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Intracranial aneurysms treatment using new generation FRED X flow diverters with antithrombotic coating and preoperative PreSize Neurovascular software simulation: literature review and own clinical observations analysis

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Objective: Evaluate the possibilities of treating giant intracranial aneurysms and complex anatomy aneurysms by implanting new generation of FRED X flow diverters (MicroVention, USA) with antithrombogenic surface subject to preoperative virtual modeling and sizing with PreSize Neurovascular software (Oxford Heartbeat Ltd, Great Britain).

Materials and Methods. FRED X flow diverters with antithrombogenic surface were implanted in 7 patients with giant cerebral aneurysms and complex anatomy aneurysms in the Endovascular Center at Mechnikov Dnipropetrovsk Regional Clinical Hospital, Dnipro, within two months (May 2, 2023 to June 27, 2023). Our study group consisted of 4 (57.1%) female patients and 3 (42.9%) male patients ($p=1.0$). The average age was 50.4 ± 13.7 . 4 patients had single intracranial aneurysms and 3 patients had multiple aneurysms. 2 patients had 2 aneurysms and 1 patient had 4 aneurysms. 3 patients had a hemorrhagic clinical course of the disease (spontaneous subarachnoid hemorrhage in the history), 3 patients had asymptomatic aneurysms, and 1 patient had a pseudotumorous aneurysm.

Results. All 7 patients underwent the ICA aneurysm(s) surgery. 3 patients had a flow diverter implanted at the level of multiple aneurysms (in 2 patients, 2 aneurysms; in 1 patient, 3 aneurysms). 2 patients, in addition to flow diverter implantation, underwent coil aneurysms embolization (using jailing technique). In all patients, the flow diverter was implanted under dual (ticagrelor and acetylsalicylic acid) antiplatelet therapy. 3 patients with a history of subarachnoid aneurysmal hemorrhage received a loading dose of dual antiplatelet therapy immediately before the flow diverter implantation. In one patient with a complex closed siphon shape, balloon angioplasty was required to optimize flow diverter opening to the arterial wall. In all other 6 patients, the flow diverters were opened in a controlled manner with a Push & Pull technique variant: Load/Tension Unsheat technique.

Conclusions: In the endovascular treatment of giant and complex aneurysms, the use of new generation FRED X flow diverters (MicroVention, USA) with antithrombogenic coating subject to proper diverters sizing with PreSize Neurovascular software does not cause technical difficulties and is controlled.

Key words: intracranial aneurysm; internal carotid artery; flow diverter; FRED X; PreSize; preoperative virtual modeling; sizing; antithrombogenic coating; antithrombotic surface

Introduction

Treatment of giant intracranial aneurysms and complex anatomy aneurysms is one of the most challenging tasks of vascular neurosurgery and interventional neuroradiology. Treatment of such types of aneurysms with flow diverters (FD) is the most effective [1, 2, 3, 4].

Aneurysms treatment with flow diverters lies in blood flow diversion due to the dense weaving of the flow diverter's wall. However, when a flow diverter is implanted, an artery is covered with metal more densely compared to intracranial stents, which can provoke

blood clots sticking in the FD. This, in turn, might cause distal embolism or FD occlusion followed by an ischemic stroke [5, 6].

Recently, cerebral aneurysms have been treated with the FDs with a special antithrombotic coating on one side [7, 8] and preoperative simulation using the 3DRA angiography. Preoperative simulation allows selecting the most optimal flow diverter size and position in the artery [9].

As of the beginning of May 2023, 79 patients had underwent the FD implantation for intracranial aneurysms treatment in the Endovascular Center,

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Mechnikov Dnipropetrovsk Regional Clinical Hospital. The FDs with Pipeline Flex with Shield Technology (Medtronic, USA) antithrombogenic covering were implanted in 57 (72%) patients [10]; flow diverters without antithrombogenic covering, in 22 (28%) patients (incl. FRED flow diverters in 15 patients).

4 patients which had the implanted FD without antithrombogenic covering had an intraluminal thrombosis near the FD walls in the acute postoperative period, which required changes in their antiplatelet therapy. The use of more aggressive antiplatelet therapy in all those patients contributed to regression of early postoperative neurological symptoms and restoration of the lumen in the flow diverter, which was confirmed by the follow-up angiography.

On the other hand, less rigid nitinol FRED flow diverters without significant oversize in the diameter were much easier to implant than cobalt-chromium flow diverters Pipeline Flex with Shield Technology. Note that 17 of 57 (30%) patients who underwent the implantation of the flow diverters Pipeline Flex with Shield Technology required balloon angioplasty to optimize the flow diverter's apposition to the artery walls compared to only two (13%) patients who had the flow diverters FRED implanted. In each case, the minimum required length was selected for the Pipeline Flex flow diverter with Shield Technology through the FD sizing and positioning by the preoperative software simulation with usage Sim&Size software (Sim&Cure Company). The minimum required FD length without significant oversizing is needed to simplify its implantation and reduce its thrombogenicity. So far, Sim&Cure (France) has not provided such preoperative virtual simulation capabilities for FRED flow diverters implantation in Europe (including Ukraine).

The FRED flow diverter is one of the world's most popular FDs for the treatment of complex aneurysms and has absolute advantages, such as the simplicity of its opening during the implantation and its conformity to the artery, but due to the lack of antithrombogenic covering and impossibility of preoperative virtual simulation, sizing, and positioning in the artery, most neurointerventional centers, including ours, do not prioritize its use [2, 11, 12, 13].

Following the publication of the FRED main trial, the product received the FDA approval in the United States in 2020. [14]. Recently introduced FRED X is a new version of FRED. The X technology, a special antithrombotic coating applied to the stent, is a brand new feature of this successor.

FRED X is a new generation of FRED flow diverters with an antithrombogenic coating, a poly-2-methoxyethyl acrylate nanopolymer covalently bound to the flow diverter's surface [15, 16]. The hydrophobic side of this amphiphilic coating is turned to the flow diverter's strata and hydrophilic side is turned to the blood flow, which shall reduce protein denaturation, and, subsequently, protect the flow diverter's surface from platelet aggregation, while not preventing its covering by endotheliocytes.

The FRESH Study [17], which included 161 patients from 9 international centers and which was published in April 2023, confirms that the risk of flow diverter thrombosis with ischemic complications significantly decreased due to the use of the new generation FRED X compared to the previous FRED.

In November 2022, with the help of ESMINT (European Society of Minimally Invasive Neurological Therapy) and Oxford Heartbeat Ltd., our clinic has installed the PreSize Neurovascular simulation software (Oxford Heartbeat Ltd., Great Britain) for preoperative software simulation and flow diverter sizing (including for FRED and its new model, FRED X). When planning a flow diverter implantation for cerebral aneurysms, the preoperative software simulation is needed due to the fact that neglecting advanced of preoperative software simulation may cause the use of more than one device (the first one being discarded or additionally opened), exceeding of the optimal minimum length of a flow diverter, or selecting its suboptimal position relative to the artery walls, which, in turn, can lead to persistent filling of the aneurysm, artery lumen stenosis in the respective segment, lateral branches occlusion, flow diverter thrombosis, and distal cerebral thromboembolism, followed by severe intra- and postoperative complications [18].

Since May 2023, a new generation of FRED X flow diverters with antithrombotic coating have been used in the Endovascular Center, Mechnikov Regional Clinical Hospital. This was made possible due to the supply of the set of such products by Professor Rocco A. Armonda as part of the RAZOM for Ukraine volunteer medical mission.

Objective: Evaluate the possibilities of treating giant intracranial aneurysms and complex anatomy aneurysms by implanting the new generation FRED X flow diverters (Microvention, USA) with antithrombogenic coating subject to preoperative software simulation and sizing with the PreSize Neurovascular software (Oxford Heartbeat Ltd., Great Britain).

Materials and Methods

Participants

The FRED X flow diverters with antithrombogenic coating were implanted in 7 patients with giant cerebral or complex anatomy aneurysms in the Endovascular Center at Mechnikov Dnipropetrovsk Regional Clinical Hospital, Dnipro, within two months (May 2, 2023 to June 27, 2023),

All patients have signed their written informed consent to participate in the study in accordance with the World Medical Association's Declaration of Helsinki on ethical principles for medical research involving human subjects (1964–2008), the European Society Directive No. 86/609 on human participation in biomedical research, and the Order of the Ministry of Health of Ukraine No. 690 dd 23.09.2009 as amended.

Inclusion Criteria

Patients aged ≥ 18 , giant or complex structure intracranial aneurysms, which were treated with the new generation FRED X flow diverters.

This article contains some figures that are displayed in color online but in black and white in the print edition.

Group Characteristics

Our study group consisted of 4 (57.1%) female patients and 3 (42.9%) male patients ($p=1.0$). The average age was 50.4 ± 13.7 . 4 patients had isolated intracranial aneurysms and 3 patients had multiple aneurysms. 2 patients had 2 aneurysms and 1 patient had 4 aneurysms. 3 patients had a hemorrhagic clinical course of the disease (SAH in the history), 3 patients had asymptomatic aneurysms, and 1 patient had a pseudotumorous aneurysm.

The generally accepted Bouthillier classification was used to categorize the ICA segments [19]. **Table 1** gives detailed clinico-angiographic characteristics of the aneurysms, including their location and size, which is important when choosing treatment tactics.

Study Design

A single-center prospective study.

Surgical Methods

All surgeries involved a right-sided three-catheter coaxial transradial access under general (inhaled and intravenous) anesthesia. In all cases, preoperative 3D software simulation was performed in the PreSize Neurovascular software to select the optimal FRED X flow diverter.

The GE Innova IGS540 (USA) angiographic system was used for all operations. After the flow diverter implantation, the follow-up DSA angiography and FD CT virtual dilution angiography were mandatorily performed – the latter enables to accurately assess the optimality of the flow diverter's opening and positioning against the artery walls on the CT images (MIP and 3D modes) with the "illuminated" flow diverter's structure. If a flow diverter was opened incorrectly or suboptimally, its position relative to the artery wall was optimized by the balloon angioplasty with a cerebral compliant balloon catheter.

Statistical Processing of the Results

Statistica 10 (StatSoft® Inc., the USE, License No. STA862D175437Q) and MedCalc V.20.218 free trial version (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org/download.php>, 2023) were used to process and analyze the data.

Results and Discussion

Today, we can discuss intermediate results in the group of patients who were treated using a new generation of FRED X flow diverters with antithrombogenic coating.

All 7 patients underwent the ICA aneurysm(s) surgery. 3 patients had a flow diverter implanted at the level of multiple aneurysms (in 2 patients, 2 aneurysms; in 1 patient, 3 aneurysms).

2 patients, in addition to flow diverter implantation, underwent coil aneurysms embolization (using jailing technique).

In all patients, the flow diverter was implanted on the dual antiplatelet therapy (ticagrelor and acetylsalicylic acid). 3 patients with a history of subarachnoid aneurysmal hemorrhage received a loading dose of dual antiplatelet therapy immediately before the flow diverter implantation.

Preoperative virtual simulation in the PreSize Neurovascular software made it possible to select the optimal FRED X flow diverter in terms of its diameter and minimum required length, as well as optimal distal and

proximal landing zones of the artery implantation. In one patient with a complex closed ICA siphon shape, balloon angioplasty was required to optimize the flow diverter's apposition to the arterial wall. In all other 6 patients, the flow diverters were opened in a controlled manner almost like conventional braided cerebral artery stents.

Table 2 gives a detailed description of the surgery performed in the study group.

The implantation and opening of a new generation FRED X flow diverter has been significantly improved due to its coverage. In addition, the ability to precisely select the optimal size and minimum required length of a flow diverter also makes it easier to open it and achieve its optimal positioning relative to the artery wall. The clinical case below confirms the above statement.

Case 6 (Tables 1 and 2)

A 31-year-old man with a confirmed subarachnoid hemorrhage was admitted to the clinic two months ago following the MRI with a non-contrast enhanced TOF angiography, which revealed a blister aneurysm in the C6 segment of the right ICA. The right-sided hypointensive signal in the basal cisterns in the T2* MRI sequence confirms subarachnoid hemorrhage due to the aneurysm rupture.

The patient underwent a digital subtraction cerebral angiography with a with a three-dimensional modality, which confirmed the right-sided blister aneurysm in the C6 segment of the ICA (**Fig. 1**), due to which, the preoperative software simulation was performed using the PreSize Neurovascular software (Oxford Heartbeat Ltd) with different sizes of the FRED X flow diverters. The final candidates were the FRED X: 5 mm x 21 mm/14 mm (**Fig. 2A**) (14 mm is exactly the length of the double-layer part of the FRED X flow diverter, excluding its "crowns") and 4.5 mm x 20 mm/13 mm (**Fig. 2B**).

Given the significant difference in diameter in the distal and proximal implantation areas, expected forced oversize in the distal area, and relatively complex closed form of the ICA siphon, the 4.5 mm x 20 mm/13 mm FRED X flow diverter with a minimum required length and minimum required diameter (without a slack fit to the artery walls proximally) was selected.

After the preoperative loading double antiplatelet therapy, an hour before the surgery (ticagrelor 180 mg, aspirin 300 mg), the FRED X flow diverter was endovascularly implanted at the level of right-sided ICA aneurysm. The transradial right-sided approach was used for the surgery: a 90 cm Ballast 6F (Balt Extrusion, France) guide-introducer was inserted into the C1 segment of the right ICA, through which a Sofia EX distal access catheter (Microvention, USA) was inserted into the C2 segment. The 4.5 mm x 20 mm/13 mm FRED X flow diverter was implanted through the Headway 27 (MicroVention, USA) microcatheter recommended for implantation of FRED nitinol flow diverters using the Push & Pull technique variant: Load/Tension Unsheath technique – when microcatheter position corresponds to the axis of the artery while saving the FD loading during implantation (**Fig. 3**). The post-implantation FD CT, including the virtual dilution angiography, confirmed the optimal opening and apposition of the walls of the flow diverter along the entire length and full compliance of the flow diverter's location with the PreSize Neurovascular software simulation results (**Fig. 4**).

Table 1. Clinico-angiographic characteristics of clinical cases

No.	Gender	Age (years)	The Number of ICA Aneurysms	Aneurysms Location	Lateralization (Right/Left)	Aneurysms Size	Clinical Type
1	M	38	4	<p>Right ICA:</p> <ol style="list-style-type: none"> C7 segment: two-chamber saccular aneurysm at the PCoA ostium, C7 segment: blister aneurysm at the ACA ostium, ICA bifurcation: blister aneurysm; <p>Left ICA:</p> <ol style="list-style-type: none"> small saccular aneurysm in the C7 segment at the ACA ostium 	<p>on the right</p> <p>— 3 AAs (including ruptured)</p> <p>on the left</p> <p>— 1 AA</p>	<p>Right ICA:</p> <p>C7 segment: two-chamber saccular aneurysm (chamber diameter 8 mm and 6 mm) with a wide neck at the PCoA ostium,</p> <p>C7 segment: blister aneurysm at the ACA ostium (2.4 mm),</p> <p>ICA bifurcation: blister aneurysm (2.6 mm);</p> <p>Left ICA:</p> <p>small saccular aneurysm in the C7 segment at the ACA ostium (S=2 mm; H=3 mm, neck=2 mm)</p>	Hemorrhagic (SAH in the history; 2 months ago; right-sided)
2	F	55	2	<p>Right ICA:</p> <ol style="list-style-type: none"> giant in the C4–C6 segments, small in the C3 segment 	on the right	<p>Giant. S=32 mm; H=28 mm (including the thrombosed part of the aneurysm);</p> <p>S=17 mm; H=28 mm (dimensions of the contrasted parts of the aneurysm body); neck=13 mm;</p> <p>Small. S=4.6 mm; H=3.5 mm; neck=4.6 mm</p>	Pseudotumorous
3	F	48	1	Left ICA C6 segment	on the left	S=8mm, H=17mm, Neck=5.4mm. Diverticulum in the proximal part of the aneurysm body (diameter 2 mm)	Hemorrhagic (SAH in the history; 3 months ago)
4	M	53	2	<p>Left ICA</p> <ol style="list-style-type: none"> C6 segment C7 segment 	on the left	<p>The C7 segment aneurysm: S=3.2 mm; H=3.5 mm; neck=3.2 mm</p> <p>The C6 segment aneurysm: S=2.6 mm; H=1.7 mm; neck=2.6 mm</p>	Asymptomatic
5	F	54	1	Right ICA C6 segment	on the right	S=7.6 mm; H=5.4 mm; Neck=7.6 mm Two cervical diverticulae (diameter, 2 mm and 1.9 mm)	Asymptomatic
6	M	31	1	Right ICA C6 segment	on the right	S=2.6 mm; H=2.3 mm; Neck=2.6 mm	Hemorrhagic (SAH in the history; 2 months ago; right-sided)
7	F	74	1	Right ICA C6–C7 segments	on the right	Fusiform, diameter up to 9 mm	Asymptomatic

Notes: *Concomitant cerebrovascular disease: Gross stenosis in the left ICA (NASCET 85%), TIA in the left carotid basin, underwent carotid stenting. **ACA=anterior choroidal artery, ***PCoA=posterior communicating artery.

Table 2. Characteristics of endovascular interventions in the treatment of giant or complex anatomy intracranial aneurysms

No.	Surgery Date	Aneurysms Location	Fred X Size	Need for Balloon Angioplasty for a Flow Diverter	Flow Diverter Implantation + Coil Embolization	Coil Embolization Density (Dense/Not Dense)	Surgery Duration	Surgeons
1	02.05.2023	Right ICA: 1. C7 segment: two-chamber saccular aneurysm at the PCoA ostium, 2. C7 segment: blister aneurysm at the ACA ostium, 3. ICA bifurcation: blister aneurysm; Left ICA: 4. small saccular aneurysm in the C7 segment at the ACA ostium	4 x23/17	None	Yes (embolized two-chamber aneurysm in the C7 segment of the right ICA in the PcoA projection)	Dense	1 h 10 min	Yu. Cherednychenko Rocco Armonda
2	04.05.2023	Right ICA: 1. giant in the C4–C6 segments, 2. small in the C3 segment	4x32/26	None	No	—	50 min	Yu. Cherednychenko Rocco Armonda
3	16.05.2023	Left ICA C6 segment	4x23/17	None	Yes	Not dense	1 h 30 min	Yu. Cherednychenko V. Perepelytsia
4	24.05.2023	Left ICA 1. C6 segment 2. C7 segment	4,5x25,0/18,0	None	No	—	55 min	Yu. Cherednychenko A. Miroshnychenko
5	31.05.2023	Right ICA C6 segment	4,5x20,0/13,0	Yes Balloon angioplasty for further FRED X opening was performed	No	—	1 h 30 min	Yu. Cherednychenko V. Perepelytsia
6	22.06.2023	Right ICA C6 segment	4,5x20,0/13,0	None	No	—	55 min	Yu. Cherednychenko V. Perepelytsia
7	27.06.2023	Right ICA , C6–C7 segments	4,5x25,0/18,0	None	No	—	55 min	Yu. Cherednychenko A. Miroshnychenko

Note: clinical cases in Tables 1 and 2 have the same numbers.



Fig. 1. Preoperative images of angiography of case No. 6. Fig. (A) Selective digital subtraction cerebral angiography, left lateral projection. Fig. (B) Three-dimensional modality of cerebral angiography. Blister aneurysm of the right internal carotid artery in the ophthalmic segment (red arrow).



Fig. 2. PreSize Neurovascular software (Oxford Heartbeat Ltd) use case. Fig. (A) Virtual view of the 5 mm x 21 mm/14 mm FRED X implantation (red arrow). Fig. (B) Virtual view of the 4.5 mm x 20 mm/13mm FRED X implantation (red arrow)

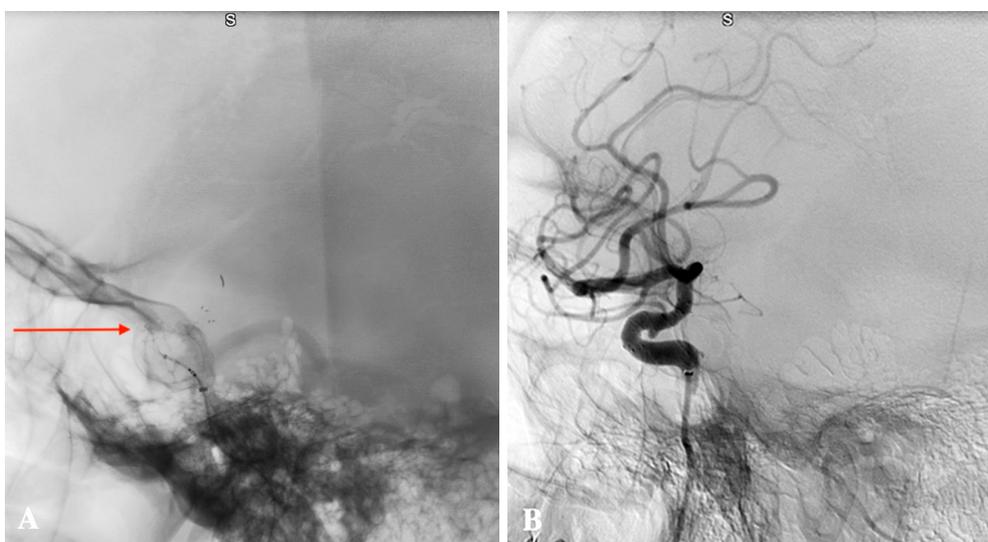


Fig. 3. Intraoperative angiography images. Fig (A) Flow diverter implantation (red arrow). Fig (B) The follow-up postoperative series of selective cerebral angiography shows satisfactory arterial patency following the flow diverter installation, with no signs of thrombosis or arterial lumen stenosis. The flow-diverted segment of the FREDX is centered on the aneurysm neck with full expansion confirmed

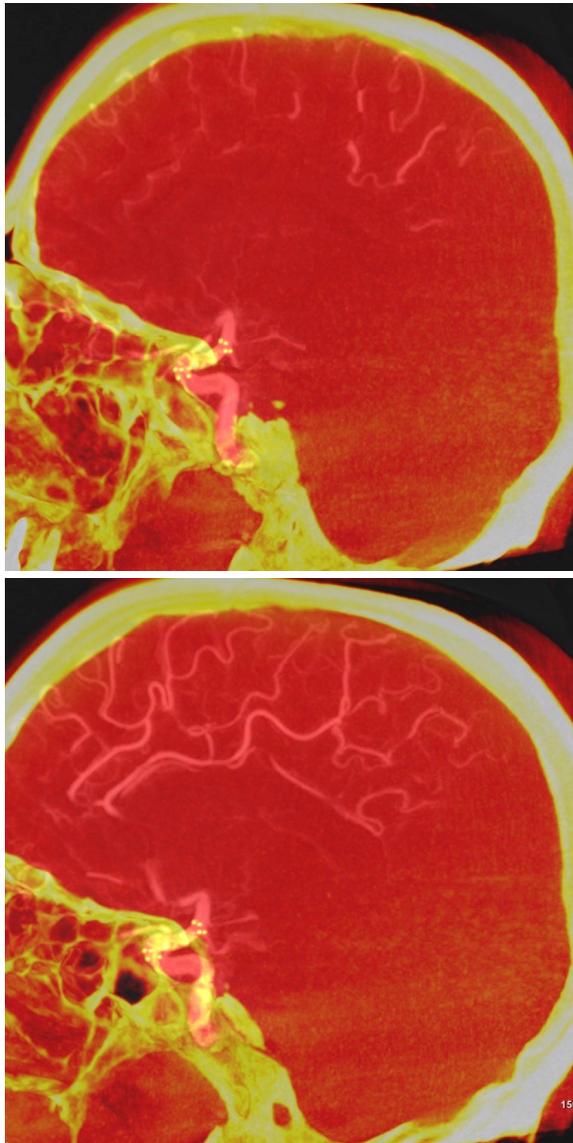


Fig. 4. The follow-up FD CT series including the virtual dilution angiography

The dual antiplatelet therapy (ticagrelor 90 mg twice a day, acetylsalicylic acid 100 mg daily) was continued. The MRI on the next day confirmed the absence of subclinical ischemic foci. The patient was discharged with no neurological symptoms. Currently, he is undergoing preparation for the follow-up at 3 months.

The opening of relatively long FRED X flow diverters has become easier and more controlled, which makes it possible to exclude multiple aneurysms with a single relatively long flow diverter with a minimal risk of technical problems. However, the diverter's excessive length can predictably increase the implantation problems and the device's thrombogenicity. The preoperative software simulation using the PreSize Neurovascular software provides an understanding of the minimum required length and optimal diameter of the FRED X flow diverter. The clinical case is described below.

Case 2 (Tables 1 and 2)

A 55-year-old woman went to the clinic with intense right-sided hemicranialgia attacks and right-sided oculomotor and abducent nerves paresis. The neuroimaging with native non-contrast enhanced head CT and CT angiography revealed a giant partially thrombosed aneurysm of the right internal carotid artery in the cavernous, clinoid, and ophthalmic segments of the right ICA and a small wide-necked aneurysm in the C3 segment of the right ICA. The patient underwent digital subtraction cerebral angiography with a three-dimensional modality (**Fig. 5**), based on which, the preoperative software simulation was performed with the PreSize Neurovascular software, where the FRED X flow diverter (4 mm x 32 mm/26 mm) was optimally sized and positioned (**Fig. 6**).

The flow diverter has the minimum possible length so that the distal edge of its bilayer part begins directly under the ostium of the posterior communicating artery and the proximal edge of its bilayer part is directly under the neck of the proximal small aneurysm. At the same time, the flow diverter does not have a lack apposition to the artery wall nor is it significantly oversized along all the segments (except for the necks of aneurysms). After the preoperative double antiplatelet therapy (ticagrelor 90 mg twice a day, aspirin 100 mg x 5 days), the FRED X flow diverter was endovascularly implanted at the level of the right-sided ICA aneurysms. The transradial right-sided approach was used for the surgery: a 90 cm Ballast 6F (Balt Extrusion) guide introducer was inserted into the C1 segment of the right ICA, through which a Sofia EX distal access catheter (Microvention) was inserted into the C2 segment. The 4 mm x 32 mm/26mm FRED X flow diverter was implanted through the Headway 27 microcatheter recommended for implantation of FRED nitinol flow diverters using the Push & Pull technique (**Fig. 7**). The post-implantation FD CT, including the virtual dilution angiography, confirmed the optimal opening and apposition of the walls of the flow diverter along the entire length and full compliance of the flow diverter's location with the PreSize Neurovascular software simulation results (**Fig. 8**).

The dual antiplatelet therapy was continued. 5 days after the surgery, glucocorticoids were prescribed in small doses. After two weeks, the patient's condition improved: the headaches intensity and frequency decreased, the patient had the ophthalmoparesis tending to regress. Currently, the patient is undergoing preparation for the follow-up at 3 months.

The FRED X flow diverters were opened in the controlled manner by simultaneous aneurysm coiling using the jailing technique. Below we present a clinical case while covering all the technical aspects of the procedure.

Case 1 (Tables 1 and 2).

A 38-year-old man went to the clinic 3.5 weeks after a severe headache attack that occurred after physical overload and regressed for 3 days; the brain MRI showed suspected cerebral aneurysms. The right-sided hypointensive signal in the basal cisterns in the T2* MRI sequence confirms subarachnoid hemorrhage due to the rupture of one of the right-sided ICA aneurysms.

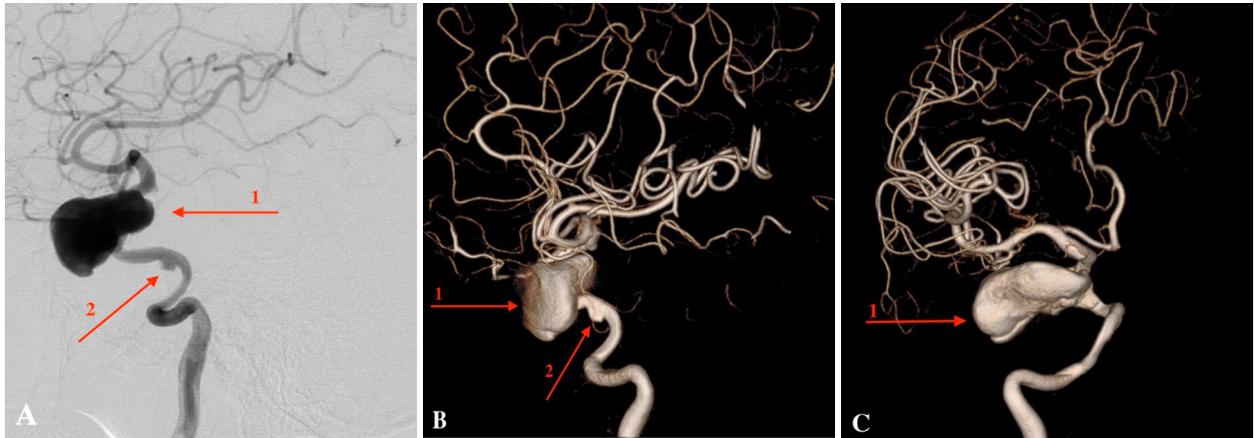


Fig. 5. Preoperative images of angiography of case No. 2. Fig. (A) Selective digital subtraction cerebral angiography. Fig. (B,C) Three-dimensional modality of cerebral angiography. Giant aneurysm of the right internal carotid artery in the cavernous, clinoid, and ophthalmic segments (red arrow 1). Wide-necked microaneurysm near the lacerum segment of the right internal carotid artery (red arrow 2)

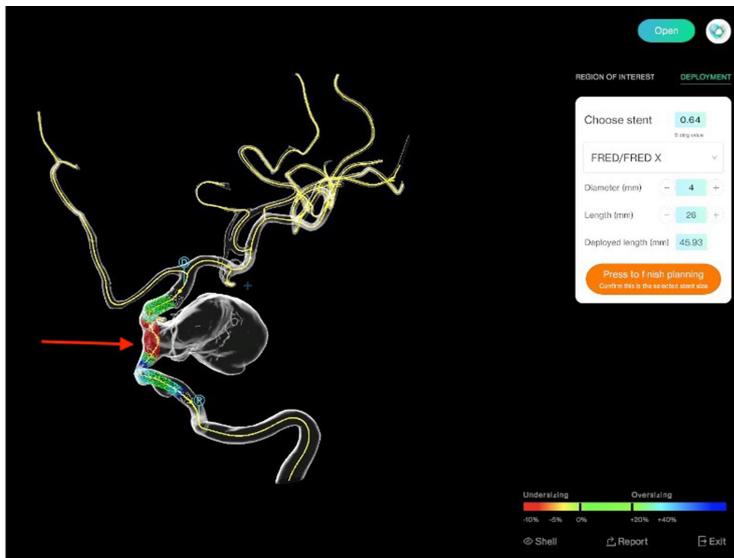


Fig. 6. PreSize Neurovascular software (Oxford Heartbeat Ltd) use case. Virtual view of the 4 mm x 32 mm/26 mm FRED X implantation (red arrow)

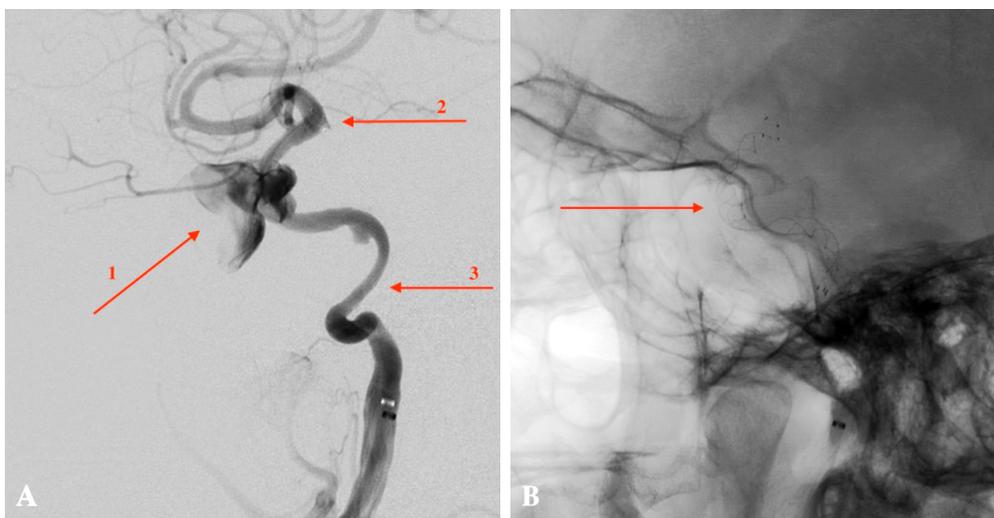


Fig. 7. Control postoperative series of selective cerebral angiography. Fig (A) The follow-up postoperative series of selective cerebral angiography shows delayed contrast of a giant aneurysm after the flow diverter implantation (red arrow 1). Shadow of the distal end (red arrow 2) and the proximal end (red arrow 3) of the FD. Fig (B) The flow diverter's shadow following the implantation (red arrow)

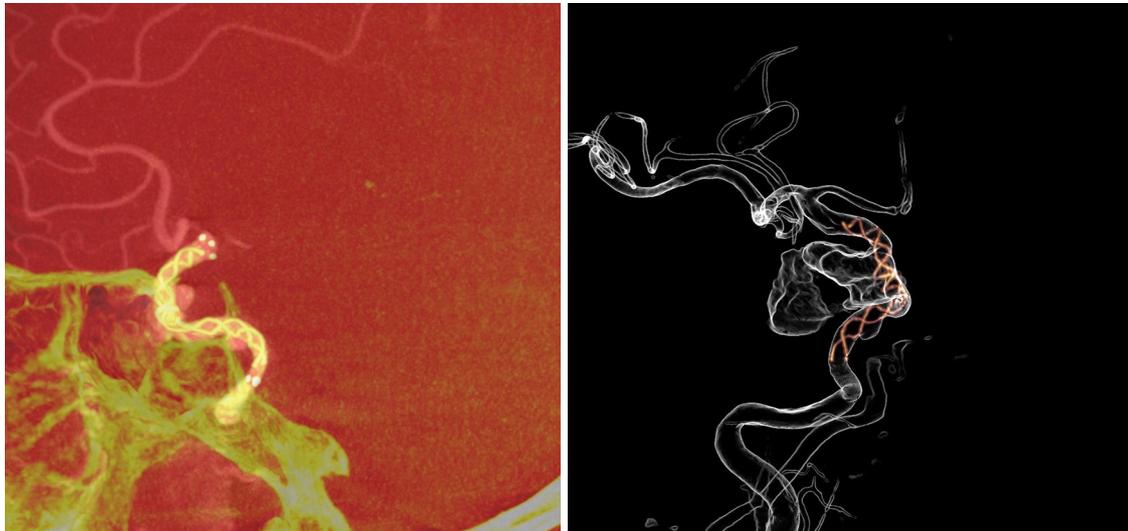


Fig. 8. The follow-up FD CT series including the virtual dilution angiography

The cerebral digital subtraction angiography with a three-dimensional modality confirmed 4 cerebral aneurysms: blister aneurysm in the bifurcation of the right ICA, blister aneurysm in the C7 segment of the right ICA in the anterior choroidal artery ostium projection, wide-necked two-sack aneurysm in the C7 segment of the right ICA in the PCoA ostium projection (diameters of the sacks are 8 mm and 6 mm) (**Fig. 9**), a small wide-necked saccular aneurysm (3 mm x 2 mm) in the C7 segment of the left ICA, at the anterior choroidal artery ostium (**Fig. 10**).

It was decided to perform the combined endovascular treatment of the right ICA aneurysms: coiling of the two-chamber C7 segment aneurysm and the FRED X flow diverter implantation from the M1 segment of the right middle cerebral artery (MCA) to the ophthalmic artery

ostium at the level of all three right-sided ICA aneurysms. The preoperative software simulation with optimum sizing and positioning of the 4 mm x 23 mm/17mm FRED X flow diverter was performed (**Fig. 11**).

One hour before the estimated time of the flow diverter implantation, the patient received loading double antiplatelet therapy (ticagrelor 180 mg plus aspirin 300 mg). The transradial right-sided approach was used for the surgery: a 90 cm Ballast 6F (Balt Extrusion, France) guide introducer was inserted into the C1 segment of the right ICA, through which a Sofia Plus distal access catheter (Microvention, USA) was inserted into the C2 segment. A Headway 17 microcatheter (Microvention, USA) was inserted into the two-sack aneurysm. The FRED X was partially opened through the Headway 27 (Microvention, USA) microcatheter from the M1 segment,

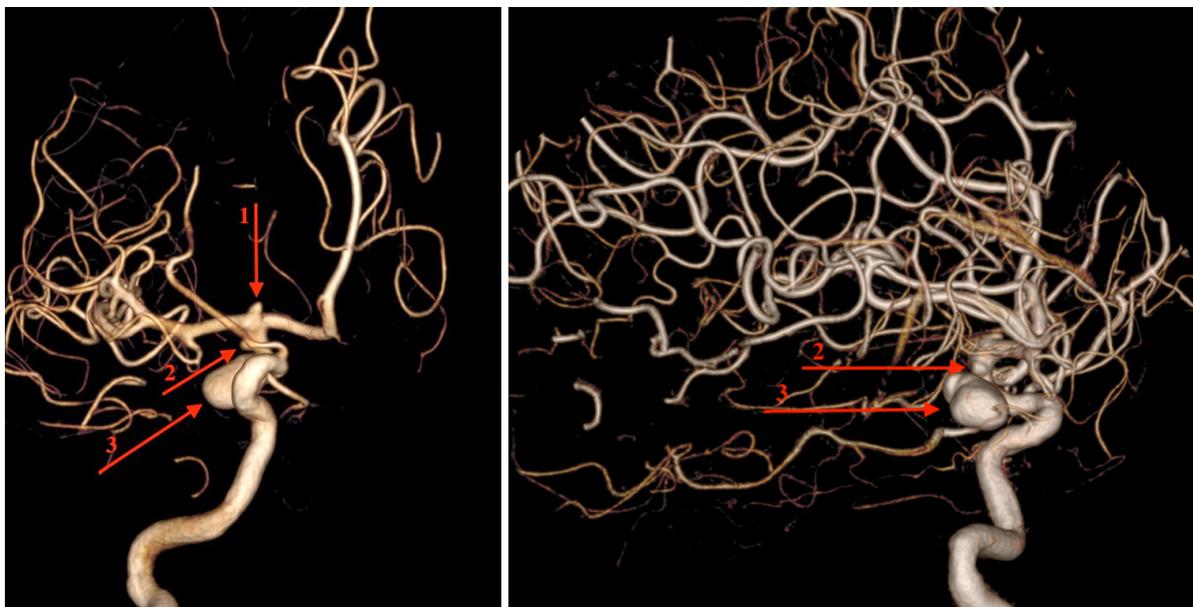


Fig. 9. Selective digital subtraction cerebral angiography in the right internal carotid artery basin. Three-dimensional modality of cerebral angiography. Blister aneurysm in the right ICA bifurcation (red arrow 1). Blister aneurysm in the supraclinoid segment of the right ICA (red arrow 2). Large two-sack aneurysm in the supraclinoid segment of the right ICA (red arrow 3)

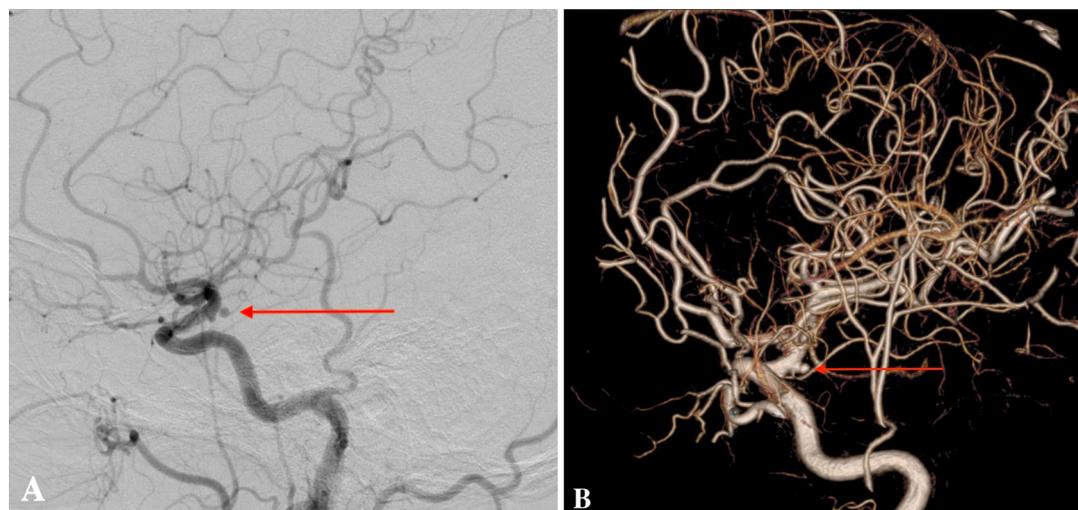


Fig. 10. Selective digital subtraction cerebral angiography in the left internal carotid artery basin. Fig (A) Two-dimensional model of cerebral angiography. (B) Three-dimensional modality of cerebral angiography. Microaneurysm in the supraclinoid segment of the left ICA (red arrow)

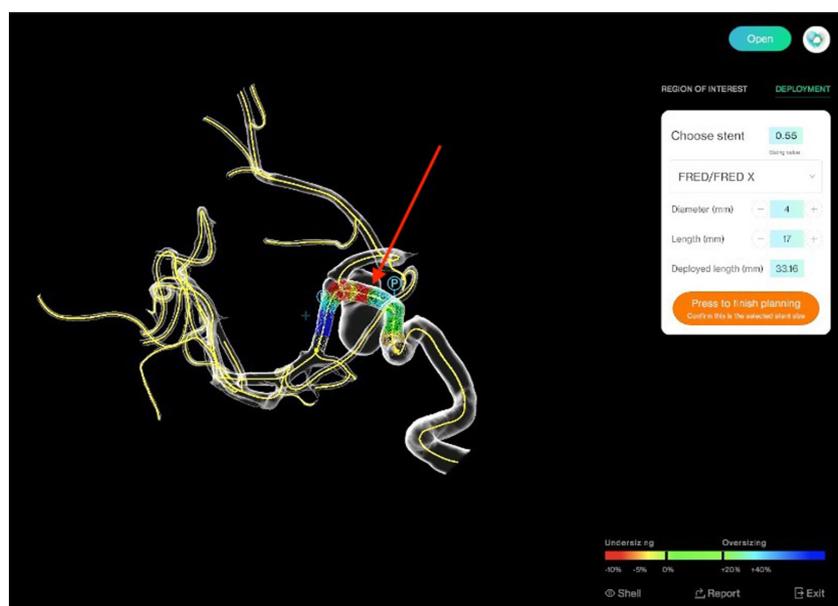


Fig. 11. PreSize Neurovascular software (Oxford Heartbeat Ltd) use case. Virtual view of the 4 mm x 23 mm/17mm FRED X implantation (red arrow)

proximal to the origin of lenticulostriate arteries to the proximal edge of the two-sack aneurysm neck and the aneurysm was embolized with the Axiom (Medtronic, USA), Target (Stryker, USA) detachable microcoils with jailing technique. Thereafter, the flow diverter was fully opened and fully implanted in conformity with the preoperative software simulation (**Fig. 12**).

The patient was discharged in a satisfactory condition, with no neurological disorders. Currently, he is undergoing preparation for the follow-up at 3 months.

In case of complex anatomy, closed complex ICA siphon, or different proximal and distal diameters, the flow diverter shall have the minimum distal oversize (if possible) — as a significant distal oversize can complicate the proximal opening of the flow diverter. In case of

suboptimal opening of the flow diverter, the balloon angioplasty in the flow diverter shall be considered. The clinical case is described below.

Case 5 (Tables 1 and 2).

A 54-year-old woman with an asymptomatic wide-necked C6 segment aneurysm and diverticulum. The aneurysm was detected by the head MRI performed due to a dizziness that had occurred once. The digital subtraction angiography with a three-dimensional modality (**Fig. 13**) was followed by the preoperative software simulation with the FRED X flow diverters of various sizes (**Fig. 14**).

Given the complex shape of the ICA siphon, it was very important to select a flow diverter without

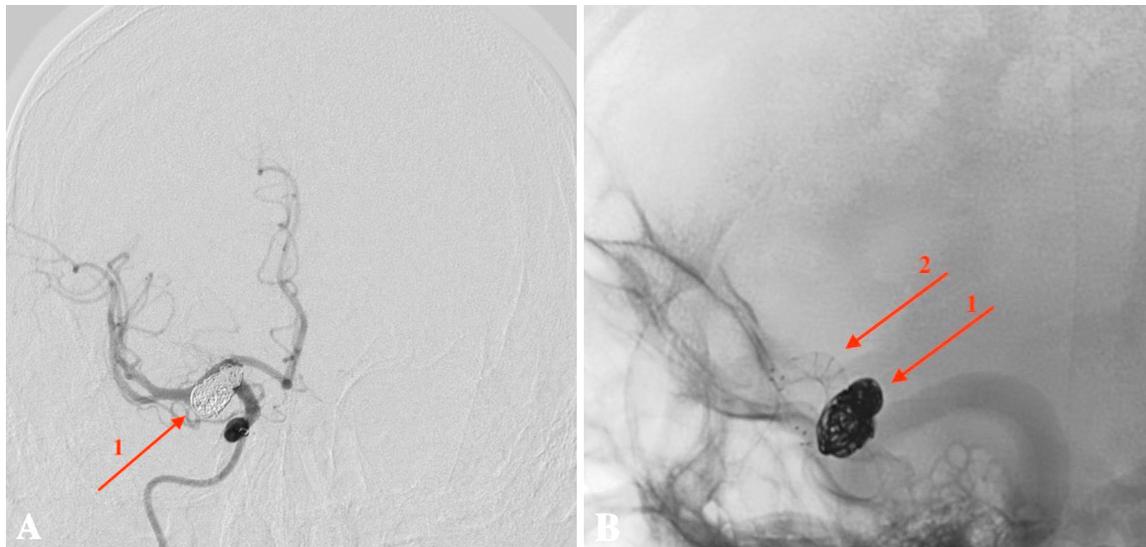


Fig. 12. Postoperative series of selective cerebral angiography Fig (A) The follow-up postoperative series of selective cerebral angiography of the right carotid basin (direct projection) shows no contrasting of the right ICA bifurcation blister aneurysm, blister aneurysm and large two-chamber aneurysm in the supraclinoid segment of the right ICA. Fig (B) The large two-sack aneurysm is completely isolated by the microcoils (red arrow 1). The flow diverter's shadow (red arrow 2)

excessive diameter and length for this patient due to possible problems with the device opening. The 5 mm x 21 mm/14 mm FRED X simulation showed the excessive diameter along the entire length (except for the aneurysm neck), which would significantly complicate the flow diverter's opening. The 4.5 mm x 25 mm/18mm simulation also demonstrated the excessive length when implanted in this artery with a small oversized segment distally. The 4 mm x 23 mm/17 mm FRED X does not fit tightly in the lower horizontal part of the siphon (C4 segment) to the artery walls, which is dangerous due to increased thrombogenicity. According to the simulation, the 4 mm x 18 mm/12 mm and 4.5 mm x 20 mm/13 mm FRED X flow diverters seemed to be the most optimal in this case (**Fig. 14**). They have the necessary length margin along of the two-layer segment covering the aneurysm neck, are tightly pressed against the artery wall, and do not have excessive length. The second flow diverter has more oversized segment distally (which, at that time, we considered not critical). We preferred the 4.5 mm x 20 mm/13 mm FRED X because the second selected FRED X (4 mm x 18 mm/12 mm; the only one in our FRED X line at that time) was also optimal for other patient. The 4.5 mm x 20 mm/13 mm FRED X was implanted using the technique and auxiliary tools as in case 1. The flow diverter was opened from the PCoA ostium to the distal part of the C4 segment. Its length turned out to be longer than was simulated, which is an additional marker that the flow diverter was not opened optimally. It can be seen that the device is opened incompletely in the corner of the C5 segment (**Fig. 15**). We optimized the flow diverter's walls positioning in this under-opened part using the ScepterC 4x10 balloon plasty. Eventually, the flow diverter was fully opened and fully implanted in conformity with the preoperation software simulation (**Fig. 16**). The post-implantation FD CT, including the virtual dilution angiography, confirmed

the optimal opening and apposition of the walls of the flow diverter to artery wall along the entire length and full consistence of the flow diverter's location with the PreSize Neurovascular software simulation results (**Fig. 17**). The patient was discharged in a satisfactory condition, with no neurological disorders. Currently, he is undergoing preparation for the follow-up at 3 months.

In our study, a series of 7 consecutive patients had no signs of spasm, dissection, or blood clots sticking to the flow diverter or artery wall during the surgery. The follow-up brain MRI the next day or the day after showed no presence of subclinical ischemic foci in the brain. The clinical condition of the patients did not deteriorate. All patients are being prepared for a follow-up examination at three months and remain under observation while taking dual antiplatelet therapy.

Results and Discussion. The FRESH Study, the largest study published at the time of this article, [17] on the use of the new generation FRED X flow diverters, included one hundred and sixty-one patients (77.6% women; mean age 55 years) with 184 aneurysms (11.2% in the acute rupture period). Most aneurysms are in the anterior circulatory region (77.0%), most often in the ICA (72.7%). The FRED X flow diverters were successfully implanted in all the procedures.

In 29.8% of the patients, additional coils were installed. Only 4 (2.5%) patients required the stent-balloon angioplasty.

3.1% of the patients had serious side effects. Thrombotic events occurred in 7 patients (4.3%): 4 intra- and 4 postoperative thrombosis in the middle of the stent (1 patient had both perioperative and postoperative thrombosis). Of these, only 2 (1.2%) thrombosis resulted in serious side effects (ischemic strokes).

In recent FRED and FRED Jr. studies, the thrombotic complications were slightly more frequent: 6.8% [13], 8.3% [14], and 7.0% [20].

1.9% of the FRESH Study patients had postoperative neurological complications and 1.2% died. In the European Flow-Redirection Intraluminal Device Study, the largest study which covered the FRED flow diverters implantation and included 531 patients, the incidence of complications and side effects was 14% [11].

The incidence of complete aneurysm occlusion after the average follow-up period of 7.0 months was 66.0%.

In our study, we managed to avoid thrombotic complications, postoperative neurological morbidity and mortality.

Prospects for further research: To formulate statistically significant conclusions, we should continue to add the patients who had the implanted FRED X to

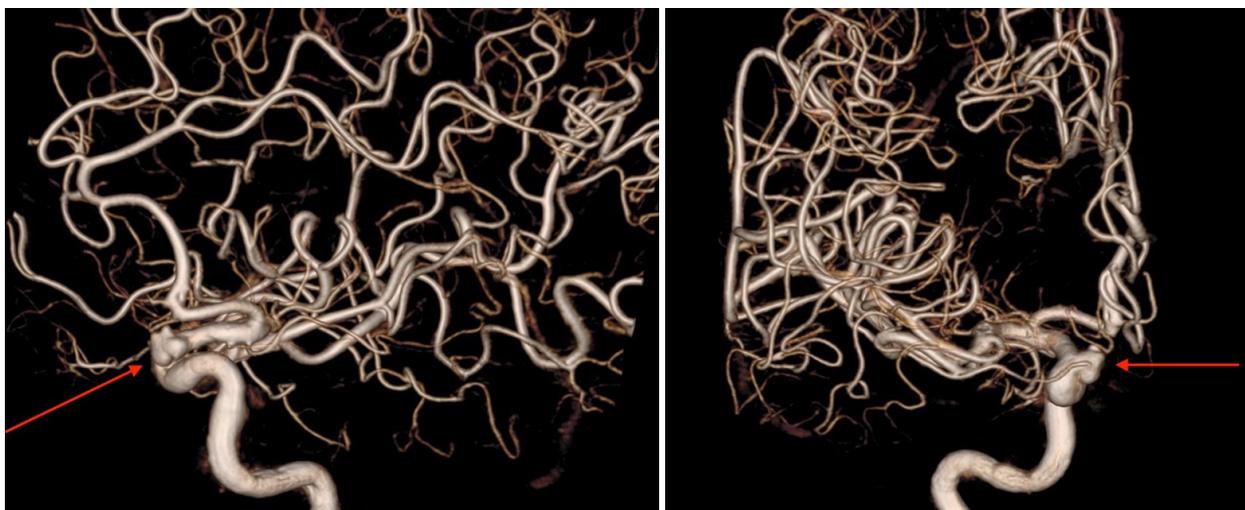


Fig. 13. Selective digital subtraction cerebral angiography in the right internal carotid artery basin. Three-dimensional modality of cerebral angiography. Aneurysm with daughter sacks in the ophthalmic segment of the right ICA (red arrow)



Fig. 14. PreSize Neurovascular software (Oxford Heartbeat Ltd) use case. The virtual projection of the 4.5 mm x 20 mm/13mm FRED X implantation

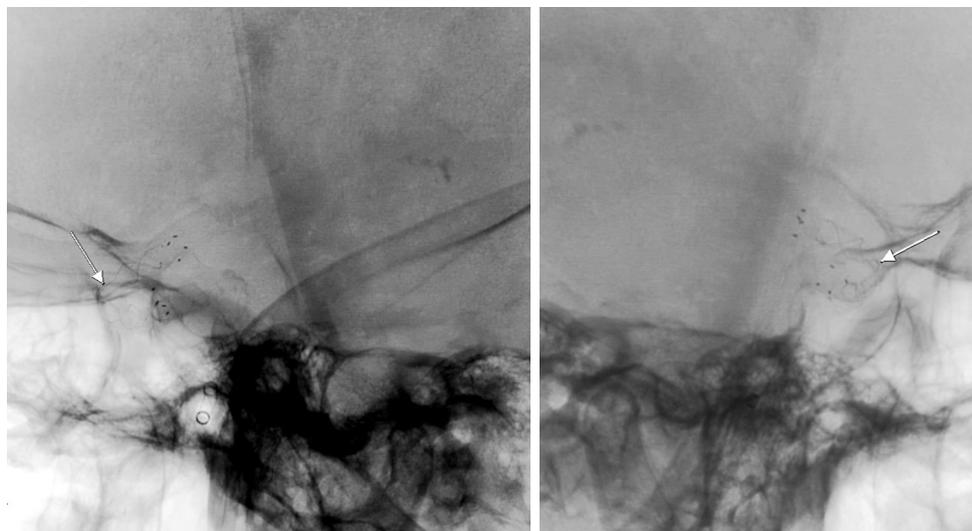


Fig. 15. Intraoperative images show an under-open flow diverter in the clinoid segment of the right ICA (white arrows)

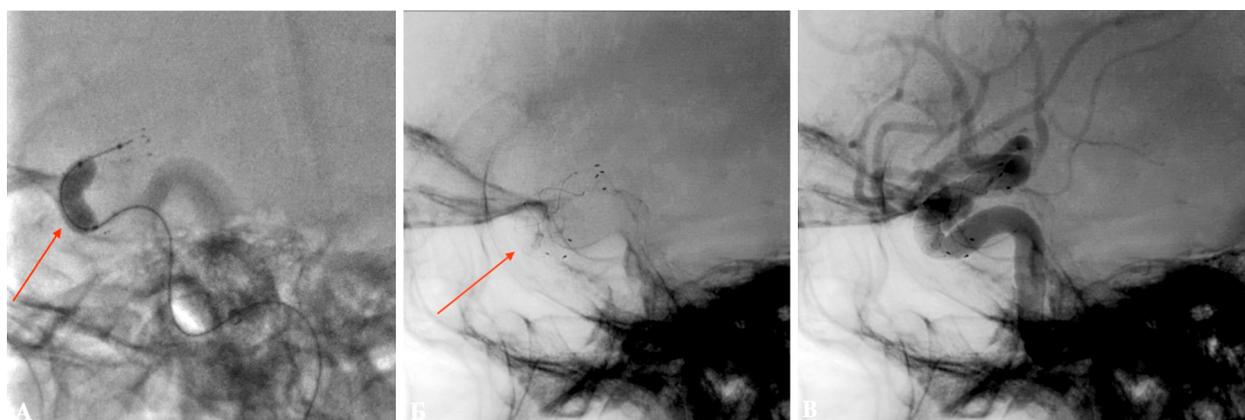


Fig. 16. Intraoperative images. Fig (A) The flow diverter's balloon plasty in the clinoid segment of the right ICA (white arrows). Fig (B) The flow diverter's shadow following the balloon plasty (red arrow). Fig (C) The follow-up angiography series shows satisfactory patency of the right ICA after the flow diverter implantation

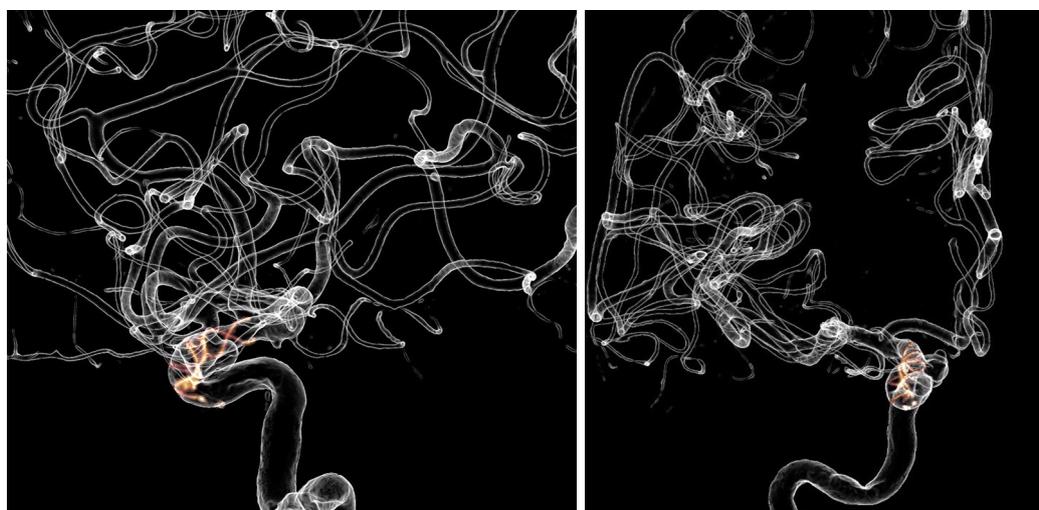


Fig. 17. The follow-up FD CT series including the virtual dilution angiography

the study group and conduct a comparative analysis with other types of flow diverters that were previously implanted in our center. To determine the incidence of complete aneurysm occlusion, all patients were assigned the follow-up angiography at 3 months and 6 months after the first follow-up DSA. We are going to include the results in our future reports.

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Conclusions:

1. In the endovascular treatment of giant and complex aneurysms, the use of new generation FREDX flow diverters (Microvention) with antithrombogenic surface subject to proper diverter sizing does not cause any technical difficulties and is controlled.

2. The use of the PreSize Neurovascular simulation software (Oxford Heartbeat Ltd.) for preoperative software simulation allows to accurately size and position a flow diverter, precisely plan the surgery, predictably reduce its duration, technical difficulties, and the risk of complications or failures, reduce the need to optimize the flow diverter's opening with the balloon angioplasty or implantation of a second flow diverter.

3. A new generation FREDX flow diverter with antithrombogenic coating is a safe and suitable device for the treatment of giant or complex structure intracranial aneurysms and multiple aneurysms. FREDX optimal sizing both diameter and length promotes proper device self-expansion and wall apposition without the need for post-deployment angioplasty in the majority of cases. When the diameter is oversized the FREDX tends not to expand fully especially around curves.

4. We have not found it necessary to use multiple FREDX in these selected cases as in the majority of Dr. Armonda's cases (>30 FREDX cases). A single FREDX may cover and treat multiple aneurysm as demonstrated in this report.

Disclosure

Conflict of Interest

None.

Ethical Standards

All procedures performed for patients during the study comply with ethical standards of institutional and national ethics committees and the Declaration of Helsinki (1964), as amended, or similar ethical standards.

Informed Consent

All patients have provided their informed and voluntary written consent to participate in the study.

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