurcation when intravascular implants are applied. When an FD stent is implanted in the context of an arterial bifurcation, the persistence of blood flow through the implanted arterial branch depends on the local anatomical features of circulation and the device itself (Alderazi et al., 2014). It has been observed that in the presence of a rich collateral network, such as when treating aneurysms of the ophthalmic artery, which has a well-developed collateral network from the external carotid artery, occlusion of the ophthalmic artery does not lead to clinical symptoms (Puffer et al., 2012; Rangel-Castilla et al., 2017). Similar principles are applied in the cases mentioned above in the series by Saleme. In cases where the artery covered by the implant is a terminal branch without collateral circulation, as is the case with the anterior choroidal artery, its patency is preserved (Neki et al., 2015). Distinctive hemodynamic changes are observed in aneurysms at the bifurcation of the middle cerebral artery, where, as mentioned in the text, collateral blood circulation varies from individual to individual. In addition to anatomical features, the selected size of the implant also plays a role in determining the changes that will occur with coverage by an FD branch. As indicated by computer analysis, choosing a larger implant size than the maximum diameter of the vessel in which it will be implanted leads to higher porosity and larger stent cell sizes, which are associated with a lower risk of compromising the covered branches. The reverse relationship is also valid, where selecting an implant with a diameter smaller than the maximum vessel diameter in which it will be implanted leads to device constriction, reduced porosity/cell size, and a higher chance of compromising the blood flow in the covered branch (Berg et al., 2016). Among our patients, a total of 52 arterial branches were covered by the implants, and follow-up for the occurring changes was conducted for 35 of them – Table 16. Over the six-month follow-up period, changes were observed in 85.8% (n = 30) of the arterial branches. In 22.9% of cases (n = 8), occlusion occurred, and in 62.9% (n = 22), a reduction in the caliber of the covered branch by the implant was documented. 14.3% of the branches (n = 5) remained unchanged. In none of the patients with occluded or reduced-sized branches as a result of the treatment, the changes were symptomatic, suggesting that potential asymptomatic occlusion of small branches may be a characteristic of using these implants. This adds to the current information that intraluminal devices redirecting blood flow from the aneurysm can be used safely in aneurysms of arterial bifurcations, but this issue requires further investigation in future studies.

Table 16. Observed changes in the jailed branches

Change	**N**	**%**
Occlusion	8	22,9
Reduction in caliber	22	62,9
No change	5	14,3
Total	35	100,0

Comparison of the obtained results between the individual groups in terms of the safety of the endovascular method used

When comparing the results regarding the pre-interventional clinical status of patients in the different groups included in this study, the highest mean values, as assessed by the mRS scale, were observed in patients from Group 1 (treated with intrasaccular implant WEB), followed by patients in Group 2 (treated with permanent stent-assisted coiling), and the lowest values were documented in patients from Group 3 (treated with a flow-diverter stent). There was no statistically significant difference in the change in mRS score measured preoperatively and six months after the intervention among patients in the three groups – Table 17. No significant correlation was found between the patient‘s clinical status at the six-month follow-up and the geometric characteristics of the aneurysms in the individual groups – Table 18.

Table 17. The Wilcoxon test was used to determine the difference between the preoperative and mRS at the six-month follow-up

Group	Parameter	N	Mean	SD	Min	Max	p
Group 1	preoperative mRS	37	1,70	0,57	1,00	3,00	0,317
	mRS at six-month follow-up	37	1,68	0,58	1,00	3,00	
Group 2	preoperative mRS	44	1,41	0,66	1,00	3,00	0,180
	mRS at six-month follow-up	44	1,52	0,95	1,00	6,00	
Group 3	preoperative mRS	46	0,96	0,59	0,00	3,00	1,000
	mRS at six-month follow-up	46	0,96	0,59	0,00	3,00	

The summary safety profile for all three groups of patients was 91.9% (137/149). Procedure-related complications directly associated with the intervention were documented in 6.7% of patients (10/149). The observed mortality rate was 1.3%, with both lethal cases not directly related to the endovascular procedure itself. To assess and compare the safety profile among the different methods, a Fisher‘s exact test was conducted, which did not show a significant difference in observed complications among the individual groups (p = 0.988) – Table 19. Group 1 and Group 3 exhibited similar levels of safety, with complications occurring in approximately 7.3% and 7.7% of cases, respectively, while Group 2 had complications observed in 9% of patients.

Table 18. Spearman's correlation analysis to assess the correlation between the patient's clinical status at follow-up and the geometric characteristics of the aneurysms in the three groups

	mRS at six-month follow-up				
	Neck size (in mm)	**Aneurysm width (in mm)**	**Height of aneurysm (in mm)**	**Dome-to-neck ratio**	**Aspect ratio**
R	0,125	0,122	0,134	0,046	0,035
p	0,164	0,175	0,134	0,606	0,693

Table 19. Fisher's exact test. Percentage distribution of complications in the individual groups

Complications		Group 1	Group 2	Group 3	Total	p
Without	N	38	51	49	137	0,988
	%	92,7%	91%	92,3%	91,9%	
Mild	N	2	3	2	7	
	%	4,9%	5,4%	3,8%	4,7%	
Moderate	N	0	0	0	0	
	%	0,0%	0,0%	0,0%	0,0%	
Severe	N	0	2	1	3	
	%	0,0%	3,6%	1,9%	2%	
Death	N	1	0	1	2	
	%	2,4%	0,0%	1,9%	1,3%	
Total	N	41	56	52	149	
	%	100,0%	100,0%	100,0%	100,0%	

Comparison of the obtained results between the individual groups in terms of the effectiveness of the endovascular method used

The registered levels of occlusion in all patients studied in this dissertation are as follows: adequate occlusion (total occlusion and residual aneurysmal neck) was observed in 81.7% (94/115) of patients, and residual aneurysm in 18.3% (21/115). After conducting a chi-square test, it was found that the differences in the achieved final degree of occlusion between the individual groups are significant ($p = 0.024$) – Table 20. The highest degree of occlusion was achieved in the group of patients treated with WEB. In this group, adequate occlusion was observed in 91.7% of cases, and residual aneurysm in 8.3%. Group 2 of patients treated with permanent stent-assisted coiling also demonstrated high levels of adequate final occlusion – 89.5%. In 10.5% of the group, a residual aneurysm was present. The lowest levels of adequate occlusion were found in the group of patients treated with „flow-diverter" implants. Adequate occlusion at the last follow-up was achieved in only 65.9%, while a residual aneurysm was observed in 34.1%. The observed low levels of occlusion in Group 3 may be related to the relatively short average follow-up period of 12 calendar months. Typically, patients treated with „flow-diverter" stents are those for whom other conventional and unconventional endovascular methods are practically inapplicable or their performance is labor-intensive. The procedure of implanting an intraluminal implant redirecting blood flow is easier compared to, for example, the technique of permanent stent-assisted coiling, which involves catheterization and navigation in the bifurcation branches, as well as the aneurysmal sac. For this reason, the average fluoroscopy time during the procedures for FD stent implantation is significantly shorter (24.87 minutes, SD ± 11.48) than during stent-assisted coiling (45.75 minutes, SD ± 18.96) – Table 21.

During the follow-up period, while monitoring the dynamic changes in the degree of occlusion in the different groups, we observed a significant difference in the change in the degree of occlusion, with the most pronounced changes occurring in Group 3 – as shown in Table 22. In Group 3, there was documented improvement in the degree

Table 20. Presentation of results by groups in terms of the degree of occlusion documented at the last available follow-up

Degree of occlusion at last available follow-up		Group 1	Group 2	Group 3	Overall	p
Adequate	N	33	34	27	94	0,024
	%	91,7%	89,5%	65,9%	81,7%	
Residual aneurysm	N	3	4	14	21	
	%	8,3%	10,5%	34,1%	18,3%	
Overall	N	36	38	41	115	
	%	100,0%	100,0%	100,0%	100,0%	

of occlusion in 31.7% of cases, compared to 11.4% in Group 1 and 10.5% in Group 2. The highest stability or lack of change in occlusion was observed in Group 2 at 84.2%, followed by patients in Group 1 at 74.3% and those in Group 3 at 68.3%. Among patients treated with an FD stent, there were no cases of worsening of occlusion observed during the follow-up. The highest frequency of worsening in occlusion was documented in patients treated with WEB (14.3%). The probability of the observed higher rate of recanalization in patients treated with WEB can possibly be explained by the fact that the initial follow-up was conducted using non-contrast MRI imaging in the early postoperative period, while the second follow-up is typically performed through conventional angiography. There may be differences in the method of interpreting findings between these two approaches. After conducting the Mann-Whitney and Kruskal-Wallis tests, we found a statistically significant correlation between the geometric factors of the aneurysm and the observed changes in the degrees of occlusion during the follow-up – as shown in tables 23 and 24. We observed a trend towards worsening occlusion with an increase in the bifurcation angle, as well as with a larger size of the aneurysmal neck, height of the aneurysm, and width of the aneurysmal sac.

Table 21. Values of fluoroscopy time (in minutes) for patients in the three studied groups

Group	N	Fluoroscopy time (in min)			
		Mean	SD	Min	Max
Group 1	41	24,59	13,21	10,00	74,00
Group 2	55	45,75	18,96	18,00	112,00
Group 3	54	24,87	11,48	10,00	70,00
Total	150	32,45	18,09	10,00	112,00

Table 22. Changes in the level of occlusion during follow-up in the three studies groups

Change in the level of occlusion between the first and last available follow-up		Group 1	Group 2	Group 3	Total	p
Stable (unchanged)	N	26	32	28	87	0,001
	%	74,3%	84,2%	68,3%	77,0%	
Improvement	N	4	4	13	18	
	%	11,4%	10,5%	31,7%	15,9%	
Worsening	N	5	2	0	8	
	%	14,3%	5,3%	0,0%	7,1%	
Total	N	35	36	41	113	
	%	100,0%	100,0%	100,0%	100,0%	

Table 23. Correlation between the observed change in occlusion degree and the bifurcation angle

Group	Parameter	Change in occlusion degree during follow-up	N	Mean	SD	Min	Max	p
Group 1	Bifurcation angle	Stable	26	150,46	24,28	116,00	207,00	n/a
		Improvement	4	175,00	13,93	157,00	186,00	
		Worsening	5	159,80	34,81	114,00	191,00	
Group 2	Bifurcation angle	Stable	32	171,31	42,16	95,00	276,00	n/a
		Improvement	1	213,00		213,00	213,00	
		Worsening	3	208,00	41,61	162,00	243,00	
Group 3	Bifurcation angle	Stable	28	178,61	37,62	94,00	251,00	0,014
		Improvement	13	189,54	33,93	125,00	245,00	
Total	Bifurcation angle	Stable	86	167,38	37,50	94,00	276,00	0,048
		Improvement	18	187,61	30,41	125,00	245,00	
		Worsening	8	177,88	42,54	114,00	243,00	

Table 24. Relationship between the geometric characteristics of the aneurysms and the observed changes in occlusion degree

Parameter	Change in occlusion degree during follow-up	N	Mean	SD	Min	Max	p
Neck size (in mm)	Stable	86	4,87	2,08	2,20	14,00	0,021
	Improvement	18	5,43	1,33	3,20	8,00	
	Worsening	8	6,66	3,28	3,90	13,30	
Aneurysm height (in mm)	Stable	86	5,35	2,59	2,20	14,80	0,027
	Improvement	18	6,88	2,99	3,30	14,00	
	Worsening	8	7,68	4,89	3,40	18,30	
Aneurysm width (in mm)	Stable	86	5,79	2,64	2,40	14,80	0,005
	Improvement	18	7,98	3,26	3,20	14,50	
	Worsening	8	7,59	4,20	4,30	16,70	
Aspect ratio	Stable	86	1,13	0,41	0,40	2,40	0,403
	Improvement	18	1,28	0,50	0,50	2,60	
	Worsening	8	1,15	0,42	0,70	1,80	
Dome-to-neck ratio	Stable	86	1,20	0,29	0,80	2,30	0,070
	Improvement	18	1,48	0,50	0,80	2,40	
	Worsening	8	1,15	0,27	0,80	1,70	

Illustrative cases

Patients treated with WEB

Case 1 – figures 15, 16 and 17

Patient with incidentally discovered, unruptured, asymptomatic saccular aneurysm located at the bifurcation of the left middle cerebral artery. Digital Subtraction Angiography (DSA) and 3D rotational angiography images demonstrate a complex aneurysm with incorporation of the upper and lower M2 segments in the aneurysmal neck. The patient underwent endovascular embolization using a WEB device. Early post-procedural follow-up, performed 6 months after the treatment using MRI, shows complete obliteration of the aneurysm.

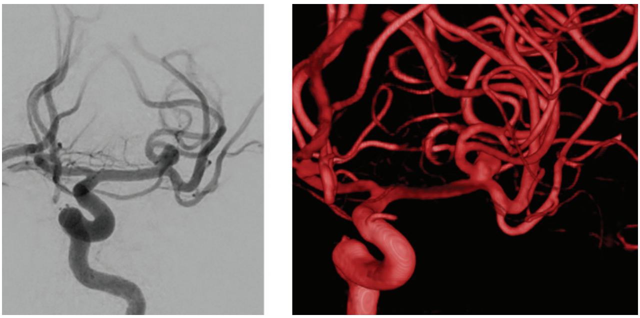


Figure 15. DSA and 3D-rotational angiography, demonstrating an aneurysm at the bifurcation of the left middle cerebral artery

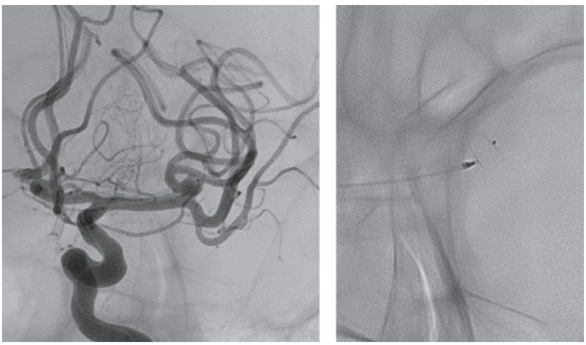
A  B

Figure 16. The final stages of endovascular embolization. A – working projection, unsubtracted angiography, with the delivered implant in the aneurysmal sac, demonstrating normal contrast material filling of the left middle cerebral artery without compromised blood flow. B – "single shot" of the device before its final deployment

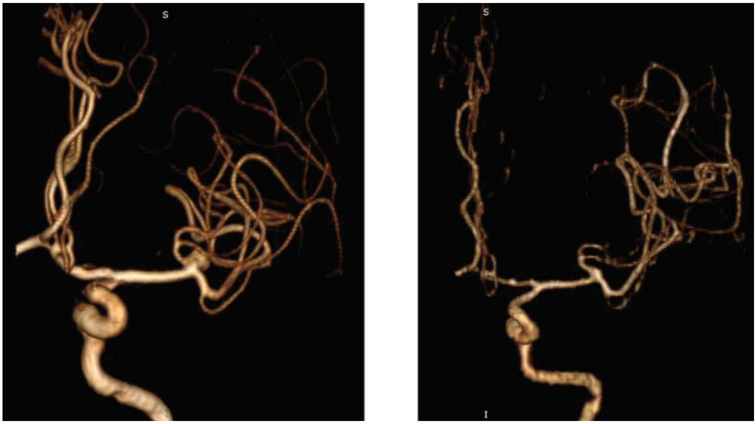
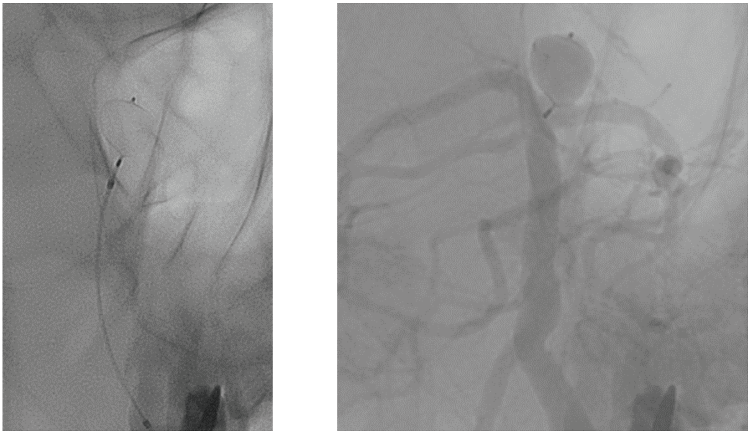
A  B

Figure 17. Preoperative (A) and postoperative (B) 3D-TOF MR angiography (VR reconstruction) demonstrating the achieved total occlusion of the aneurysm

Case 2 – figure 18, 19 and 20

Patient with incidentally discovered saccular aneurysm located at the basilar tip. Endovascular embolization of the aneurysm was performed using WEB device. Follow-up at 12 months after the procedure via MR angiography demonstrates total obliteration of the aneurysm.

Figure 18. DSA and 3D rotational angiography demonstrating a saccular aneurysm at the tip of the basilar artery



A B

Figure 19. Steps of the endovascular procedure. A – “Single shot” before the final delivery of the implant, and B – unsubtracted angiography illustrating the implant and its position entirely within the aneurysmal sac

Figure 20. 3D-TOF MR angiography (VR reconstruction) at 12 months, demonstrating complete obliteration of the aneurysm

Patients treated via permanent stent-assisted coiling

Case 1 – figures 21, 22, 23, 24 and 25

A patient with an unruptured, saccular aneurysm located at the bifurcation of the left middle cerebral artery. During the procedure, a 3D rotational angiography revealed that both M2 segments from the bifurcation were incorporated into the aneurysmal neck. In this case, the aneurysm was treated through stent-assisted coiling using two Atlas stents in a Y-configuration. Follow-up via conventional angiography at 7 months post-procedure revealed complete occlusion of the aneurysmal sac.

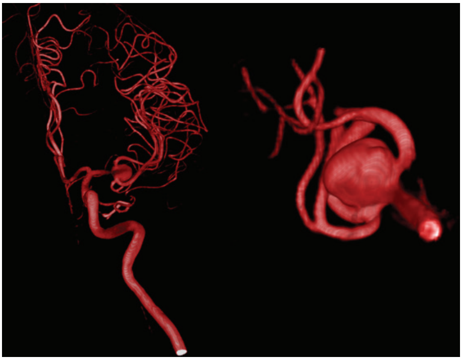
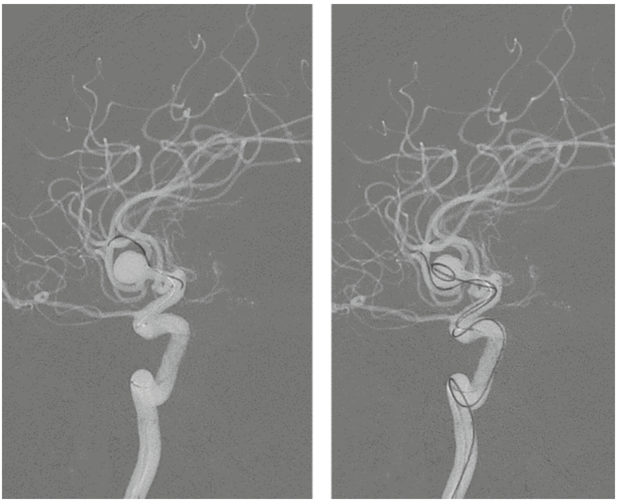
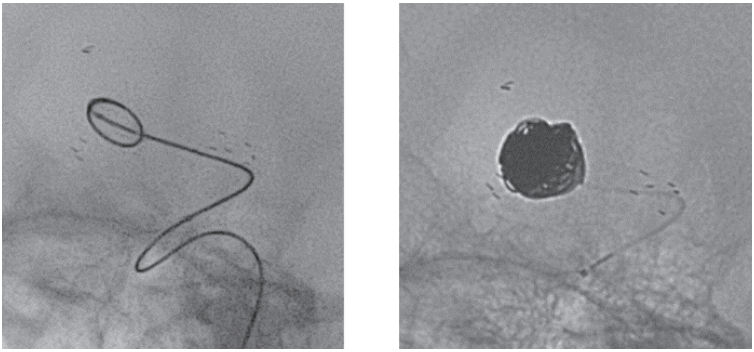


Figure 21. 3D rotational angiography demonstraring a complex, saccular aneurysm with a wide neck at the bifurcation of the left middle cerebral artery



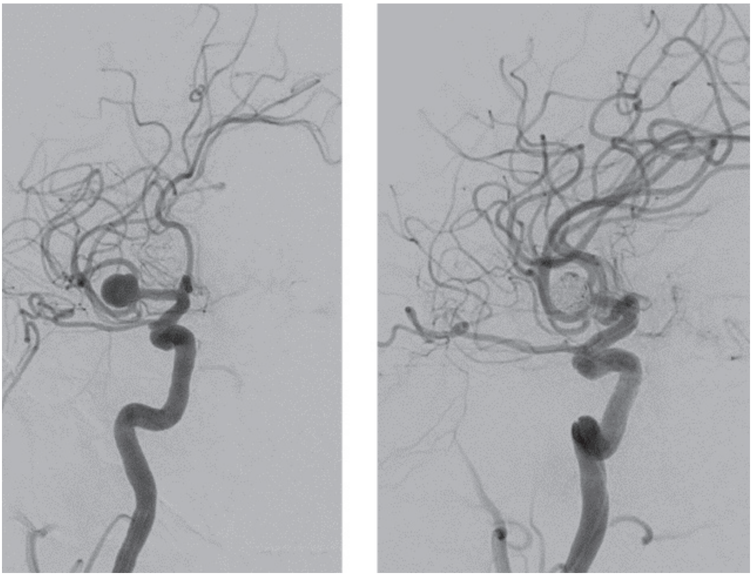
A **B**

Figure 22. Technical stages of the procedure. A – Selective catheterization of the upper M2 segment. B – Selective catheterization of the lower M2 segment and delivery of coils into the aneurysmal sac



A B

Figure 23. “Single shot” images. A – At the beginning of coiling. B – The final result with a densely formed mass of coils in the aneurysm sac



A B

Figure 24. DSA at the beginning and end of the procedure in the working projection. A – Start of the procedure. B – Working projection at the end of the procedure, demonstrating the achieved satisfactory obliteration of the aneurysmal sac

Figure 25. DSA in the working projection, at seven months post-procedure, demonstrating complete occlusion of the treated aneurysm

Case 2 – figures 26, 27, 28, 29 and 30

The clinical case involves a patient with an unruptured, incidentally discovered, saccular aneurysm located on the bifurcation of the right middle cerebral artery. The aneurysm has an indistinctly defined neck. The patient underwent Y-stent-assisted coiling, with the permanent implantation of two Atlas devices. A satisfactory obliteration of the aneurysmal sac was achieved during the procedure. The follow-up MRI conducted at the 6-month mark post-procedure confirmed the achieved total occlusion of the embolized aneurysm.

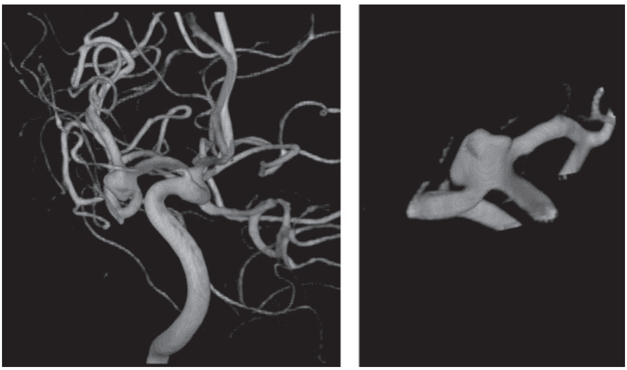


Figure 26. 3D rotational angiography providing a clear definition of the complex anatomy of the aneurysm and its relationship with adjacent vessels

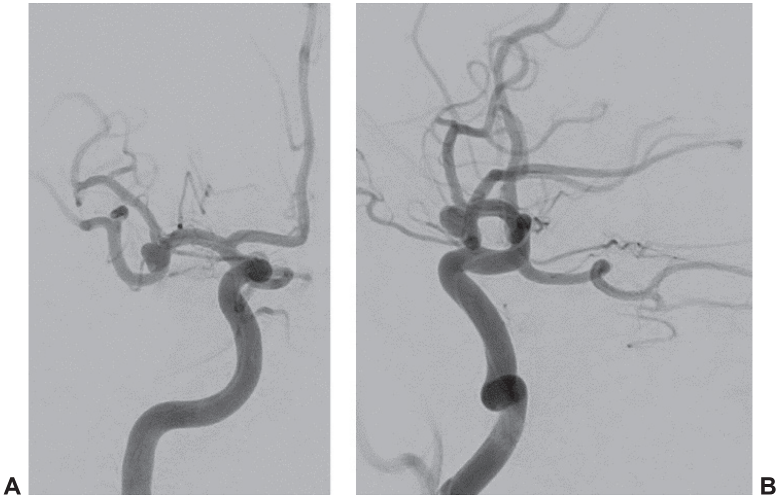


Figure 27. DSA in working projection at the beginning of the procedure. A – frontal projection, B – lateral projection

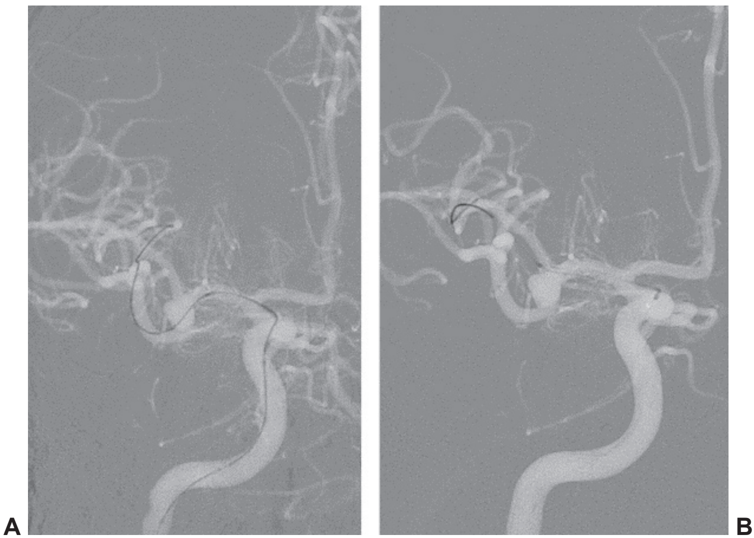


Figure 28. Technical steps during embolization. Sequential catheterization of the lower (A) and upper M2 segments (B) of the bifurcation

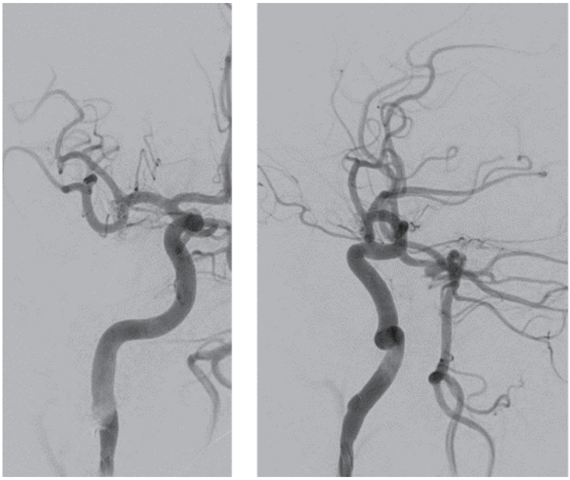


Figure 29. DSA in a working projection at the end of the procedure, demonstrating the achieved satisfactory occlusion of the aneurysm. A – frontal projection, B – lateral projection

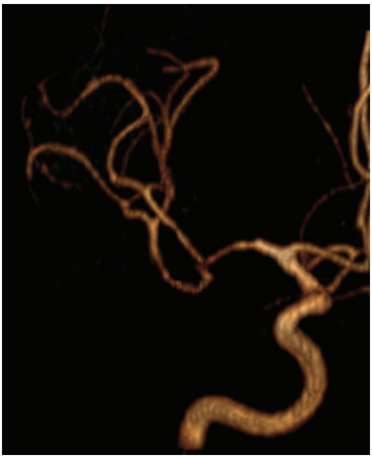


Figure 30. 3D TOF MR angiography (VR reconstruction), performed 6 months after the procedure, demonstrating a completely obliterated aneurysm

Patients treated with flow-diverter stents

Case 1 – figures 31 and 32

This is a case of a patient with an incidentally discovered saccular aneurysm located at the bifurcation of the left middle cerebral artery. The patient underwent endovascular embolization of the aneurysm using the p48 device. Follow-up evaluation of the procedure's outcome was conducted with angiographic imaging at the 18-month mark after the procedure, revealing total obliteration of the aneurysm, accompanied by asymptomatic occlusion of the covered M2 segment of the bifurcation.

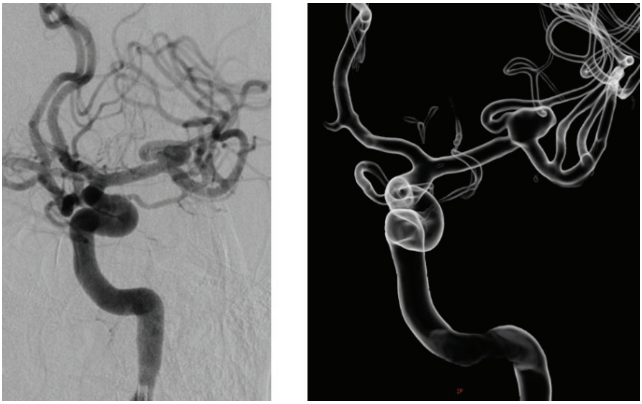
A  B

Figure 31. Saccular aneurysm with an ill-defined neck, located at the bifurcation of the left middle cerebral artery, as depicted by DSA (A) and 3D rotational angiography (B)

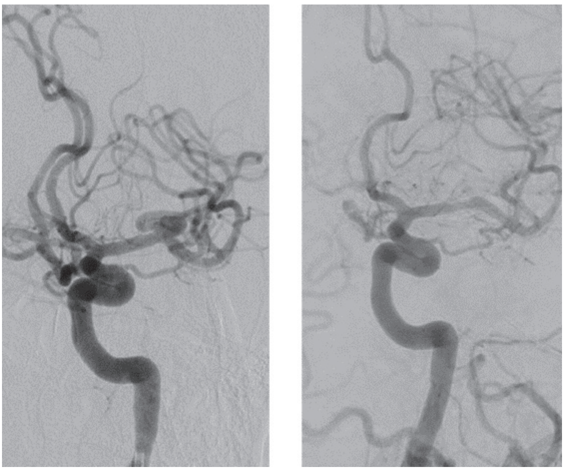
A  B

Figure 32. Presentation of the treatment outcome. A – DSA in a working projection before implantation of the p48 device. B – DSA at 18 months after the procedure, showing total obliteration of the aneurysm and asymptomatic occlusion of the upper M2 segment

Case 2 – figures 33, 34 and 35

The patient had an unruptured, wide-necked saccular aneurysm located at the bifurcation of the left middle cerebral artery. Treatment was performed using a ‚flow-diverter‘ stent p64. The observed total occlusion of the aneurysm during angiographic follow-up was accompanied by asymptomatic obliteration of the covered upper M2 segment of the bifurcation.

A B

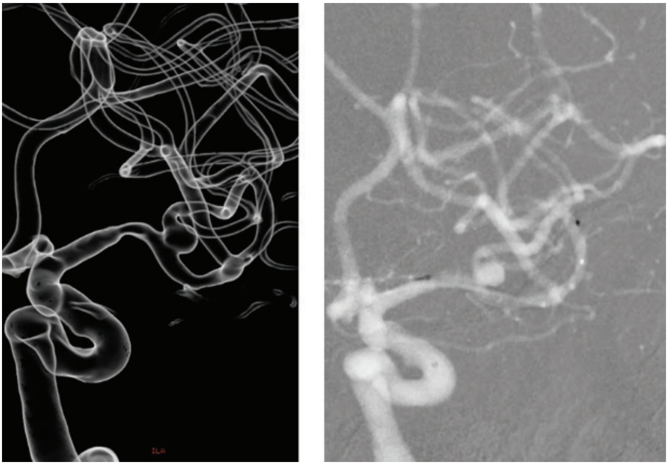


Figure 33. Technical stages of the endovascular intervention. A – 3D rotational angiography depicting an aneurysm with a wide neck located at the bifurcation of the left middle cerebral artery. B – Deployment of the intraluminal flow-modulating device – p64

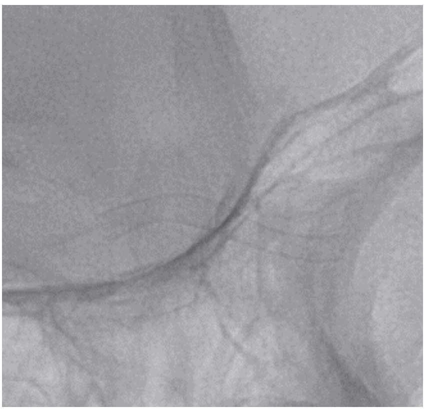
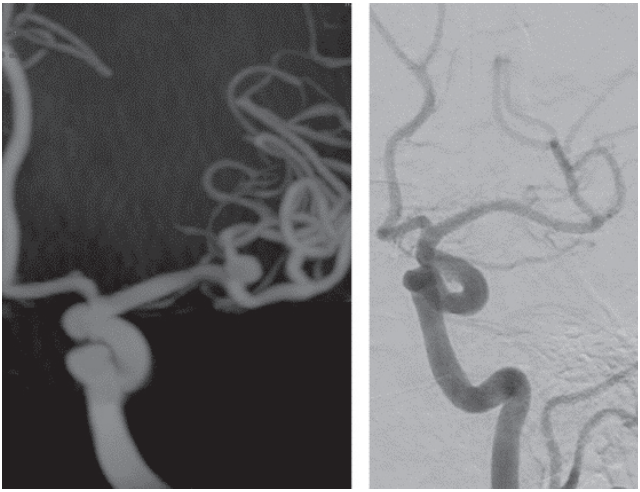


Figure 34. „Single shot“ image illustrating the delivered implant



A B

Figure 35. Assessment of the treatment outcome – comparison of angiographic studies during the procedure – A, and the follow-up conducted after 12 months – B. Image B visualizes complete occlusion of the aneurysm, accompanied by asymptomatic obliteration of the upper M2 segment which is covered by the implant

CONCLUSIONS

After analyzing and interpreting the results obtained from the application of non-conventional endovascular methods in the patients included in this study with unruptured wide-neck bifurcation cerebral aneurysms, we have reached the following conclusions:

1. The studied non-conventional endovascular methods are associated with a good safety profile, and complications related to the procedure were absent in 91.9% of treated patients..
2. The three methods included in this study showed similar complication rates.
3. Significant differences were observed in the achieved occlusion rates among the studied treatment methods for bifurcation cerebral aneurysms with wide necks. The use of permanent stent-assisted coiling and the intrasaccular implant WEB were associated with high levels of adequate occlusion, at 89.5% and 91.7%, respectively.
4. Treatment of aneurysms with flow-diverter stents was associated with a lower degree of adequate occlusion in our series, at 65.9%
5. The application of „flow-diverter“ devices in the treatment of bifurcation aneurysms with wide necks led to a significant improvement in the level of occlusion during follow-up.
6. We identified the characteristic features of typical unruptured bifurcation cerebral aneurysms with wide necks treated with non-conventional methods in our series, including localization on the middle cerebral artery, a neck size of 4.98 mm (SD ± 1.97), dome-to-neck ratio of 1.25 (SD ± 0.35), aspect ratio of 1.19 (SD ± 0.47), and a bifurcation angle of 171.58 (SD ± 38.47).
7. The geometric characteristics of the aneurysms, such as the bifurcation angle, neck size, height, and width of the aneurysmal sac, have an effect on the degree of occlusion in all studied methods. Higher values of these parameters are associated with a significantly adverse impact on the degree of occlusion.

CONTRIBUTIONS

Theoretical contributions

- Some of the most commonly used unconventional endovascular methods for treating unruptured bifurcation brain aneurysms with wide necks have been compared in terms of their safety and effectiveness
- The studied methods demonstrate “non-inferiority” in terms of their safety
- For the first time in Bulgaria, an advantage has been identified in terms of achieving adequate occlusion with stent-assisted coiling and WEB compared to “flow-diverter” implants
- The relationship between the geometric characteristics of brain aneurysms (neck size, height, and width of the aneurysmal sac) and occlusion levels when using the intrasaccular WEB implant, permanent stent-assisted coiling, and “flow-diverter” stent has been studied

Practical contributions

- For the first time worldwide, a correlation has been established and validated between the bifurcation angle and occlusion for patients treated with the intrasaccular WEB implant, persistent stent-assisted coiling, and “flow-diverter” stents.
- The documented relationship would have practical significance in choosing a treatment method and predicting the final effect of the performed intervention

JOURNAL PUBLICATIONS RELATED TO THE DOCTORAL THESIS

Publications in international journals with ISI impact factor

1. Matanov S., Sirakov A., Sirakova K., Sirakov S. Nautilus-Assisted Coiling of an Unruptured Wide-Necked Aneurysm of the Posterior Communicating artery. World Neurosurg. 2021 Jul; 151:117. doi: 10.1016/j.wneu.2021.04.139.Epub 2021 May 12. PMID: 33989820, IF: 2.21

Publications in national journals withour impact factor

1. Matanov S. Current concepts regarding the endovascular management of unruptured wide-necked bifurcation cerebral aneurysms. Рентгенология и Радиология, брой 1-2/2023г.
2. Matanov S., Sirakova K., Sirakov A., Sirakov S. The impact of the bifurcation angle on the occlusion rate in patients with unruptured wide-necked bifurcation aneurysms treated via WEB. Рентгенология и Радиология, брой 1-2/2023г.

APPENDICES

Appendix No. 1. Modified Rankin Score

It is used to assess the degree of disability or the inability to perform daily activities in patients who have survived a stroke or other causes leading to neurological deficits. The scale consists of 7 levels, expressed by numbers from 0 to 6, with a higher value indicating a higher level of impairment (Rankin, 1957; Bonita and Beaglehole, 1988; van Swieten et al., 1988).

Table 25. Modified Rankin Score. The values on the scale are presented, along with their corresponding symptoms.

Values	Symptoms
0	No symptoms
1	Presence of symptoms, but without significant impairment. Patients can perform daily activities.
2	Mildly impaired condition. Patients cannot perform all previous activities but do not need assistance in carrying out their daily activities.
3	Moderately impaired condition. Patients need assistance with daily activities but can move independently.
4	Moderately to severely impaired condition. Patients cannot move independently and require assistance, including for daily sanitary needs.
5	Severely impaired condition. Patients are in a passive forced bed position, requiring constant assistance and care.
6	Death.

Appendix No. 2. Table for selecting the appropriate size of the intrasaccular implant – WEB SL

Table 26. Selecting an appropriate size of the WEB SL device. Provided with permission for use by MicroVention (Microvention, Aliso Viejo, California, USA)

	2.0–2.6	2.7–3.1	3.2–3.6	3.7–4.1	4.2–4.6	4.7–5.5	5.6–6.5	6.6–7.4	7.5–8.3	8.4–9.2	9.3–10
9.5–10.4											SL 11x9
8.5–9.4										SL 10x8	SL 11x8
7.5–8.4									SL 9x7	SL 10x7	SL 11x7
6.5–7.4								SL 8x6	SL 9x6	SL 10x6	SL 11x6
5.5–6.4							SL 7x5	SL 8x5	SL 9x5	SL 10x5	
4.5–5.4						SL 6x4	SL 7x4	SL 8x4	SL 9x4		
3.5–4.4			SL 4x3	SL 4.5x3	SL 5x3	SL 6x3	SL 7x3	SL 8x3			
2.5–3.4	SL 3x2	SL 3.5x2	SL 4x2	SL 4.5x2	SL 5x2						