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# Advances in flow-diversion devices for cerebral aneurysms

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# Advances in flow-diversion devices for cerebral aneurysms

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# Editorial: Advances in flow-diversion devices for cerebral aneurysms

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KEYWORDS

**flow-diversion, cerebral, aneurysm, endovascular, treatment**

Editorial on the Research Topic
Advances in flow-diversion devices for cerebral aneurysms

I am honored to co-edit the topic "*Advances in flow-diversion devices for cerebral aneurysms*" with Pervinder Bhogal and Alexander Sirakov. The material of this Research Topic has published cutting-edge research on this subject from all over the world, including clinical application research of new flow-diversion devices (FDs), FD treatment of distal aneurysms, ruptured and unruptured dissecting aneurysms, bifurcation aneurysm, antiplatelet therapy and hemodynamic study of FDs.

In the past 60 years, great success has been achieved in endovascular surgery of cerebral aneurysms. From the iron-acrylic compound (1), electrocoagulation, detachable balloon in the 1960s to the electrolytic coil in 1990s, the endovascular surgery became an alternative to surgical clipping for cerebral aneurysm treatment. The FD emerged in 2007 has fundamentally changed the previous concept of endovascular surgery of cerebral aneurysms, from intra-aneurysm filling, occlusion of the parent artery, clipping of the aneurysm neck, remodeling of the aneurysm orifice to repair the pathological arterial wall (2). This is undoubtedly correct, because the basic pathological changes for the occurrence of an aneurysm are the weakness of the intima, atherosclerosis, injury, or infection of the arterial wall. FD has greatly expanded the scope and improved the outcome of endovascular surgery of cerebral aneurysms, from large and giant to tiny aneurysms, from unrupture to ruptured blister-like/dissecting aneurysms, from side-wall to bifurcation aneurysms (3). FDs make those complex aneurysms, which are incurable by previous endovascular techniques, to be curable.

The concept of FD is derived from the experiences and lessons learned in the development of stent-assisted coiling, which provides the denser coil filling, better angiographic and clinical results. Stent-assisted coiling directly interrupts the blood flow from the parent artery into the aneurysm and leads to the thrombosis in the aneurysm sac. The concept FD is based on two principles: (1) placing woven mesh device in the parent artery changes the blood flow away from the aneurysm sac and (2) the device structure provides a scaffold for the growth of endothelial cells. This process of "new endothelialization" separates the aneurysm from the circulation and allows the gradual thrombosis of the aneurysm (4). The advantage of FD is that it can repair the weakened arterial wall with a very low recurrence rate contrasting to the high recurrence rate associated with coil embolization. In addition, when deploying the FD, the devices does not need to enter the aneurysm sac directly, thus lowered the risk of aneurysm rupture during treatment.

As the first FDA certified FD, the pipeline embolization device (PED; Medtronic Neurovascular, Irvine, California, USA) is still the most popular FD at present. Its safety and effectiveness of the off-label use have been widely published. Its clinical use has expanded from unruptured internal carotid artery aneurysms to the most cerebral aneurysms, such as anterior cerebral artery, middle cerebral artery and posterior circulation aneurysms (including posterior cerebral artery and posterior inferior cerebellar artery aneurysms; Figures 1A–D). It is a good option for ruptured and unruptured aneurysms with incorporated perforating arteries. FD has become the first-line treatment for blister-like aneurysms (5). There are also reports on the FD treatment of carotid cavernous fistulas. In our center, the FD has replaced the coil embolization in most of unruptured aneurysms due to its low complication rate, low recurrence rate and high occlusion rate (3). In a meta-analysis including 11 studies (6), the occlusion rates of unruptured aneurysms at 1 year, 1–2 years, 2 years, 3 years, and 5 years follow-up were 77%, 87.4%, 84.5%, 89.4%, and 96%, respectively. There were 5% long-term in-stent stenosis, one delayed ischemic stroke and no delayed hemorrhage of aneurysm.

There are many other FDs with different designs (2), such as Silk, Silk+ and Silk vista baby (Balt Extrusion; Montmorency, France); Surpass Streamline and Surpass Evolve (Stryker Neurovascular, Fremont, CA); The FRED and FRED Jr (Microvention, Aliso Viejo, California); p64, p48MW, and p48-HPC (Phenox, Bochum, Germany); Derivo Embolization Device (Acandis GmbH, Pforzheim, Germany); Tubridge (MicroPort, Shanghai, China) and Lattice (Accumedical, Beijing, China). Up to date, the FDA approved PED in 2011, Surpass in 2018 and FRED in 2019, all of which are used to treat large or large wide-necked intracranial aneurysms along the internal carotid artery (FDA.gov). All FDA-approved FDs consist of Nitinol or Co-Cr alloy. If the clinical scenario requires, the endovascular neurosurgeon must be proficient in at least one or two of them as well as maintain a certain understanding and familiarity with the advantages/limitations of these devices.

The main limitation of FD is ischemic stroke associated with intra-stent thrombosis, which requires dual antiplatelet therapy or GP IIb/IIIa inhibitors (7). Therefore, we must bear their related bleeding risks. Different manufacturers have designed antithrombotic coating FDs to reduce the risk of thrombosis since 2014. At present, the available antithrombotic coating FDs include Pipeline Flex embolic device with shielding technology (Medtronic Neurovascular, Irvine, California, USA),

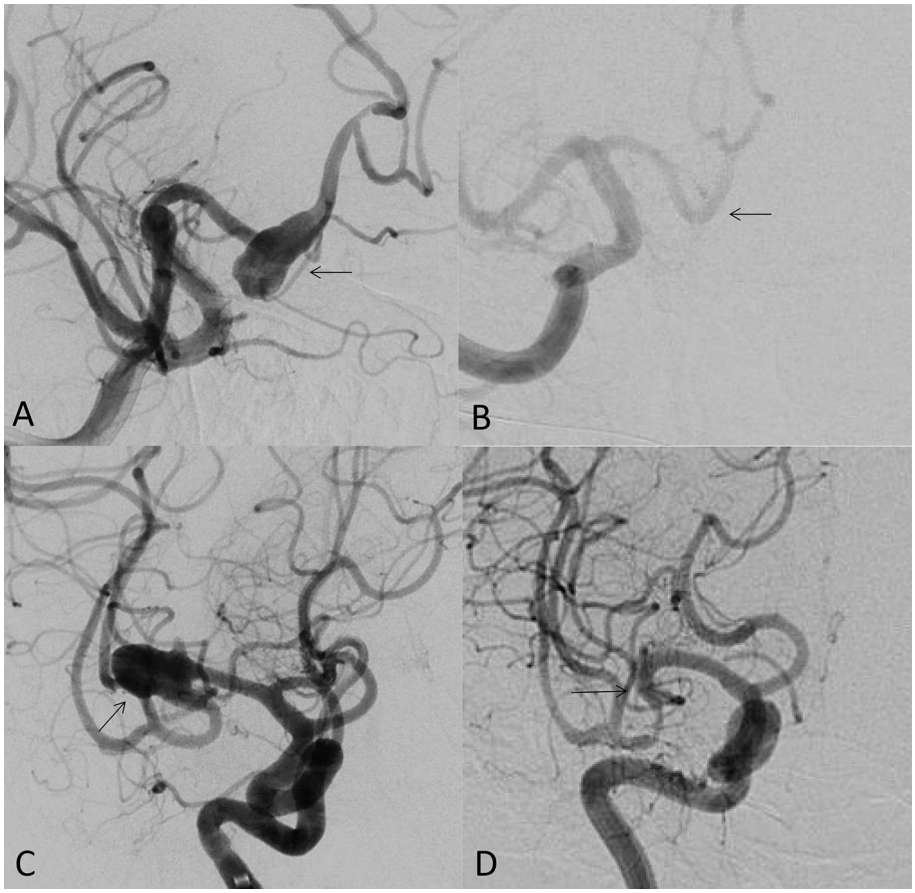


FIGURE 1
**(A)** 49-year-old male, unruptured aneurysm of the right anterior cerebral artery (arrow); **(B)** the 7 months control angiogram after PED treatment showed that the aneurysm was completely occluded (arrow); **(C)** 53-year-old female, the right middle cerebral artery bifurcation aneurysm (arrow); **(D)** the control angiogram after 9 months showed that the aneurysm was completely occluded (arrow).

Derivo embolic device (Acandis GmbH, Pforzheim, Germany) and p48-HPC (Phenox, Bochum, Germany). Preliminary follow-up data shows that the incidence of ischemia related to FDs is low and their angiographic occlusion rate is comparable to uncoated FDs.

With the increase in the off-label use of FDs in a broader clinical scenario (8), it is necessary to design and customize the specific aneurysm anatomical structure, location and shape to cover a broader range of clinical indications. The use of FDs in small arteries has been widely reported (9). The most commonly used device is PED, as well as FRED and SILK series. Few studies support the efficacy of Surpass, p64, Derivo, and Tubridge FDs in small arteries.

Finally, we thank all the authors and endovascular centers who have contributed to this topic and congratulate their great success in the use of FDs. This topic will undoubtedly continue to arouse the enthusiasm of the research, development and clinical use of FDs, and pursuit of excellent endovascular surgery results of cerebral aneurysms.

## Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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ORIGINAL RESEARCH
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# Endovascular Treatment of Intracranial Aneurysms in Small Peripheral Vessel Segments—Efficacy and Intermediate Follow-Up Results of Flow Diversion With the Silk Vista Baby Low-Profile Flow Diverter

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**Background and Purpose:** Low-profile flow diverter stents (FDS) quite recently amended peripheral segments as targets for hemodynamic aneurysm treatment; however, reports on outcomes, especially later than 3 months, are scarce. This study therefore reports our experience with the novel silk vista baby (SVB) FDS and respective outcomes after 8 and 11 months with special respect to specific adverse events.

**Materials and Methods:** Forty-four patients (mean age, 53 years) harboring 47 aneurysms treated with the SVB between June 2018 and December 2019 were included in our study. Clinical, procedural, and angiographic data were collected. Follow-ups were performed on average after 3, 8, and 11 months, respectively. Treatment effect was assessed using the O'Kelly Marotta (OKM) grading system.

**Results:** Overall, angiographic follow-ups were available for 41 patients/45 aneurysms. Occlusion or significant reduction in aneurysmal perfusion (OKM: D1, B1–B3 and A2–A3) was observed in 98% of all aneurysms after 8 months. Only 2% of the treated aneurysms remained morphologically unaltered and without an apparent change in perfusion (OKM A1). Adverse events in the early post-interventional course occurred in seven patients; out of them, mRS-relevant morbidity at 90 days related to FDS treatment was observable in two patients. One death occurred in the context of severe SAH related to an acutely ruptured dissecting aneurysm of the vertebral artery.

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**Conclusion:** The SVB achieves sufficient occlusion rates of intracranial aneurysms originating from peripheral segments, which are comparable to prior established conventional FDS with acceptably low complication rates. However, alteration of a hemodynamic equilibrium in distal localizations requires special attention to prevent ischemic events.

**Keywords: flow diversion, low-profile flow diverter, silk vista baby, small cerebral vessels, cerebral aneursym**

# INTRODUCTION

Endovascular treatment of intracranial aneurysms has experienced significant improvements in recent years (1). Most importantly, the introduction of flow diversion has driven the strategy away from intra-aneurysmal manipulation toward stepwise reconstruction of the affected segment. The comparatively novel technique allows one to circumnavigate the probation of the fragile aneurysm sac, which bears the risk for procedural rupture—and hence, fatal outcome in about a third of these cases (2). By implanting the densely woven mesh into the parent vessel, the aneurysm neck is covered and blood flow is directed away from the aneurysm orifice. Subsequently, thrombus is formed in the aneurysm sac and a novel layer of endothelium grows along the scaffold of the device (3).

Initially, flow diverter stents (FDS) were indicated for aneurysms arising from the petrous to the clinoid segment of the internal carotid artery (4). After this technique has been securely established and convincing outcomes in otherwise untreatable cases (5), flow diverters were used for smaller branches of the anterior intracranial and even the posterior circulation (6, 7). Accompanying the success of the technique, low-profile flow diverters, for example, the Silk Vista Baby (SVB, Balt, France), the p48MW (Phenox, Germany), and the FRED Junior (Mircovention, USA), have been developed and are now applied with increasing frequency to small and peripherally located, aneurysm-harboring segments of the intracranial arteries (8).

Few studies on the safety and feasibility of these FDS are available; however, reports on intermediate or long-term outcomes after treatment with low-profile FDS, especially concerning peripheral segments of the cerebral vessels, are lacking (9). Our institution has participated on the pre-market release of the SVB and reported first experience with the device (10). However, only early follow-up results were available. Therefore, our presented study aims to report the intermediate outcomes of patients treated with the Silk Vista Baby (SVB) low-profile FDS in our neurovascular center.

# MATERIALS AND METHODS

## Ethics Approval

The institutional ethics committee approved our retrospective analysis of a prospectively maintained database including cases between June 2018 and October 2020 (local IRB no AZ 208-15-0010062015). Informed consent was waived from the IRB regarding the scientific use of anonymized clinical data.

## Study Design

The study comprises patients suffering from unruptured and ruptured aneurysms as well as clinically manifesting segmental arterial disease (for example, dissecting aneurysms) of the internal carotid artery terminus, anterior cerebral artery complex, middle cerebral artery, and vertebral and basilar artery who were treated with the SVB. Unruptured aneurysms were treated primarily with the SVB or had undergone endovascular pre-treatment (coiling or flow diversion) and exhibited significant relapse after initial treatment. Decision for endovascular therapy was made after discussion of each case in the interdisciplinary cerebrovascular board, consisting of neurosurgeons, neuroradiologists, and neurologists.

Demographic data, localization, size, and morphology of each aneurysm as well as procedural and post-procedural adverse events in combination with angiographic follow-ups were collected for analysis. **Table 1** provides an overview of our patient database.

## Antiplatelet Regimen and Endovascular Treatment

In the elective setting, dual antiplatelet therapy (DAPT) was initiated 24 h prior to treatment. The loading dose consisted of 500 mg of acetylic salicylic acid (ASA) and 180 mg of Ticagrelor. DAPT was then continued for 12 months with 100 mg of ASA and 180 mg of Ticagrelor given daily; the latter was administered in two doses of 90 mg every 12 h. In one case, DAPT was performed with 100 mg of ASA and 75 mg of Clopidogrel, as the patient already had been on DAPT for cardiac indication. Mono anti-platelet therapy with 200 mg of ASA twice a day (SAPT) was performed in one case of acute subarachnoid hemorrhage, related to a ruptured fusiform-dissecting vertebra-basilar aneurysm.

All interventions were performed under general anesthesia. Prior the procedure, a bolus of 5000 international units of heparin was given via the introducer sheath prior catheterization of the supra-aortic vessels. For the endovascular procedure, tri-axial access was established via the right common femoral artery using an 8F introducer sheath, a 6F guiding catheter (Neuron Max, Penumbra, Alameda, California, USA), and a 6F distal access catheter (Sofia, Microvention, Aliso Viejo, California, USA). In proximal locations (ICA, M1, V4, and BA) the Headway 17 (Microvention, Aliso Viejo, California, USA ) was used for SVB implantation. In distal segments, mostly in the anterior cerebral artery segments, the Excelsior SL10 (Stryker Neurovascular, California, USA) was used for implantation of the smaller SVB models (2.75 mm and 2.25 mm diameter), as reported previously.

**TABLE 1 |** Demographic data and follow-up results.

| Patient | Location | Previous SAH | Neck width (mm) | Dome width (mm) | Dome height (mm) | Parent artery diameter (mm) | Treatment strategy | Device dimensions | OKM after FD | OKM 1st FU (mean FU after 2.6 'months) | OKM 2nd FU (mean FU after 7.7 months) | OKM 3rd FU (mean FU after 10.6 months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | A1/2–left | Fisher IV*[1] | 2.2 | 3 | 2.3 | 2 | Primary | SVB 2.25 × 15 | A1 | D1 | D1 | n.a. |
| 2 | M2–right | no | 2 | 5.6 | 6.6 | 2 | Primary | SVB 2.25 × 15 | C3 | D1 | D1 | n.a. |
| | | | 3 | 3.8 | 3 | | | | A1 | D1 | D1 | |
| 3 | A1/2–left | Fisher IV | 3.8 | 5.5 | 7.3 | 2.5 | Plug and pipe | SVB 2.25 × 1520 | A1 | D1 | D1 | n.a. |
| 4 | A2/3–right | no | 1.2 | 1.7 | 2.2 | 1.8 | Primary | SVB 2.25 × 1510 | A1 | D1 | n.a. | n.a. |
| 5 | A1/2–left | no | 2 | 4.5 | 4.3 | 2.2 | Primary | SVB 2.25 × 1510 | A2 | D1 | n.a. | n.a. |
| | | | | | | | | SVB 2.25 × 15 | | | | |
| 6 | A1/2–right | Fisher IV | 2.5 | 3.6 | 5.5 | 2 | Plug and pipe | SVB 2.25 × 15 | A1 | D1 | D1 | n.a. |
| 7 | PICA left | Fisher IV | 2.3 | 3.2 | 5 | 2.5 | Plug and pipe | SVB 2.25 × 10 | A1 | D1 | D1 | n.a. |
| 8 | AcomA*[2] | No | 2 | 3.4 | 4.1 | 1.9 | Primary | 3 × SVB 2.25 × 15 | A3 | C2 | n.a. | n.a. |
| 9 | A1/2–right | Fisher IV | 2 | 4 | 5 | 2.5 | Plug and pipe | SVB 2.25 × 15 | A1 | D1 | D1 | D1 |
| 10 | C6–right | no | 4.5 | 5.8 | 8.6 | 3 | Primary | SVB 3.25 × 20 | A2 | D1 | D1 | n.a. |
| 11 | RCP–right | Fisher IV*[1] | 3.8 | 5.4 | 5.3 | 3.3 | Primary | SVB 3.25 × 25 | A1 | A1 | A3*[3] | A2 |
| 12 | PICA–left | Fisher IV | 2 | 5.3 | 5.8 | 2.8 | Plug and pipe | SVB 3.25 × 10 | A1 | B1 | B1 | n.a. |
| 13 | A1/2–right | Fisher IV | 2.5 | 4 | 5 | 2.5 | Plug and pipe | SVB 2.25 × 15 | A1 | D1 | D1 | n.a. |
| 14 | A1/2–left | Fisher IV | 2 | 3.3 | 3.9 | 2.1 | Plug and pipe | SVB 2.25 × 15 | A1 | D1 | n.a. | n.a. |
| 15 | RCP–left | Fisher IV*[1] | 4.1 | 4.6 | 3 | 3.5 | Primary | SVB 3.25 × 20 | A1 | B1 | D1 | n.a. |
| | | | | | | | | SVB 3.25 × 25 | | | | |
| | | | | | | | | 1 WEB | | | | |
| 16 | A2/3 right | no | 1.8 | 2.9 | 3.2 | 1.8 | Plug and pipe | SVB 2.25 × 10 | A1 | D1 | n.a. | n.a. |
| 17 | C7 – left | Fisher | 2.8 | 2.2 | 4 | 3.2 | Plug and | SVB 3.25 × 20 | A1 | C1 | C2 | n.a. |
| | RCP–left | IV | 1.9 | 1.7 | 2 | | pipe | | A3 | A3 | A3 | |
| 18 | M1–left | Fisher IV | 2 | 4.6 | 5.1 | 3 | Plug and pipe | SVB 3.25 × 20 | A1 | B1 | D1 | D1 |
| 19 | A1/2–left | no | 2 | 2.5 | 3.5 | 2 | Primary | SVB 2.25 × 15 | A1 | B2 | B2 | B2 |
| 20 | C6–left | Fisher IV | 2.4 | 3 | 5.3 | 3.5 | Plug and pipe | SVB 3.25 × 25 | A1 | D1 | D1 | n.a. |
| 21 | PICA–left | Fisher IV | 3.9 | 3.9 | 8.3 | 2.6 | Plug and pipe | SVB 2.75 × 25 | A3 | D1 | D1*[4] | n.a. |
| 22 | M1–right | no | 3.5 | 6 | 6 | 2.6 | Plug and pipe | SVB 2.25 × 15 | A1 | A1 | A1 | n.a. |
| | | | | | | | | SVB 2.75 × 15 | | | | |
| 23 | A1/2–left | Fisher IV | 4.9 | 5.9 | 4.8 | 2.6 | Plug and pipe | SVB 2.75 × 20 | A1 | B1 | B1 | B1 |
| 24 | A1/2–right | Fisher IV | 3.9 | 5.3 | 3.9 | 2.2 | Plug and pipe | SVB 2.25 × 20 | A1 | D1*[5] | D1 | n.a. |
| 25 | A1/2–right | Fisher IV | 2.2 | 3.3 | 3.3 | 2.2 | Plug and pipe | SVB 2.25 × 15 | A2 | D1 | D1 | D1 |
| 26 | A1/2–left | no | 2.5 | 2.8 | 2.9 | 1.8 | Primary | SVB 2.25 × 15 | B1 | D1*[5] *[6] | n.a. | n.a. |
| 27 | V4/PICA–left | no | 2.8 | 6.0 | 7.0 | 3.0 | Primary | SVB 2.75 × 15 | A3 | B3 | C2 | n.a. |
| 28 | M1–right | Fisher IV*[1] | 2.3 | 2.6 | 3.7 | 2.2 | Primary | SVB 2.25 × 15 | A1 | A1 | D1 | D1 |
| 29 | RCA | Fisher IV | 8 | 14 | 12 | 2.6 | Plug and pipe | SVB 2.75 × 20 | A2 | A2 | D1*[5] | D1*[5] |

*(Continued)*

**TABLE 1** | Continued

| Patient | Location | Previous SAH | Neck width (mm) | Dome width (mm) | Dome height (mm) | Parent artery diameter (mm) | Treatment strategy | Device dimensions | OKM after FD | OKM 1st FU (mean FU after 2.6 'months) | OKM 2nd FU (mean FU after 7.7 months) | OKM 3rd FU (mean FU after 10.6 months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | A1/2–left | No | 1.7 | 2.1 | 1.7 | 1.7 | Primary | SVB 2.25 × 15 | A2 | n.a. | n.a. | n.a. |
| 31 | A1/2–right | Fisher IV | 3.2 | 3.4 | 3.4 | 2.2 | Plug and pipe | SVB 2.25 × 15<br>SVB 2.25 × 20 | A1 | C2 | n.a. | n.a. |
| 32 | BA | No | – | – | – | 2.5 | Primary | 2 × SVB 2.75 × 15 | – | – | – | – |
| 33 | A1/2–right | Fisher IV | 2.7 | 2.6 | 2.9 | 2.4 | Revision | SVB 2.25 × 20 | A2 | D1 (right)<br>C3 (left) | n.a. | n.a. |
| 34 | M1–left<br>M1/2–left | Fisher III | 3<br>5.8 | 3.2<br>10 | 3.1<br>18 | 2 | Primary<br>Plug and pipe | SVB 2.25 × 20 | A2<br>A3 | A2<br>D1 | A2<br>D1 | A2<br>D1 |
| 35 | BA | No | 1.6 | 1.6 | 2 | 1.8 | Primary | SVB 2.25 × 15<br>Rebel 2.5 × 8 | A1<br>Reconst. | n.a. | n.a. | n.a. |
| 36 | V4–right | Fisher III | – | – | – | 3.1 | Primary | SVB 2.75 × 15<br>SVB 2.75 × 20<br>4 x p48_HPC 3 × 18 (4)<br>3 x p48_HPC 3 × 15 (3)<br>P48_HPC 3 × 12<br>Rebel 4.5 x 12 | A1 | A2 | n.a. | n.a. |
| 37 | C6–right | No | 6 | 7.1 | 5.1 | 3.5 | Plug and pipe | SVB 2.75 x 15<br>SVB 2.75 x 20<br>SVB 3.25 x 20<br>SVB 3.25 x 25<br>3 x p48_HPC 3 x 18<br>ilk 5 x 40 | A2 | A2 | n.a. | n.a. |
| 38 | C6–left | No | 4 | 7 | 9 | 3.2 | Primary | SVB 3.25 x 25 | A3 | D1 | D1 | D1 |
| 39 | C6–left | No | 5.4<br>3.6 | 7<br>3 | 7.5<br>3.4 | 3.1 | Primary | SVB 3.25 x 25 | A3<br>A2 | C1<br>D1 | n.a. | n.a. |
| 40 | A2/3–left | No | 3.6 | 5 | 5 | 2 | Plug and pipe | SVB 2.25 x 15 | A1 | A2 | B2 | n.a. |
| 41 | C6/7–right | Fisher IV | 1.9 | 8.3 | 6 | 3.1 | Plug and pipe/ revision | SVB 3.25 x 15 | A3 | B2 | n.a. | n.a. |
| 42 | A2/3–left | No | 1.8 | 2.3 | 2.6 | 1.9 | Primary | SVB 2.25 x 10 | B2 | D1 | n.a. | n.a. |
| 43 | A1/2–left | Fisher IV | 2 | 3 | 2.4 | 2.7 | Plug and pipe | SVB 2.75 x 15 | A1 | D1 | n.a. | n.a. |
| 44 | M1/2–left | No | 5 | 9 | 14 | 2.3 | Primary | SVB 2.75 x 20<br>2 Coils | A3 | B2 | C2 | n.a. |

*[1]*Patient priorily suffered SAH due to aneurysm of different location.*

*[2]*Both right and left A1-A2 junctions were treated via flow diversion as the AcomA aneurysm got influx from both A1 segments (Double-C-stenting).*

*[3]*Patient underwent aneurysm retreatment with PED as the initially implanted SVB had contracted.*

*[4]*Angiographic FU after 5months revealed asymptomatic occlusion of the parent artery (left V4).*

*[5]*FU shows sufficient flow diversion of the A1-A2 junction, however, angiography revealed contralateral aneurysm influx.*

*[6]*Patient underwent retreatment and flow diversion of the contralateral A1-A2 junction with further SVB (look at patient 33).*

Sufficient opening of the implanted device and patency of the parent artery were controlled immediately after flow diverter implantation and again 15 min later. Also, potentially delayed perfusion of covered branches was controlled angiographically after deployment. In two cases, a covered branch exhibited significantly delayed perfusion and required further pharmaceutical intervention. For this, a bolus of Eptifibatid (©Integrilin, GlaxoSmithKline, Ireland) was given initially (180 μg/kg) and was continued as infusion therapy for 24 h (0.2 μg/kg per min). In both cases, no further treatment was necessary.

## Post-interventional Course

Electively treated patients were extubated directly after the procedure and were monitored continuously at our intensive care unit (ICU) for at least 24 h. Emergency patients were extubated in the further course at the ICU depending on their neurologic condition. Moreover, non-enhanced cranial computed tomography (CCT) and standardized neurologic examination were performed for every patient within 48 h post procedure in order to detect or exclude potential haemorrhagic or ischemic complications.

## Follow-Up Regimen

Efficacy of flow diversion was assessed immediately after flow diverter deployment using the O'Kelly-Marotta (OKM) grading scale (11). Efficacy of the treatment was re-assessed angiographically aiming for follow-up DSAs 3, 9, and 24 months after implantation and compared to the initial OKM grading.

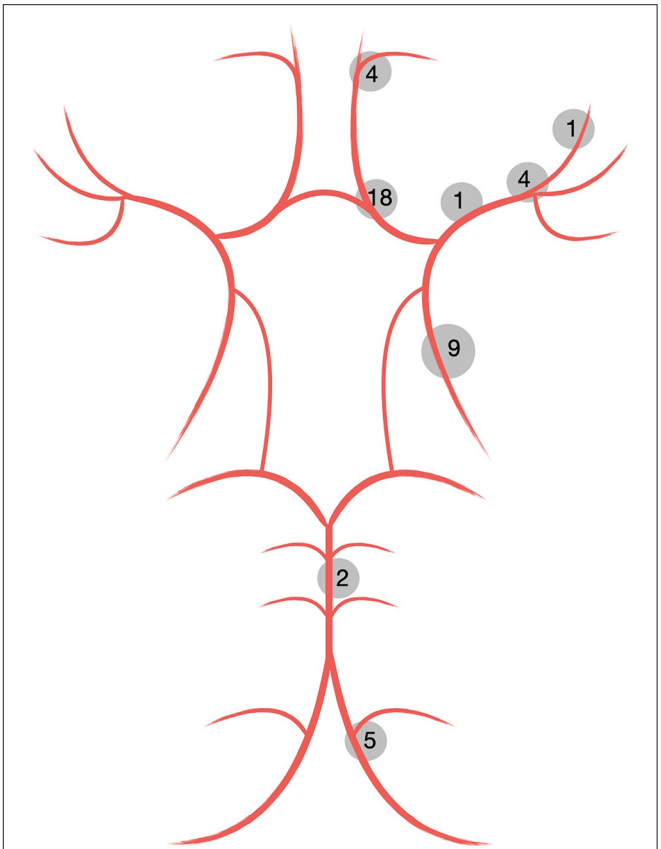


**FIGURE 1 |** Distribution of cerebral aneurysms treated with the SVB.

# RESULTS

## Patient Population and Aneurysm Characteristics

Intermediate follow-up results from patients treated with the low-profile SVB flow diverter were available in 44 individuals (31 female and 13 male patients with a mean age of 52.6 years ranging from 18 years to 83 years) in our analysis. Those 44 patients harbored a total of 47 aneurysms and were treated between June 2018 and December 2019 in our institution.

The majority—41 cases—were suffering from saccular intracranial aneurysms. The remaining three patients suffered from dysplastic segmental, partially stenosive basilar artery disease and presented as acute stroke in our emergency department.

**Figure 1** graphically summarizes the anatomical distribution and corresponding frequencies of all included aneurysms. **Table 1** provides an overview of the treated patients and the corresponding lesions.

## Treatments

Overall, 44 patients were treated with the SVB. Of those, 21 were primarily treated with flow diversion, 22 underwent retreatment after preceding coil embolization, and 1 patient underwent revision of an unsuccessful case of flow diversion with insufficient aneurysm occlusion in follow-up imaging.

In 36 cases, a single SVB was implanted, and in 6 patients, two overlapping SVB were used for sufficient coverage of the target lesion. One patient required implantation of three SVB (two unilaterally, one contralaterally) due to a wide-necked aneurysm of the anterior communicating artery (AcomA) with significant additional contralateral perfusion.

Four patients required implantation of additional devices to achieve technically sufficient results. The first patient suffered from an aneurysm originating from the left-hand M1-M2 segment that measured 9 × 14 mm and revealed signs of substantial mural inflammation, i.e., contrast enhancement of the thickened aneurysm wall together with peri-aneurysmal edema. To promote immediate stasis and relief of transmural force, two coils were loosely implanted in jailing technique as reported earlier (12).

In three patients, further stents were implanted synergistically. In the first of those cases, four SVB were implanted to treat an aneurysm located in a segment with large-caliber differences and a highly challenging, short distal landing zone. Primary attempt was to implant a first-generation Silk+ flow diverter (Balt Extrusion, Montmorency, France), which had failed due to insufficient definition of the distal landing zone with significant subsequent retraction.

Another patient was treated with a balloon-mounted coronary stent (REBEL, Boston Scientific, Maple Grove, USA) to

reconstruct a high-grade stenosis proximal to the aneurysm-bearing segment. The remaining patient was treated with an additional low-profile FDS (p48MW_HPC, Phenox, Bochum, Germany) to treat extensive, long-segmental alterations with large differences in the proximal and distal landing zones.

## Technical and Clinical Adverse Events

### Material-Related Adverse Events

In four patients, the SVB shortened immediately after insertion. In two of those cases, undersizing was decisive in retrospect. In the remaining two patients, the tortuosity of the target vessel was the underlying cause for malplacement requiring additional implantation of a second SVB in telescoping (stent-in-stent) technique.

In a fifth patient, the second follow-up after 5 months revealed distal device shortening resulting in insufficient aneurysm coverage. Related to significant differences in size of the proximal and distal landing zone, which were causative for shortening, retreatment was performed using an appropriately sized Pipeline 2 Shield (Medtronic, Covidien, USA).

All cases of shortening exclusively occurred during the first months after introduction of the SVB related to the rationale of implanting as little foreign material into the target vessel as possible.

### Peri-Interventional Adverse Events

Two patients experienced peri-interventional branch occlusion or significantly delayed perfusion in the downstream territory. In one of the patients, the distal left-hand side ACA territory showed delayed perfusion after implantation of the SVB. To avoid stroke and permanent disability, body weight adapted intravenous application of Eptifibatid (GlaxoSmithKline, Ireland) was started immediately. The treatment significantly improved perfusion of the ACA territory in the angio suite. However, after waking up from general anesthesia, the patient exhibited a right-hand side hemiparesis and aphasia. Immediate cranial computed tomography revealed focal hypodensity in the left-hand side cortical MCA territory as an early sign of infarction, causative for the neurological deficit. Opacification of the MCA territory had been unremarkable during and at the end of the procedure. We therefore attribute the infarction to be a consequence of the long duration of the technically challenging intervention (ca. 4 h) together with comparatively low blood pressure during the procedure. At the last follow-up, 10 months after flow diversion, only mild speech disturbances remained.

The second patient experienced an asymptomatic transient occlusion of a temporal MCA branch, which was successfully treated with Eptifibatid as described above.

### Adverse Events During the Early Post-interventional Period

Delayed adverse events occurred in seven patients.

Permanent stent occlusion with transient neurologic deficits was observed in one individual. The patient had suffered from acute aneurysmal SAH caused by one of two aneurysms originating from the left-sided MCA bifurcation and developed delayed ischemia due to classic SAH-associated vasospasm. He was initially treated with endovascular coiling; however, retreatment was required related to aneurysm relapse. After the patient had recovered completely, SVB was implanted for definitive treatment of both aneurysms. Three days post procedure, the patient presented with fluctuating aphasia and subtle facial paresis. Re-angiography revealed absent opacification of the distal, SVB-covered M1–M2 segments with sufficient antegrade perfusion of the proximal M1, as well as SVB-covered segment and its side branches. Overall, no territorial or segmental perfusion deficit was apparent, as compensatory leptomeningeal collaterals originating from the ipsilateral ACA, which had developed during subacute vasospasm after SAH, were supplying the distal portion of the M1–M2 segments retrogradely. **Figure 2** provides a detailed illustration of the case. At the last follow-up, 8 months after flow diversion, the patient revealed subtle residual speech disturbance.

Transient stent occlusion occurred in one patient after FDS implantation for treatment of an ICA aneurysm originating from the orifice of the left posterior communicating artery. Five h post procedure, the patient suddenly presented with a right-sided hemiparesis. Re-angiography revealed in-stent thrombosis resulting in distinctly reduced perfusion of the downstream ICA territory. After administration of Eptifibatid (GlaxoSmithKline, Ireland, 180 μg/kg) the angiogram revealed complete resolution of the thrombus and improved perfusion. No further treatment was required and the patient's neurologic deficits resolved completely.

Acute infarction in the aftermath of flow diversion appeared in one patient, who had initially suffered from aneurysmal SAH, which was treated with coiling. The broad-based AcomA aneurysm relapsed and required an additional intervention. Flow diversion in crossover technique was considered to be the only sufficient option. SVB was implanted from the right A2 segment into the left A1 segment. After implantation of the flow diverter, control injection revealed a delayed opacification of the left ACA territory. Eptifibatid was given as described above and improved perfusion of the depending ACA territory. However, the patient presented with reduced vigilance during the postinterventional course and developed partial bilateral cortical infarction in the ACA and MCA territory.

Two patients suffered from hemodynamically relevant vasospasm manifesting between 1 and 3 weeks after endovascular treatment, a phenomenon that we reported earlier (13).

In one case, MRI revealed extensive wall enhancement of a large MCA bifurcation aneurysm together with substantial peri-aneurysmal edema. In this patient, transient worsening of the pre-existing brachial paresis occurred 6 h after SVB implantation related to the progressive inflammatory mass effect of the aneurysm. Prophylactic anti-inflammatory medication (Dexamethasone 4 mg every 8 h) had already been given and was then amended by additional Celecoxib 100 mg daily. Neurologic deficits resolved completely after a period of 5 days. **Figure 3** provides an overview of the respective case.

One patient died in the aftermath of extensive endovascular treatment of an acutely ruptured, multi-segmental dissecting vertebra-basilar aneurysm causing major SAH due to episodes of uncontrollable intracranial pressure.

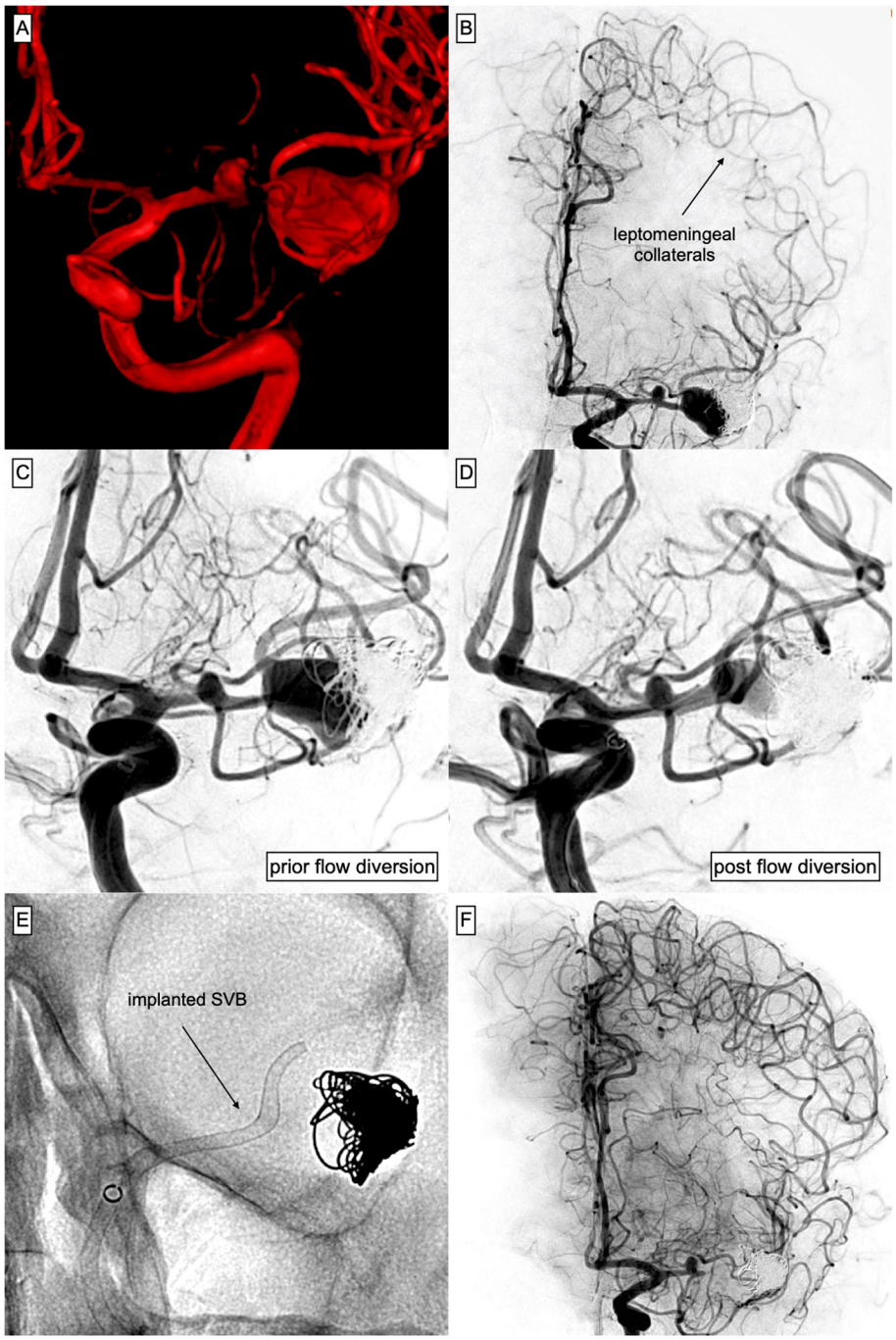


**FIGURE 2 |** Complex course of a ruptured aneurysm arising from the MCA-bifurcation, treated with Plug & Pipe. **(A)** 3D reconstruction of the acutely ruptured, complex MCA-bifurcation aneurysm measuring 10 mm × 18 mm. **(B)** DSA 3 weeks after protective coiling of the ruptured aneurysm aiming for fundus protection and preservation of the bifurcation. Note the distinct ACA–MCA collaterals that had developed with SAH-associated subacute vasospasm. **(C)** Aneurysm after coiling, prior TO SVB implantation. Also note the coincidental aneurysm arising from the M1 segment and the stenosis preceding the aneurysmal orifice. **(D)** Control injection after implantation of the SVB [**(E)** shows the corresponding radiograph] into the MCA. The device covers the proximal M1 aneurysm and extends into the superior branch of the bifurcation, significantly reducing aneurysmal inflow. **(E)** Non-enhanced radiograph corresponding to **(D)**. **(F)** Three days after SVB implantation, the patient had developed a subtle right-sided facial paresis and fluctuating aphasia. Immediate DSA revealed no opacification of the distal MCA including the bifurcation-aneurysm but patency of the proximal SVB including the coincidental M1 aneurysm and a temporal MCA branch arising from the aneurysm base. However, ACA–MCA collaterals completely supplied the peripheral MCA territory distal to the occluded segment. A significant perfusion gradient between the proximal M1 segment and the stenotic pre-bifurcation segment had developed, which culminated in the manifestation of a distinct watershed zone after SVB implantation. Blood pressure was raised and the neurological deficit ceased subsequently. The patient had recovered completely after 48 h.

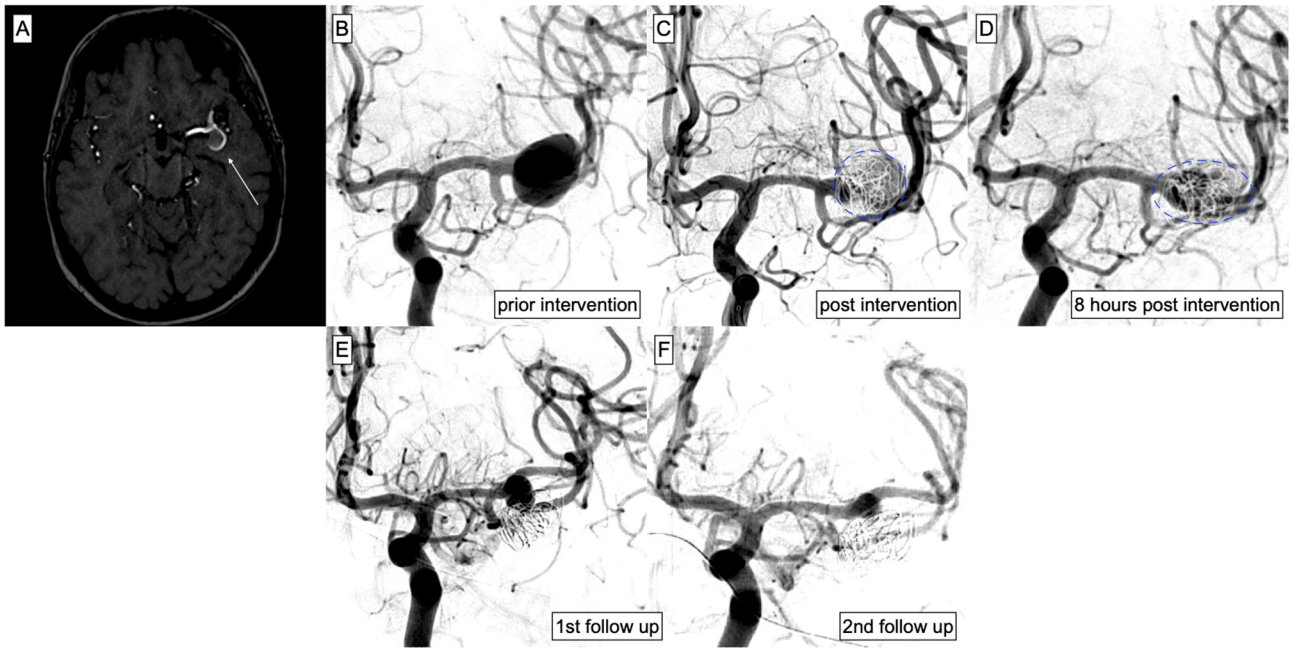


**FIGURE 3 |** Endovascular treatment of an MCA aneurysm on the left side. MRI was performed due to fluctuating aphasia and hemiparesis. **(A)** Time of flight angiography revealed the aneurysm (white arrow) located at the left MCA bifurcation measuring 15 mm × 14 mm × 11 mm. **(B)** DSA confirmed the broad-based aneurysm. The patient refused open surgery and decided for endovascular treatment. **(C)** The aneurysm had grown 2 mm in size and its morphology had changed within 24 h, justifying again the prompt treatment by indicating a highly unstable situation. Therefore, decision was made for immediate protective coiling and flow diversion. The SVB was successfully implanted after loose coiling of the aneurysm sac (proximal landing zone: M1, distal landing zone: superior branch of the MCA bifurcation). **(D)** Eight h post intervention, the patient developed increasing hemiparesis of the left side. DSA was performed to exclude potential stent occlusion. The vessel proved patent; however, the morphology of the aneurysm and the coil package had changed again (highlighted in blue), indicating inflammatory changes of the aneurysm. Anti-inflammatory medication was given and the patient's symptoms resolved completely within 5 days. **(E)** The first regular follow-up 3 months post-treatment revealed a stable situation and decrease of the perfused aneurysm part/lumen. **(F)** One month later, DSA was performed again to decide on the further course of anti-inflammatory therapy. The perfused part of the aneurysm had further decreased and anti-inflammatory medication was discontinued.

## Early and Intermediate Aneurysm Occlusion Rates

Overall, angiographic follow-ups were available for 41 patients, harboring a total of 45 aneurysms. The occlusion rates after approximately 3, 8, and 11 months, were evaluated according to the O'Kelly-Marotta scale.

### Early Follow-Up Results (Mean of 2.6 Months)

Early angiographic follow-ups revealed subtotal or complete aneurysm occlusion (OKM C1–C3 and D1) in 28 aneurysms (62%) and significant reduction of the residually perfused portion of the aneurysm sac (OKM B1-B3) in eight further aneurysms (18%).

In summary, the first follow-up indicates early sufficiency of the treatment in approximately 80% of the cases.

In one case, implantation of a singular SVB in the A1–A2 segment for treatment of a predominantly unilaterally filled AcomA aneurysm resulted in an angiographically sufficient result post implantation (OKM D1). However, after establishing a novel hemodynamic equilibrium after 4 months, the aneurysm was re-perfused from the contralateral A1 segment and required retreatment with a second contralaterally placed SVB.

Prolonged aneurysm opacification with delayed washout (OKM A2–A3) was achieved in six aneurysms (13%). Only three aneurysms (7%) did not show early apparent changes in perfusion after implantation (OKM A1).

### Intermediate Follow-Up Results (Mean of 7.7 and 10.6 Months)

The third follow-up did not reveal relevant changes compared to the second follow-up. Therefore, results are presented together. At both time points, 34 aneurysms (76%) revealed subtotal or complete occlusion (OKM: D1 and C1–C3).

Significant reduction of the residually perfused portion of the aneurysm sac (OKM B1–B3) was evaluated in 10 aneurysms (22%). Five of the latter (10%) revealed a small remnant (OKM B1–B3), indicating significant but yet incomplete neo-intimalization. The remaining five aneurysms showed prolonged intra-aneurysmal opacification representing significantly reduced influx accompanied by stagnation of intraaneurysmal blood (OKM A2–A3). Only one aneurysm (2%), which was located at the MCA bifurcation, demonstrated an unaltered aneurysm influx (OKM A1). **Figure 4** provides an illustration of the particular case.

In summary, successful treatment was observed in 98% of treatments after approximately 8 months. **Figure 5** provides an example of a successfully treated distal ACA aneurysm with complete occlusion 5 months after SVB implantation. Two percent remained morphologically unaltered.

In conclusion, 45 aneurysms were available for angiographic follow-up imaging. Occlusion or significant reduction in aneurysmal perfusion (OKM: D1, C1–C3, B1–B3, and A2–A3) were observed in 44 aneurysms (98% of all aneurysms) after approximately 8 months, while the patients remained under dual platelet inhibition. Only 2% of the aneurysms remained morphologically unaltered and did not show an apparent change in perfusion (OKM A1).

## DISCUSSION

To our best knowledge, this study is the first report on intermediate follow-up results after aneurysm treatment with the Silk Vista Baby flow diverter. Reporting efficacy, technical experiences, and adverse events that occurred in our patients is of significance, as the novel FDS is indicated and has been CE-approved for treatment of small peripheral segments of the distal intracranial arteries, a territory that is not accessible for the comparatively large flow diverters of earlier generations and thus has been applied in flow diversion therapy only recently (10).

Efficacy of endovascular treatment with the Silk Vista Baby appears to be at least comparable to earlier reports after flow diversion in more proximal locations with occlusion rates ranging from 73.3% to 89.2% at 12 months post intervention (14–16).

A major difference between these investigations and our study is the origin of the aneurysms from distal cerebral vessels, oftentimes involving bifurcations of the peripheral anterior and posterior intracranial circulation. A previous investigation by Michelozzi and colleagues reported a mean time to occlusion for bifurcation-associated aneurysms of approximately 12 months after endovascular flow diversion using the PED (Medtronic), FRED (Microvention), and Silk (Balt Extrusion) (17). Considering the available studies and our results, aneurysm treatment with the Silk Vista Baby is equally effective in distal cerebral vessels, despite the involvement of hemodynamically complex bifurcation aneurysms.

Another factor requiring consideration in this context is the duration of dual antiplatelet treatment, an essential prerequisite for the avoidance of thrombo-embolic complications, which inevitably decelerates intra-aneurysmal thrombosis, formation of the neo-intima, and, thus, aneurysm occlusion. A general guideline for DAPT in flow diversion is lacking.

In our institution, DAPT is routinely administered for 12 months aiming to avoid FDS-associated ischemic complications, which are exemplarily caused by intimal hyperplasia and delayed device induced vasospasm, as reported earlier (12). In contrast, the aforementioned studies applied DAPT for <6 months in average, followed by ASA monotherapy. Considering the significantly greater duration of DAPT in our patients, the actual efficacy of the SVB is probably even superior to the distinct FDS in those reports, as aneurysm occlusion times and rates are comparable despite the difference in hindering platelet function medication.

Technical issues were dominated by device shortening either during or shortly after implantation (5/44 patients, 11.4%). In our experience, it seems advisable to include device shortening as a relevant technical epiphenomenon into calculation for device selection. Empirically, if the proximal landing zone equals the diameter of the device or is even larger, a proximal shortening of 50% must be expected if only half of the stent is already implanted. Therefore, it seems advisable to consider the next longer version of the device in order to avoid proximal foreshortening into the aneurysm, which may jeopardize re-catheterization and further synergistic device implantations if necessary.

In seven patients, clinically apparent adverse events occurred, and one already critically ill patient died in the aftermath of the treatment during intensive care.

Two of the seven patients experienced clinically relevant prolonged or persisting neurological deficits. According to our patient population, we consider a comparatively low rate of permanent neurologic deficits of 4.8% (2 out of 41 patients). Prior studies, in contrast, reported distinctly increasing rates of clinical adverse events with persisting neurologic disorder after flow diversion of aneurysms arising from distal segments of the anterior cerebral artery and the middle cerebral artery ranging from 10% to 13% (18, 19).

The majority of symptomatic (but predominantly transient) adverse events in our patients were the sequel to focal hypoperfusion of eloquent brain parenchyma after flow diverter implantation. The latter, especially when performed in peripheral segments, causes immediate changes in loco-regional blood flow potentially manifesting with TIA-like episodes, which cease as soon as perfusion is restored to a sufficient level. In our experience, the adjustment of local perfusion, which happens within the first days after SVB implantation, can culminate in neurologically apparent ischemia despite sufficient dual platelet inhibition, especially if long-lasting episodes of vasospasm accompanied a preceding aneurysmal SAH. An exemplary case is discussed and shown in **Figure 2**.

The occurrence of this distinct phenomenon is more likely, if the perfusion of the MCA-bifurcation undergoes alteration via flow diversion. Especially in cases where the flow diverter requires implantation into an inferior branch of the MCA bifurcation, the orifices of one or more superior MCA branches must inevitably be covered by the hemodynamically active implant. Then, anterograde blood flow in those covered branches supplying the MCA territory close to the ACA territory is decreased and the perfusion of the border zone is further restricted. Corresponding to the pressure drop in the border zone, which is predominantly supplied by the MCA, perfusion via the ACA and its downstream leptomeningeal collaterals increases in a compensatory manner, potentially causing flow stagnation or even flow reversal within functionally connected MCA branches. During this hemodynamic adjustment, the formation of a thrombus in the respective branch is possible and—independently—the manifestation of focal neurological symptoms is comparatively frequent.

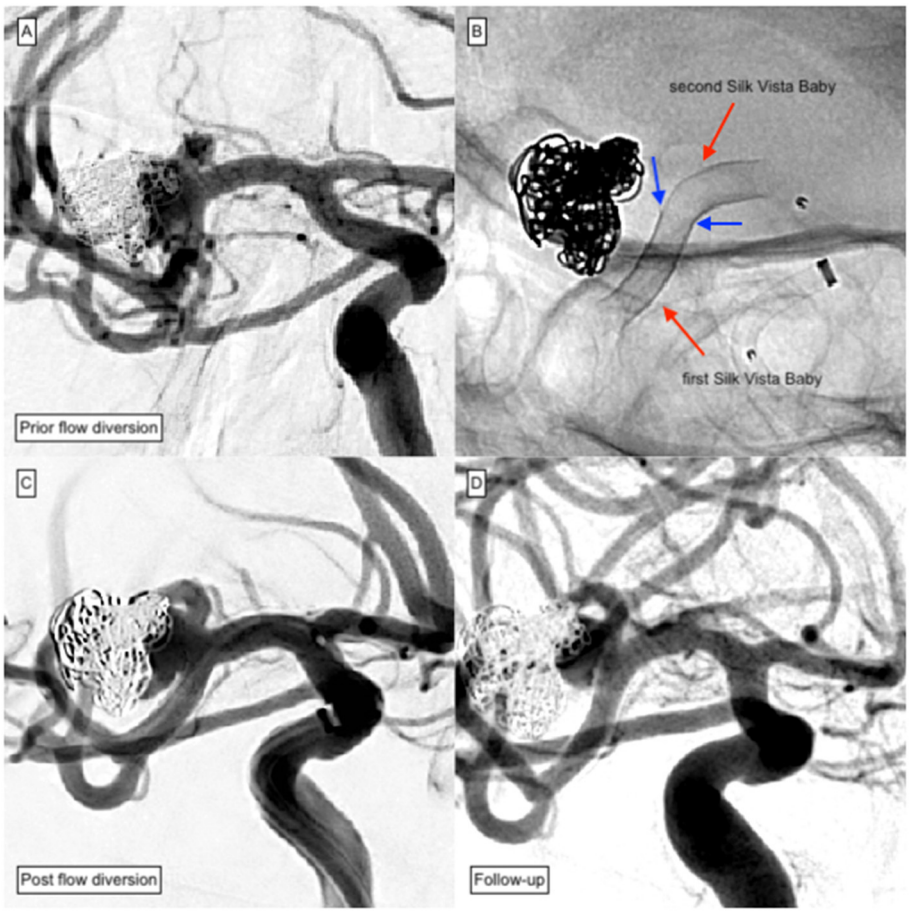


**FIGURE 4 |** Plug and Pipe treatment of a previously ruptured MCA aneurysm of the right-handed side. Due to the difference in diameter between the M1 and M2 segments, extensive proximal shortening occurred after implantation of the first SVB and required complementary implantation of a second SVB. **(A)** DSA of a non-ruptured saccular aneurysm located at the right-handed side MCA bifurcation after protective coiling shows significant reperfusion and coil compaction. Decision was made for retreatment with SVB. **(B)** The first implanted SVB had shortened proximally (blue arrows) and did not sufficiently cover the aneurysm. Consequently, implantation of an additional device in telescoping technique was performed. **(C)** The control injection showed the timely opacification of all MCA branches including the covered superior truncus. **(D)** To avoid ischemic complications, DAPT was extended to 16 months. However, a significant remnant was observable at 15 months follow-up.

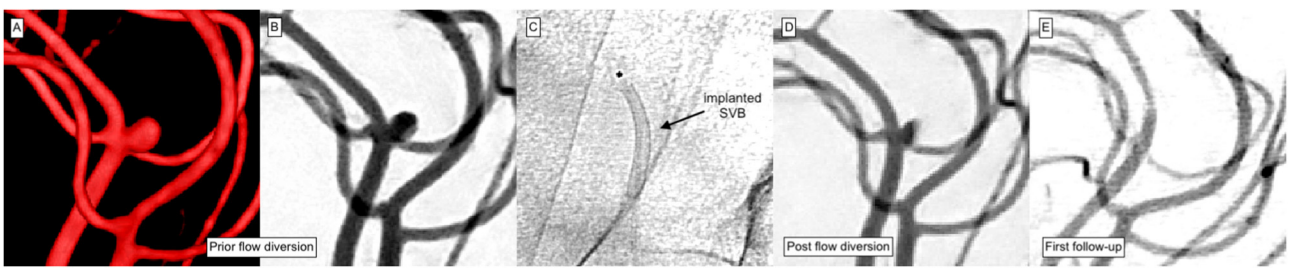


**FIGURE 5 |** Treatment of a peripheral left ACA aneurysm. The patient exhibited further aneurysms at the contralateral MCA bifurcation and the right SUCA. **(A)** 3D angiogram demonstrates an incidental peripherally located aneurysm of the left ACA. Interdisciplinary consent for treatment using the SVB was made. **(B)** The working projection was used to quantify the target lesion and the parent artery. The saccular aneurysm measured 2.3 mm × 2.6 mm. **(C)** The SVB was implanted using the Excelsior SL10 microcatheter (Stryker Neurovascular) for device delivery. SVB was positioned within the pericallosal artery; the aneurysm arising from the callosomarginal orifice was used to center the device. **(D)** Control injection revealed immediate reduction of aneurysmal perfusion. **(E)** The first follow-up after 5 months showed the exclusion of the aneurysm from the intracranial circulation. The covered branch remains patent but exhibits a slightly reduced diameter without delayed flow.

Therefore, presence of peripheral collaterals, which may cause conflicting retrograde flow in branches distal to a FDS-treated segment, has to be evaluated critically and included into treatment planning as well as patient information.

Notably, in our study, no further events occurred up to and including the last follow-up. Most importantly, delayed aneurysm rupture as a well-known critical postprocedural complication did not occur in any of our patients (20).

Comparable studies with the SVB are lacking; however, a meta-analysis investigating complication rates of flow diversion using the Pipeline Embolization Device (Medtronic) and Silk flow diverter (Balt Extrusion) revealed peri-procedural technical complications between 6.6% and 12.2%, while mortality was reported to range between 1.2 and 4.4% (21).

Our study suffers from a number of limitations. The presented results represent only a small patient collective treated in our singular institution. We therefore suggest the prospective collection of patients treated with the SVB in different centers. Furthermore, long-term angiographic follow-up data of our cohort are yet not available and should be reported as soon as they become available.

## CONCLUSION

Our study demonstrates the effectiveness of the Silk Vista Baby flow diverter for aneurysm treatment in small peripheral vessel segments after 8 and 11 months. Despite our comparatively long prophylactic DAPT regimen, occlusion rates are comparable to prior studies of flow diversion in more proximal locations applying significantly shorter periods of DAPT.

However, alteration of the hemodynamic equilibrium in distal localizations demands special attention to prevent ischemic events including careful supervision of patients especially in the very early post-treatment phase and a quick and comprehensive way to react to such emerging events. Therefore, a patient's collateral status and the potential effect of inevitably covered non-aneurysmal side branches should be considered in detail prior to flow diversion.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB University Hospital Leipzig. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

UQ performed the interventions. EW and MS were responsible for patient monitoring and data acquisition of the post-interventional period. JM performed image analysis. NB performed review of the clinical information. FA performed vascular analysis. CR performed interventions and post-processed imaging data. K-TH wrote and reviewed the paper. CS performed interventions and follow-up imaging and analysis. SS designed the study, wrote the paper, and performed interventions. M-SS wrote the paper, performed image analysis, and statistical review. All authors contributed to the article and approved the submitted version.

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# Flow Diversion for Intracranial Aneurysms Beyond the Circle of Willis

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**Background:** Few reports have shown the therapeutic outcomes of flow diversion (FD) for intracranial aneurysms beyond the circle of Willis, and the efficacy of this technique remains unclear.

**Materials and methods:** A retrospective study was performed on 22 consecutive patients, diagnosed with intracranial aneurysms beyond the circle of Willis, and treated with pipeline embolization device (PED) (Medtronic, Irvine, California, USA) between January 2015 and December 2019.

**Result:** The 22 patients were between 16 and 66 years old (mean 44.5 ± 12.7 years), and six patients were male (27.3%, 6/22). Twenty-two patients had 23 aneurysms. The 23 aneurysms were 3–25 mm in diameter (12.2 ± 7.1 mm on average). The diameter of the parent artery was 1.3–3.0 mm (2.0 ± 0.6 mm on average). The 23 aneurysms were located as follows: 17 (73.9%, 17/23) were in the anterior circulation, and 6 (26.1%, 6/23) were in the posterior circulation. PED deployment was technically successful in all cases. Two overlapping PEDs were used to cover the aneurysm neck in 3 cases. One PED was used to overlap the two tandem P1 and P2 aneurysms. Other cases were treated with single PED. Coil assistance was used to treat 7 aneurysms, including 4 recurrent aneurysms and 3 new cases requiring coiling assistance during PED deployment. There were no cases of complications during PED deployment. All patients were available at the follow-up (mean, 10.9 ± 11.4 months). All patients presented with a modified Rankin Score (mRS) of 0. During angiographic follow-up, complete embolization was observed in 22 aneurysms in 21 patients, and one patient had subtotal embolization with the prolongation of stasis in the arterial phase.

**Conclusion:** PED deployment for intracranial aneurysms beyond the circle of Willis is feasible and effective, with high rates of aneurysm occlusion.

**Keywords: pipeline embolization device, endovascular treatment, circle of Willis, distal aneurysm, complex aneurysm**

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## INTRODUCTION

Currently, flow diversion (FD) has revolutionized the treatment of intracranial aneurysms into a safe and efficacious therapy for large or giant wide-necked aneurysms. However, the off-label uses of FD have increased for intracranial aneurysms, including those in distal locations and bifurcation aneurysms (1).

Currently, FD for aneurysms beyond the circle of Willis is effective, but there are some uncertain factors (2). This is because smaller arteries, the technical challenges of distal navigation, and the coverage of bifurcation branches and perforators may increase the risk of treatment-related complications (3). Thus, these aneurysms remain difficult to treat (4, 5).

Therefore, this study planned to evaluate the safety and efficacy of pipeline embolization device (PED) (Medtronic, Irvine, California, USA) treatment of intracranial aneurysms beyond the circle of Willis, including distal anterior circulation aneurysms and posterior circulation aneurysms.

## MATERIALS AND METHODS

From January 2015 to December 2019, consecutive 22 patients, who underwent PED treatment for intracranial aneurysms beyond the circle of Willis, were retrospectively reviewed.

### Inclusion Criteria

(1) The location of intracranial aneurysms was beyond the circle of Willis. (2) These aneurysms, including previously coiled aneurysms, underwent treatment with a PED.

### Perioperative Data Collection

The data collected and recorded included age, sex, clinical presentation, aneurysm side, aneurysm size, number of PED deployments, coiling assistance, and procedural complications.

### Scheme of Treatment

#### Medication Management

Dual-antiplatelet medication with aspirin 100 mg and clopidogrel 75 mg was given for at least 5 days before the treatment. In the case of platelet inhibition of 40% to adenosine diphosphate (ADP), an additional 300-mg loading dose of clopidogrel was administered before the procedure. Dual-antiplatelet therapy was maintained for 6 months. Then, aspirin 100 mg was given for a minimum of 6 months or for life.

#### Treatment Procedure

All patients were treated under general anesthesia via a transfemoral approach. A coaxial system consisting of a Shuttle sheath, a guide catheter, an intermediate catheter and a microcatheter was used. Under roadmap guidance, the 0.027-inch Marksman or Phenom catheter (Medtronic, Irvine, California, USA) was navigated beyond the aneurysm neck. Based on the aneurysm neck and parent artery parameters, a PED was chosen to allow enough wall apposition and coverage of the aneurysm. If the aneurysm was ruptured or when necessary, PED deployment plus coiling was performed. Control angiography was performed at 10 and 20 min intervals after PED deployment to observe platelet aggregation within the stent (5).

### Prognostic Evaluation

The modified Rankin Scale (mRS) was used for clinical outcome assessment. During the follow-up imaging, follow-up angiography was analyzed. If the treatment was incomplete, the degree could be evaluated with the prolongation of stasis, which was divided into arterial, capillary, and venous phases.

## RESULTS

### General Information

Twenty-two patients were identified, with ages ranging from 16 to 66 years (mean, 44.5 ± 12.7 years), and six patients were male (27.3%, 6/22). Seventeen patients were admitted for accidental findings, 1 had subarachnoid hemorrhage (SAH), and 4 recurrent aneurysms were treated with previous coiling with or without stenting assistance.

### Imaging Characteristics

Twenty-two patients had 23 aneurysms, of which 12 aneurysms were on the left side and 11 were on the right side. In 23 aneurysms, 2 aneurysms were in tandem. The other 21 patients had single aneurysms. The 23 aneurysms were 3–25 mm in diameter (12.2 ± 7.1 mm on average). The diameter of the parent artery was 1.3–3.0 mm (2.0 ± 0.6 mm on average). The locations of 23 aneurysms were as follows: the first segment of the middle cerebral artery (MCA) (M1), 6 aneurysms; the second segment of the MCA (M2), 2 aneurysms; the third segment of the MCA (M3), 6 aneurysms; the second segment of the anterior cerebral artery (ACA) (A2), 3 aneurysms; the first segment of the posterior cerebral artery (PCA) (P1), 3 aneurysms; the second segment of the PCA (P2), 2 aneurysms; and the third segment of the posterior inferior cerebellar artery (PICA) (p3), 1 aneurysm.

### Treatment Procedure

PED deployment was technically successful in all cases. Two overlapping PEDs were used to cover the aneurysm neck in 3 cases. One PED was used to overlap the tandem P1 and P2 aneurysms. The other cases were treated with single PED. In 23 aneurysms, coiling assistance was performed for 3 aneurysms, including one ruptured aneurysm. In total, coiling was used to treat 7 aneurysms, including 4 recurrent aneurysms and 3 new cases requiring coiling assistance during PED deployment. During PED deployment, the branches were covered by the PED in 15 cases (68.2%, 15/22), according to the results of immediate angiography.

### Follow-Up Outcomes

All patients were available at the clinical follow-up, and the clinical and imaging follow-up ranged from 3 to 48 months (mean, 10.9 ± 11.4 months). All patients presented with a mRS score of 0 (100%). The degree of embolization was 100% occlusion in 22 aneurysms (95.6%, 22/23), and one aneurysm exhibited <90% occlusion (subtotal embolization with the prolongation of stasis in the arterial phase). Representative cases are shown in **Figures 1**, **2**. Clinical data in this study are summarized in **Table 1**.

## DISCUSSION

FD involves 24–55% metal coverage, and after FD deployment, the blood flow within the aneurysm is disturbed, causing stasis

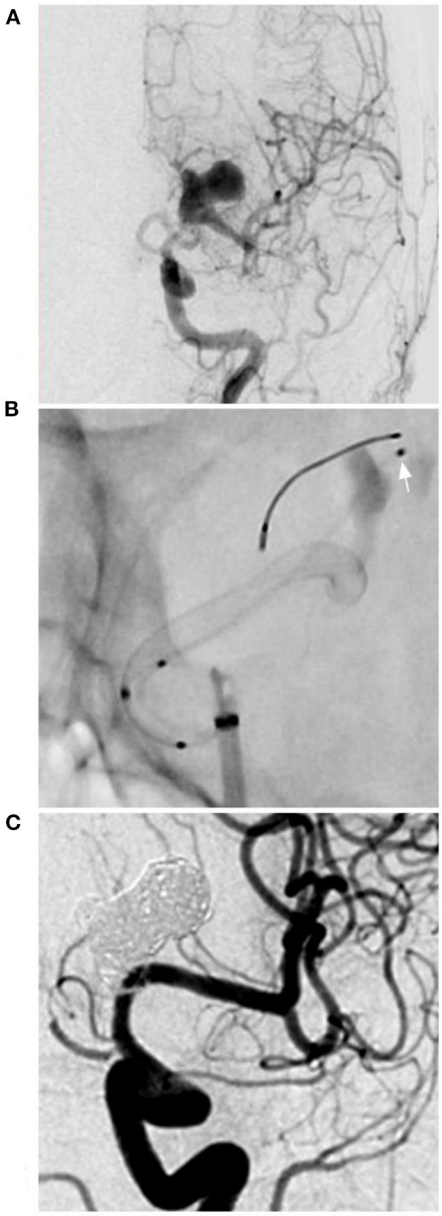


**FIGURE 1 |** PED for an M1 complex aneurysm. **(A)** DSA of the anterior-posterior view of the ICA showing a complex lobulated aneurysm on the M1 segment of the middle cerebral artery. **(B)** X-ray film showing the deployment of the PED and the microcatheter (arrow) in the aneurysm to plan coiling. **(C)** Follow-up DSA showing complete aneurysm occlusion. DSA, digital subtraction angiography; ICA, internal carotid artery; PED, pipeline endovascular device.

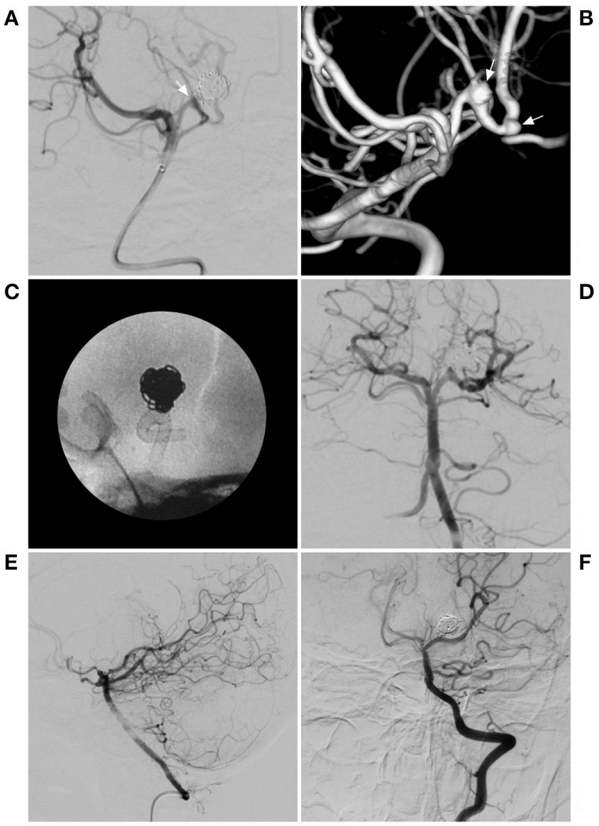


**FIGURE 2 |** PED for a previously coiled recurrent aneurysm. **(A)** DSA of the BA showing the previous coiled aneurysm in posterior cerebral artery. The arrow indicates the recurrent neck of the aneurysm. **(B)** 3D reconstruction of DSA showing the 2 aneurysms, including the previous coiled aneurysm and another aneurysm (arrows). **(C)** X-ray film showing the deployment of the PED. **(D)** Immediate angiography showing the deployment of the PED. **(E,F)** Follow-up DSA of the VA showing complete aneurysm occlusion. BA, basilar artery; DSA, digital subtraction angiography; PED, pipeline endovascular device; VA, vertebral artery.

that leads to thrombosis, followed by endothelialization of the parent artery (6). Currently, FD technology has revolutionized the treatment of intracranial aneurysms that are suboptimal for surgical or traditional interventional treatment (7). For aneurysms beyond the circle of Willis, classic endovascular approaches to the treatment of these aneurysms include selective coiling or parent artery occlusion, which imparts risks of recurrence and distal infarction (8).

The Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial showed the safety and effectiveness of the use of PEDs in the treatment of large and giant wide-neck aneurysms of the internal carotid artery in adult patients (9). At the same time, based on their ability to reconstruct the parent artery, the off-label uses of FD are constantly extended, including aneurysms beyond the circle of Willis (1). These aneurysms are often dissected and located in sub-2.0-mm vessels, where small-diameter PEDs have been used (5). In this study, we also tried to treat 22 patients with 23 aneurysms with the deployment of PEDs.

The deployment of FDs in arteries beyond the circle of Willis is technically challenging due to the smaller caliber of the parent vessel and the relative stiffness of the high-metal coverage stent. Sometimes, telescoping PEDs with 25–30% overlap is a feasible low-risk treatment option for long-segment aneurysms, using larger-diameter PEDs more proximally (10).

**TABLE 1 |** Clinical data in this study.

| No. | Age/sex | Onset | Side | Aneurysm location | Parent artery diameter (mm) | Size (diameter, mm) | Flow diversion | Coiling assistance | Covered branch | Immediate angiography | Follow-up time | Occlusion (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 43/M | Accidental | L | M1 | 3 | 15 | 1 Pipeline | N | Lenticular artery | Incomplete | 37 mon | 100 |
| 2 | 59/F | Recurrent | R | M1 | 2.7 | 20 | 1 Pipeline | N | Lenticular artery | Incomplete | 7 mon | 100 |
| 3 | 16/F | Recurrent | R | M2 | 2 | 10 | 1 Pipeline | N | Lenticular artery, superior trunk | Incomplete | 24 mon | 100 |
| 4 | 66/M | Accidental | R | M2 | 2.2 | 7 | 1 Pipeline | N | Lenticular artery, superior trunk | Incomplete | 6 mon | <90 |
| 5 | 36/F | Accidental | R | M3 | 1.7 | 8 | 1 Pipeline | N | No | Incomplete | 6 mon | 100 |
| 6 | 55/F | Accidental | L | M3 | 1.5 | 8 | 1 Pipeline | N | No | Incomplete | 48 mon | 100 |
| 7 | 57/F | Accidental | R | M3 | 1.8 | 9 | 2 Pipelines | N | No | Incomplete | 6 mon | 100 |
| 8 | 50/F | Accidental | L | M1 | 3 | 13 | 2 Pipelines | N | Lenticular artery | Incomplete | 8 mon | 100 |
| 9 | 54/F | SAH | R | M1 | 2.8 | 25 | 1 Pipeline | Y | Lenticular artery | Incomplete | 3 mon | 100 |
| 10 | 60/F | Accidental | L | P1 | 1.5 | 7 | 1 Pipeline | N | Perforating artery | Incomplete | 11 mon | 100 |
| 11 | 23/F | Recurrent | L | P1 | 2 | 3 | 1 Pipeline | N | Perforating artery | Incomplete | 18 mon | 100 |
| 12 | 54/M | Accidental | L | P1 and P2 | 2 | 3 and 4 | 1 Pipeline | N | Perforating artery | Incomplete | 6 mon | 100 |
| 13 | 37/M | Accidental | L | M1 | 2.9 | 25 | 1 Pipeline | Y | Lenticular artery | Incomplete | 6 mon | 100 |
| 14 | 45/M | Accidental | L | M1 | 2.7 | 10 | 1 Pipeline | N | Lenticular artery | Incomplete | 6 mon | 100 |
| 15 | 46/F | Accidental | L | M3 | 2 | 12 | 1 Pipeline | N | No | Incomplete | 7 mon | 100 |
| 16 | 49/F | Accidental | R | M3 | 1.9 | 20 | 1 Pipeline | N | No | Incomplete | 8 mon | 100 |
| 17 | 28/F | Accidental | R | A2 | 1.5 | 20 | 1 Pipeline | N | Pericallosal artery | Incomplete | 3 mon | 100 |
| 18 | 40/M | Accidental | L | A2 | 1.6 | 5 | 1 Pipeline | N | Pericallosal artery | Incomplete | 6 mon | 100 |
| 19 | 30/F | Accidental | R | A2 | 1.4 | 20 | 1 Pipeline | Y | Pericallosal artery | Incomplete | 6 mon | 100 |
| 20 | 37/F | Accidental | L | M3 | 1.5 | 20 | 2 Pipelines | N | No | Incomplete | 6 mon | 100 |
| 21 | 48/F | Accidental | R | P2 | 1.3 | 12 | 1 Pipeline | N | Perforating artery | Incomplete | 6 mon | 100 |
| 22 | 46/F | Recurrent | R | p3 | 1.5 | 6 | 1 Pipeline | N | No | Incomplete | 6 mon | 100 |

*A2, anterior cerebral artery (2 was the second segment); DSA, digital subtraction angiography; F, female, L, left, M, male, M1-3, middle cerebral artery (1–3 was the first-third segment); Mon, month; N, no; P1-2, posterior cerebral artery (1–2 was the first-second segment); p3, posterior inferior cerebellar artery (3 was the third segment); R, right; SAH, subarachnoid hemorrhage; Y, yes.*
*Note, in the onset column, "recurrent" refers to previous coiling.*

FD among aneurysms beyond the circle of Willis is effective (5). In the Ravindran et al. study of the use of FD for distal circulation aneurysms, complete and near-complete occlusion was noted in 78.2% of aneurysms (11). Our study demonstrates that PED treatment for aneurysms beyond the circle of Willis is effective, with rates of complete occlusion close to 95.6%.

FD can be applied alone or in combination with coiling, which includes the retreatment of previously coiled lesions, theoretically, which allows higher rates of occlusion than treatment with FDs alone, such as the case shown in **Figure 2** (11). However, coiling assistance is controversial, especially for large and giant aneurysms, and despite coiling assistance in FD deployment, delayed rupture cannot completely be avoided. Moreover, after coiling assistance, the effect may not be complete, and the coiling could result in the occlusion of a perforating artery.

Intracranial aneurysms beyond the circle of Willis are often dissecting and long but not large. Delayed rupture was uncommon after FD deployment, so the aim of coiling assistance was not to reduce the rupture risk; coiling may increase the degree of aneurysm occlusion. The coiling assistance during FD deployment was the same as that during conventional stent-assisted coiling. For instance, in the case shown in **Figure 1**, follow-up showed excellent occlusion after coiling assistance. However, coiling assistance is selectively applied for intracranial aneurysms beyond the circle of Willis, because in these aneurysms, the blood flow is not abundant, and FDs alone may be sufficient in most of these cases. In our study, 7 aneurysms were treated with coils in the aneurysms, including 4 recurrent aneurysms and 3 new cases requiring coiling assistance during PED deployment, and complete occlusion was obtained. Coiling assistance was feasible, but whether there is a difference between aneurysms with or without previously coiling requires further study. In our study, due to the small number of cases, it was difficult to identify such a difference. However, PED deployment was safe and effective.

However, the complications associated with FD deployment are not negligible and include ischemic/thromboembolic and hemorrhagic complications (9, 12). In addition, for small vessels, after FD deployment, segmental vasospasm can occur as a frequent vascular reaction, potentially causing symptomatic ischemia or even stroke ∼1 month after the procedure (13). Safety concerns regarding FD within small vessels can originate with vessel trauma from robust support to deliver and open the PED in the distal circulation, often in the presence of significant tortuosity, acute stent thrombosis, and delayed in-stent stenosis (5, 14).

The ASPIRe (Aneurysm Study of Pipeline in an Observational Registry) meta-analysis reported outcomes with a major morbidity of 6.8% and mortality of 1.6% across on-label PED treatments (15). In the Bender et al. study of FD for aneurysms in distal vessels measuring <2.0 mm, the major morbidity of 4.5% and mortality of 1.5% observed were lower than the on-label PED series outcomes (5). In the Primiani et al. report of A2, M2, and P2 aneurysms and beyond, the procedural compilation rate of 7.7% indicates a need for further studies as flow diversion technology constantly evolves (16). Our study reported no complications because the choice of cases was appropriate.

To reduce ischemic complications, instead of a PED with 30% metal coverage, an intermediate-porosity braided LEO stent (Balt Extrusion, Montmorency, France) with 14% metal coverage can be used with the help of a flow-diversion effect (17). In the Cagnazzo et al. study of 76 intracranial aneurysms and 98 side branches covered by LEO stents, the rate of flow remodeling on the covered arteries and perforators was 9 and 4%, respectively, and complete occlusion of aneurysms treated with sole stent-placement therapy was 70% (18).

In addition, a new low-profile visualized intraluminal support device (LVIS Blue; MicroVention, Tustin, California, USA) is a braided stent that provides a higher degree of metal coverage (22–28%) than first-generation devices (19). Although the coverage of the LVIS Blue stent is lower than that of FDS, the LVIS Blue stent may be beneficial for complete obliteration of an aneurysm due to not only its support of a high occlusion rate using coils inside of the aneurysm but also its flow-diversion effect (20, 21).

## CONCLUSIONS

The PED is an effective tool for managing aneurysms beyond the circle of Willis, especially those that are difficult to reconstruct with clipping and residual or recanalizing aneurysms after coiling.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

JY: draft. XL: review, editing, and submitting. All authors read and approved the final version of the manuscript.

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# Flow Diversion for Reconstruction of Intradural Vertebral Artery Dissecting Aneurysms Causing Subarachnoid Hemorrhage—A Retrospective Study From Four Neurovascular Centers

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**Objective:** Dissecting aneurysms (DAs) of the vertebrobasilar territory manifesting with subarachnoid hemorrhage (SAH) are associated with significant morbi-mortality, especially in the case of re-hemorrhage. Sufficient reconstruction of the affected vessel is paramount, in particular, if a dominant vertebral artery (VA) is impacted. Reconstructive options include stent-assisted coiling and flow diversion (FD). The latter is technically less challenging and does not require catheterization of the fragile aneurysm. Our study aims to report a multicentric experience with FD for reconstruction of DA in acute SAH.

**Materials and Methods:** This retrospective study investigated 31 patients (age: 30–78 years, mean 55.5 years) who had suffered from SAH due to a DA of the dominant VA. The patients were treated between 2010 and 2020 in one of the following German neurovascular centers: University Hospital Leipzig, Katharinenhospital Stuttgart, BG Hospital Bergmannstrost Halle/Saale, and Heinrich-Braun-Klinikum Zwickau. Clinical history, imaging, implanted devices, and outcomes were reviewed for the study.

**Results:** Reconstruction with flow-diverting stents was performed in all cases. The p64 was implanted in 14 patients; one of them required an additional balloon-expandable stent to reconstruct severe stenosis in the target segment. One case demanded additional liquid embolization after procedural rupture, and in one case, p64 was combined with a PED. Further 13 patients were treated exclusively with the PED. The p48MW-HPC was used in two patients, one in combination with two additional Silk Vista Baby (SVB). Moreover, one patient was treated with a single SVB, one with a SILK+. Six patients died [Glasgow Outcome Scale (GOS) 1]. Causes of death were periprocedural re-hemorrhage, thrombotic occlusion of the main pulmonary artery, and delayed parenchymal hemorrhage. The remaining three patients died in the acute–subacute phase related to the severity of the initial hemorrhage and associated

comorbidities. One patient became apallic (GOS 2), whereas two patients had severe disability (GOS 3) and four had moderate disability (GOS 4). Eighteen patients showed a complete recovery (GOS 5).

**Conclusion:** Reconstruction of VA-DA in acute SAH with flow-diverting stents is a promising approach. However, the severity of the condition is reflected by high overall morbi-mortality, even despite technically successful endovascular treatment.

**Keywords: ruptured dissecting aneurysm, dominant vertebral artery dissection, endovascular reconstruction, subarachnoid hemorrhage, flow diverter**

## INTRODUCTION

Intracranial dissections of the vertebral artery (VA) represent rare but potentially critical cerebrovascular lesions associated with a significant variety of unspecific symptoms (1). The dissection of an intracranial VA may remain clinically silent but more frequently manifests with posterior circulation stroke, subarachnoid hemorrhage (SAH), or, less frequently, spinal ischemia (2, 3). More than 80% of patients with intracranial VA dissections of the steno-occlusive type develop posterior circulation stroke. However, the majority of those improve without the imperative for endovascular treatment (4, 5).

Ruptured dissecting aneurysms of the intracranial VA are associated with worse outcomes. Between 24 and 72 h after the segmental vascular injury, frequently indicated by a characteristic occipital and nuchal headache, severe SAH manifests in almost every case (6). Subsequently, re-hemorrhage occurs in more than 70% of patients, culminating in mortality rates of ∼50% (7). As a consequence, early and sufficient therapy of ruptured dissecting aneurysms of the intracranial VA is mandatory.

Depending on the hemodynamic situation in the posterior circulation and the localization of the ruptured dissecting aneurysm, different endovascular approaches must be considered (8, 9). In case the rupture site is associated with a hypoplastic VA, segmental sacrifice, ideally sparing the posterior inferior cerebellar artery (PICA) orifice, has shown promising results (8, 10). However, segmental sacrifice and proximal VA occlusion carry significant risk for ischemia and, in some cases, re-bleeding (11).

In particular, if the ruptured dissecting aneurysm arises from a dominant VA or involves the PICA origin, a reconstructive technique is recommendable (11, 12). Reconstruction can be achieved with different approaches, for example, stent-in-stent implantation, stent-assisted coiling, and flow-diverting stents (12–16). However, related to the rarity of the condition, only retrospective reports on the different strategies exist, and the most suitable treatment remains to be determined (17).

Flow-diverting stents offer several advantages over the alternative endovascular techniques; most importantly, they allow the reconstruction of the vessel without primary catheterization of the highly fragile dissecting aneurysm, and their increased surface coverage provides a superior seal of the potentially extensive intimal tear in comparison to conventional, low-porosity laser-cut stents. However, reports on flow diversion (FD) in this specific context are lacking.

This study, therefore, aims to report our multicenter experience of FD for the reconstruction of acutely ruptured, dissecting aneurysms of the dominant intracranial VA, including clinical and procedural aspects as well as follow-up data in order to present feasibility, safety, and effectiveness of this approach.

## MATERIALS AND METHODS

Our retrospective study of multicenter data regarding the reconstructive approach with flow-diverting stents to treat ruptured dissecting aneurysms of the vertebrobasilar system was approved by the institutional ethics committee (local institutional review board, IRB, nr. AZ 208-15-0010062015). The patients were treated between 2010 and 2020 in one of the following German neurovascular centers: University Hospital Leipzig ($n = 13$), Katharinenhospital Stuttgart ($n = 16$), BG Klinikum Bergmannstrost Halle/Saale ($n = 1$), and Heinrich-Braun-Krankenhaus Zwickau ($n = 1$). Informed consent of each patient regarding the use of radiological and clinical data was obtained in written form by either the patient or his or her legal representative.

Clinical, procedural, and imaging data including anatomical aspects of the aneurysm (size, location, and morphology), post-procedural aneurysmal status, devices used, technical aspects, and clinical follow-up data using the modified Rankin scale (mRS) were analyzed. Any clinical events in the postoperative course were documented. Initial and follow-up occlusion rates were graded according to the O'Kelly-Marotta (OKM) grading scale, as reported previously (18).

Platelet function testing was not mandatory and was routinely performed only in one center (Katharinenhospital Stuttgart, 9/16 patients). No cases of hypo-response were recorded in the included patients. Dual platelet inhibition was performed in all patients if necessary. Those patients who received platelet function testing and revealed no insufficient response were treated with a combination of Clopidogrel (1 × 75 mg PO daily) and acetylsalicylic acid (ASA) (1 × 100 mg PO daily). The remaining 15 patients received a combination of Ticagrelor (2 × 90 mg PO, bid) and ASA (1 × 100 mg PO daily). Ticagrelor was chosen as a simple measure to avoid insufficient platelet function inhibition, in line with earlier studies (19).

All interventions were performed under general anesthesia using biplane neuroangiography suites. In 19 cases, a triaxial system with guiding catheter, distal access catheter (11× 6F

SOFIA, MicroVention, Alajuela, Costa Rica; 8× 6F Heartrail II, Terumo Europe, Belgium), and microcatheter was used. In an additional 12 cases, a coaxial setup consisting only of guiding catheter and microcatheter was applied. Guiding catheters used were 13× 6F Neuron Max (Penumbra, Alameda, USA), 7× 6F Guider Softtip (Boston Scientific, Marlborough, USA), and 11× 6F Envoy MP (Cerenovus, Irvine, CA USA).

As each flow diverter has its specific requirements for delivery, the microcatheters were chosen accordingly. The Pipeline Embolization Device (Medtronic, Irvine, USA) was implanted using the Phenom$^{TM}$ 27 (Medtronic, Irvine, USA) microcatheter. The p64 Flow Modulation Device (phenox, Bochum, Germany) was implanted using the Excelsior XT 27 (Stryker Neurovascular, Fremont, USA) microcatheter, whereas the novel p64MW-HPC was implanted using the Rebar 18 (Medtronic, Irvine, USA). The Silk+ (Balt Extrusion, Montmorency, France) was implanted using the Vasco 25 (Balt Extrusion, Montmorency France) microcatheter. The p48MW (phenox, Bochum, Germany) was implanted using the Prowler Select Plus (Cerenovus, Irvine, CA, USA) microcatheter. The Silk Vista Baby (SVB) (Balt Extrusion, Montmorency, France) was implanted *via* a Headway 17 (MicroVention, Tustin, USA) microcatheter.

**Table 1** summarizes the relevant information of all included patients.

# RESULTS

## Patients

Thirty-one patients (17 male and 14 female) between 30 and 78 years who had suffered from SAH caused by the rupture of a dissecting aneurysm of the dominant intradural VA were included. Of those, 11 had the dissecting aneurysm at the right-hand side dominant VA, while the remaining patients had the dissecting aneurysm at the left-hand side dominant VA. In six patients, the dissecting aneurysm morphologically involved the basilar artery.

## Implanted Devices and Adjunctive Techniques

Reconstruction with one flow-diverting stent was sufficient in 15 cases. A single p64 was used in seven patients and one PED was used in five patients, whereas a single p48 and a single SVB were applied in one case each. Reconstruction with two flow diverter stents in overlapping fashion was necessary for 10 patients. Of those, 2× p64 in overlapping fashion were used in four patients, 2× PED in overlapping fashion was implanted in five further patients, and 1× p64 together with 1× PED were implanted in one patient. Examples of endovascular reconstruction with overlapping flow diverters of a relatively confined and extensive dissecting aneurysm are given in **Figures 1**, **2**. Multiple overlapping flow diverter stents were implanted in the remaining six patients. One patient was treated with five overlapping PED flow diverters, and two patients were treated with three overlapping PED flow diverters. One additional patient received four overlapping p64 flow diverters, and the next patient required nine overlapping p64 flow diverters together with a balloon-mounted coronary stent. A further patient was treated with eight overlapping p48MW-HPC combined with two additional SVB flow diverters and one balloon-mounted coronary stent. In the last two patients, the dissecting aneurysm had associated high-grade stenosis, which required implantation of a balloon-mounted coronary stent to prevent occlusion of the respective segment. Balloon angioplasty was necessary in six other cases (4× p64, 1× p48MW, and 1× PED) to achieve sufficient wall apposition of the implanted flow diverters after initially insufficient opening.

Additional occlusive techniques—coiling and liquid embolization—were necessary in four cases. Coiling was performed based on the jailing technique in three patients, aiming for enhanced thrombosis of the large pseudoaneurysm in all of those cases. An exemplary case is shown in **Figure 3**. Liquid embolization resulting from periprocedural re-rupture was necessary in one case, which is demonstrated in **Figure 4**.

## Ischemic Complications

In this series, 9.6% (3/31) of the patients experienced an ischemic stroke. Two of them suffered from a partial PICA infarction, and one developed a subtle thalamic stroke. One of the PICA infarctions occurred in a patient with a fusiform dissecting, partially thrombosed aneurysm extending into the basilar artery, responsible for a Hunt and Hess grade V SAH. The patient succumbed to the severity of the hemorrhage in the early post-interventional phase (11 days after treatment), and the PICA infarct was irrelevant to the outcome. The two remaining patients had good outcomes. One of both developed a partial PICA infarct due to an in-stent thrombosis within a PED2 shield 3 days after the implantation. Platelet function inhibition had been initiated with acetylsalicylic acid (ASA, 500 mg IV per day) only in order to reduce the risk for hemorrhage, as was suggested earlier (20). The in-stent thrombosis was treated successfully with IV application of eptifibatide according to the manufacturer's instruction. The patient experienced an overall good recovery [Glasgow Outcome Scale (GOS) 4].

The third patient suffered from thalamic infarction secondary to post-hemorrhagic vasospasm in the vertebrobasilar territory, from which he recovered utterly (GOS 5).

## Hemorrhagic Complications and Re-hemorrhage

Hemorrhagic complications, on the other hand, occurred in three further patients. One patient suffered from a periprocedural re-rupture of the dissecting aneurysm. Salvage embolization with n-butyl cyanoacrylate (Histoacryl, B. Braun) was performed immediately, but the patient succumbed to the sudden rise of intracranial pressure. The second patient suffered from cerebellar hemorrhage within the first 24 h after flow diverter implantation and did not recover well from the hemorrhage (GOS 2). The third patient experienced a large parenchymal hemorrhage 3.5 months after the endovascular therapy while being under dual antiplatelet therapy (ASA and Clopidogrel, dosage according to the manufacturer's instruction) and died in the aftermath of this event (GOS 1).

**TABLE 1 |** Clinical data of all included patients.

| Case | Sex | Age | Location, hemodynamic situation | Hunt and Hess | Fisher grade | Lesion dimension (mm) | Pseudo aneurysm max. diameter (mm) | Endovascular approach | EVD | Craniectomy | GOS at time of review |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | 30 | Dominant left vertebral artery; right hypoplastic | IV | 4 | 14 × 2 | 9 | Flow Diverter + Coiling (1× p64) | Right frontal, VP-Shunt | No | 4 |
| 2 | Male | 57 | Dominant right vertebral artery; left hypoplastic | IV | 4 | 11 × 2 | 4 | Flow Diverter (2× PED) | Right frontal | No | 4 |
| 3 | Male | 48 | Dominant right vertebral artery; codominant left | III | 4 | 10.7 × 3 | 4.7 | Flow Diverter (4× p64) | Right frontal | No | 5 |
| 4 | Male | 78 | Dominant left vertebral artery; right hypoplastic V4 | V | 4 | 30 × 4 | 8 | Flow Diverter + Drug Eluting Stent (9× p64, 1× Corofle× ISAR) | Right frontal | No | 1 |
| 5 | Male | 40 | Dominant right vertebral artery; codominant left | III | 4 | 9 × 3 | 3 | Flow Diverter (1× PED) | None | No | 5 |
| 6 | Male | 52 | Left dominant vertebral artery; codominant right | IV | 3 | 7 × 2 | 1.3 | Flow Diverter (1× p64) | Left frontal | No | 5 |
| 7 | Male | 67 | Left dominant vertebral artery; codominant right | IV | 4 | 14 × 2 | 3 | Flow Diverter (1× p64) | Bifrontal, VP-Shunt | No | 5 |
| 8 | Male | 78 | Hypoplastic right vertebral artery with PICA ending; dominant left vertebral artery | 1 | 2 | 20 × 4 | 8 | Flow Diverter + Coiling (2× p64) | None | No | 1 |
| 9 | Female | 57 | Dominant left vertebral artery; codominant right | III | 4 | 19 × 2 | 4 | Flow Diverter (1× p64, 1× PED) | Right frontal, VP-Shunt | No | 4 |
| 10 | Female | 66 | Dominant right vertebral artery; left hypoplastic V4 | III | 4 | 28 × 4 | 6 | Flow Diverter + Liquid Embolizate (2× p64) | None | No | 1 |
| 11 | Male | 58 | Dominant right vertebral artery; codominant left | I | 2 | 18 × 4 | 4 | Flow Diverter (2× PED) | None | No | 5 |
| 12 | Male | 51 | Dominant left vertebral artery; codominant right | V | 4 | 24 × 3.5 | 6 | Flow Diverter (2× PED) | None | No | 5 |
| 13 | Male | 49 | Dominant right vertebral artery; hypoplastic left vertebral artery with PICA ending | IV | 4 | 18 × 3 | 7 | Flow Diverter (1× PED) | Left frontal | No | 5 |
| 14 | Male | 67 | Dominant left vertebral artery; codominant right | II | 3 | 15 × 2 | 2 | Flow Diverter (1× p64) | None | No | 3 |
| 15 | Male | 57 | Dominant right vertebral artery; dissection stenosis vertebral artery left | I | 2 | 18 × 4 | 6 | Flow Diverter (1× p64) | None | No | 5 |
| 16 | Female | 41 | Dominant left V4 with equally important right V4 | III | 4 | 12 × 4 |  | Flow Diverter (2× p64) | None | No | 5 |
| 17 | Female | 54 | Dominant right vertebral artery; codominant left | I | 4 | 8 × 3 | 4,5 | Flow Diverter (1× p64) | None | No | 5 |
| 18 | Male | 53 | Dominant left vertebral artery; right hypoplastic vertebral artery | II | 4 | 12 × 4 | 4 | Flow Diverter (2× p64) | VP-Shunt | No | 5 |
| 19 | Female | 67 | Dominant left vertebral artery; codominant right | IV | 4 | 10 × 3 | 5 | Flow Diverter + Coiling (1× PED) | Right frontal, VP-Shunt | Yes | 5 |
| 20 | Female | 52 | Dominant left vertebral artery; hypoplastic right vertebral artery with PICA ending | IV | 4 | 12 × 4 | 6 | Flow Diverter (3× PED) | Right frontal, VP-Shunt | No | 1 |
| 21 | Male | 44 | Dominant left vertebral artery; codominant right | IV | 4 | 19 × 3 | 2 | Flow Diverter (2× PED) | None | No | 5 |
| 22 | Male | 50 | Dominant left vertebral artery; codominant right | I | 4 | 9 × 3 | 2.3 | Flow Diverter (1× PED) | None | No | 5 |
| 23 | Male | 67 | Dominant left vertebral artery; codominant right | III | 4 | 21 × 3 | 3 | Flow Diverter (2× PED) | Right frontal, VP-Shunt | No | 5 |
| 24 | Female | 66 | Dominant left vertebral artery; codominant right | IV | 4 | 8 × 4 | 4 | Flow Diverter (3× PED) | None | No |  |
| 25 | Female | 71 | Dominant left vertebral artery; codominant right | III | 4 | 30 × 4 | 3 | Flow Diverter (5× PED) | Left frontal | No | 1 |
| 26 | Female | 57 | Dominant right vertebral artery; left hypoplastic | No relation to dissection |  | 17 × 4 | 4 | Flow Diverter (1× PED) | None | Yes | 3 |
| 27 | Female | 47 | Dominant right vertebral artery; left hypoplastic | IV | 3 | 42 × IV | 6.6 | Flow Diverter + Coronary stent (8× p48MW_HPC, 2× SVB, 1× Rebel) | Left frontal | Yes | 1 |
| 28 | Female | 44 | Dominant left vertebral artery; right hypoplastic V4 | – | – | 30 × 4 | 4 | Flow Diverter (1× p48MW_HPC) | None | No | 2 |
| 29 | Female | 69 | Dominant left vertebral artery; right hypoplastic | – | – | 11.5 × 4 | 7 | Flow Diverter (1× Silk) | None | No | 5 |
| 30 | Female | 35 | Dominant right vertebral artery; equally strong left | II | 4 | 15 × 3 | 3 | Flow Diverter (1× SVB) | None | No | 5 |
| 31 | Female | 49 | Dominant left vertebral artery; hypoplastic right | III | 4 | 11.5 × 4 | 4 | Flow Diverter (1× p64) | None | No | 5 |

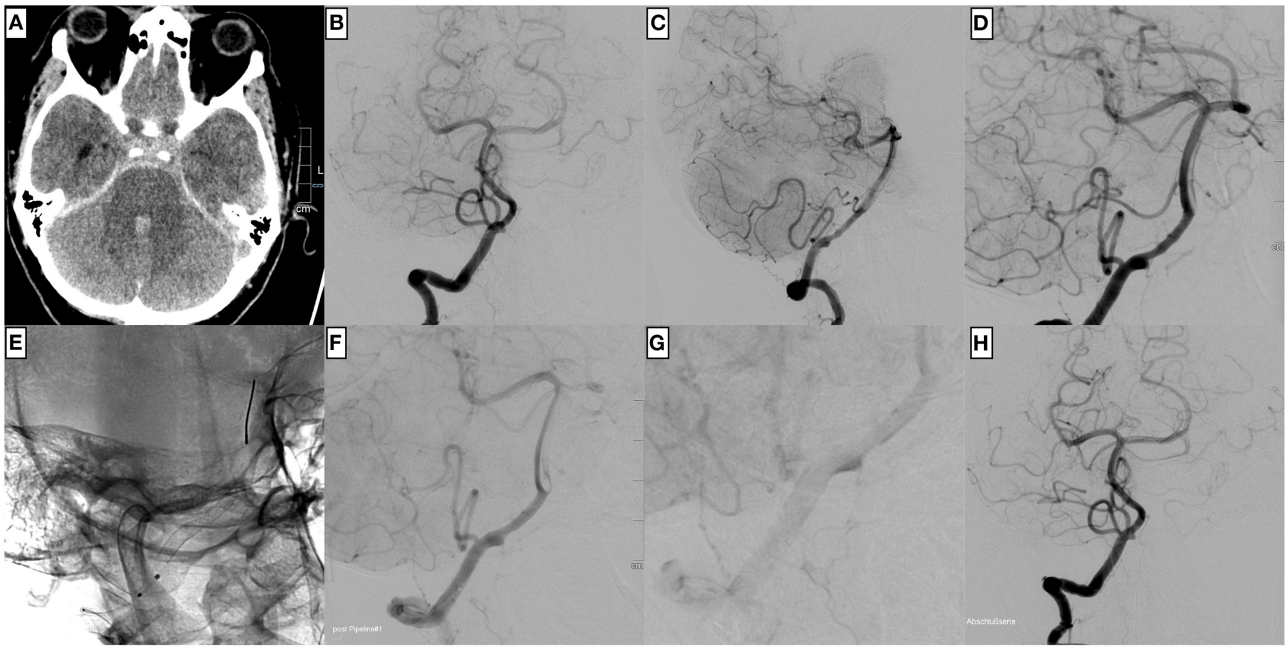


**FIGURE 1 |** An example of uncomplicated PED implantation for treating a ruptured, dissecting aneurysm of the right dominant intradural vertebral artery in a 57-year-old male patient. **(A)** Non-enhanced cranial computed tomography shows Fisher grade 3 subarachnoid hemorrhage. **(B)** The injection of the right vertebral artery in posterior–anterior, **(C)** lateral, and **(D)** working projection demonstrates the comparatively confined ruptured dissecting aneurysm close to the posterior inferior cerebellar artery (PICA) orifice. After unimpeded catheterization with a Phenom$^{TM}$ 27, a PED **(E)** is implanted. The flow diverter is centered over the dissecting aneurysm. The control injection **(F)** shows the reconstruction of the vessel, now without irregularities in the post-PICA segment, which were apparent before implantation **(D)**, and significant stasis of contrast agent within the aneurysm **(G)**. The final angiogram in posterior–anterior projection **(H)** reveals timely opacification of the posterior circulation.

## Outcomes

Six patients died (GOS 1), two of those patients in the context of hemorrhagic complications. Thereby, one case was related to a periprocedural re-hemorrhage, which was angiographically controlled with immediate liquid embolization after flow diverter implantation but culminated in uncontrollable high intracranial pressure, as demonstrated in **Figure 4**. The second case suffered from delayed major parenchymal hemorrhage 3.5 months after successful endovascular treatment. A third patient, Hunt and Hess SAH grade I, developed a fulminant and eventually fatal pulmonary embolism. The fourth patient, who had suffered from a sizeable dissecting aneurysm extending from the V3 segment into the basilar artery, died within the first week after reconstruction due to repeated episodes of uncontrollable intracranial pressure. The fifth patient had suffered from SAH Hunt and Hess grade IV and depended on a left-ventricular assist device, and therefore required dual antiplatelet medication together with oral anticoagulation, and died after discharge from the hospital without, in retrospect, precisely determinable cause. The last patient of the GOS 1 group presented with Hunt and Hess grade V and developed an outcome-wise insignificant PICA infarction after treatment before he succumbed to the severity of the SAH. The only GOS 2 case resulted from early re-hemorrhage within 24 h after treatment. Two patients had severe disabilities (GOS 3), in one case as a result of the initial ictus, whereas the other patient already presented with a reduced general condition (alcoholism) and required permanent ventriculoperitoneal shunting.

The remaining three patients died in the acute–subacute phase related to the severity of the initial hemorrhage and associated comorbidities. One patient became apallic (GOS 2) as a consequence of re-hemorrhage within 24 h post-procedure. Two patients had severe disability (GOS 3) and four had moderate disability (GOS 4). Eighteen patients (58.1%) showed a complete recovery (GOS 5).

# DISCUSSION

This study summarizes our multicenter experience with flow diverter implantation, using different flow diverter models, to treat acutely ruptured dissecting aneurysms of dominant intracranial vertebral arteries.

Flow-diverting stents are designed to reconstruct parent vessels of cerebral aneurysms. The reconstruction after implantation is achieved stepwise. Firstly, the dense mesh of the flow diverter covering the aneurysmal entry reduces inflow and causes redirection of blood flow along the physiological axis of the parent vessel (21). That way, intra-aneurysmal pressure, and thus transmural force, is reduced immediately. Subsequently, a thrombus is formed in the aneurysm sac, and neointima formation along the lattice of the flow diverter

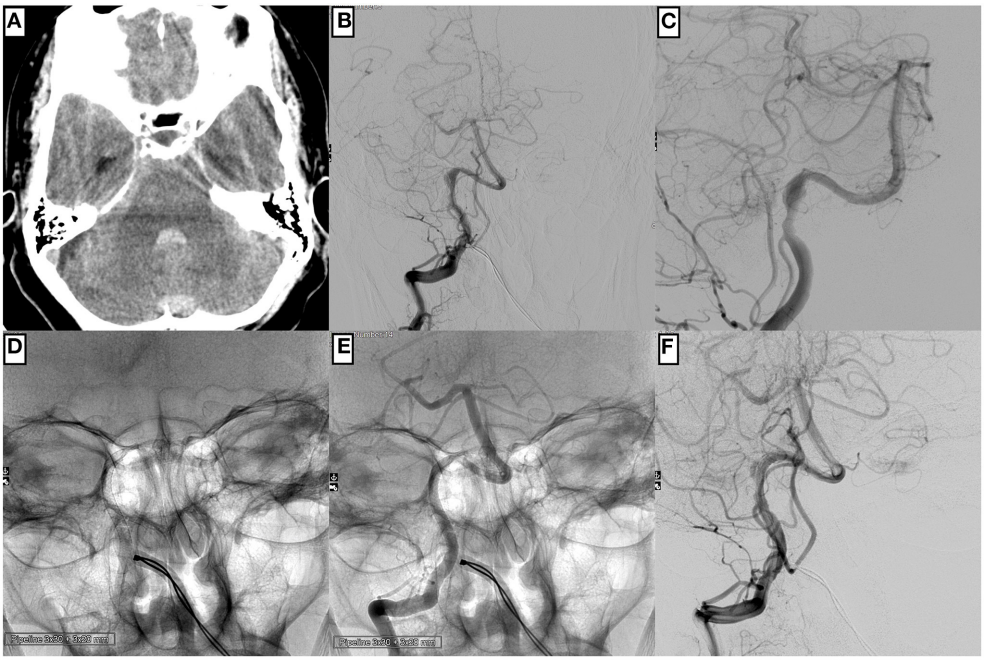


**FIGURE 2 |** An example of technically unremarkable PED implantation is to reconstruct a right-hand side distal V4 segment affected by an extensive dissecting aneurysm in a 58-year-old male patient. **(A)** Cranial computed tomography prior intervention displays SAH Fisher grade 3. The injection of the right-hand side vertebral artery in posterior–anterior **(B)** and working projection **(C)** demonstrates an extensive, hourglass-shaped dissecting aneurysm directly distal to the PICA orifice. After uneventful catheterization with a Phenom$^{TM}$ 27 microcatheter, two PED flow diverters are implanted in telescoping fashion **(D,E)**. The control injection demonstrates timely opacification of the PICA and the distal vertebrobasilar vessels together with delayed and prolonged opacification of the pseudoaneurysm **(F)**.

begins (22). This concept has been proven to be clinically successful for treating anatomically challenging aneurysms in the anterior circulation, particularly for wide-neck sidewall or complex fusiform aneurysms, and long-term follow-up data after flow diverter implantation substantiate good safety and efficacy (23, 24). However, ruptured dissecting aneurysms of the intradural VA are biologically distinct from incidental aneurysms, particularly the anterior circulation, and very little data on the use of flow diverters for treatment of dissecting intracranial VA aneurysms have been made available (16). Considering the data mentioned above, together with the imperative for immediate reconstruction of dominant V4 segments affected by ruptured dissecting aneurysms, further investigations of FD for ruptured dissecting VA aneurysms are required (8).

Overall, the results of our study underline the safety and feasibility of FD as a strategy for the treatment of acutely ruptured dissecting aneurysms affecting dominant and thus indispensable vertebral arteries. However, significant clinical adverse events, as well as technical adverse events, must be reflected critically. Therefore, those points are addressed in the following paragraphs.

Morbidity and mortality associated with ruptured dissecting aneurysms of the VA are mainly related to the severity of the initial hemorrhage, ischemic complications, the occurrence and magnitude of re-hemorrhage, and comorbidities (6, 25).

## Ischemic Complications

In our cohort, <10% of the patients suffered from posterior circulation ischemic stroke in association with the SAH, its treatment, or its early sequelae. Two of the infarctions affected the PICA territory, but neither those nor the singular thalamic infarction were relevant for the individual outcome. Recent reports indicated that the major branches of the intradural VA, most notably the PICA, remain patent and functionally unaffected in most cases after flow diverter implantation (26, 27). Our results are not entirely in accordance with those reports, underlining the pathophysiological inequality of ruptured dissecting aneurysms of the intracranial VA compared to electively treated aneurysms in the exact location. More specifically, the different fate of the PICA in our patients is explainable as follows. Firstly, it is comprehensible that the dissection itself or the mass effect of the dissecting aneurysm can affect the PICA directly and therefore cause significant stenosis or even occlusion with subsequent infarction. Secondly, acute SAH is associated with significant and prolonged platelet activation and aggregation, facilitating device-associated thrombo-embolism and occlusion of covered side branches (28). Aside from that, our findings suggest that single antiplatelet therapy, instead of dual antiplatelet therapy, after implantation of devices with reduced thrombogenicity due to hydrophilic coating, must be evaluated critically in acute SAH. However, several investigations suggested the feasibility and safety of this approach

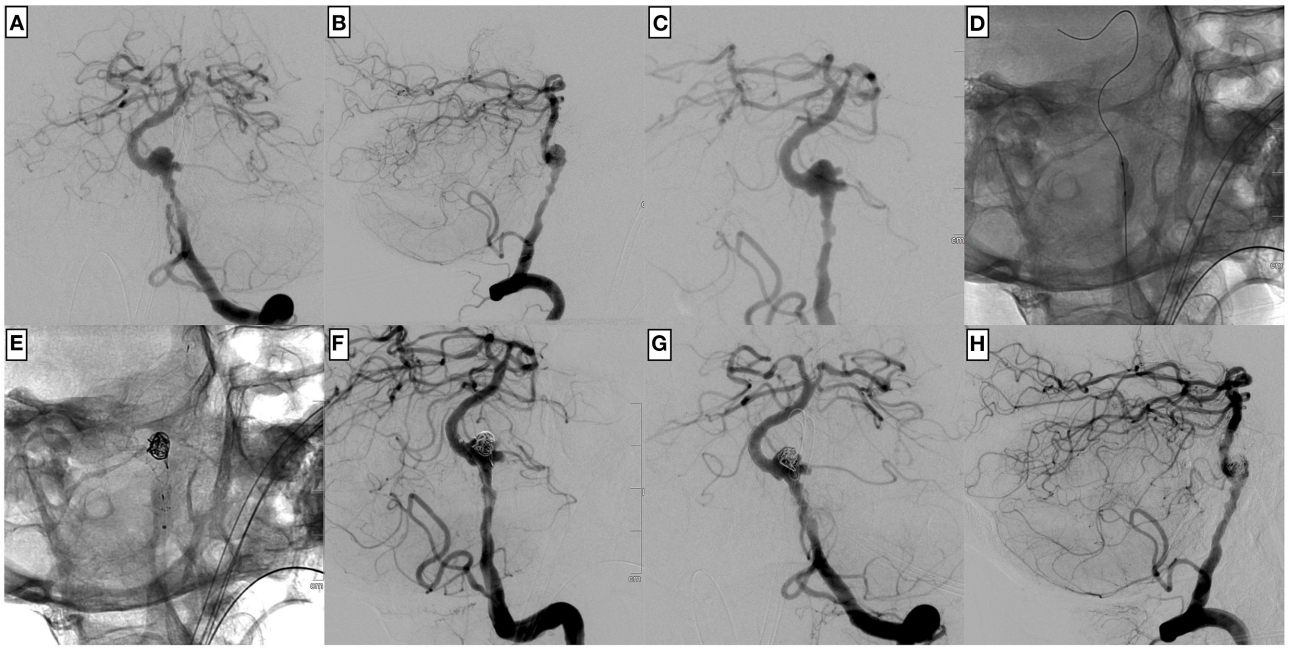


**FIGURE 3 |** An example of a complex endovascular treatment including balloon angioplasty, coiling in jailing technique, and p64 implantation of a large ruptured, dissecting aneurysm of the left dominant intradural vertebral artery in a 78-year-old male patient. **(A)** The injection of the left vertebral artery in posterior–anterior, **(B)** lateral, and **(C)** working projection demonstrates an extensive, multi-lobulated dissecting aneurysm close to the vertebral artery junction. A stenosis proximal to the aneurysm requires balloon angioplasty **(D)** before implanting the flow diverter. **(E)** Few coils are placed in jailing position within the large pseudoaneurysm to promote thrombus formation and reduce the risk for re-rupture. The p64 was distally anchored within the basilar artery, and the proximal landing zone was defined slightly above the PICA orifice. The control injection **(F–H)** shows a less irregular shape of the affected V4 segment and a still markedly opacified pseudoaneurysm.

(25, 29). Prior experience has shown that the hemorrhage-induced platelet activation requires a tailored dosage based on response tests (e.g., Multiplate, Roche Diagnostics; VerifyNow, Accriva), with prasugrel being more efficient than ASA (30).

## Hemorrhagic Complications

Significant hemorrhagic complications occurred in the same proportion as ischemic complications, affecting 3/31 patients. However, contrary to the ischemic complications, all hemorrhagic complications were causative for the death of the respective patient or persisting and severe neurological deficit. Our findings in this regard are in line with earlier reports, underlining the significance of re-hemorrhage for the patient's outcome (31). Concerning the time point of hemorrhagic complications, our results are also in accordance with earlier studies showing that hemorrhagic complications occur either during intervention or in the vulnerable early phase post-intervention (17, 32, 33). However, few reports also showed markedly delayed parenchymal hemorrhages with insignificant distance to the dissecting aneurysm—which we encountered in one patient after the implantation of a PED2 shield together with additional coiling. They hypothesized an association with hemorrhagic transformation of small, imaging-negative lesions under dual antiplatelet therapy (34).

## Outcome—Synopsis

Overall, 9/31 patients (29%) had unfavorable outcomes (GOS 1–3). Five of the six patients who died (GOS 1) in the context of the SAH already presented with severe deficits (Hunt and Hess grade III-V). Five of them also required treatment with adjunctive techniques (1× Histoacryl embolization, 2× coiling, and 2× coronary stent to reconstruct high-grade stenosis of the flow diverter-bearing segment), indicating technically particularly complicated cases. One of the six GOS 1 patients presented with Hunt and Hess grade I SAH but developed a fulminant and eventually fatal pulmonary embolism, an infrequent but recognized complication in acute SAH (35). The only GOS 2 case resulted from early re-hemorrhage within 24 h after treatment. The remaining 22 patients either recovered completely ($n = 18$) or regained independence in their daily routine (GOS 4: $n = 4$). In summary, high Hunt and Hess grades and the necessity for adjunctive techniques in ruptured dissecting VA aneurysms and respective comorbidities were associated with poor outcomes in our patients, according to earlier studies (11, 17, 30).

## Technical Issues and Device Considerations

A total of six cases required additional endovascular maneuvers related to purely technical issues. In two patients, foreshortening of the flow diverter (1× PED2; 1× p64) resulted in insufficient coverage of the proximal portion of the dissecting aneurysms

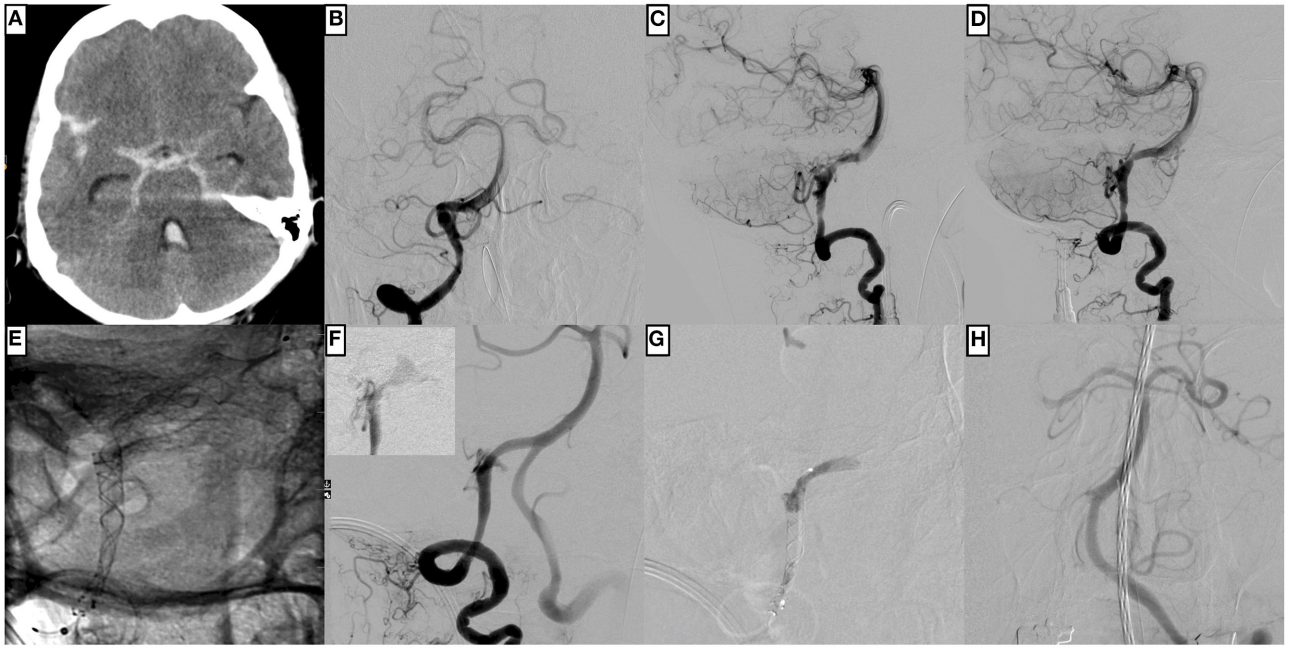


**FIGURE 4 |** An example of complicated p64 implantation for treating a ruptured, dissecting aneurysm of the right dominant intradural vertebral artery in a 66-year-old male patient. **(A)** Non-enhanced cranial computed tomography shows Fisher grade 4 subarachnoid hemorrhage. **(B)** The injection of the right vertebral artery in the posterior–anterior and **(C)** lateral projection demonstrates the underlying fusiform dissecting aneurysm with the PICA at its center. **(D)** represents the working projection for flow diverter implantation, which is subsequently evaluated in **(E)**; two p64 are implanted in telescoping technique with sufficient overlap of both devices at the center of the dissecting aneurysm. Note the distal intraluminal position of the p64 wire and the olive at its tip. **(F)** shows the control injection moments after unremarkable p64 implantation, revealing significant contrast extravasation from the distal V4 segment (the smaller image in the upper left corner shows extravascular pooling of contrast agent seconds later). The procedural re-rupture after flow diverter implantation prompted embolization of the respective segment with Histoacryl, which immediately stopped the bleeding **(G)**. A small proportion of the liquid embolic agent dislocated into the right posterior cerebral artery. The control injection *via* the left vertebral artery **(H)** demonstrates the basilar artery's timely perfusion and branches, except for the right posterior cerebral artery, which exhibits a slightly delayed filling.

and required implantation of a second device in telescoping technique. In two other cases, the insufficient opening of the device (1× p64: distal landing zone; 1× PED 2: mid-section) demanded balloon angioplasty to achieve adequate wall apposition. These four procedures were not associated with unfavorable outcomes. In the remaining two cases, the dissecting aneurysm exhibited a partly stenotic portion that compressed the flow diverter construct and required implantation of a balloon-expandable coronary stent to prevent impending occlusion. Despite the technical success, both patients died within the first week post-procedure.

Notably, all flow-diverting stents applied in the present study were sufficiently implantable and technically effective for treating the respective dissecting aneurysm. However, depending on the anatomy of the target vessel, the hemodynamic situation at hand, together with the necessity for subsequent surgery and relevant comorbidities, device selection can be decisive for the outcome. Therefore, the subsequent consideration aims to summarize our experience with the different device models in acutely ruptured dissecting VA aneurysms.

FD in acute SAH requires dual antiplatelet therapy, which delays obliteration of the aneurysm, increases the risk for re-rupture, and has been associated with a complication rate of 18% (36). In this regard, the selection of a coated device with biomimicry properties that prevent interactions with blood cells—most importantly platelets—is advantageous, as this strategy allows early reduction of platelet function inhibition or even single antiplatelet treatment (25). Current options are the Pipeline Flex with Shield Technology, the p48MW HPC, and the p64MW HPC. In our experience, the PED shield practically displays the most significant empirical outward force with optimal wall apposition—and thus the reconstructive potential for intradural dissecting aneurysms. However, the device requires a 0.027" inner diameter (ID) microcatheter for implantation, which is comparatively stiff, less maneuverable than a 0.021" microcatheter, and can therefore be distinctly problematic in challenging segments, especially in a situation with a preexisting mural injury.

The p48MW HPC and the p64MW HPC only require a 0.021" ID, and therefore a more versatile microcatheter, and come with a movable inner wire that can be placed up to 6 cm distally within the target vessel. This setup not only stabilizes the system during implantation (37), it also can be used to navigate the microcatheter through and distal to the implanted stent after implantation without losing access to the true lumen, which is a beneficial feature in large-scale dissecting aneurysms

(21). However, in our experience, balloon angioplasty is required more frequently to achieve sufficient wall apposition when implanting a p48MW HPC or a p64MW HPC compared to a PED Flex Shield.

Although not available with anti-thrombotic surface modification, the SVB can be the device of choice for dissecting aneurysms of the intracranial VA and basilar artery. The low-profile flow diverter is designed for the treatment of vessels ranging from 1.5 to 3.5 mm diameter and can be implanted *via* a 0.017" microcatheter. This feature is uniquely advantageous in challenging anatomies, as the 0.017" microcatheter allows atraumatic navigation in very elongated and curved vessels and provides a maximum of controllability (38). Remarkably, the SVB also achieves high rates of early obliteration in challenging cerebral aneurysms (38).

The Silk+, representing an older-generation flow-diverting stent, requires a rather stiff 0.025" microcatheter, which can be a significant limitation in the posterior circulation anatomy and especially in case of VA-DA. However, if a VA with a large diameter requires FD, the Silk+ may be the device of choice, as it is available in dimensions up to 5.5 × 40 mm and can be used to treat segments of 5.75 mm diameter.

## CONCLUSION

Reconstructive treatment in ruptured dissecting VA aneurysms of the dominant VA with flow-diverting stents is a technically safe and effective approach; however, the severity of the condition is reflected by high rates of morbidity and mortality, even despite technically successful endovascular treatment. Different flow-diverting stents are available, and case-adapted device selection is essential, as each flow diverter has a unique combination of features. In our experience, the size of the microcatheter required for implantation, anti-thrombotic surface modification, and radial force are the most significant features that should be taken into consideration when choosing the flow diverter model for treatment of ruptured dissecting VA aneurysms.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of University Hospital Leipzig. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JM, HH, WH, K-TH, and SS designed the manuscript and drafted the final version. HH, UQ, SS, JM, VH, MA-P, DM, AR, and K-TH performed the interventions. M-SS, GG, JM, and RB were responsible for data curation and statistical analysis. M-SS and SS designed the figures. All authors contributed to the article and approved the submitted version.

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# Treatment of Intracranial Aneurysms Using the New Silk Vista Flow Diverter: Safety Outcomes at Short-Term Follow-Up

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**Background:** Flow diverters are widely used as the first endovascular treatment option for complex brain aneurysms due to their high percentage of occlusion and low morbi-mortality. The Silk Vista device is a new generation of flow diverters designed to facilitate full visibility, improve apposition to the vessel wall, and enhance navigability. Indeed, its greatest advantage is that it enables the easier navigation of stents between 3.5 and 4.75 mm through a 0.021 microcatheter. The objective of this study was to evaluate the safety and effectiveness of Silk Vista systems for treating cerebral aneurysms.

**Methods:** This prospective observational study included 25 consecutive patients with 27 wide-necked unruptured aneurysms treated with SILK Vista who were retrospectively analyzed for safety and efficacy.

**Results:** Endovascular treatment was successfully performed in all patients. The final morbidity and mortality rates were both 0.0%. Short-term (3–5 months) angiographic follow-up revealed 21 complete occlusions and 6 near-complete occlusions. No significant parent artery stenosis was observed.

**Conclusions:** This report demonstrates the efficacy of Silk Vista in treating brain aneurysms, although longer experiences should be carried out to confirm our results.

**Keywords: flow-diverter, aneurysm, embolization, silk vista, stent**

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## INTRODUCTION

The introduction of flow diverter stents represented a new treatment option for those cerebral brain aneurysms that could not be managed with the usual endovascular techniques (1–3).

Since the Food and Drug Administration (FDA), in 2011, authorized the use of the first Flow diverter (Pipeline Embolization Device, Medtronic, Dublin, Ireland), flow diverters (FDs) began to be used representing an important option in the treatment of large and long brain aneurysms, obtaining satisfactory results both in the degree of occlusion and in the clinical efficacy (1–8). The neurovascular community has been progressively increasing their use, developing a new-generation the FDs, with different structures, in order to produce better parent artery reconstruction and

improve endothelial cells formation across the aneurysm neck (Silk flow diverter, Balt Extrusion, Montmorency, France; FRED, MicroVention, Tustin, CA; Derivo Embolization Device, Acandis GmbH, Germany; Surpass stent, Stryker Neurovascular, Kalamazoo, MI, USA; p64, Phenox GmbH, Bochum, Germany) (9–14).

Recently, novel devices have been introduced several systems have been designed in order to reduce thromboembolic complications, facilitate navigability, improve radial force and radiopacity, including the development of FDs specifically designed for the treatment of aneurysms beyond the Willis Circle (PED Shield, Medtronic, Dublin, Ireland; p48, Phenox GmbH, Bochum, Germany; Silk Vista Baby, Balt Extrusion, Montmorency, France; Fred Junior, MicroVention, Tustin, CA, USA) (15–21).

The SILK Vista (SV) system represents a new generation of Silk flow diverters with a redesigned delivery system. Its greatest advantage is that it allows a better navigation and more controlled stent delivery through a 0.021 microcatheter, presenting a full radiopacity and resheathability capacity after deployment of up to 90%. We report our preliminary results using this device in the management of brain aneurysms.

# MATERIALS AND METHODS

## The SILK Vista System

The SV is a novel self-expanding stent designed to treat complex brain aneurysms that received the CE mark on June 6, 2020. The SV contains 48 drawn filled tubing (DFT) Nitinol/platinum wires, of a slightly larger caliber and a mesh density three times less dense than the Silk Vista Baby (SVB). This technology facilitates a good radiopacity and the precise controlled deployment of the entire device (**Figures 1A,B**).

This device and the p64 MW HPC are the only systems designed to treat vessels between 3 and 5 mm in diameter that navigate through a microcatheter of 0.021 in diameter. SV is currently available in 26 references, with a length between 15 and 40 mm and a diameter between 3.5 and 4.75 mm.

The stent is folded in a plastic sheath, the distal end of which is protected by a metal cannula that allows it to be safely inserted into the microcatheter. The delivery system presents an improved pusher profile to achieve the best compromise between flexibility and pushability. It has a delivery wire of nitinol with a 9-mm distal atraumatic platinum coil at a 45° angle.

Its design is similar to that of a SVB with the same instructions, precautions, and technical features (**Figure 1**), except that it has no present flared ends, which, together with its greater radial force, facilitate its better apposition to the vessel wall.

## Patient Population

This was a prospective observational study that included 25 consecutive patients with 27 wide-necked aneurysms treated with SV system at four Spanish university tertiary care centers, each of whom had experience with more than 30 SILK plus implanted. This study was approved by the institutional ethics committee. Written informed consent was obtained from all patients.

Patients between 18 and 80 years of age, with a pre-treatment modified Rankin scale (mRS) of 0–2, anterior circulation wide-neck unruptured aneurysm, or beyond 30 days since the hemorrhage, regardless of prior treatments, were included. Exclusion criteria included the presence of hemodynamically significant atherosclerotic lesions in the carotid artery on the same side, intolerance to heparin or resistance to antiplatelet therapy, coagulopathies, and an abnormal platelet count. The indication for endovascular treatment was made by a vascular neuroscience team of neurologists, neuroradiologists, and neurosurgeons.

## Data Collection and Follow-Up

We recorded each patient's demographic data, clinical presentation, aneurysm location, size of the SV, clinical and radiological follow-up information, and adverse events Clinical status was assessed during hospitalization, at discharge, and at short-term (3–5 months), using the modified Rankin scale (mRS). Any decrease in grade on the mRS scale was identified as morbidity.

Angiographic follow-up was performed at short-term (3–5 months). The imaging was reviewed and compared by two senior endovascular neurosurgeons who were not involved in the procedure for initial and follow-up occlusion grades. The degree of aneurysm occlusion was assessed according to the O'Kelly Marotta (OKM) grading scale (22).We considered grade C or D as a satisfactory outcome.

## Endovascular Procedure

All procedures were performed under anesthesia. All patients received double antiplatelet therapy before and after treatment as well as complementary heparinization according to our protocol for brain stenting (9).

The SV deployment strategy aimed at strict compliance with the recommendations of the SV manufacturer (Balt Extrusion, Montmorency, France). The choice of SV was selected by three-dimensional angiography, and the stent length was determined to be 30% longer than the aneurysm neck overlapping both sides of the aneurysm neck, by at least 4 mm. The diameter was chosen by oversizing the proximal diameter of the parent artery by 0.25 mm. Selection of the FDs, deployment of multiple devices, and implementation of adjunctive coiling were carried out at the discretion of the individual neurointerventionalist (**Figures 2A–F**). In cases in which additional aneurysm coiling was performed, a microcatheter was initially positioned inside the aneurysmal sac, followed by semi-jailing of the microcatheter between the parent vessel wall and the FDs on deployment.

Deployment failure was assessed in terms of the following aspects: failure to advance through the delivery catheter, poor opening, poor positioning, shortening, and stent displacement.

## Statistical Analysis

Data are presented as means and SD for continuous variables and as numbers and percentages for categorical variables. Statistical analyses were performed using a Student's *t*-test, Chi-square test, Mann-Whitney test, ANOVA, and multivariate analysis using IBM® SPSS® statistics v. 22 (IBM Co., Armonk, NY, USA).

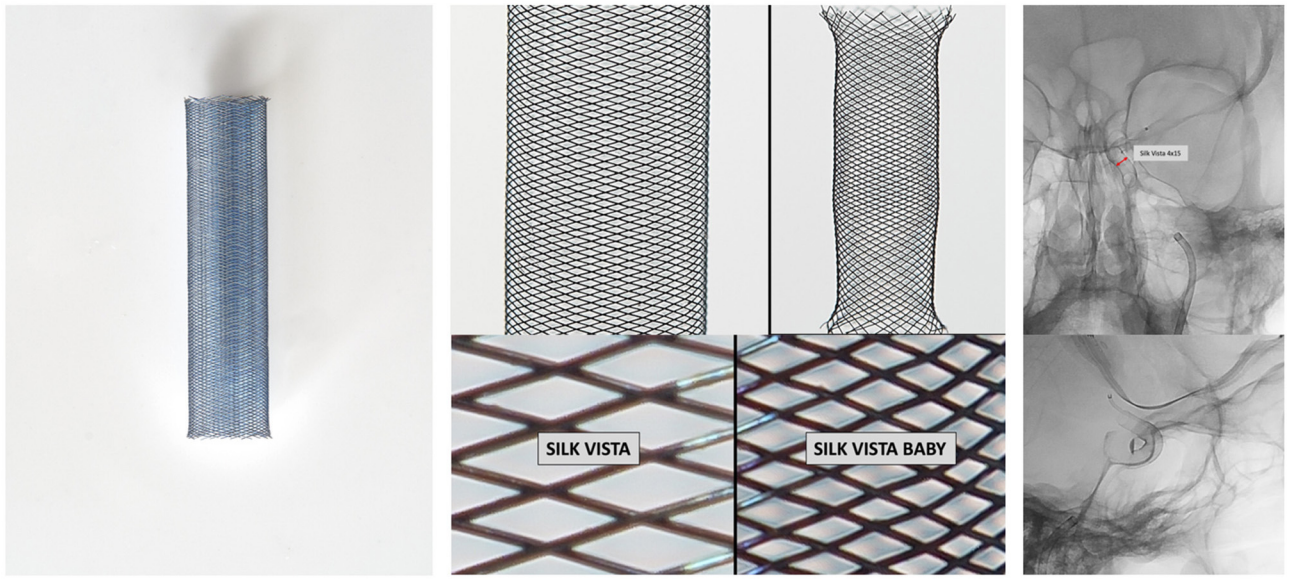


**FIGURE 1 |** Schematic graphic representation of the SV delivery system. **(A)** SV appearance fully open; **(B)** comparison between SV and SVB, both with 48 DFT. The SV, however, are three times less dense and no present flared ends. **(C)** Good radiopacity SV. SV, Silk Vista; SVB, Solk Vista Baby.

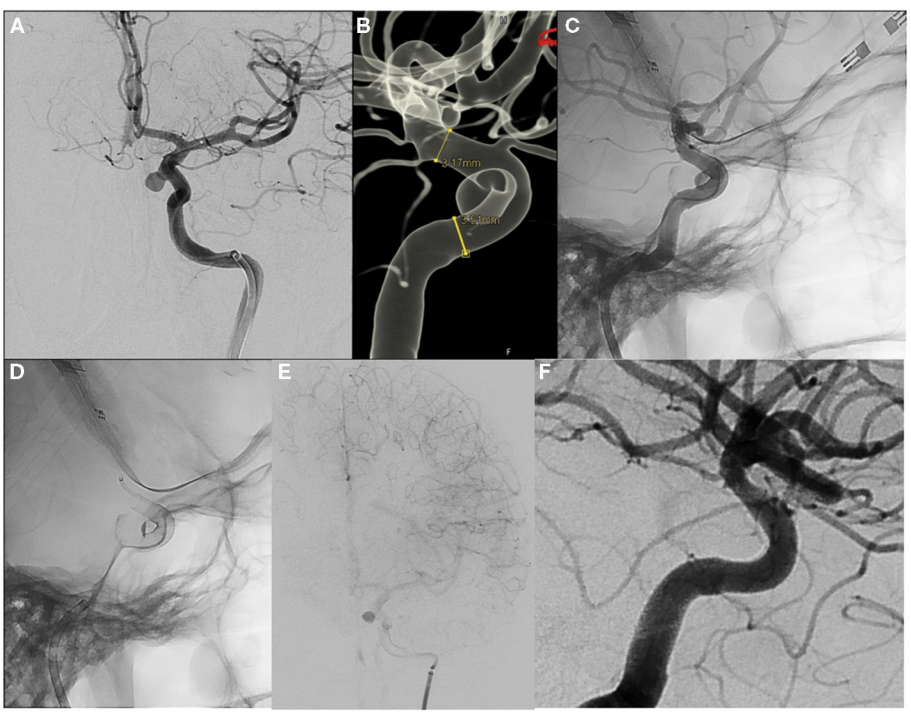


**FIGURE 2 |** DSA and reconstruction of 3D rotational of the right internal carotid artery **(A,B)** show a paraclinoid aneurysm. Silk Vista device 3.75 × 20 mm is deployed through the Rebard 18 microcatheter, covering the neck of the aneurysm with a safety margin **(C)**, after which the microcatheter is advanced through the interior of the stent **(D)**. Postoperative angiography reveals a flow reduction **(E)**. The 4-month follow-up DSA shows complete occlusion of the aneurysm **(F)**.

For statistical analyses, values of $p < 0.05$ were considered statistically significant.

# RESULTS

## Patient and Aneurysm Characteristics

Between August 15, 2020, and November 31, 2020, 25 patients (11 female, 14 male; mean age, 58-years-old; age range, 32–80) with 27 aneurysms who fulfilled the criteria of inclusion were enrolled in our study. Angiography follow-ups were carried out prior to February 2020; data locking took place in March 2020.

Aneurysms locations were: cavernous internal carotid artery (ICA; n.4), paraophthalmic ICA (n.8), superior hypophyseal artery (n.5), paraclinoid ICA (n.2), supraclinoid ICA n.5), posterior communicating artery (PcomA; n.2), and anterior cerebral artery (ACA; n.1).

Four aneurysms had previously ruptured and had recurrence after initial coiling. Two patients had two aneurysms. The aneurysm size ranged from 2 to 16 mm (median, 7 mm). The neck size ranged from 1.5 to 10 mm (average, 4 mm). The neck to sac ratio ranged from 0.3 to 1 (average 0.8).

## Intraprocedural Technique

The Silk Vista advanced easily into a Rebard 18 microcatheter (Medtronic) in all cases. Stent deployment was successfully achieved in all patients. One patient was implanted with two devices. The mean procedure duration was 92.7 min (range, 40–235 min), and the mean cumulative fluoroscopy time was 31.4 min.

We implanted 26 SV in 25 patients. Each patient was treated using a single SV, except in one patient with a large paraophthalmic aneurysm, where the length of the SV was underestimated, who was treated with two overlapping stents. In three cases, a semi-jailing technique was used for coiling. In two patients, with tortuous vascular anatomy, the adaptation of the SV to the vessel in its middle part was not complete, and an angioplasty (PTA) was performed with a Scepter balloon (MicroVention, Tustin, CA) to fully open the stent and improve its apposition to the vessel. A postoperative VasoCT showed excellent wall apposition in both cases.

## Immediate Angiographic and Clinical Results

Following FD deployment, 22 aneurysms showed contrast stasis in the venous phase. No aneurysm showed the complete absence of contrast fill (OKM grade D), 13/27 (%) showed persistent filling (OKM grade B), and 14/27(50%) showed complete filling (OKM grade A).

No periprocedural thrombus formation was observed. No new neurological deficits developed after endovascular treatment in any of the patients, and no bleeding or ischemic events occurred during or after the endovascular treatment.

## Clinical and Imaging Follow-Up

Clinical and imaging follow-up data were available for all 25 patients at a mean of $3.45 \pm 0.8$ post-procedure months (range, 3–5). No new neurological deficits were observed in any patient.

Short-term anatomical results revealed a complete aneurysm occlusion (OKM D) in 21/27 (77.7%) aneurysms. A near-complete occlusion (OKM C) was detected in another 6/27 (22.3%) aneurysms. No cases of in-stent stenosis or in-stent thrombosis were observed.

In one case, delayed migration of the SV was detected. A 52-year-old woman presented an aneurysm in the left superior hypophyseal segment of the ICA ($6.43 \times 6.97$ mm with a neck of 3.6 mm). The diameter of the petrous segment of the internal carotid artery was 4.1 mm, and the diameter of the paraclinoid segment was 2.7 mm. The aneurysm was treated with flow diversion and coiling. A $4 \times 20$-mm SILK Vista was deployed across the aneurysms without difficulty. Immediate post-procedure angiography control showed adequate SV placement with contrast stasis in the aneurysm (**Figures 3A–D**) and a VasoCT demonstrated adequate stent apposition to the vessel wall with covering of the aneurysm neck. The procedure and postoperative course were uneventful, and the patient was discharged the following day.

Three months later, angiography showed proximal displacement of the stent with partial filling of aneurysms. A VasoCT confirmed the complete non-coverage of the neck. The deployment of an additional stent was necessary, and an overlapping $4 \times 25$-mm SV was subsequently deployed beyond the first stent to bridge the neck of the aneurysm and disrupt the inflow jet (**Figures 3E,F**). A VasoCT subsequently performed demonstrated adequate apposition to the interior of the prior SV and to the vessel wall with covering of the aneurysm neck.

# DISCUSSION

Some aneurysms have morphological characteristics that hinder conventional endovascular treatment, requiring the use of new systems such as in the form of FDs. Many studies have demonstrated the feasibility and effectiveness of FDs in the treatment of nearly all types of aneurysms, which are now widely accepted as a suitable alternative to conventional intracranial aneurysm treatment, especially for complex aneurysms (3, 6, 9, 12, 15, 19). This preliminary clinical experience of aneurysm treatment (26 SV implanted in 25 patients) with SV devices was technically successful in all cases and showed excellent feasibility, safety, and short-term efficacy at the 3–5 month follow-up.

Although the short- and mid-term results after FD use have demonstrated good aneurysm occlusion as well as low morbidity and mortality, one of the major limitations of the FD implantation technology between 3 and 5 mm in diameter is that most systems are compatible with microcatheters with a lumen >0.027 inches (Silk + -Balt-extrusion; Pipeline Vantage-Medtronic; FRED Jr. -Microvention; DERIVO mini – AcandisGmbH; P48 MW -Phenox).

In 2020, a redesigned "third-generation SILK," called the SILK Vista was introduced, representing the most significant technical improvement, being a FD for vessels diameters between 3 and 5 mm compatible with 0.021 inner diameter microcatheters, which facilitates the navigability of the system while minimizing technical complications during treatment.

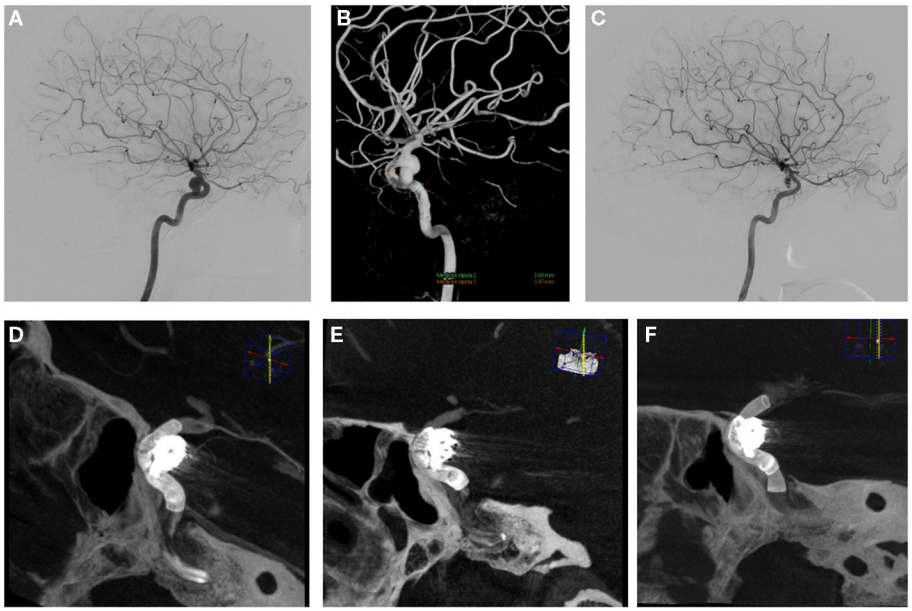


**FIGURE 3 |** A 52-year-old woman referred for embolization of an incidental aneurysm. Digital subtraction angiography **(A)** and 3D rotational angiography **(B)** show a wide-neck left para-ophthalmic aneurysm. Stent deployment (SV 4 × 20 mm) and compartmental coiling (semi-jailing technique) was performed **(C)**. A Vaso CT shows adequate stent apposition to the vessel covering of the aneurysm neck **(D)**. A follow-up at 3 months, shows shortening of SV without completely covering the aneurysmatic neck **(E)**. An overlapping 4 × 25 mm SV was deployment covering of the aneurysm neck **(F)**.

Previous experiences using first-generation silk devices had relatively high morbidity and mortality rates (2, 3, 9, 23–25), resulting in specific problems mainly related to deployment difficulties. In these studies, the rate of successful deployment reported varied between 75 and 96%, with an average of 88.6%, which contrasts with the rate of technical feasibility of 100% reported in our results and those reported in other series with P48-MW (20, 21). However, a direct comparison between our results and the reported results is not possible given the variations in key factors, such as patient selection criteria and population size. We believe that such differences are due to the fact that significant experience in the management of the silk system is needed to implant SV devices, as such a procedure is slightly different than that followed for the implantation of other FDs stents.

To date, no published short-term aneurysm occlusion or clinical outcome data exist with regard to the SV systems. Recently, Martínez-Galdámez et al. (26) described the first experience assessing, in a retrospective revision, the technical success and procedural safety in the management of a consecutive succession of 57 patients with 60 brain aneurysms between September 2020 and January 2021. In a prospective study, we report our experience assessing both the procedural safety of the system and its effectiveness in a clinical and radiological follow-up at short-term (3–5 months) in a case series of patients treated with SV system. This clinical study was carried out to conduct a *post-hoc* multicenter study.

In this preliminary clinical experience, aneurysm treatment (26 SV implanted in 25 patients) with SV deployment was technically successful in all cases. It is great percentage of success in deployment is probably related to the FD construction design, which enables the visibility of the entire device, better apposition to the vessel wall, and compatibility with a 0.021 delivery microcatheter, facilitating navigability. Our preliminary impression compared with the other current FDs is that it is technically simpler to deliver, deploy, maneuver, and perform crossings, presenting much lower friction, more flexibility, and better radiopacity.

In two patients with very tortuous anatomy, immediate post-deployment control angiograms showed an incomplete opening of the SV in its middle part without a good wall apposition, and an in-stent PTA was performed with excellent wall apposition in both cases. The 8% post-deployment angioplasty rate reported was similar to 5.6% of PED and markedly lower than 28% for Surpass and although malapposition is still a complication of the system, new FDs (FRED; P48 MW HPC; P64 MW HPC; SV.)have been specifically designed provide higher radial forces and better navigation systems to facilitate wall apposition in difficult opening situations.

According to our experience, adequate stent opening is achieved only when the stent is slowly deployed from the microcatheter, and it is also important to ensure that the stent is steadily placed at the vessel wall by pushing the microcatheter distally through the stent; we have generally avoided excessive compaction or stretching of the SV during deployment to reduce the risk of damaging the flow diverter.

In this experience, we have reported one case of delayed shortening or migration of the SV in the angiography follow-up

performed at 3 months, evidencing that the neck of the aneurysm is no longer covered by the device. Lubicz et al. (23) previously described the delayed migration of a Silk stent in a patient with a giant saccular carotid ophthalmic aneurysm. Although Chalouhi et al. (27) reported 5 cases of FD migration or shortening with serious and potentially fatal complications in our case, the patient did not present any clinical complications. There are various potential mechanisms to be contemplated which might cause FD shortening or migration, involving the undersizing the caliber of the stent in relation to the diameter of the target vessel, substantial diameter differences of the target vessel diameters, faulty wall apposition of the FD, and excess manipulation of the device during implantation. In our case, we believe that due to the vascular tortuosity, the radial force of the stent exerted a non-uniform pressure on the wall of the vessel, facilitating the displacement toward the proximal part of greater caliber.

At the 3-month angiographic follow-up, 21 aneurysms (77.7%) showed complete occlusion (OKM score D), and 6 aneurysms showed near-complete occlusion (OKM score C). This rate is comparable with the rates reported in the literature (10, 13, 17), such as those reported by Pierot et al. (28) in the SAFE study, where an adequate occlusion rate of 81.1% was reported using the FRED device. Although the sample size was small, and the follow-up period was short, SV system appear to be a safe and effective form of treatment for unruptured ICA aneurysms. Based on our results, we believe that a prospective multicenter study to validate the safety and effectiveness of the SV stents would be worthwhile.

The major limitations of this prospective study include the limited cohort of 25 patients, a short-term follow-up period of 3-5 months. Another major limitation is the heterogeneity of the aneurysms and the fact that the majority of aneurysms were located in the ICA, which supposes a lower risk of complications compared with those located elsewhere in the anterior circulation.

## CONCLUSION

Based on the results obtained in this study with a small series of cases the efficacy of Silk Vista seems to be promising as a flow diverter with special characteristics, enabling easy deployment with low friction, very good radiopacity, predictable opening, and operator-friendliness. To confirm the apparent high safety of the device, long-term follow-up and a larger cohort is necessary to determine this.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comite etico del SERGAS. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JP, AM, and JO: conception and design of the study. JP, CR-F, EG-D, and AM: data acquisition and analysis. CR-F and JO: manuscript drafting. EG-D and JO: critical revision for important intellectual content. All authors have reviewed and approved the manuscript.

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**Conflict of Interest:** JP was a consultant for Balt.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Endovascular Treatment of Posterior Circulation Saccular Aneurysms With the p64 Flow Modulation Device: Mid-and Long-Term Results in 54 Aneurysms From a Single Center

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**Objective:** Flow diverter (FD) stents have become one of the most common tools for treating intracranial aneurysms; however, their role in treating posterior circulation aneurysms is still discussed with controversy. In this study, we evaluated the safety and effectiveness of p64 FD for the treatment of saccular, unruptured aneurysms in the posterior circulation over a long-term follow-up period in a single center.

**Methods:** From our prospectively maintained database, we retrospectively identified patients who underwent treatment of an intracranial saccular aneurysm arising from the posterior circulation with ≥1 p64 FD implanted or attempted between October 2012 and December 2019. Aneurysms could have been treated with prior or concomitant saccular treatment (e.g., coiling, intra-aneurysmal flow diversion). Aneurysms with parent vessel implants other than p64, fusiform aneurysms, and dissections were excluded. Peri- and postprocedural complications, clinical outcome, and clinical and angiographic follow-up results were evaluated.

**Results:** In total, 54 patients (45 female, 9 male; mean age 55.1 years) with 54 intracranial aneurysms met the inclusion criteria. In 51 cases (94.4%), one p64 was implanted; in 2 cases (3.7 %), two p64s were implanted; in one case, deployment of the p64 was not feasible. Procedural complications occurred in 3.7% and postprocedural complications in 9.3 %, respectively. Hemorrhagic complications occurred in 2/54 patients (3.7%), thereof one fatal parenchymal hemorrhage. Ischemic complications were observed in 5/54 patients (9.3%). Early, mid-term, and long-term angiographic follow-up examinations showed complete or near-complete aneurysm occlusion, defined according to the O'Kelly –Marotta (OKM) scale as OKM C + D in 56, 75.6, and 82.9 %, respectively. Asymptomatic side vessel occlusions occurred in 3.8%, each during the first follow-up.

**Conclusions:** The implantation of a p64 FD is a safe and effective device for endovascular treatment of posterior circulation saccular aneurysms with a high success rate and low morbi-mortality.

**Keywords: p64, posterior circulation aneurysms, flow diversion, unruptured aneurysm, saccular aneurysm**

# INTRODUCTION

Flow diverter (FD) implantation has become one of the most common tools for treating intracranial aneurysms (IAs). In the last years, the number of available FDs has increased continuously. One of these FDs is the p64 FD (phenox, Bochum, Germany). Its unique feature is that it can be deployed entirely and resheated due to its mechanical detachment system allowing for potentially necessary repositioning. Several published studies have reported the long-term efficacy of the p64 (1–3). However, these studies have focused mainly or exclusively on aneurysms in the anterior circulation. There is only limited data for treating aneurysms with the p64 in the posterior circulation.

Furthermore, FD in the posterior circulation is still discussed more controversially due to higher rates of ischemic complications and morbidity and mortality (4–6).

In the present study, we report the experience of treating intracranial saccular unruptured aneurysms arising from the posterior circulation endovascularly with the p64 FD. To the best of our knowledge, this is the most extensive study to report data for saccular aneurysms in the posterior circulation treated exclusively with the p64 FD.

# METHODS

## Device Description

The p64 Flow Modulation Device is braided from 64 nitinol wires and two platinum wires wrapped around opposing nitinol wires for visibility under x-ray fluoroscopy. At the proximal end, the 64 wires form 8 bundles, each carrying a radiopaque marker. The unique feature of the p64 is that after full deployment, it is entirely resheatable and repositionable due to its mechanical detachment. It is delivered via a 0.027-inch inner diameter microcatheter.

## Patient Population

We retrospectively reviewed our prospectively maintained database to identify all patients with intracranial saccular unruptured aneurysms in the posterior circulation treated with at least one p64 FD between October 2012 and December 2019. Inclusion criteria for this series were all aneurysms treated endovascularly with p64 implantation only or with p64 and simultaneous or prior coiling. Only patients with unruptured aneurysms or past the acute stage of SAH (>30 days) were included. Fusiform, dissecting, or blister-like aneurysms, as well as dolicho-ectatic basilar artery aneurysms, were excluded. Aneurysms treated with other parent vessel implants such as other FDs or stents were also excluded. We recorded demographic data, anatomical features, location of the aneurysm, procedural and post-procedural complications, and clinical and angiographic outcomes according to the latest available follow-up for each of these patients.

## Endovascular Procedure

In each case, patients had given written informed consent at least 24 hours before the procedure after being informed about the intended treatment and potential alternatives.

All treatments were performed under general anesthesia using bi-plane digital subtraction angiography (DSA) units (Axiom Artis, Siemens, Erlangen, Germany). A 6F short sheath with a 6F guiding catheter was used via right-sided femoral access as the standard approach. In cases with severe vessel elongation and the need for an intermediate catheter, an 8F right femoral approach was used. Heparin was administered intravenously immediately after groin puncture (usually 3,000 IU unfractionated heparin IV). All flushing solutions, including the guiding catheters and microcatheters, were heparinized (5,000 IU unfractionated heparin/l).

The p64 was deployed via an Excelsior XT27 (Stryker Neurovascular, Kalamazoo, MI, USA) microcatheter. The diameter and length of the p64 were chosen based on intraprocedural 2D and 3D calibrated measurements of the diameter of the parent artery, the distance between the proximal and distal landing zones, the discrepancy of the diameter between the landing zones, and the aneurysm neck size taking into account potential device foreshortening. Once satisfactory deployment and positioning were achieved, the p64 was mechanically detached.

## Medication

All patients received dual antiplatelet therapy (DAPT) with 1 × 100 mg acetylsalicylic acid (ASA) PO daily and either 1 × 75 mg clopidogrel or 2 × 90 mg ticagrelor or 1 × 10 mg prasugrel PO daily for at least five days before treatment. Alternatively, a loading dose of 500 mg ASA and either 600 mg clopidogrel or 180 mg ticagrelor or 30 mg prasugrel 24h before the treatment was given. From 2012 until 2015 the standard approach was DAPT with ASA and clopidogrel and ticagrelor was only used in case of non-responders to clopidogrel. From 2015 on the standard approach was switched to ASA and ticagrelor to avoid issues due to non-responders to clopidogrel and to achieve a stronger DAPT. Prasugrel was given in case of insufficient DAPT under ticagrelor or in case of intolerance to ticagrelor. The response tests of the antiplatelet regime were done with the Multiplate Analyzer (Roche Diagnostics, Mannheim, Germany) and with the Verify Now (Accriva, San Diego, CA, USA). No p64 was implanted unless adequate platelet inhibition was confirmed. Postprocedural medication consisted of a daily dose of 100 mg ASA and either 1 × 75 mg clopidogrel or 2 × 90 mg

ticagrelor or 1 × 10 mg prasugrel PO daily for at least one year. Then DAPT was stopped and switched to 1 × 100 mg ASA PO daily lifelong. According to our institutional protocol, postmedication in patients with an anticipated increased risk of ischemic complications (e.g., if many perforating arteries were covered with an undersized p64) consisted of 2 × 3,000 IU certoparin s.c. (Mono-Embolex, Mylan Healthcare, Germany), daily for 4–6 weeks after flow diversion treatment. The decision to add heparin to the therapy regimen was made based on the device location in perforator-rich areas and the size of the device in relation to the parent vessel.

## Data Collection and Follow-Up

Patency of the parent vessel and distal and side branches and flow characteristics within the flow diverter was assessed angiographically immediately after deployment of the p64 and during follow-ups.

Patients were scheduled for clinical and angiographic follow-up examinations as follows: early follow-up (3–6 months), mid-term follow-up (9–12 months), and long-term follow-up (>24 months). Assessment of the aneurysm occlusion was evaluated according to the O'Kelly-Marotta (OKM) – scale, based on the degree of aneurysm perfusion (7). Adequate occlusion was defined as OKM C and D. Neurological examinations were performed in the peri-procedural period (≤24h), post-procedural period (>24 h ≤ 30 days), and during the follow-up (>30 days) by a neurologist or a certified stroke nurse, and recorded using the modified Rankin Scale (mRS) (8). The clinical sequelae of any complication were classified as "transient neurological deficit," "permanent minor neurological deficit" (i.e., mRS 1 or 2), "permanent major neurological deficit" (i.e., mRS 3–5) or "death." (9).

# RESULTS

## Patient's Demographics and Aneurysm Characteristics

Between October 2012 and December 2019, a total of 54 patients with 54 aneurysms of the posterior circulation were identified who met the inclusion criteria. There were 45 female patients in our cohort (83 %), and the mean age of the patients was 55.1 years (range 29–76) (**Table 1**).

The mean aneurysm dome size was 3.6 mm (range 0.8–18 mm). Of the 54 aneurysms treated, 51 (94.6 %) aneurysms were small (<10mm), 3 (5.5%) were large (10–25mm), and 0 (0 %) was giant (>25mm). In 51 cases (94.4%), one p64 was implanted, in 2 cases (3.7%), 2 p64 were implanted, and in one case (1.9%), the deployment of a p64 was not feasible even though two different p64 were tried. The implantation of the p64 was the first procedure in 39 aneurysms (72.2%), whereas the remaining 15 aneurysms (27.8%) had been treated before as follows: coiling $n = 12$, coils + Medina $n = 1$, WEB $n = 1$, microsurgical clipping ($n = 1$, the attempted clipping failed). In 10 procedures (18.5%), coils were used as additional devices; in one case (1.9%), additional coiling was attempted but failed. Out of the 54 treated patients 17 patients (31.5%) with an anticipated increased risk of ischemic complications were given additional heparin for 4–6 weeks. Three patients still presented symptoms due to perforator ischemia.

**TABLE 1 |** Baseline patient demographics and clinical presentation of the study population.

| **Patients characteristics** | |
|---|---|
| Number of patients | 54 |
| Gender (m/f) | 9/45 |
| Number of aneurysms | 54 |
| **Previously treated aneurysms** | 15/54 (27.8%) |
| Coiling | 12 |
| Coiling +Medina | 1 |
| WEB | 1 |
| Microsurgical clipping (failed) | 1 |
| **Aneurysm location** | |
| Basilar artery bifurcation | 10 (18.5%) |
| Basilar artery trunk | 6 (11.1%) |
| Posterior cerebral artery | 3 (5.6%) |
| Posterior inferior cerebellar artery | 18 (33.3%) |
| Superior cerebellar artery | 14 (25.9%) |
| Vertebral artery (V4) | 3 (5.6%) |

The distribution of the location of the aneurysms in the posterior circulation was: basilar artery (BA)-bifurcation $n = 10$ (18.5%), BA-trunk $n = 6$ (11.1%), posterior cerebral artery (PCA) $n = 3$ (5.6%), posterior inferior cerebellar artery (PICA) $n = 18$ (33.3%), superior cerebellar artery (SCA) $n = 14$ (25.9%) and vertebral artery (VA) intradural $n = 3$ (5.6%) (**Table 1**).

The mean diameter of the distal landing zone was 2.4 mm (range 1.3–4.4mm), and of the proximal landing zone, 3.0 mm (range 1.6–4.2 mm); the mean discrepancy of the diameter between the proximal and distal landing zone was 0.5 mm, ranging from −1.2 to 1.8 mm.

## Angiographic Follow-Up

An early follow-up (FU) DSA examination (3–6 months) was available for 50 of the 53 (94.3%) aneurysms in which the implantation of the p64 was successful. The FU was performed after a median of 96 days ranging from 42–379 days. The angiographic findings were as follows: complete aneurysm occlusion (OKM D) was observed in 22 (44 %), and a neck remnant (OKM C) in 6 (12%) aneurysms. For 17 (34%) aneurysms, subtotal aneurysmal filling (OKM B) was found. Five aneurysms (10%) remained unchanged (OKM A). In-stent stenosis was found in 3 patients (6%) thereof two moderate ones (50–75%), and one (2%) was graded severe (>75%). All of the patients mentioned above were asymptomatic. Furthermore, there were 2 (4%) side vessel occlusions observed, both asymptomatic.

A mid-term follow-up (9–12 months) was available in 49/53 aneurysms (92.5 %) after a median of 275 days (range 93–522), showing complete aneurysm occlusion (OKM D) in 31/49 (63.3%), neck remnant (OKM C) in 6 (12.3%) aneurysms, and a sac remnant (OKM B) in 8 (16.3 %) aneurysms. Four (8.2 %) aneurysms remained still unchanged (OKM A). In-stent

**TABLE 2 |** Angiographic results and occlusion rates.

| **Available FU** | |
|---|---|
| 1st FU | 50/53 (94.3%) |
| 2nd FU | 49/53 (92.5%) |
| 3rd FU | 41/53 (77.4%) |
| **Occlusion rates OKM C+D** | |
| 1st FU | 28/50 (56%) |
| 2nd FU | 37/49 (75.6%) |
| 3rd FU | 34/41 (82.5%) |
| Parent vessel patency at FU | 100 % |
| Side vessel occlusion at FU | 4/53 (7.5%) |

*FU, Follow-up; OKM, O'Kelly Marotta. OKM C+D stand for "entry remnant" and "no filling", and signify sufficient occlusion.*

**TABLE 3 |** Aneurysmal location and angiographic occlusion rates at each time point.

| Location | 1st FU OKM C+D | 2nd FU OKM C+D | 3rd FU OKM C+D |
|---|---|---|---|
| BA- bifurcation | 71.4% (7/50) | 85.7% (6/7) | 100% (5/5) |
| BA-trunk | 83.3% (5/6) | 100% (6/6) | 100% (6/6) |
| PCA | 66.7% (2/3) | 100% (3/3) | 100% (2/2) |
| PICA | 44.4% (8/18) | 62.5% (10/17) | 78.6% (12/15) |
| SCA | 38.5% (5/13) | 61.5% (8/13) | 63.9% (7/13) |
| V4 | 100% (3/3) | 100% (3/3) | 100% (2/2) |

stenosis improved in all cases: 2 (4.1%) were now graded as mild (<50%), and one (2%) was moderate (50–75%). No additional patient developed in-stent stenosis between the first and second FU. There was one other asymptomatic side vessel occlusion (2.0%) observed.

The long-term follow-up (>24-months) was performed after a median of 686 days (range 240–1505) in 41/53 aneurysms (77.4%), revealing complete occlusion (OKM A) in 33 (80.5%), neck remnant (OKM C) in 1 (2.4%), and an aneurysm remnant (OKM B) in the remaining 6 (14.6%), respectively. One aneurysm remained unchanged (2.4%). Therefore, an adequate occlusion (OKM D & C) was seen in 82.9% of aneurysms during the follow-up period. Intimal hyperplasia had resolved entirely, and one new side vessel occlusion (2.4%) had occurred at this FU (**Tables 2, 3**).

Retreatment of the target lesion was performed in 5/53 patients (9.4%). In all these patients, the effect of the first implant was considered insufficient, and retreatment was performed by deploying another FDS. Re-treatment was performed if the aneurysms were graded OKM A or B more than 6 months after stopping of DAPT. Of the 5 re-treated aneurysms were three PICA aneurysms and two SCA aneurysms. The jailed vessel had remained patent after the first FD presumably leading to reduced flow diversion effect hence failing to occlude the aneurysm.

During these retreatments, no adverse event occurred. Follow-up DSA examinations confirmed an adequate occlusion (OKM D & C) of the concerning aneurysms in 4 patients. One aneurysm showed reduction in size in follow-up DSA, but was still graded OKM B after the 3rd FU DSA. Patient refused a second re-treatment (**Figure 1**).

Out of the 53 patients in which the FD implantation had been feasible, angiographically visible side vessel branches had to be covered in 48 patients (90.6%). Acute occlusion of the covered branches was not observed in any of these patients. During the first FU in two patients, the covered branches were occluded (4%), and during the second and third FU, one more side vessel occlusion was observed (2 and 2.4%) (**Figure 2**). The occluded side vessels were 1 × PICA, 1 × SCA, and 2 × the V4 segment of the VA distal of the PICA. All of these side vessel occlusions were asymptomatic. In 22 patients (41.5%), the origin of the PCA was covered by the p64. In 13 of the 22 cases (59%), the PCA was predominantly or solely supplied by the posterior communicating artery (PcomA) in the FU angiography combined with caliber reduction or occlusion of the P1 segment of the respective PCA (**Figure 3**). None of these hemodynamic changes were symptomatic.

## Complications

Intraprocedural complications occurred in 2 out of the 54 procedures (3.7%). In one patient, the FD dislocated after detachment, causing incomplete coverage of the aneurysmal neck. Therefore, a second FD was placed.

One patient suffered a subarachnoid hemorrhage (SAH) Hunt & Hess II, Fisher 2 due to a suspected microwire perforation and a dissection of the vertebral artery in the V2 segment that was reconstructed with the implantation of 2 Solitaire Stents (Solitaire AB, Medtronic). The implantation of the p64 failed in this patient due to unstable access. Therefore, the aneurysm was treated with partial coiling of the dome, accepting a neck remnant. The clinical outcome of these patients was rated as mRS 3, equivalent to the condition before the treatment.

Postprocedural complications (24h−30d) were observed in 5 patients (9.3%).

A hemorrhagic complication was observed in one patient (1.9%). This patient suffered a fatal hemorrhage on the day of discharge. The other four patients (7.4%) suffered from symptomatic ischemia resulting in permanent deficits in three patients, and transient symptoms in one patient. A delayed complication (>30 days) occurred in one patient (1.9%) who presented with an internuclear ophthalmoplegia (INO) 15 months after the implantation of the p64 (**Tables 4, 5**).

We did not observe any device-related thromboembolic complications in our series during the procedural and postprocedural period nor any in-stent thrombosis.

## Clinical Follow-Up

Clinical deterioration with a permanent worsening of the mRS was reported in 5 of the 54 patients (9.3 %) as follows: one fatal hemorrhage (mRS 6, 1.9%), one shift of the mRS from 0 =>2 (1.9%), and 3 patients with a shift from mRS 0=>1 (5.6 %) (**Table 3**).

**Tables 2**, **3** show a breakdown of aneurysm occlusion rates and **Tables 4**, **5** of complication rate.

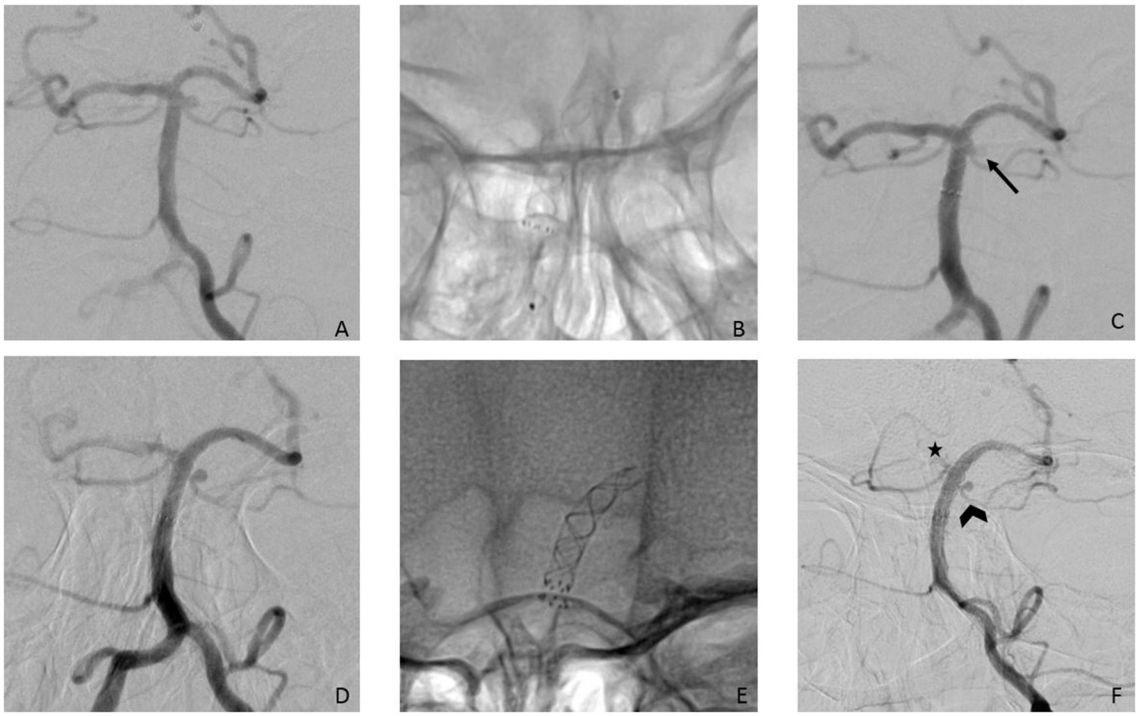


**FIGURE 1 | (A)** Posterior-anterior view after injection of the left VA showing a 2 mm aneurysm of the left SCA; **(B)** successful implantation of a p64 3/12 mm from the left PCA to the BA; **(C)** final run after the FD implantation showed already reduction of the perfusion (arrow); **(D)** 3rd FU after 20 months shows aneurysm unchanged as well as a significant caliber reduction of the right P1- segment. **(E)** a second FD- p64 3/9 mm- was implanted coaxial with the first FD without any complications. **(F)** FU after 12 months after the second confirms that the aneurysm has shrunken, but remains still patent. The left SCA shows significant reduction in size (arrowhead) but is also still patent. The right P1 segment (asterisk) is reduced in caliber now.

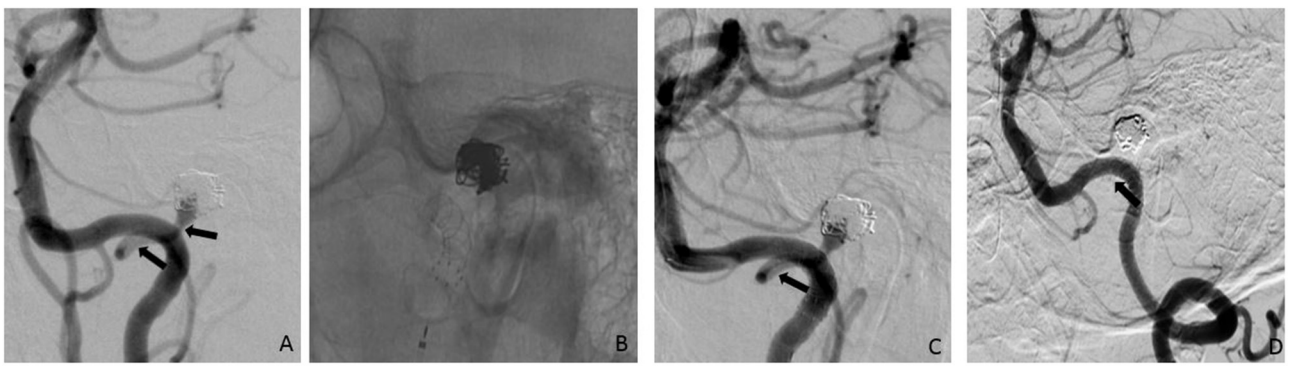


**FIGURE 2 |** 45° LAO injection of the left VA showed a recurrence of a formerly ruptured and coiled left PICA aneurysm; arrows indicating the PICA; **(B)** implantation of a p64 3,5/15 mm; **(C)** final run after the p64 implantation confirmed that the PICA was patent and the aneurysm neck completely covered (arrows = PICA); **(D)** FU angiography after three months reveal an asymptomatic occlusion of the left PICA (arrow) as well as complete occlusion of the aneurysm. LAO, left anterior oblique; VA, vertebral artery; PICA, posterior inferior cerebellar artery.

## DISCUSSION

Flow diversion has gained an essential role in treating IAs in the last decade, especially in wide-necked, giant, or fusiform aneurysms. This is even more distinct for the so-called "challenging" aneurysm in the anterior circulation. The implantation of FDs for the treatment of posterior circulation aneurysms remains controversial due to the significantly higher rates of ischemic complications and higher morbidity and mortality that have been reported throughout the literature (4, 6, 10). However, the composition of the respective study populations has to be considered as they did not solely focus on saccular aneurysms but also included giant, fusiform, and dissecting aneurysms. It has been shown that these non-saccular

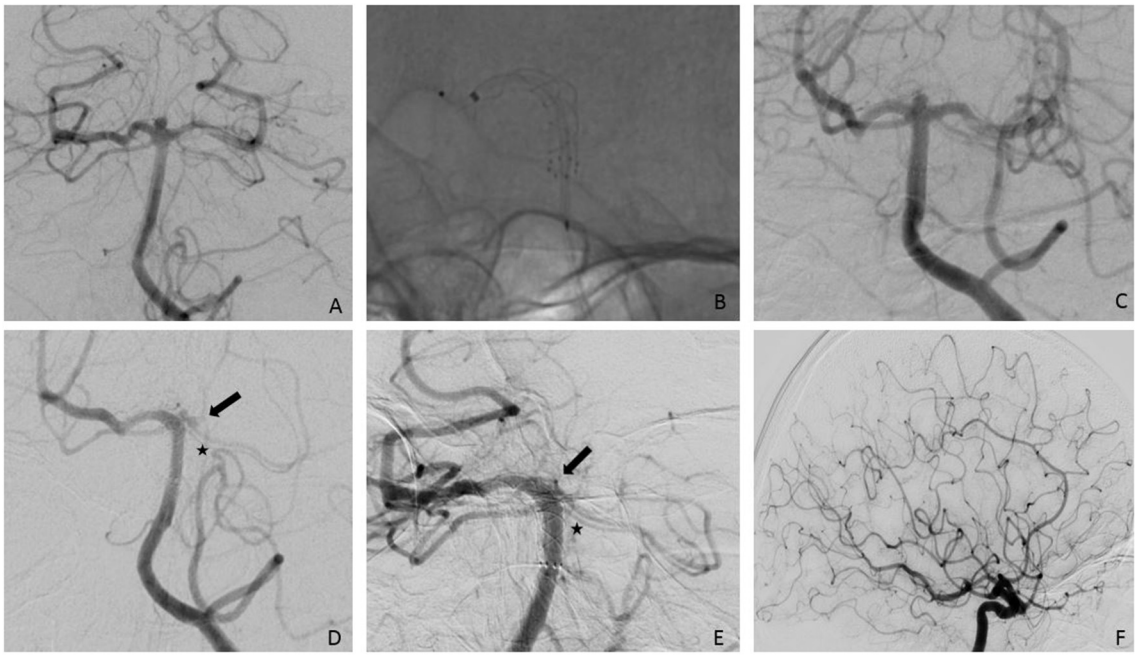


**FIGURE 3 | (A)** Posterior-anterior view after injection of the left VA showing a 2.5 mm aneurysm of the basilar bifurcation, slightly more to the right side; **(B)** successful implantation of a p64 3/15 mm from the right PCA to the BA; **(C)** final run after the FD implantation.; **(D)** first FU after four months shows a small aneurysm remnant as well as a significant caliber reduction of the left P1- segment (arrow). The SCAs on the left side remain the same (asterisk); **(E)**. second FU after nine months shows complete occlusion of the aneurysm as well as the left P1-segment; **(F)**. injection of the left ICA confirms supply of the left PCA via PcomA. pa, posterior-anterior; VA, vertebral artery; PCA, posterior cerebral artery; BA, basilar artery; FD, flow diverter; SCA, superior cerebellar artery; ICA, internal carotid artery; PcomA, posterior communicating artery.

aneurysms are especially prone to ischemic complications due to extensive thrombus formation (5, 11). In this series, only saccular aneurysms were included. We observed ischemic complications in 4/54 patients (7.4%), with 1/54 (1.9%) patients suffering a deterioration of the mRS from 0=>2. According to previously published data, these results confirm that smaller (usually saccular) aneurysms carry a lower risk of ischemic complications (12).

The porosity of the FD is another crucial factor regarding ischemic complications and aneurysm occlusion rates. The porosity is defined as the ratio of metal-free surface area to the entire surface area, and pore density is the number of pores per unit surface. It has been shown that FD with a porosity of 70% achieves a high rate of aneurysm occlusion without affecting the covered branches (13).

The p64 is braided using 64 nitinol wires with a lower porosity of 51–60%, depending on the device size in relation to the parent vessel diameter (14). Lower porosity is supposed to lead to higher occlusion rates but might also be prone to more ischemic complications. Aguilar et al. reported high complete or near-complete occlusion rates of 89.7% at mid-term FU and 94.5 % at long-term FU (>24 months) in saccular aneurysms in the anterior circulation in the most extensive study with the p64 from a single center (2). Despite the higher porosity of the p64, they observed similar ischemic complication rates- reported as 4.8% in their study- that have been reported for other FDs such as the Pipeline Embolization Device (PED) (Medtronic, Dublin, Ireland), Silk (Balt Extrusion, Montmorency, France), and Surpass (Stryker Neurovascular, Fremont, CA, USA) (15). As compared to these data, we observed a higher rate of ischemic complication of 9.3 % overall in this study, as is to be expected due to the increased vulnerability of the covered perforating arteries of the posterior circulation compared to FD in the anterior circulation. However, there was only one major stroke (1.9%) despite the higher porosity of the p64. In comparison, Bender et al. report major stroke complications of 8% with the PED in the posterior circulation, and Kulcsar et al. report 25% with the SILK FD (12, 16). Despite the higher porosity of p64, the significantly lower rate of severe stroke complications might be attributed to the device's sizing. We always choose to slightly oversize the FD, avoiding foreshortening and preserving perforating arteries. In addition, for patients with a high risk of perforator stroke, low molecular weight heparin is administered for 4–6 weeks after the FD implantation in addition to the DAPT.

In our analysis concerning occlusion rate, we observed a progressive increase in aneurysm occlusion with a complete or near-complete obliteration rate of 56% at 3-month, 75.6% at 9-month, and 82.5% at the last angiographic follow-up. The lowest occlusion rates at the last FU were observed for PICA aneurysms with 78.6 % and SCA aneurysms with 63.3%. These low occlusion rates might be because the parent vessels stayed patent in most cases, leading to a reduced flow-diverting

effect by sucking blood from the BA or VA to the respective parent vessel, hence failing to occlude the aneurysm. Similar observations have been reported for fetal PcomA aneurysms (2, 17). Occlusion rates, regardless of location, have been reported very heterogeneously in literature ranging from approximately 50% up to 96–100 % even (5, 16, 18). The meta-analysis of Brinjikji et al. analyzed 29 articles with 1,451 patients and 1,654 aneurysms and found an occlusion rate of 80% (69–88 %) for small posterior circulation aneurysms (11). The wide range of reported occlusion rates reflects the heterogeneous nature of posterior circulation aneurysms as almost all the studies also included giant and fusiform aneurysms. Another reason might be the small study populations in some of the articles prone to statistically less meaningful data. Our results are in line with the meta-analysis as mentioned above. Oversizing of the device did not lead to a significantly lower occlusion rate while preserving the perforating arteries. Therefore moderate oversizing of the FD seems to be an essential factor for the treatment in posterior circulation aneurysms, achieving a reasonable occlusion rate without increasing the risk of complications. As concerning complications, it has been suggested that the lower porosity of

**TABLE 4 |** Complications.

| Complications | |
|---|---|
| Technical | 2/54 (3.7%) |
| Hemorrhagic | 2/54 (3.7%) |
| Ischemic | 5/54 (9.3%) |
| Transient | 1/54 (1.9%) |
| Permanent | 4/54 (7.4%) |
| Permanent worsening of the mRS | 5/54 (9.3%) |
| Fatal hemorrhage, mrs 6 | 1/54 (1.9%) |
| Shift from mrs 0 => mRS 1 | 3/54 (5.6%) |
| Shift from mrs 0=> mRS 2 | 1/54 (1.9%) |

*mRS, modified Ranking Scale.*

**TABLE 5 |** Clinically relevant complications overview.

| No. | Location of the aneurysm | Aneurysm size (width × height in mm) | device | Location of the device | Antiplatet regimen | Platelet-Inhibition at the time of FD-implantation confirmed with Multiplate or Verify Now | Description | Transient vs. permanent | mRS pre | Last mRS |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | BA tip | 4.2 × 3.4 | 1 × p64 4/21 1 × p64 4.5/21 (both failed) | - | 100 mg ASA p.o. 2 × 90 mg ticagrelor p.o. | ADP 12 ASPI 1 | postprocedural SAH on CCT, transient drowsiness and headache, resolved spontaneously | Transient | 3 | 3 |
| 2 | BA tip | 2.9 × 2.2 | 1 × p64 3/15 | left PCA to BA | 100 mg ASA p.o. 75 mg Plavix p.o. | ADP 47 ASPI 42 | Fatal cerebellar IPH on the day of discharge | Permanent | 1 | 6 |
| 3 | BA trunk | 4.6 × 2.3 | 1 × p64 4.5/15 | BA trunk | 100 mg ASA p.o. 10 mg prasugrel p.o. | ADP 19 ASPI 8 | Bi-lateral pontine perforator infarction with left-sided hemiparesis, dysphagia and dysarthria, at last FU remaining mild dysarthria | Permanent | 0 | 1 |
| 4 | SCA | 1.8 × 1.0 | 1 × p64 3/15 | left PCA to BA | 100 mg ASA p.o., 75 mg Plavix p.o. | ADP 7 ASPI 6 | INO 15 months after treatment, 3 month after stop of DAPT | Permanent | 0 | 1 |
| 5 | PICA | 2.3 × 2.1 | 1 × p64 3.5/15 | right V4 segment | 100 mg ASA p.o. 75 mg Plavix p.o. | ADP 71 ASPI 19 ARU 391 P2Y12 (20/139) = 92 % | Scattered diffusion restriction in both cerebellar hemispheres with vertigo, vomiting and dizziness | Transient | 0 | 0 |
| 6 | SCA | 1.8 × 2.2 | 1 × p64 3.5/15 | left PCA to BA | 100 mg ASA p.o. 75 mg Plavix p.o. | ADP 25 ASPI 6 | Bilateral pontine perforator infarction with right-sided hemiparesis | Permanent | 0 | 2 |
| 7 | BA tip | 1.5 × 1.2 | 1 × p64 3/12 | right PCA to BA | 100 mg ASA p.o. 2 × 90 mg ticagrelor p.o. | ADP 13 ASPI 6 | Left pontine perforator infarction with discrete finger movement impairment | Permanent | 0 | 1 |

*BA, basilar artery; SAH, subarachnoid hemorrhage; CCT, cranial computed tomography; mRS, modified Ranking Scale; IPH, intra-parenchymal hemorrhage; INO, internuclear ophthalmoplegia; SCA, superior cerebellar artery; PICA, posterior inferior cerebellar artery; ASA, acetylisalicylic acid; p.o., per os.*

p64 may lead to a higher rate of ischemic complications, which is primarily an essential concern in the posterior circulation. However, an increased number of ischemic complications was not observed in our series, with a total of 5 events (9.3%) consisting of 4 permanent minor neurological deficits (7.4%) and one case (1.9%) of transient neurological symptoms. We observed no permanent major neurological deficit. There was one device-unrelated, treatment-related mortality of 1.9%. This is significantly lower than previous studies reported for FD in the posterior circulation (4, 10). Bender et al. report major stroke complications in 8% (12). Toth et al. report mortality rates and permanent neurological deficits of each 14.3 % with the PED in predominantly saccular aneurysms (19). These numbers are significantly higher than the results from our series with the p64 that carries a supposedly higher risk of ischemic complications. Possible explanations may be the oversizing of the device and the additional use of low molecular weight heparin combined with DAPT during the first 4 to 6 weeks after FD implantation as bridging of the most thrombogenic and, therefore, most vulnerable period after FD implantation.

Of course, DAPT in combination with heparin poses an increased risk for hemorrhagic complications. Hemorrhagic transformation of clinically silent microinfarcts observed after endovascular procedures have been reported as one of the significant drawbacks of FD implantation (20–22). Our series report one fatal hemorrhage three days after the p64 implantation, most likely to be attributed to delayed parenchymal hemorrhage due to microischemia. Additionally, this patient had been a hyper-responder for clopidogrel.

The recent introduction of surface- modified, hydrophilic coated FDs such as the p64MW HPC and p48MW HPC (phenox, Bochum, Germany) and the Pipeline Shield (Medtronic, Dublin, Ireland) allows the implantation of FD under single platelet inhibition (SAPT) only (23–25).

## LIMITATIONS

The limitations of this study include those inherent in a retrospective study, and this study reports the experience of a single center with a single specific flow diverter. Secondly, this study dealt with unruptured, saccular aneurysms of the posterior circulation only, explicitly excluding fusiform, giant, and dissecting aneurysms of the posterior circulation.

## CONCLUSION

The p64 is safe and effective for treating intracranial saccular unruptured aneurysms arising from the posterior circulation with acceptable occlusion rates on mid-term and long-term follow-ups and low morbi-mortality rate. This represents the most extensive study to date on the use of p64 in saccular posterior circulation aneurysms exclusively.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Landesärztekammer Baden-Württemberg. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

MA-P, EH, CS-C, and VH: data gathering and manuscript preparation. CW, OG, and HB: review and editing. HH: guarantor, overall review, and study design. All authors contributed to the article and approved the submitted version.

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# Computational Study of Hemodynamic Changes Induced by Overlapping and Compacting of Stents and Flow Diverter in Cerebral Aneurysms

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**Purpose:** The flow diversion effect of an intracranial stent is closely related to its metal coverage rate (MCR). In this study, the flow diversion effects of Enterprise and low-profile visualized intraluminal support (LVIS) stents are compared with those of a Pipeline flow diverter, focusing on the MCR change. Moreover, the changes in the flow diversion effect caused by the additional manipulations of overlapping and compaction are verified using computational fluid dynamics (CFD) analysis.

**Methods:** CFD analysis was performed using virtually generated stents mounted in an idealized aneurysm model. First, the flow diversion effects of single Enterprise, LVIS, and Pipeline devices were analyzed. The Enterprise and LVIS were sequentially overlapped and compared with a Pipeline, to evaluate the effect of stent overlapping. The effect of compacting a stent was evaluated by comparing the flow diversion effects of a single and two compacted LVIS with those of two overlapped, uncompacted LVIS and uncompacted and compacted Pipeline. Quantitative analysis was performed to evaluate the hemodynamic parameters of energy loss, average velocity, and inflow rate.

**Results:** Statistically significant correlations were observed between the reduction rates of the hemodynamic parameters and MCR. The single LVIS without compaction induced a reduction in all the hemodynamic parameters comparable to those of the three overlapped Enterprise. Moreover, the two overlapped, uncompacted LVIS showed a flow diversion effect as large as that induced by the single uncompacted Pipeline. Compacted stents induced a better flow diversion effect than uncompacted stents. The single compacted LVIS induced a flow diversion effect similar to that induced by the two uncompacted LVIS or single uncompacted Pipeline.

**Conclusions:** The MCR of a stent correlates with its flow diversion effect. Overlapping and compaction can increase the MCR of an intracranial stent and achieve a flow diversion effect as large as that observed with a flow diverter.

**Keywords: stent, flow diverter, flow diversion effect, metal coverage rate, overlapping, compaction, computational fluid dynamics**

## INTRODUCTION

Intracranial, self-expanding stents were originally designed as scaffolding to protect aneurysmal necks against coil protrusion or migration (1, 2). Recently, the flow diversion effect of intracranial stents has received considerable attention (3). This effect describes a phenomenon in which the blood flow into an aneurysmal sac is redirected by a stent implanted in the parent artery (4). The flow diversion effect promotes the potential for postembolization thrombosis, which improves the success rate of aneurysm treatment (5, 6).

Stents currently available on the market have different mechanical properties depending on their design and manufacturing methods (7, 8). The mechanical properties of a stent affect the results of aneurysm treatment, and the metal coverage rate (MCR) of a stent is closely related to the flow diversion effect (9). The MCR indicates the percentage of the aneurysmal neck covered by metal after the application of a stent (10). According to previous studies, the aneurysm occlusion rate correlates positively with the MCR (11, 12). Therefore, achieving a high MCR is a key factor in the success of stent-assisted aneurysm treatment.

Each stent has a constant range of MCR that depends on its mechanical properties. However, a higher MCR can be achieved by using an adjuvant method. Overlapping multiple stents is one of the methods commonly used to increase the MCR. Previous studies have reported that sequentially placing stents across the aneurysm neck can enhance the flow diversion effect (13–15). Another way to increase the MCR is to use the properties of braided stents, whose MCR can be changed by compaction. Unlike a laser-cut stent, a braided stent can produce various mesh densities as the wires of the stent are rearranged according to the device size, vessel diameter, and curvature (16). Compacting a braided stent using the push-pull technique can result in a higher MCR around the aneurysm neck, which can improve the aneurysm occlusion rate (17–19).

In actual aneurysm treatment, stents are overlapped or compacted to induce the flow diversion effect, and sometimes these manipulations are used together. Therefore, a comprehensive understanding of the flow diversion effect induced by overlapping or compacting a stent is necessary. However, no study conducted so far has compared the effect of overlapping and compacting intracranial stents in a single configuration on the flow diversion effect. Although previous studies have demonstrated the flow diversion effect of stents that were separately overlapped or compacted, variations in the configurations used in these studies should be considered while comparing their results (20, 21).

In this study, we compared the flow diversion effects of an Enterprise laser-cut stent (Cerenovus, Raynham, Massachusetts, USA) and a low-profile visualized intraluminal support (LVIS) braided stent (MicroVention, Tustin, California, USA) with that of a Pipeline flow diverter (Medtronic Neurovascular, Irvine, California, USA). The MCR was calculated and compared to evaluate the flow diversion effect of each stent numerically, considering additional manipulations, namely, overlapping and compaction. All the studies were conducted under the same experimental conditions using an idealized aneurysm model to control for variables that could affect the results. Thus, we compared the flow diversion effects of the Enterprise and LVIS stents with that of the Pipeline flow diverter, focusing on the MCR changes. Furthermore, we verified the changes in the flow diversion effect caused by the additional manipulations of overlapping and compaction using computational fluid dynamics (CFD) analysis.

## MATERIALS AND METHODS

### Aneurysm and Stent Modeling

An idealized sidewall-type saccular aneurysm model that was minimally affected by lesion geometry was established to compare the characteristics of the stents (**Figure 1A**). The ideal sidewall aneurysm model had a radius of 5 mm and a neck diameter of 5.27 mm, and the diameter of a parent artery was 4 mm. The sizes of the ideal aneurysm and its parent artery were set by assuming a large aneurysm in the internal carotid artery.

A silicone model of the ideal aneurysm was fabricated, and the real stents were deployed inside the silicone model *in vitro* to examine the configurations of the stents in the aneurysm neck. After installing each real stent inside the silicone model, we captured the images of the stent shapes in the aneurysm neck. Based on the information obtained from the images of deployed stents, we generated virtual stents for subsequent CFD analyses.

CFD analyses were performed using an idealized aneurysm model with virtually created stents placed across the aneurysmal neck. We considered three different kinds of stents: a laser-cut stent (Enterprise, 4.5 × 39 mm), a braided stent (LVIS, 3.5 × 22 mm), and a flow diverter (Pipeline, 4.0 × 35 mm). The size of each stent was set to match the size of the parent artery as much as possible. In the absence of a stent of the same size as the parent artery, an undersized stent was chosen to maximize the MCR (22). This study aims to answer the following questions:

① How large is the flow diversion effect of the Enterprise and LVIS stents compared with that of the Pipeline flow diverter?
② What is the influence of an overlap of the Enterprise or LVIS stents on the flow diversion effect compared with that of a single placement?
③ What is the influence of compaction of an LVIS stent or Pipeline flow diverter on the flow diversion effect compared with that of an uncompacted state?

First, the flow diversion effects of a single Enterprise stent, LVIS stent, and Pipeline flow diverter were analyzed separately. Then, the Enterprise and LVIS stents were sequentially overlapped virtually, and their flow diversion effects were compared with that of the Pipeline flow diverter. The virtual stents were overlapped to have a constant gap between them, to investigate the results of ideal overlapped stents. The CFD results for the LVIS and Pipeline devices were compared with and without compaction to evaluate the flow diversion effect according to stent compaction. The compaction study did not include the Enterprise device because it cannot be compacted owing to its manufacturing method (8). During the compaction study, the maximum compaction rate was achieved by examining

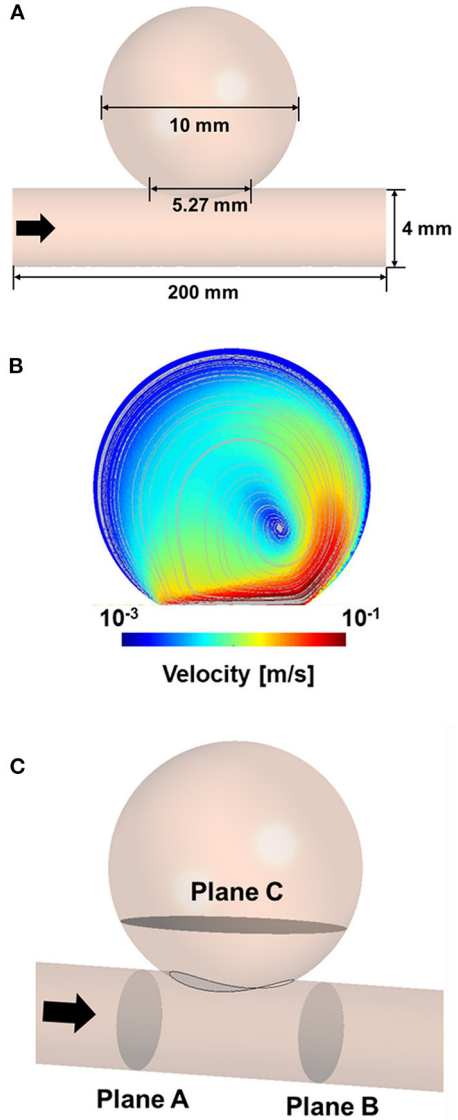


**FIGURE 1 |** Three-dimensional model of idealized sidewall-type aneurysm for CFD analysis **(A)**. CFD velocity and streamline results for CFD process validation **(B)**. Position of the planes for extracting the hemodynamic parameters **(C)**. CFD, computational fluid dynamics.

the configuration of the real stent mounted in the silicone model aneurysm.

## Validation of the CFD Process

To verify our CFD process, we used the experimental data of Tupin et al. (21), who conducted a particle image velocimetry (PIV) experiment for an idealized sidewall-type saccular aneurysm. We used the inlet and outlet boundary conditions measured in their experiment in our CFD validation to ensure that our results were comparable to their results. Meshing and CFD analyses were conducted using ANSYS Workbench Fluent (version 19.2; ANSYS Inc., Canonsburg, Pennsylvania, USA). An element of size 0.2 mm was used for the validation model, and the density and viscosity of the fluid were set to 1,200 kg/m$^3$ and 0.0038 Pa·s, respectively. The inlet boundary condition was constructed using the Womersley profile, and the pressure profile was applied to the outlet boundary condition. The velocity and streamline were extracted after three cardiac cycles to compare the results of the PIV experiment with the CFD results. The velocity contour and streamline calculated via CFD analysis were consistent with the results of the PIV experiment (**Figure 1B**).

## CFD Analysis With Stent

Three-dimensional models of the aneurysm and stents were constructed using CATIA computer-aided design software (V5-6R2012; Dassault Systèmes, Paris, France). A stent was constructed only at the aneurysm neck to improve the efficiency of the CFD analysis (23). An element of size 0.2 mm was used for the aneurysm, and an element of size 0.005 mm was generated near the location where the stent was deployed. Overall, 30–50 million elements were used in the CFD analysis. The blood was assumed to be an incompressible Newtonian fluid (24) with the density and viscosity of 1,055 kg/m$^3$ and 0.004 Pa·s, respectively (25). The pulsatile flow of the internal carotid artery with a Womersley profile was used as the inlet boundary condition, and zero pressure was used as the outlet boundary condition (26). The blood vessel was assumed to have a rigid wall under non-slip conditions. All the hemodynamic parameters were calculated as systolic after three cardiac cycles.

To evaluate the results of the CFD analysis quantitatively, we compared the following hemodynamic parameters: inflow rate, average velocity, and energy loss (EL). The average velocity and inflow rate into the aneurysm were calculated at plane C, which is located near the aneurysm neck (**Figure 1C**). The velocity and pressure in planes A and B were extracted to calculate the EL based on the following equation (27):

$$EL = \frac{v_{in}A \cdot \{(\frac{1}{2}\rho v_{in}^2 + P_{in}) - (\frac{1}{2}\rho v_{out}^2 + P_{out})\}}{V_m}$$

where $V_m$ represents the volume of the model between planes A and B. $\rho$ and A are the density and area at the inlet, respectively. $v_{in}$ and $P_{in}$ represent the average velocity and pressure, respectively, at the inlet (plane A), and $v_{out}$ and $P_{out}$ represent the average velocity and pressure, respectively, at the outlet (plane B). The EL indicates the amount of blood flowing into the aneurysm. We calculated the reduction rate of the EL to indicate the effect of stenting compared with the unstented case. Therefore, a higher EL reduction rate indicates less blood flow into the aneurysm.

# RESULTS

## Comparison of the Flow Diversion Effect and MCR

The changes in the MCR and hemodynamic parameters caused by overlapping and compacting the stents are summarized in **Table 1**. As the MCR was increased by overlapping and compaction, the reduction rate of the hemodynamic parameters

**TABLE 1 |** Summary of changes in the MCR and hemodynamic parameters caused by overlapping or compacting the stents used in this study.

| Device | MCR (%) | EL (W/m$^3$) (reduction rate %) | Avg. velocity (m/s) (reduction rate %) | Inflow rate (mm$^3$/s) (reduction rate %) |
|---|---|---|---|---|
| Control | 0.0 | 66.09 (0.00) | 0.0114 (0.00) | 224.4 (0.00) |
| Enterprise (single) | 7.0 | 58.01 (12.23) | 0.01 (12.28) | 196.4 (12.33) |
| Enterprise (double) | 13.0 | 46.7 (29.34) | 0.00543 (52.37) | 119.0 (47.36) |
| Enterprise (triple) | 18.0 | 36.05 (45.45) | 0.00415 (63.60) | 48.5 (78.43) |
| LVIS (single) | 20.4 | 34.38 (47.98) | 0.00339 (70.26) | 54.0 (75.89) |
| LVIS (double) | 36.3 | 20.49 (69.00) | 0.00241 (78.86) | 26.5 (88.24) |
| LVIS compaction (single) | 35.4 | 22.21 (66.39) | 0.00254 (77.72) | 20.1 (91.15) |
| LVIS compaction (double) | 63.9 | 6.72 (89.83) | 0.00156 (86.32) | 15.9 (92.93) |
| Pipeline | 26.8 | 30.68 (53.58) | 0.00241 (78.86) | 24.9 (88.82) |
| Pipeline compaction | 47.8 | 12.9 (80.48) | 0.0019 (83.33) | 15.7 (92.90) |
| Pearson correlation* (coefficient, *p*-value) | | −0.961 (≤0.001) | −0.82 (0.004) | −0.805 (≤0.001) |

**Correlation between the actual value of each hemodynamic parameter and the MCR.*
*MCR, metal coverage rate; EL, energy loss.*

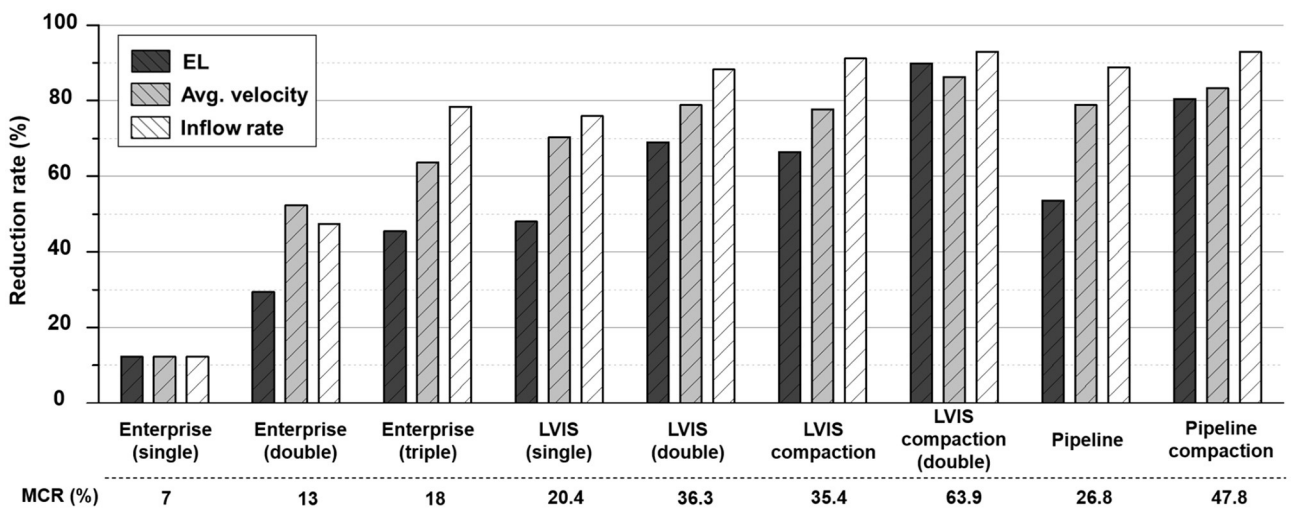


**FIGURE 2 |** Comparison of the MCR and reduction rates for the hemodynamic parameters according to the overlapping and compaction of Enterprise, LVIS, and Pipeline devices. MCR, metal coverage rate.

increased accordingly, and the correlation was statistically significant (**Figure 2**).

## Comparison of the Flow Diversion Effects of Single Stents

First, we compared the hemodynamic modifications induced by each stent (**Figure 3**). An intra-aneurysmal flow diversion was observed with all the three stents compared with the unstented ideal aneurysm model used as the control. However, the changes in flow pattern and velocity magnitude differed according to the MCR. As the MCR of the different stents increased in the order of Enterprise, LVIS, and Pipeline, the velocity magnitude showed a tendency to decrease. With the Enterprise stent, the velocity magnitude of the jet flow decreased compared with that of the control, but the flow pattern (inflow from the distal part of the aneurysmal neck and outflow to the proximal) did not change.

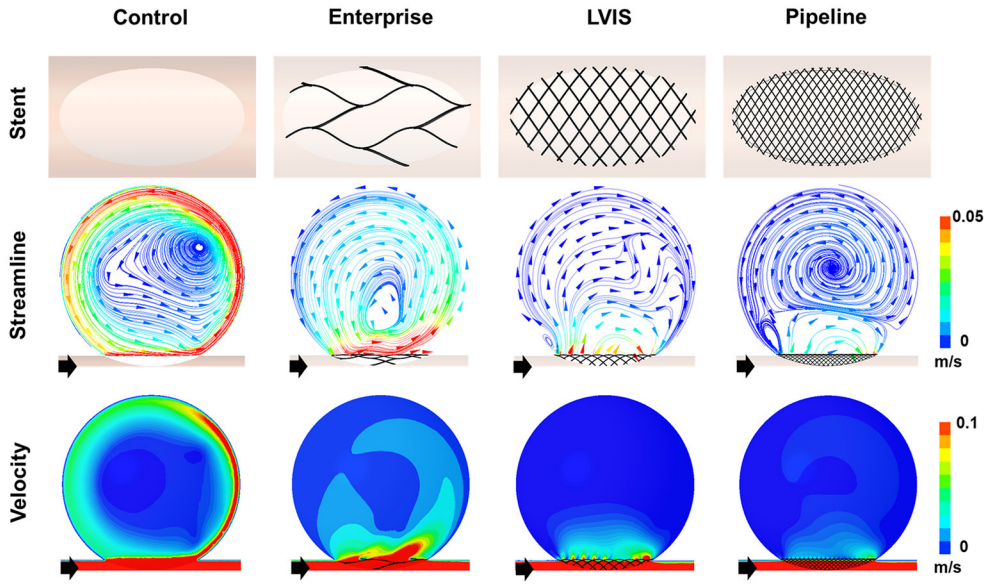


**FIGURE 3 |** Visualization of the hemodynamic modification of the idealized aneurysm model by each stent. The stent configurations in the idealized aneurysm model and the streamlines and velocity contours calculated using CFD analysis are displayed. The black arrows indicate the flow direction. With the Enterprise stents, the velocity magnitude of the jet flow was decreased compared with that of the control, but the flow pattern of inflow from the distal part of the aneurysmal neck and outflow to the proximal side did not change. In contrast, the LVIS and Pipeline devices disrupted and changed the direction of the inflow jet. Particularly with the Pipeline device, the jet flow was not transferred into the aneurysmal dome due to the remarkable reduction of inflow jet. This led to a silent vortex in the aneurysmal sac due to a separation in the hemodynamics of the aneurysmal dome and neck. CFD, computational fluid dynamics.

In contrast, both the LVIS and Pipeline devices disrupted and changed the direction of the inflow jet. In particular, the Pipeline device did not transfer the jet flow into the aneurysmal dome because of its remarkable reduction of the inflow jet. This led to a silent vortex in the aneurysmal sac due to a separation in the hemodynamics of the aneurysmal dome and neck.

The Pipeline device (MCR 26.8%, EL 53.58%, average velocity 78.86%, inflow rate 88.82%) showed the most pronounced reduction rate for all the three parameters. The LVIS stent (MCR 20.4%, EL 47.98%, average velocity 70.26%, inflow rate 75.89%) showed a higher reduction rate for all the three parameters than the Enterprise stent (MCR 7.0%, EL 12.23%, average velocity 12.28%, inflow rate 12.33%) (**Table 1**; **Figure 2**).

## Comparison of Stent Overlapping Effects

The results of the CFD analysis for stent overlapping are shown in **Figure 4**. Simulations were performed to overlap one, two, and three Enterprise stents and one and two LVIS stents, using the Pipeline device as the control, to confirm the overlapping effects of the Enterprise and LVIS stents. The changes in the velocity magnitude with stent overlapping tended to follow the change in the MCR. However, the change in the flow pattern according to the stent overlap differed for each stent. With the overlapped Enterprise devices, the volume of the inflow jet decreased due to the disruption of the jet flow. However, the direction of the intra-aneurysmal jet flow did not change even when three Enterprise stents were used together. In contrast, a change in the direction of the inflow jet was observed with a single LVIS stent without overlapping. Moreover, when two LVIS stents were overlapped, the separation of the hemodynamics of the aneurysmal dome and neck was similar to that observed with a single Pipeline device.

In terms of parameter reduction, a single LVIS stent (MCR 20.4%, EL 47.98%, average velocity 70.26%, inflow rate 75.89%) induced a reduction in all the hemodynamic parameters comparable to the effect of three overlapped Enterprise stents (MCR 18.0%, EL 45.45%, average velocity 63.60%, inflow rate 78.43%). Two uncompacted LVIS stents showed a better flow diversion effect (MCR 36.3%, EL 69.00%, average velocity 78.86%, inflow rate 88.24%) than a single LVIS stent. Moreover, the effect of two uncompacted LVIS stents was similar to that of a single uncompacted Pipeline device (MCR 26.8%, EL 53.58%, average velocity 78.86%, inflow rate 88.82%).

## Comparison of Stent Compacting Effects

To demonstrate the effect of stent compaction, we performed simulations in the following order: a single uncompacted LVIS stent, a single compacted LVIS stent, two uncompacted LVIS stents, two compacted LVIS stents, a single uncompacted Pipeline device, and a single compacted Pipeline device (**Figure 5**). Compaction induced a better flow diversion effect than the lack of compaction with either device. The single compacted LVIS stent induced a similar decrease in the velocity magnitude and change in the flow pattern as the two uncompacted LVIS stents or single uncompacted Pipeline device. In particular, vortex formation within the aneurysm and the separation of the hemodynamics of the aneurysmal dome and neck were observed with the single compacted LVIS stent. The flow diversion effect of the Pipeline device was also improved by compaction, which reduced the

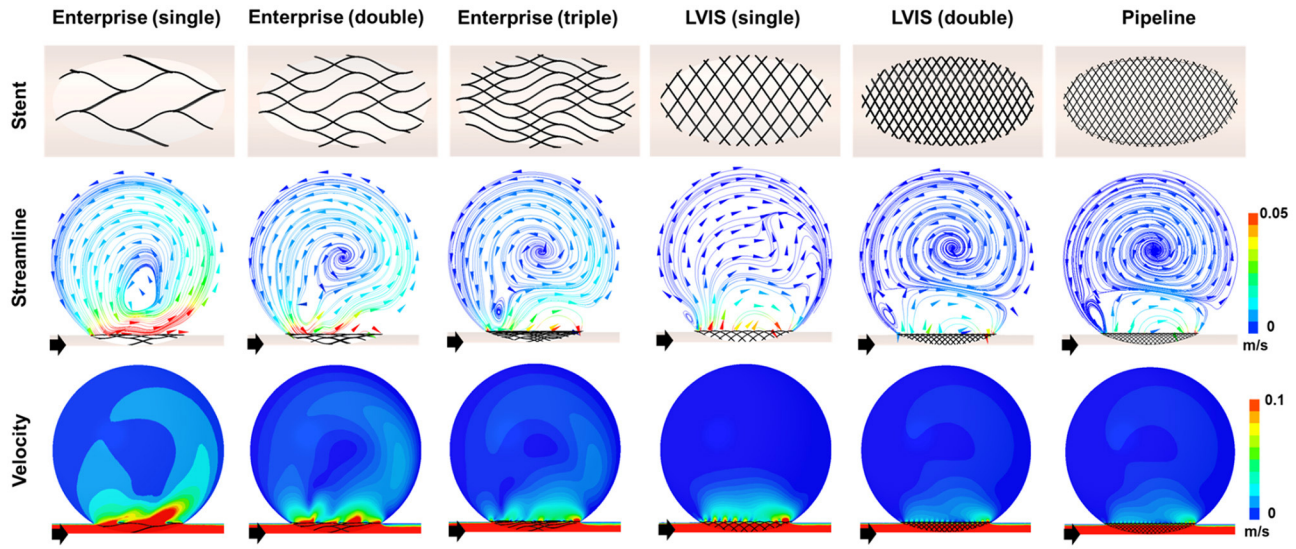


**FIGURE 4 |** Visualization of the hemodynamic modifications induced by overlapping the stents. The stent configurations deployed in the idealized aneurysm model and the streamlines and velocity contours calculated using CFD analysis are displayed. The black arrows indicate the flow direction. The overlapped Enterprise stents decreased the volume of the inflow jet by disrupting the jet flow, but they did not change the direction of the intra-aneurysmal jet flow even when three stents were used. In contrast, the single LVIS stent without overlapping changed the direction of the inflow jet. A separation of the hemodynamics of the aneurysmal dome and neck, similar to that observed with the Pipeline device, was observed when the two LVIS stents were overlapped. CFD, computational fluid dynamics.

size of the inflow jet compared with that of the uncompacted Pipeline device. The two compacted LVIS stents eliminated most of the jet flow and almost completely separated the flow inside the aneurysm from the flow near the aneurysm neck.

The single compacted LVIS stent (MCR 35.4%, EL 66.39%, average velocity 77.72%, inflow rate 91.15%) induced a reduction in all the hemodynamic parameters comparable to the effect of the two uncompacted LVIS stents (MCR 36.3%, EL 69.00%, average velocity 78.86%, inflow rate 88.24%) or the single uncompacted Pipeline device (MCR 26.8%, EL 53.58%, average velocity 78.86%, inflow rate 88.82%). Similarly, the two compacted LVIS stents (MCR 63.9%, EL 89.83%, average velocity 86.32%, inflow rate 92.93%) showed a flow diversion performance comparable to that of the single compacted Pipeline device (MCR 47.8%, EL 80.48%, average velocity 83.33%, inflow rate 92.90%).

## DISCUSSION

The purpose of this study was to analyze quantitatively the flow diversion effects of stents with different MCRs and the effects of stent overlapping and compaction. We observed that (1) a single LVIS stent showed a comparable flow diversion effect to three overlapping Enterprise stents, (2) two-overlapped, uncompacted LVIS stents had a similar flow diversion performance to a single uncompacted Pipeline device, and (3) a single compacted LVIS stent and two-overlapped, uncompacted LVIS stents produced a similar performance. These findings support the following conclusions: (1) A stent with a high MCR can reduce intra-aneurysmal flow activity better than a stent with a low MCR. (2) Increasing the MCR through stent overlapping can induce a flow diversion effect as large as that induced by a flow diverter. (3) It is important to increase the MCR through stent compaction to induce a sufficient flow diversion effect. The proper compaction of a braided stent induces a better flow diversion effect compared with that induced by multiple overlapped, uncompacted stents.

Intra-aneurysmal hemodynamics plays an important role in aneurysmal growth and rupture (28). Previous studies have reported that the flow diversion effect induced by a stent can alter intra-aneurysmal hemodynamics and that the MCR is an important parameter for determining the flow diversion effect induced by a stent (12, 29). As shown in **Figure 3**, the Enterprise, LVIS, and Pipeline devices all exhibited a flow diversion effect compared with the unstented control case. The Pipeline and Enterprise devices had the highest and lowest flow diversion effects, respectively, which were consistent with their MCRs. Dholakia et al. (30) compared the flow diversion effects of five neurovascular stents using contrast concentration–time curves within the aneurysm. They reported that the LVIS stents showed better flow diversion effects than the Enterprise stents, which is consistent with the results of this study. Jankowitz et al. (31) studied the flow diversion effects of two low-metal-coverage stents (Neuroform Atlas and Enterprise), the LVIS blue stent, and the Pipeline device and observed trends similar to our results. These findings indicate that the MCR of a stent is associated with flow diversion.

As the MCR of a stent is determined by its mechanical properties, such as its number, thickness, and the weave angle of the stent wire (5, 32), each commercialized stent has a constant MCR and thus produces a constant flow diversion effect. Although each stent has a unique MCR, the MCR can

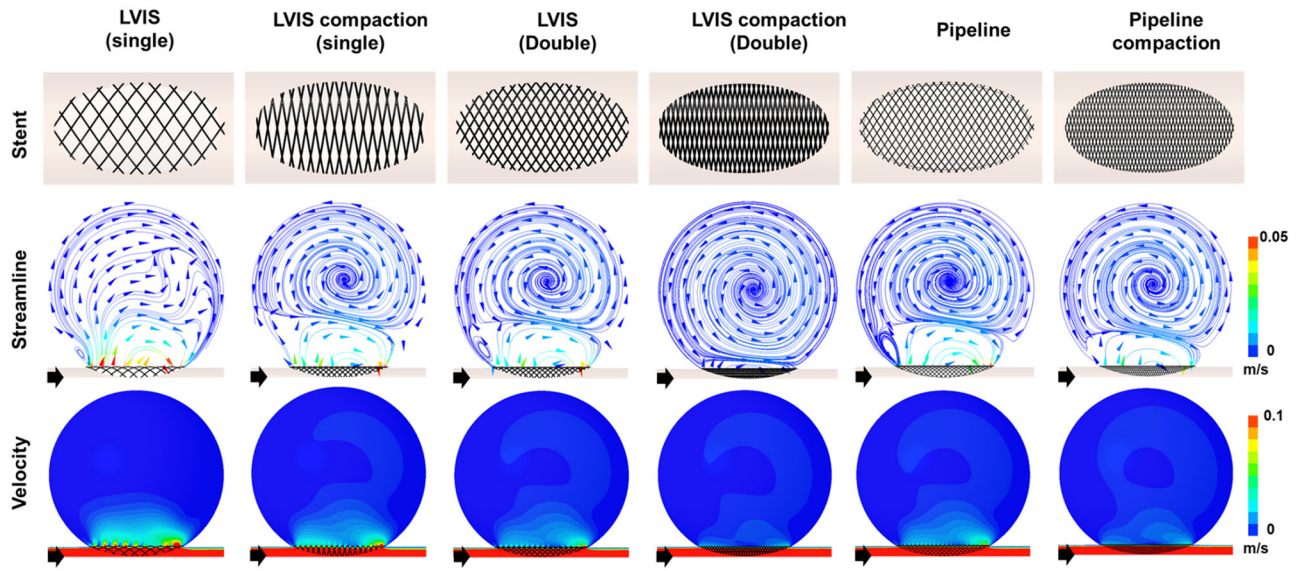


**FIGURE 5 |** Visualization of the hemodynamic modification induced by compacting the stents. The stent configuration deployed in an idealized aneurysm model and the streamlines and velocity contours calculated using CFD analysis are displayed. The black arrows indicate the flow direction. Stent compaction improved the flow diversion effect of both the LVIS and Pipeline devices. The compacted LVIS stent induced a similar decrease in the velocity magnitude and change in the flow pattern as the two uncompacted LVIS devices or single uncompacted Pipeline device. CFD, computational fluid dynamics.

be increased by overlapping multiple stents. Tremmel et al. (33) used CFD to study the hemodynamic changes induced by overlapping Enterprise stents and reported that overlapping two or three Enterprise stents sequentially decreased hemodynamic parameters, such as wall shear stress, velocity, turnover time, and pressure. Kojima et al. (34) studied the flow diversion effects of implanting multiple Enterprise stents. They reported that two Enterprise stents yielded a greater reduction in the intra-aneurysmal pressure and wall shear stress compared with a single Enterprise stent, but the reduction in velocity did not differ significantly. Furthermore, the flow diversion effect of two Enterprise stents in Kojima's study was not as large as that of a single Pipeline device. On the other hand, Roszelle et al. (13) conducted a PIV experiment and reported that overlapping three Enterprise stents produced a flow diversion effect similar to that of a Pipeline device. All the three studies on the effects of overlapping Enterprise stents confirmed that overlapping correlated with an increase in the flow diversion effect. However, the flow diversion effect of Enterprise stents varied among the studies, possibly because of the differences in study designs, such as the geometry and size of the aneurysm and stent, and the validation tools and hemodynamic parameters used. In this study, we set an ideal sidewall aneurysm formed on a straight parent artery to control for factors other than the MCR of the stent that affect the flow diversion effect. As we overlapped one to three Enterprise stents, the MCR increased from 7 to 13 and 18%, and the reduction rate of the velocity, EL, and inflow increased sequentially. However, the MCR of the three overlapped Enterprise stents were still inferior to those of a single uncompacted LVIS stent and the flow diversion effect of three overlapped Enterprise was not better than a single uncompacted LVIS stent (**Figure 5**). Therefore, when the MCR of a single stent is low, overlapping multiple stents results in a limited increase in the MCR. Therefore, clinicians using a stent to create flow diversion for the treatment of aneurysms must consider the MCR of the stent.

In this study, we investigated the effects of overlapping LVIS stents. Overlapping two uncompacted LVIS stents induced a flow diversion effect as large as that induced by a single Pipeline device. Wang et al. (14) also used CFD to compare the flow diversion effects of LVIS, Enterprise, and Pipeline devices. They reported that two LVIS stents can induce a greater flow diversion effect than a single Pipeline device, which is consistent with our results. The LVIS is a braided stent made by braiding a single nitinol wire. Braided stents are characterized by the ability to rearrange the filament to adapt to vascular geometry, which induces various MCRs. The MCR of an uncompacted deployed LVIS is 11–12% (8). However, an MCR more than 20% is possible, depending on the size discrepancy between the parent artery and the stent (35). In this study, the MCR of the 3.5 mm LVIS stent installed in the 4 mm parent artery was 20.4%, and the MCR of the two overlapped LVIS stents was 36.3%. Therefore, the overlapping effect of LVIS stents can yield hemodynamic advantages in real-world practice.

Compaction can also increase the MCR. A braided stent can generate various mesh densities as the wires of the stent are rearranged, making it possible to increase the MCR during stent deployment by using the push-pull technique (19). Previous studies have shown that increasing the MCR of Pipeline devices through compaction improves their flow diversion effect (9, 17). Furthermore, Tian et al. (36) reported that compacted LVIS stents could induce a flow diversion effect comparable to that

induced by uncompacted Pipeline devices. We also observed that stent compaction affects the flow diversion effect. As shown in **Figure 5**, compaction increased the MCR of both the LVIS and Pipeline devices, which improved the flow diversion effect. We also observed that compacting a single LVIS stent induced a flow diversion effect as large as that induced by two overlapping LVIS stents or a single, uncompacted Pipeline device. Moreover, overlapping two compacted LVIS stents induced a flow diversion effect as large as that induced by a single compacted Pipeline device. The results of this study on stent compaction may differ from those in real-world practice because our results are derived from an assumed ideal condition to maximize the MCR. However, as all the stent experiments in this study were conducted under the same conditions, our results showing the relative flow diversion effects of the stents with and without overlapping or compaction may still be informative for actual clinical practice.

This study has some limitations. First, as explained, our experiments were conducted under the assumption of an ideal condition; therefore, the results obtained in real practice may be different. We assumed an idealized sidewall-type saccular aneurysm to exclude factors other than the stent properties that affect the flow diversion effect. However, the flow diversion effects of the stents could vary in real practice depending on factors, such as the shape of the aneurysm, the geometry of the parent artery, and the degree of wall apposition between the stent and the parent artery (37–39). Moreover, our hemodynamic study was performed under the assumption that the virtual stent covered the entire aneurysm neck uniformly with a maximum MCR. When multiple stents are overlapped in a clinical setting, they cannot be placed such that they divide the stent cells equally, as assumed in the CFD simulations. In addition, when a braided stent is compacted, the metal coverage on the aneurysm neck can vary along different segments, even on a single device (16). Second, our CFD analysis has technical limitations. Several assumptions for the CFD analysis, such as the properties of blood and the boundary conditions, were set for the generalized conditions of intracranial circulation; however, they might not reflect all patient-specific conditions. Therefore, the flow diversion effects of the stents in real-world practice may differ from the results presented here. Nonetheless, this proof-of-concept study demonstrates the maximum capacity of the flow diversion effects of the stents, including the effects of overlapping and compaction. To prove the effects of overlapping and compaction, we needed to control for other conditions affecting the flow diversion effect. Although our results may differ somewhat from the actual flow diversion effects of the stents, our objective comparison of the changes in aneurysm hemodynamics induced by overlapping and compaction extends the current understanding of how the flow diversion effect depends on the type of stent, overlapping, and compaction.

## CONCLUSIONS

We observed that a single LVIS stent exhibited a flow diversion effect similar to that of three overlapped Enterprise stents. Compacting a single LVIS stent was as effective in terms of flow diversion as overlapping two LVIS stents, and similar results were confirmed for the Pipeline device. The MCR of a stent correlates with its flow diversion effect. Overlapping and compcation can increase the MCR of an intracranial stent and improve the flow diversion effect to match that of a flow diverter.

## DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

SK and HY gathered the data and drafted the manuscript in collaboration. IH assisted in the discussions and reviewed the manuscript. JO and YK conceptualized the study and supervised the process, corresponding to each field of specialty. All authors approved the final version of the manuscript.

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# First Experience of Three Neurovascular Centers With the p64MW-HPC, a Low-Profile Flow Diverter Designed for Proximal Cerebral Vessels With Antithrombotic Coating

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**Background:** In the last decade, flow diversion (FD) has been established as hemodynamic treatment for cerebral aneurysms arising from proximal and distal cerebral arteries. However, two significant limitations remain—the need for 0.027" microcatheters required for delivery of most flow diverting stents (FDS), and long-term dual anti-platelet therapy (DAPT) in order to prevent FDS-associated thromboembolism, at the cost of increasing the risk for hemorrhage. This study reports the experience of three neurovascular centers with the p64MW-HPC, a FDS with anti-thrombotic coating that is implantable *via* a 0.021" microcatheter.

**Materials and methods:** Three neurovascular centers contributed to this retrospective analysis of patients that had been treated with the p64MW-HPC between March 2020 and March 2021. Clinical data, aneurysm characteristics, and follow-up results, including procedural and post-procedural complications, were recorded. The hemodynamic effect was assessed using the O'Kelly–Marotta Scale (OKM).

**Results:** Thirty-two patients (22 female, mean age 57.1 years) with 33 aneurysms (27 anterior circulation and six posterior circulation) were successfully treated with the p64MW-HPC. In 30/32 patients (93.75%), aneurysmal perfusion was significantly reduced immediately post implantation. Follow-up imaging was available for 23 aneurysms. Delayed aneurysm perfusion (OKM A3: 8.7%), reduction in aneurysm size (OKM B1-3: 26.1%), or sufficient separation from the parent vessel (OKM C1-3 and D1: 65.2%) was demonstrated at the last available follow-up after a mean of 5.9 months. In two cases, device thrombosis after early discontinuation of DAPT occurred. One delayed rupture caused a caroticocavernous fistula. The complications were treated sufficiently and all patients recovered without permanent significant morbidity.

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**Conclusion:** Treatment with the p64MW-HPC is safe and feasible and achieves good early aneurysm occlusion rates in the proximal intracranial circulation, which are comparable to those of well-established FDS. Sudden interruption of DAPT in the early post-interventional phase can cause in-stent thrombosis despite the HPC surface modification. Deliverability *via* the 0.021" microcatheter facilitates treatment in challenging vascular anatomies.

**Keywords: flow diverter, p64MW-HPC, hydrophilic coating, HPC, navigability, anti-platelet therapy**

## INTRODUCTION

In the past decade, flow diversion (FD) has been well-established as a functional treatment option for cerebral aneurysms. The distinct architecture of fine-meshed flow diverter stents (FDS), characterized by an optimized ratio of porosity and surface area metal coverage, allows maintained perfusion of covered arteries while decreasing aneurysmal perfusion below the threshold required for intra-aneurysmal thrombosis (1). Following the immediate reduction of aneurysmal inflow with subsequent thrombosis, the FDS serves as scaffolding for the development of an increasingly resilient neo-intima (2–4).

Both events, flow reduction and formation of a neo-intima, depend on FDS porosity (5). Regarding the latter, computational fluid dynamics revealed that porosities of 70% or less are sufficient to trigger occlusion (6). Definite reconstruction of the aneurysm-bearing segment depends on the ingrowth of smooth muscle cells together with endothelial cells along the FDS at the level of the aneurysmal orifice, according to histological findings (7). The process of vascular remodeling starts at the peripheral landing zones of the FDS, continues inwardly, and strongly depends on sufficient wall apposition of the implant (7). In this study, completely occluded aneurysms were covered entirely with a thin but continuous layer of smooth muscle and endothelium at the neck level, whereas substantial aneurysmal remnants were associated with discontinued islands of inflammatory cells, mostly monocytes and macrophages, incompletely covering the FDS struts at the aneurysm neck. As a consequence, the immediate flow diverting effect of FDS should be considered only as a prerequisite for the proper therapeutic mechanism of FD, which is the establishment of a novel functional vessel wall that results from the complex interaction between a variety of cell types and the metal surface of the stent (8). Neo-endothelialization is initiated by activated platelets that bind to surface adsorbed fibrinogen *via* GPIIb/IIIa (9, 10). Those platelets not only mediate the recruitment of circulating endothelial progenitor cells to the FDS' surface and strongly support their proliferation and differentiation to functioning endothelial cells (11), but also trigger and further amplify local coagulation (12). Therefore, FD requires concomitant dual anti-platelet therapy (DAPT) to prevent thromboembolic complications, which are responsible for stroke with permanent neurological impairment in up to 7.4% of cases (13). However, DAPT reduces the risk for thromboembolic events at the cost of increasing the risk for hemorrhagic complications (14), and both hemorrhagic and ischemic events remain a significant concern in clinical practice, especially in ruptured aneurysms (15). Therefore, the ability to implant FDS in cerebral vessels without the imperative for DAPT would be a major improvement (10).

The p64MW-HPC (phenox, Bochum, Germany) is a novel FDS designed for cerebral vessels with diameters between 3.0 and 5.0 mm and can be implanted with 0.021" microcatheters. The device was developed with a special focus on enhanced hemocompatibility, which is achieved by a glycan-based, multilayer hydrophilic polymer coating (HPC) that inhibits the initial step of platelet adhesion to surface adsorbed fibrinogen (16). *Ex vivo* testing has demonstrated that platelets in contact with HPC-covered FDS are significantly less activated than platelets in contact with uncoated FDS (16). Additionally, first clinical evidence indicates that applying the HPC technology to FDS allows reduction of DAPT in selected cases of unruptured and even ruptured cerebral aneurysms (17–20). Whether the HPC technology may delay neo-endothelialization, and thus aneurysm occlusion, remains to be elucidated. As a consequence, this study aims to report the early experiences with the p64MW-HPC from three German neurovascular centers (University Hospital Leipzig, Heinrich-Braun-Hospital Zwickau, and Klinikum Chemnitz GmbH), specifically focusing on technical issues, thromboembolic or hemorrhagic complications, and aneurysm occlusion rates.

## MATERIALS AND METHODS

### Ethics Approval

This retrospective study was approved by the institutional ethics committee (local IRB no. AZ 208-15-0010062015). Written consent was obtained from the patient or his or her legal representative.

### Study Design

The study was designed as a multi-center, single-arm retrospective analysis of a prospectively maintained database comprising all endovascular treatments with the p64MW-HPC performed in the following neurovascular centers: University Hospital Leipzig ($n = 27$), Heinrich-Braun-Hospital Zwickau ($n = 3$), and Klinikum Chemnitz ($n = 2$). Demographic data, aneurysm characteristics, procedural aspects, technical and clinical adverse events, as well as early angiographic follow-up results were systematically reviewed for all cases. **Table 1** provides an overview of the ascertained data from all three neurovascular centers.

**TABLE 1 |** Demographic data.

| Patient | Age | Sex | Location | Aneurysm configuration | Neck width (mm) | Dome width (mm) | Dome height (mm) | Treatment strategy | Antiplatelet therapy | Device | Size | OKM after FD | 1st FU | OKM 1st FU | Last available FU | OKM last FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 64 | Female | Right C6/ C7 | Saccular | 2 | 4.7 | 3.3 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 3.5 × 18 | B3 | 3 months | B3 | 3 months | B3 |
| 2 | 60 | Female | Right M1 | Saccular | 3.3 | 4.2 | 3.3 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 3.5 × 18 | A2 | 2.5 months | B2 | 10 months | B2 |
| 3 | 34 | Male | Left C6 | Saccular | 4.5 | 4.7 | 4.3 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 5 × 30 | B3 | 3.5 months | D1 | 12 months | D1 |
| 4 | 74 | Female | Right C6 | Saccular | 3.7 | 4.3 | 2.7 | Primary | ASA + Ticagrelor* | 1× p64MW-HPC | 4.5 × 27 | B3 | 1.5 weeks | B3 | 11 months | B3 |
| 5 | 27 | Male | Left C6 | Saccular | 2.7 | 3.3 | 4 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 4 × 18 | B2 | 3.5 months | B3 | 10 months | B2 |
| 6 | 65 | Female | Left C6/ C7 | Saccular | 3.5 | 3.8 | 4.2 | Primary | ASA + Clopidogrel | 1× p64MW-HPC | 5 × 30 | A1 | 3.5 months | A3 | 3.5 months | A3 |
| 7 | 49 | Male | Right C7 | Saccular (2×) | 3<br>2.8 | 3.5<br>2.8 | 4.8<br>3.2 | Primary<br>Primary | ASA + Ticagrelor | 1× p64MW-HPC + Coil | 4.5 × 15 | A3<br>A3 | 4 months | D1<br>C2 | 10 months | D1<br>C2 |
| 8 | 56 | Female | Right C4 | Saccular | 4.5 | 5.3 | 3.5 | Primary | ASA + Ticagrelor | 2× p64MW-HPC | 4 × 15<br>4.5 × 18 | A3 | 3 months | D1 | 6.5 months | D1 |
| 9 | 55 | Female | Basilar artery | Saccular | 6.3 | 18 | 50 | Revision | ASA + Ticagrelor + De×amethason | 1× p64MW-HPC | 3.5 × 21 | A3 | 4 months | B3 | 9 months | B3 (but distinctly decreased in aneurysm size) |
| 10 | 63 | Female | Left C4/ C5 | Saccular | 2.1 | 3.1 | 5.4 | Primary | Ticagrelor | 1× p64MW-HPC | 4 × 21 | A2 | 4 months | C1 | 4 months | C1 |
| 11 | 36 | Male | Right C7 | Blister | - | - | - | Primary (acute SAH) | ASA + Ticagrelor | 1× p64MW-HPC | 4 × 21 | C2 | 1.5 weeks | D1 | 9 months | D1 |
| 12 | 68 | Female | Left C6 | Saccular | 2.9 | 3.2 | 4.5 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 4 × 15 | A3 | 3.5 months | C3 | 7 months | D1 |
| 13 | 72 | Female | Right C3/ C4 | Saccular | 4 | 8 | 9 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 4 × 21 | A3 | 3 weeks | A1 | 4 months | C2 |
| 14 | 72 | Female | Right C3/ C4 | Barrow A fistula | - | - | - | Revision | ASA + Ticagrelor | 2× p64MW-HPC + venous coiling | 4 × 18<br>4 × 21 | A1 | 5 days | A1 | 3 months | C2 |
| 15 | 58 | Male | Right C6 | Saccular | 4 | 4.2 | 3.6 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 4.5 × 18 | B3 | 2 months | C3 | 5.5 months | D1 |
| 16 | 62 | Male | Left C4 | Stenosis | - | - | - | Primary | ASA + Ticagrelor | 2× p64MW-HPC | 3.5 × 12<br>3.5 × 21 | n.a. | n.a. | n.a. | n.a. | n.a. |
| 17 | 56 | Female | Left V4/ PICA orifice | Saccular | 3 | 3.6 | 5.6 | Primary | Prasugrel ** | 1× p64MW-HPC | 3 × 12 | A3 | 3 months | D1 | 3 months | D1 |
| 18 | 68 | Female | Left C3/C4 | Saccular | 8.4 | 14.2 | 14.3 | Primary | Prasugrel ** | 1× p64MW-HPC + 2× PED2 | 5 × 30 | A3 | 3.5 months | A3 | 3.5 months | A3 |

*(Continued)*

**TABLE 1** | Continued

| Patient | Age | Sex | Location | Aneurysm configuration | Neck width (mm) | Dome width (mm) | Dome height (mm) | Treatment strategy | Antiplatelet therapy | Device | Size | OKM after FD | 1st FU | OKM 1st FU | Last available FU | OKM last FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 19 | 64 | Female | Right C6/ C7, Pcom orifice | Saccular | 5.2 | 6.3 | 8.2 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 5 × 30 | B3 | 3 months | B2 | 3 months | B2 |
| 20 | 48 | Female | Right C4 | Saccular | 3.2 | 5.2 | 4.3 | Revision | ASA + Ticagrelor | 2× p64MW-HPC | 3.5 × 15<br>3.5 × 18 | A3 | n.a. | n.a. | n.a. | n.a. |
| 21 | 48 | Male | Left C6 | Saccular | 5 | 26 | 17 | Primary | Prasugrel + Celebre× + De×amethason | 1× p64MW-HPC + Coiling | 4.5 × 21 | B3 | 3 months | C2 | 3 months | C2 |
| 22 | 24 | Female | Right C6 | Saccular | 2.9 | 3.5 | 3.3 | Primary | ASA + Prasugrel | 1× p64MW-HPC | 3.5 × 18 | A2 | 3 months | D1 | 3 months | D1 |
| 23 | 60 | Male | Right C6, AChA orifice | Saccular | 1 | 1.8 | 2.9 | Revision | ASA + Prasugrel | 1× p64MW-HPC | 3.5 × 15 | B2 | n.a. | n.a. | n.a. | n.a. |
| 24 | 68 | Female | Right C6 | Saccular | 2.6 | 3.4 | 3.8 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 3.5 × 18 | A2 | n.a. | n.a. | n.a. | n.a. |
| 25 | 50 | Female | Left V4/ PICA orifice | Saccular | 2.8 | 5 | 4 | Primary | ASA + Prasugrel | 1× p64MW-HPC | 4 × 12 | A2 | n.a. | n.a. | n.a. | n.a. |
| 26 | 46 | Female | Right C6 | Saccular | 2.3 | 3 | 4.3 | Primary | ASA + Ticagrelor | 1× p64MW-HPC + 1× SVB | 3 × 15 | A3 | n.a. | n.a. | n.a. | n.a. |
| 27 | 82 | Female | Right C7 | Saccular | 4.5 | 4.5 | 5 | Primary | ASA + Clopidogrel ** | 1× p64MW-HPC | 3.5 × 18 | A3 | n.a. | n.a. | n.a. | n.a. |
| 28 | 43 | Female | Basilar artery tip | Saccular | 7 | 5 | 5 | Primary | ASA + Ticagrelor | 1× p64MW-HPC | 3.5 × 21 | A2 | n.a. | n.a. | n.a. | n.a. |
| 29 | 58 | Female | Left V4 | Dissection | - | - | - | Primary (acute SAH) | ASA + Ticagrelor | 1× p64MW-HPC | 3 × 18 | D1 | n.a. | n.a. | n.a. | n.a. |
| 30 | 52 | Male | Left C6, Pcom orifice | Saccular | 4 | 4 | 5 | Primary | ASA + Clopidogrel | 1× p64MW-HPC | 4 × 15 | A2 | n.a. | n.a. | n.a. | n.a. |
| 31 | 75 | Female | Left C6, AChA orifice | Saccular | 4 | 4 | 3 | Primary | ASA + Prasugrel | 2× p64MW-HPC | 4 × 18<br>4 × 21 | A2 | 1 week | A2 | 6 months | C2 |
| 32 | 71 | Male | Basilar artery/ left V4 | Fusiform | 20 | 10 | 10 | Primary | ASA + Clopidogrel | 3× p64MW-HPC | 4.5 × 27<br>5 × 24<br>5 × 30 | A2 | 1 week | C1 | 1 week | C1 |

**Two months after flow diversion, the DAPT was changed to ASA + Prasugrel due to recurrent events of inadaequate administration of ticagrelor. **In addition, oral anticoagulation was administered due to cardiologic indication.*

## The p64MW-HPC—Features

The p64MW-HPC has been designed and approved for the therapy of cerebral aneurysms arising from vessels with 3.0–5.0 mm in diameter. The device consists of 64 braided wires, composed of nickel–titanium alloy with an inner platinum core. Contrary to the majority of other FDS, which were approved for similarly sized cerebral vessels but require a 0.027" microcatheter for delivery (for example: Surpass—Stryker Neurovascular, FRED—Microvention, Pipeline Embolization Device—Medtronic, Derivo—Acandis), the p64MW-HPC only requires a 0.021" microcatheter. The smaller microcatheter allows enhanced access and less traumatic catheterization in anatomically demanding cerebral vessels (21). The stent-carrier module of the p64MW features an independently movable wire that can be placed 6 cm distal to the stent in order to provide increased stability during placement and preserve distal access after deployment. The potentially most significant improvement is its availability with a hydrophilic polymer coating that inhibits platelet adhesion and activation, and thus allows early reduction of DAPT or even single anti-platelet therapy (SAPT) (17, 22–26).

## Endovascular Procedure and Antiplatelet Regimen

All interventions were performed under general anesthesia using a biplane digital subtraction angiography system (Philips AlluraClarity, Best, The Netherlands). DAPT was performed as follows: each patient received a loading dose of 500 mg acetylsalicylic acid (ASA) together with either 180 mg ticagrelor, 30 mg prasugrel, or 300 mg clopidogrel 24 h prior to the procedure. DAPT was continued with 100 mg ASA daily and either 90 mg ticagrelor every 12 h (twice a day), 10 mg prasugrel daily, or 75 mg clopidogrel daily, for an average of 12 months. Clopidogrel as second anti-platelet drug was chosen only in patients who had already been treated with clopidogrel in an earlier occasion. Ticagrelor or prasugrel was chosen in patients who required DAPT for the first time, as platelet function testing is not routinely performed in all institutions and both agents are not associated with high-on-treatment platelet reactivity, as it is the case for clopidogrel (10). Overall, the majority of patients (20/32) received DAPT consisting of ASA and ticagrelor. DAPT with ASA and prasugrel or ASA and clopidogrel was administered in eight patients, four received prasugrel as second drug, and four received clopidogrel as second drug. In further four cases, decision was made for SAPT (ticagrelor in one or prasugrel three patients) based on a preexisting anticoagulation (2/4 patients) and a case of ASA intolerance, respectively. In the remaining case, SAPT with prasugrel was amended by celecoxib and dexamethasone in regard of a giant aneurysm with distinct mass effect. A bolus of 5,000 international units heparin was administered at the beginning of each procedure.

In all patients, triaxial endovascular access was established *via* the right common femoral artery using an 8 French introducer sheath (Terumo radifocus II, Leuven, Belgium). For supra-aortic extra-cranial access either the Neuron Max 088 (6F; Penumbra, Alameda, CA, USA) or the Cerebase (Cerenovus, Miami, FL, USA) were used. Either a 6F Sofia distal access catheter (115 cm; MicroVention, Aliso Viejo, CA, USA; $n = 25$) or a 6F Navien distal access catheter (Covidien Vascular Therapies, Mansfield, MA, USA) was used to enhance intracranial stability. Finally, the Headway 21 (MicroVention) microcatheter was used for device delivery in 20 cases, followed by the Rebar 18 (Medtronic, Covidien, USA) in nine cases, and the Prowler Select Plus (Codman Neurovascular, Raynham, MA., USA) in three cases.

## Procedure Assessment, Radiological and Clinical Follow-Up

After the implantation, the patency of the parent artery and covered side branches as well as FDS efficacy employing the O'Kelly–Marotta scale [OKM; (27)] were angiographically assessed in each case. The OKM grading scale defines the degree of residual aneurysm filling (A-D) and the angiographic opacification referring to the intra-aneurysmal stasis lasting up to the arterial, capillary, or venous phase. After the procedure, all patients were transferred to the intensive care unit (ICU) ensuring continuous monitoring of the patient's neurological status for at least 24 h. Cranial computed tomography (CCT) was performed 24 h after the intervention as a post-interventional standard imaging. Angiographic follow-up examinations were aimed at 3, 9, and 24 months after FDS implantation.

# RESULTS

## Patients and Aneurysms

Overall, 32 patients (22 female, 10 male) were treated with the p64MW-HPC. The average age at presentation was 57 years, ranging from 24 to 82 years. One patient had two adjacent aneurysms, which were treated in one session with a singular FDS. Twenty-eight lesions were saccular side-wall aneurysms. The remaining lesions were one blister aneurysm, one fusiform aneurysm, and two dissecting aneurysms. Another patient

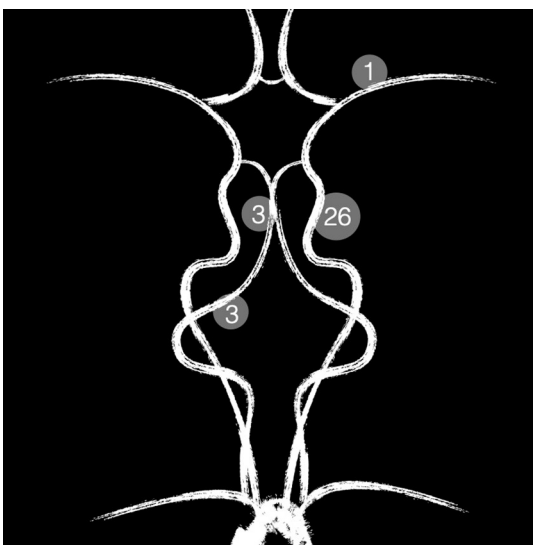


**FIGURE 1 |** Summary of the anatomical distribution of the treated lesions.

**TABLE 2 |** Procedural aspects.

| | |
|---|---|
| Number of patients | $n$ =32 |
| Number of treated lesions | $n$ = 33 |
| Number of implanted devices | $n$ = 39 |
| Number of implanted p64MW(HPC) per patient | |
| 1 | 26 |
| 2 | 5 |
| 3 or more | 1 |
| Adjunctive devices | 6 |
| Technical adverse events | $n$ = 5 |
| Twist of the FDS | 3 |
| Insufficient wall adaption | 1 |
| Device shortening | 1 |
| Periinterventional adverse events | $n$ = 6 |
| Delay in distal perfusion | 3 |
| Thrombus formation/ vessel occlusion | 2 |
| Extravasate | 1 |
| Clinical adverse events | $n$ = 3 |
| Transient stent occlusion | 2 |
| Delayed aneurysm rupture | 1 |
| Clinically manifest adverse events at last follow up | 0 |

suffered from a high flow carotid-artery-cavernous-sinus-fistula (Barrow A). **Figure 1** summarizes the anatomical distribution of the treated lesions.

## Treatments and Procedural Aspects

In sum, 39 p64MW-HPC were successfully implanted. Detailed information about the procedural aspects are given in **Table 2**. The vast majority (28 patients; 87.5%) was treated with FD using the p64MW-HPC as primary and only endovascular implant. In four patients (12.5%), flow diversion was performed as a second step after initial embolization (plug and pipe). An example of flow diversion after coiling is shown in **Figure 2**, whereas **Figure 3** demonstrates flow diversion as a sole strategy for an aneurysm associated with a growth-hormone secreting pituitary adenoma prior to transsphenoidal surgery.

Supplementary devices were required in six cases. In two patients who suffered from aneurysms >8 mm diameter, additional coiling of the aneurysm was performed aiming to promote intra-aneurysmal flow reduction and thrombus formation. **Figure 4** illustrates an exemplary case—the treatment of a giant sidewall aneurysm with FDS and coiling. Another patient, who presented with a symptomatic high-flow carotid artery cavernous sinus fistula, was treated with flow diversion and transvenous coil embolization of the affected cavernous sinus compartment. The patient with the megadolicho-basilar artery was treated with FD and coil occlusion of the contralateral distal vertebral artery in order to prevent thromboembolism from the covered branch. In further two patients, FD was augmented with implantation of a second FDS within the previously implanted p64MW-HPC. One patient, who presented with a giant aneurysm arising from the cavernous ICA, received two additional PED2 shield, which were implanted as stent-in-stent construct. The second patient, who suffered from an incidental, para-ophthalmic aneurysm, received a p64MW-HPC that initially showed poor wall adaption and then shortened after catheterization with the microcatheter in order to promote wall approximation. A Silk Vista Baby (SVB; Balt, Montmorency, France) was subsequently implanted, which improved wall adaption and achieved an anatomically optimal result.

Delayed perfusion of covered branches occurred in two patients immediately post implantation. An intravenous bolus of body weight-adapted integrilin (= eptifibatid, GlaxoSmithKline, Dublin, Ireland) was given intravenously, which resolved the issue in all cases without further sequelae.

## Adverse Events

### Technical Adverse Events

Purely technical adverse events in the early phase were observed in five cases (15.6%). Among them, twisting of the p64MW-HPC occurred in three patients and was related to distinct ICA tortuosity in all cases. The movable wire, however, allowed successful re-probation of the segment distal to the implanted FDS with some effort. Balloon angioplasty was performed subsequently, resulting in complete opening and wall adaption of the FDS in each of the cases. As described above, in a case of poor wall adaption and shortening, the technical issues were compensated by implantation of an additional low profile FDS (Silk Vista Baby). In a further patient, shortening of the distal end post implantation caused incomplete aneurysm coverage. A second p64MW-HPC was successfully implanted, resolving the issue completely. Clinical sequelae related to those technical obstacles were not observed in any case.

In one patient presenting with a PICA aneurysm, secondary dislocation of the FDS occurred after implantation in the V4 segment. Although the p64MW-HPC was initially well-positioned confirmed by digital subtraction angiography (DSA) immediately after deployment, the first angiographic follow-up revealed significant distal migration of the FDS. However, the device still covered the aneurysm neck, and the aneurysm was completely excluded from the intracranial circulation.

### Clinical Adverse Events

Overall, clinical complications occurred in three patients (9.4%), two were of thromboembolic and one of hemorrhagic nature. Both thromboembolic complications occurred in patients who initially presented with a right-sided ICA aneurysm that was sufficiently treated with a singular p64MW-HPC. However, 1½ weeks after implantation, each of the patients presented with an acute onset, left-sided hemiparesis. Thrombus formation within the implanted devices causing impaired perfusion of the ICA territory was revealed by the immediately performed DSA. Both patients received integrilin as outlined above. The thrombus and patients' neurological deficits resolved completely. Both cases were related to abandoned anti-platelet medication. DAPT was re-initiated and then continued without further adverse events.

In one patient, delayed aneurysm rupture 2.5 weeks after FDS implantation for treatment of a right-sided cavernous ICA aneurysm caused a high-flow carotid artery cavernous sinus

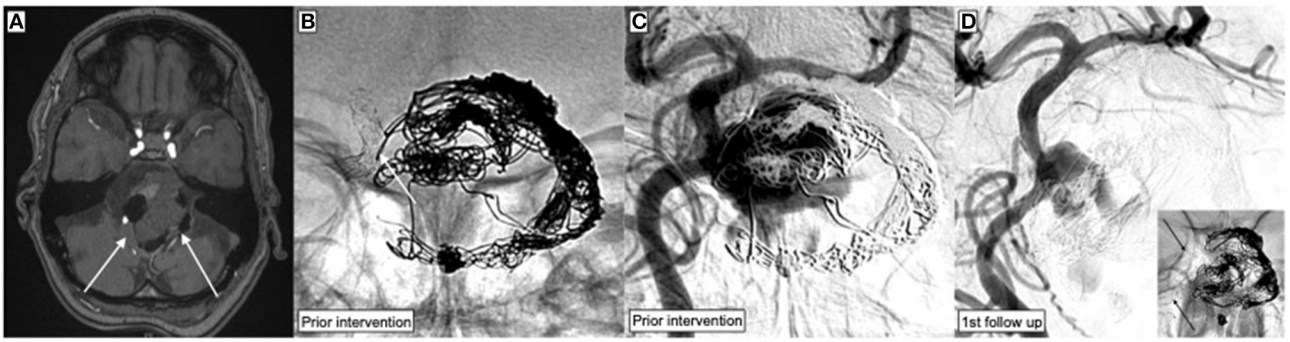


**FIGURE 2 |** Endovascular treatment of a wide-necked, partially thrombosed giant aneurysm arising from the side wall of the basilar artery, which had been treated with stent-assisted coiling 6 years earlier but without any follow-up. The aneurysm relapsed and caused brain stem compression. **(A)** Time of flight angiography (TOF) shows the partially thrombosed basilar artery aneurysm (white arrows) compressing the brain stem. **(B)** Device radiography demonstrates the separation of the previously implanted Neuroform stents (white arrow) and substantial deformation of the coil package. **(C)** DSA image corresponding to the radiography in **(B)**. The gap between the stents corresponds to the broad neck of the aneurysm. The same projection was used for FDS implantation. **(D)** The p64MW-HPC was implanted within the Neuroform stents in order to bridge the gap between the separated devices and provide a scaffold for the formation of a neo-intima along the neck of the aneurysm.

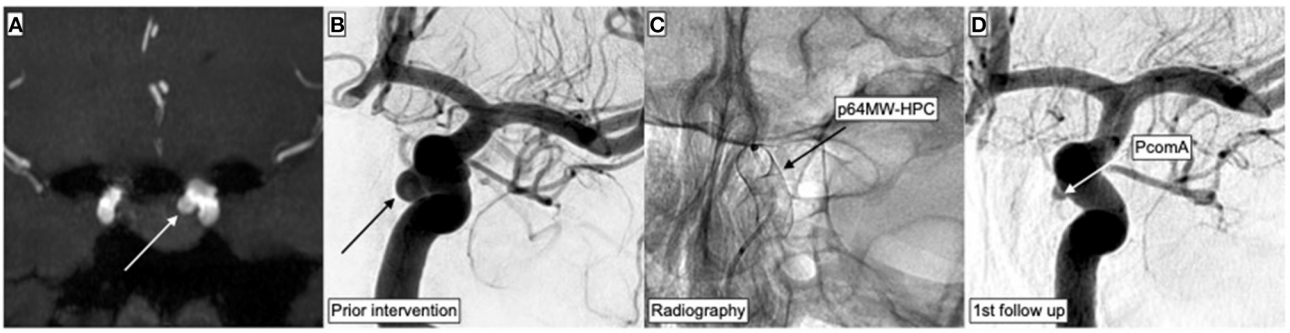


**FIGURE 3 |** Endovascular treatment of an incidental aneurysm arising from the left-handed side ICA. MRI was performed as preoperative imaging for planning of pituitary adenoma surgery. The growth-hormone-secreting adenoma had caused acromegaly. After detection of the aneurysm, decision was made for preceding flow diversion in order to facilitate future transsphenoidal resection without increased risk for arterial bleeding. **(A)** TOF-angiography maximum intensity projection (MIP) demonstrates the 4.5-mm measuring ICA aneurysm and its anatomical relationships. **(B)** Corresponding DSA in posterior–anterior projection demonstrates the aneurysm (black arrow) prior to treatment. **(C)** Radiography immediately after implantation of the p64MW-HPC in a posterior–anterior projection, matching **(B,D)**. **(D)** First follow-up DSA after 3.5 months in posterior–anterior projection; the aneurysm is completely occluded.

fistula (Barrow A). The patient had acutely developed headache, ipsilateral tinnitus, and exophthalmos. After confirmation of the diagnosis, the fistula was treated in two separate sessions. Firstly, two additional p64MW-HPC were implanted, aiming to reduce the volume of the AV-shunt. Complementarily, *via* a transfemoral venous approach, cavernous sinus coiling was performed, but only resulted in reduction, not occlusion of the shunt. In a second session, complete occlusion was achieved after coiling of a venous pouch *via* the ophthalmic vein. At the last clinical follow-up, the patient had recovered completely from the complication.

## Angiographic Follow-Up

### Hemodynamic Effect Immediately After Implantation

Angiographic evaluation of the therapeutic effect was performed immediately after FDS implantation using the OKM grading scale. From a total of 32 assessed aneurysms, 20 (62.5%) revealed a distinctly delayed perfusion, corresponding to OKM grades A2–A3. In eight cases (25%) the aneurysm dome remained partially perfused (OKM grades B1–B3). A residual neck perfusion (OKM grades C1–C3) was observed in one case (3.1%). In the case of a fusiform dissecting aneurysm of the dominant vertebral artery, which was associated with an additional blister aneurysm, functional reconstitution of the lumen verum with separation of the pseudoaneurysm was achieved immediately after FDS implantation, corresponding to OKM grade D1. In sum, all but two aneurysms (93.75%) already showed a marked delay in perfusion (OKM grades A2–A3) or additional reduction of the opacified aneurysmal volume, corresponding to OKM grades B1–B3, C1–C3, and D1 immediately after treatment with the p64MW-HPC. Two aneurysms (6.25%) revealed no substantial

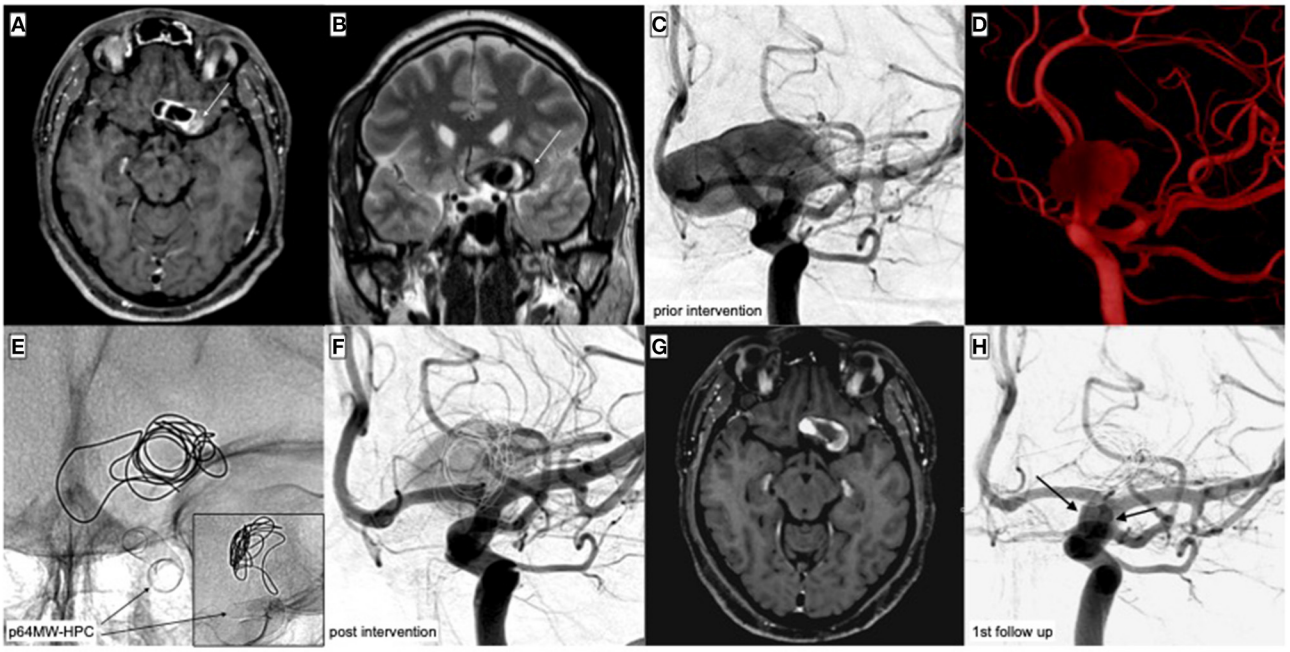


**FIGURE 4 |** Treatment of a partially thrombosed, giant aneurysm of the C6 segment of the left-handed side ICA. The aneurysm had compressed the ipsilateral optic nerve and caused unilateral blindness. The cause for unilateral blindness had remained unclear for months—finally, MR imaging was performed and demonstrated the underlying pathology. The decision was made for flow diversion together with loose additional coiling, in order to further decrease intra-aneurysmal flow. **(A)** Contrast-enhanced, axial T1-weighted imaging shows the partially thrombosed (white arrow) giant aneurysm of the left-handed side ICA. **(B)** Coronal T2-weighted imaging demonstrates the multi-compartmental (white arrow) aneurysm and its significant space-occupying effect. **(C)** DSA in posterior–anterior projection shows the 26 × 17 mm perfused compartment of the aneurysm. **(D)** Reconstruction of the 3D rotational angiogram demonstrating the neck level of the giant aneurysm. **(E)** Radiography in posterior–anterior projection post implantation and coiling. The distal end of the p64MW-HPC was positioned in the C7 segment of the ICA, avoiding affection of the ICA-T. One coil was placed inside the aneurysm in order to further disrupt intra-aneurysmal flow. The image in the lower right corner displays the lateral projection after FDS implantation and supplementary coiling. **(F)** DSA immediately after implantation of the FDS. Note the already decreased volume of the residually perfused compartment. Compared to **(C)**, aneurysmal perfusion is markedly delayed. **(G)** Contrast-enhanced, axial T1-weighted imaging 5 weeks post procedure demonstrating the significantly decreased volume of the aneurysm together with progressive thrombosis of the peripheral compartments. **(H)** First angiographic follow-up in posterior–anterior projection 3 months post intervention. The aneurysm is sufficiently separated from the parent vessel (OKM C2).

residual opacification after implantation (OKM grades C3 and D1).

## Hemodynamic Effect at the First Follow-Up Imaging

The first angiographic follow-up after a mean of 2.5 months was available for 23 lesions in 22 patients. Twelve of the 23 aneurysms (52.2%) revealed sufficient exclusion from the intracranial circulation, corresponding to OKM grades C1–C3 and D1. In six cases (26.1%), the aneurysm dome remained partially opacified (OKM grades B1–3), but showed a markedly reduced residual volume. Three lesions (13%) revealed a significantly delayed perfusion without changes in volume (OKM grades A2–A3). In conclusion, similar to the initial evaluation, all but two aneurysms (91.3%) showed a significant reduction of aneurysm perfusion (OKM grades A2–A3) or decreased, residually perfused volumes together with prolonged stasis of the contrast agent (OKM grades B1–B3, C1–C3, and D1). Thus, successful early hemodynamic remodeling, corresponding to OKM grades C1–C3 and D1, was achieved in 52.2% of the lesions at the first follow-up after 2.5 months. Only 2 of the 23 aneurysms (8.7%) remained morphologically unaltered (OKM A1).

## Hemodynamic Effect at the Second Follow-Up Imaging

A second imaging follow-up, on average 6 months post procedure, was performed in 13 of the 22 patients (=14 aneurysms), who had received the first follow-up. Eight of the 14 aneurysms (57.1%) were completely or subtotally excluded from the intracranial circulation (OKM grades C1–C3 and D1). Residual perfusion (OKM grades B1–B3) was observed in four aneurysms (28.6%). Two aneurysms (14.3%) showed a significant delay of contrast outwash (OKM A3). There was no case of unaltered aneurysm perfusion (OKM A1).

## Overall Hemodynamic Outcome at the Last Available Follow-Up Imaging

Considering the last available imaging follow-up of all patients, i.e., five patients after ∼7.5 months, seven patients (eight aneurysms) after 6 months and 10 patients after 2.5 months,

15 aneurysms (65.2%) were already functionally separated from the intracranial circulation (OKM grades C1–C3 and D1). A significant decrease of the residually perfused aneurysm volumes (OKM grades B1–B3) occurred in six cases (26.1%). Two aneurysms (8.7%) showed no reduction in perfused volume, but significantly prolonged opacification (OKM grade A3). Overall, reduction of aneurysm influx and morphological improvement was achieved in all aneurysms treated with the p64MW-HPC. No case of unaltered aneurysm perfusion (OKM A1) was observed.

Overall, in-stent stenosis, probably representing endothelialized mural thrombus, as reported recently (28), occurred in eight patients. Six cases were mild, two were moderate, and none was hemodynamically significant.

## DISCUSSION

Our retrospective three-center study reports the efficacy of aneurysm treatments employing the p64MW-HPC, a newly developed low-profile FDS with improved hemocompatibility, together with complications, clinical aspects, technical pitfalls, and their management. Besides first clinical evidence for the safety and feasibility of the novel FDS for treatment of cerebral aneurysms in a German patient collective, our study addressed the question of FD efficacy in the presence of the HPC surface modification, and provided case-based clinical evidence for the necessity of DAPT in the early post-interventional phase despite the use of HPC-modified FDS.

In general, our findings demonstrated a good efficacy of the p64MW-HPC for aneurysms arising from proximal cerebral vessels, i.e., the intradural internal carotid artery, the M1 segment of the middle cerebral artery, and the proximal posterior circulation including the basilar and vertebral arteries. After ∼6 months, 65% of the aneurysms treated with the p64MW-HPC were sufficiently isolated from the parent vessel. These findings are largely in accordance with earlier studies investigating the efficacy of nowadays well-established bare-metal FDS, for example, the first-generation "classic" p64 or the Pipeline Embolization Device (PED), which demonstrated occlusion rates for proximally located aneurysms between 58.3 and 73.6%, 3–6 months post implantation (29–32).

However, recent studies on the efficacy of the third-generation PED with Shield Technology, a phosphorycholine-based surface coating that mimics the red blood cell's outer membrane and significantly reduces platelet activation, reported even higher rates of early occlusions in up to 79.7% after 6 months (33–35). Considering the central role of platelets for the induction of neo-endothelialization (11), it appears somewhat conflicting that application of a platelet-inhibitory surface modification on a FDS is associated with enhanced occlusion rates (36). This dissonance is further contrasted by the fact that the hydrophilically coated p64MW, which is composed of a more densely woven and hemodynamically impactful mesh than the PED, achieved an inferior rate of early occlusions in our patient collective. The discrepant occlusion rates (65% vs. almost 80%) may simply reflect a greater hemodynamic complexity in the subset of aneurysms, which were treated with the p64MW-HPC (37). Aside from that, the anti-thrombogenic surface modifications either based on phosphorylcholine (Medtronic: Shield Technology) or hydrophilic glycan-containing polymers (Phenox: HPC) may interact differently with the circulating blood cells and the migratory cells from the vessel wall that are required for the formation of a neo-intima (9, 10), and hence, influence its progress in a divergent way. Indeed, an experimental study compared the uncoated with the coated PED and revealed faster neo-endothelialization together with decreased thrombus formation for the PED with Shield technology (38), supporting this hypothesis. Unfortunately, comparable investigations on the p64MW-HPC and its bare metal counterpart are lacking. As a consequence, further investigations are needed to better understand the impact of the distinct anti-thrombotic coatings on the process of vascular healing after FDS implantation (36, 39).

Moreover, the anti-platelet medication in our study differed considerably from the standard DAPT regimen in the aforementioned PED Shield studies, which comprised ASA and clopidogrel. High on-treatment platelet reactivity occurs with clopidogrel in up to 50% of patients (40) and is associated with thromboembolic complications in neurovascular stenting (41). As current methods of platelet function testing are not sufficiently reliable to predict treatment efficacy of DAPT, the clinical value of platelet function testing in FD remains doubtful (10, 42, 43). As a consequence, either ticagrelor or prasugrel was predominantly administered as a second anti-platelet drug in our cohort, in order to avoid the pitfalls associated with clopidogrel. Large-scale clinical trials demonstrated superiority of ticagrelor and prasugrel over clopidogrel regarding the prevention of ischemic complications without excess risk of hemorrhage (44). However, neo-endothelialization of a FDS seems to depend on the preceding formation of thrombus along its surface to some extent, and *vice versa*, excessive DAPT delays the process of arterial healing (36, 38). Hence, using the more potent anti-aggregants ticagrelor or prasugrel for DAPT in our patients may have contributed to prolonged vascular remodeling and, thus, decelerated aneurysm occlusion. Aside from platelet inhibition, circulating anti-aggregants impact the physiology of the endothelium directly *via* the P2Y12 receptor and through paracrine mechanisms that involve other circulating blood cells (45, 46). A growing number of *ex vivo* and clinical studies in this regard indicate that the currently used P2Y12-receptor antagonists, i.e., clopidogrel, prasugrel, and ticagrelor, have a very different effect on injury-repair process that immediately begins after stenting (47). The latter anti-platelet drug reduces neo-intimal hyperplasia together with the local inflammatory response and excessive proliferation of smooth muscle cell proliferation while preserving re-endothelialization (48). Schnorbus et al. compared the three P2Y12 anti-aggregants and postulated that prasugrel is associated with improved endothelial function, stronger platelet inhibition, and a lower inflammatory response compared to ticagrelor and clopidogrel (49). Other authors claimed the superiority of ticagrelor over prasugrel

and clopidogrel regarding the extent of platelet inhibition and endothelial function (44).

In summary, the P2Y12 inhibitors not only inhibit platelet activation to very different extents, but also exert a number of drug-specific pleiotropic effects that influence vascular physiology after stenting. However, in particular, which P2Y12 antagonist provides the best pharmaceutical profile for flow diversion remains to be elucidated, and prospective studies in this regard are urgent. From the current perspective, a certain degree of customization of anti-platelet medication, accounting for the type and surface modification of the respective implant in the context of the patient's hemostaseologic condition and potentially required level of care, should be considered to achieve an optimal outcome. In our patient collective, for example, two ischemic complications manifested as a result of suddenly abandoned anti-platelet medication within the 3rd week post intervention. The respective patients required a moderate level of care related to their preexisting comorbidities and were supported in day care centers. In retrospect, DAPT, consisting of ASA and ticagrelor in both cases, was given incompletely after returning to day care, resulting in acute in-stent thrombosis. Both cases were treated sufficiently as described above and the patients recovered well from the complications. However, ticagrelor, although having a low rate of hypo-response, has a very short duration of action, requires the intake of two pills every 12 h and skipping just one pill can cause device thrombosis (10). Therefore, prasugrel, exhibiting a longer duration of action and requiring only 1 pill every 24 h, may have been the more appropriate anti-aggregant in this situation.

The occurrence of complications in the especially sensitive, early post-interventional phase is well-known and our observations in this regard are in accordance with previous studies (50, 51). Both thromboembolic and hemorrhagic events are comparatively rare, but oftentimes manifest within 6 weeks post FDS-implantation (52). However, the complications in our patients were treated with good outcomes and no patient suffered from severe, permanent device-related morbidity. The rate of clinical complications in our preliminary study on the p64MW-HPC is in line with or below the complication rates of earlier reports (20).

The five technical adverse events in our study were dominated by twisting of the p64MW-HPC in highly tortuous cavernous or ophthalmic ICA segments, which were successfully resolved by balloon angioplasty. In those cases, the movable wire of the stent-carrier module maintained distal endovascular access and facilitated the introduction of the balloons markedly. However, recognition and immediate elimination of twisting or device collapse are paramount, as they functionally equal the occlusion of the vessel (20). Secondly, foreshortening or migration of the p64MW-HPC occurred as further technical issues. In our study, peri-interventional shortening was sufficiently compensated by implantation of a second low-profile FDS, and the distal migration did not require a further intervention. Nevertheless, both phenomena can culminate in fatal SAH, for example, if the distal end of the FDS dislocates into the aneurysm sac, directing blood flow toward the aneurysm wall, or major ischemic stroke, if the device migrates distally and obstructs a downstream bifurcation (53). Migration and foreshortening are related to suboptimal wall adaption and the specific low-porosity closed cell design of FDS (54). Hence, their occurrence is limitable by appropriate sizing and optimal placement. However, as they also may manifest several months after implantation, regular follow-ups during the 1st year are important (54).

Our study suffers from a number of limitations. Firstly, it is a retrospective analysis of a prospectively maintained database. Related to the novelty of the device, only a small number of patients with limited numbers of follow-up examinations were available. The lack of routinely performed platelet-function testing, in addition, limits the assessment of the efficacy of the administered anti-platelet regimen and its potential impact on the aneurysm occlusion rate. Furthermore, intraluminal imaging, for example optical coherence tomography, which is well-suited to assess the process of neo-endothelialization, was not performed (55).

## CONCLUSION

This study highlights the safety and feasibility of the novel p64MW-HPC for the treatment of intracranial aneurysms arising from proximal segments of the anterior and posterior intracranial circulation. The early follow-up results indicate good early occlusion rates, which appear comparable to bare-metal FDS. The compatibility with small 0.021" microcatheters limits the necessity for potentially traumatic catheterization maneuvers and facilitates FDS implantation in tortuous, elongated vessels. However, further studies and long-term data are required in order to assess the efficacy of the p64MW with HPC surface modification. A comparative prospective study between the uncoated p64MW and the p64MW-HPC employing intraluminal imaging is wanted.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission des Universitätsklinikums Leipzig. The patients/participants or his or her legal representative provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

HW was responsible for data acquisition, performed statistical review, and wrote the paper. M-SS was responsible for data acquisition, wrote the paper, and performed image analysis. CS performed interventions and follow-up imaging analysis. DM and JT performed interventions, follow-up imaging, and vascular analysis. WH reviewed and drafted the paper. AD performed

image analysis and reviewed the paper. JM and NB performed follow-up imaging and analysis. KH wrote and reviewed the paper. UQ performed interventions. SS designed the study, wrote the paper, and performed interventions. All authors contributed to the article and approved the submitted version.

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# Pipeline Embolization Device for the Treatment of Unruptured Intracranial Dissecting Aneurysms

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**Background:** Intracranial dissecting aneurysms (IDAs) are rare but pose significant challenges to treatment. The pipeline embolization device (PED) has been demonstrated to be an effective treatment option with excellent outcomes. Herein, we report our experience with patients treated with the PED for unruptured IDAs.

**Methods:** We retrospectively reviewed our hospital database and identified patients who were treated with PEDs for unruptured IDAs between March 2016 and September 2020. Data including demographics, clinical presentation, aneurysm characteristics, procedural details, intra- or peri-procedural complications, and follow-up details were collected.

**Results:** Eighty patients (61 men, 76.25%) were treated with PED for unruptured IDAs. The most common symptoms were headache (34, 42.5%), dizziness (29, 36.25%), and nausea or vomiting (15, 18.75%). Of these patients, 73 had one aneurysm, and seven harbored two aneurysms. All of them achieved successful PED deployment. Six patients experienced intra- or peri-procedural complications including perforator artery occlusion, thromboembolic, hemorrhagic events, and falling of the stent into the aneurysm sac. Follow-up with digital subtractive angiography was available for 29 patients with a median of 6 months, and 28 (96.56%) patients had aneurysm occlusion. Late thrombosis occurred in four patients, and two of them had unfavorable outcomes. Clinical follow-up showed that a favorable clinical outcome was achieved in 76 (95%) patients, and the mortality rate was 3.75%.

**Conclusion:** Treating unruptured IDAs is safe and effective with long-term favorable clinical and angiographic outcomes. However, the complications of this treatment should be noted. Careful selection of appropriate patients and individualized antiplatelet therapy might be needed.

**Keywords: unruptured intracranial dissecting aneurysms, pipeline endovascular device, outcomes, complications, treatment**

# INTRODUCTION

Intracranial dissecting aneurysms (IDAs) are uncommon types of cerebrovascular lesions caused by a disruption of the internal elastic lamina and account for only 3% of all intracranial aneurysms (1). Even though they are less frequent than saccular aneurysms, IDAs have been recognized as an important source of subarachnoid hemorrhage (SAH) in children, young adults, and middle-aged adults, especially in the East Asian population (2, 3). The risk of SAH has shifted treatment for unruptured IDAs away from initial conservative therapy toward more invasive approaches. However, these lesions still pose a major challenge to endovascular treatment due to their unique location and anatomic characteristics (4, 5).

The flow-diverting pipeline embolization device (PED) has been approved in 2011 by the United States Food and Drug Administration for the treatment of large or giant wide-necked intracranial aneurysms of the internal carotid artery. Later, multiple studies demonstrated the safety and efficacy of expanding indications for PED including ruptured aneurysms, blister aneurysms, and dissecting aneurysms (6). The PED can be used as an endoluminal reconstruction device that preserves the parent artery and major side branches. These characteristics of a PED make it ideal for the treatment of IDAs.

The treatment of unruptured IDAs with a PED has been reported by several studies (7–14). The outcomes seemed to be excellent, and no unfavorable outcomes or adverse events were reported by these studies (6). However, most of these studies have not investigated the use of a PED specifically for unruptured IDAs (8, 9, 12, 13), and all of them used a small number of cases. Owing to these limitations, we present a retrospective analysis of the procedure-related complications, angiographic outcomes, and clinical outcomes for patients with unruptured IDAs who received PED treatment in a high-volume center.

# METHODS

## Study Design

This study was approved by the institutional review board of Beijing Tiantan Hospital, and the need for informed consent was waived due to the retrospective design. We reviewed our hospital database to identify consecutive patients who were admitted to our department for the treatment of unruptured IDAs between March 2016 and September 2020.

The inclusion criteria for this study were as follows: (1) IDAs diagnosed by digital subtraction angiography (DSA). The diagnosis for IDAs was established according to imaging findings including intimal flap, pearl and string sign, double-lumen sign, luminal dilation adjacent to a stenotic segment, or a simple fusiform dilation with delayed clearance of contrast media (1); (2) aneurysms treated by PED alone or a PED with adjunctive coiling. The exclusion criteria were as follows: (1) aneurysms treated by non-PED approaches; (2) history of SAH; (3) major diseases such as stroke, cerebral artery stenosis, injury, or tumor that would affect patients' outcomes; and (4) incomplete clinical data. Clinical and angiographic data were reviewed by two experienced neurologists. Finally, 80 consecutive patients were included in this study.

The following variables were collected for eligible patients: demographics, aneurysm characteristics, antiplatelet treatment, procedural details, immediate or delayed complications, radiographic data, and functional outcomes. Complications were considered if new symptoms emerged that could attribute to either thromboembolism or hemorrhage.

## Treatment Details

Before treatment, each case was discussed with neurovascular team members, and the treatment decision was made based on demographics, symptoms, location, and morphology. There were no strict criteria for aneurysm size.

Patients in this series were preloaded with a daily oral antiplatelet regimen consisting of 100 mg of aspirin and 75 mg of clopidogrel for 5 days before treatment. Patients' reactivity to these two antiplatelet drugs was routinely tested; if a low response to clopidogrel was indicated, it was replaced with ticagrelor.

Treatments were performed with the patient under general anesthesia and via a transfemoral approach, and systemic heparinization was administered after placement of the sheath. The Marksman microcatheter (Medtronic, Dublin, Ireland) was manipulated under high-magnification fluoroscopic roadmap control across the aneurysm neck. We attempted to cover the aneurysm neck with a minimal number of PEDs, and multiple PEDs were considered when a single PED could not bridge the wide neck. The PED position was adjusted from multiple angles before releasing it carefully. Stent apposition was evaluated by DynaCT (Siemens Healthcare GmbH, Erlangen, Germany). Flow stagnation inside the aneurysm was assessed to decide whether to insert additional coils. After the operation, patients were asked to take 75 mg of clopidogrel and 100 mg of aspirin daily for 6 months for the rest of their life.

## Assessment and Follow-Up

Technical success was defined as complete coverage of the aneurysm neck after PED deployment and preserved patency of the parent artery without clinically evident adverse events. Patients were advised to undergo both clinical and angiographic follow-up 3, 6, and 12 months after the treatment and annually thereafter. An independent neurologist was responsible for the neurologic assessment. Any residual filling of the aneurysms was interpreted as incomplete occlusion. Functional outcomes were evaluated using the modified Rankin scale (mRS), of which a score of 0 to 2 was defined as a favorable outcome and a score of 3–6 as an unfavorable outcome. This score was obtained during a follow-up visit at our clinic or by telephone interview for those referred from distant locales.

# RESULTS

Over a 5 year study period, 80 patients (61 male, 76.25%) were treated with PEDs due to unruptured IDAs (**Table 1**). Their age ranged from 10 to 71 years (median, 53 years), and 61 (76.25%) of them were male. The most common symptoms were headache

**TABLE 1 |** Baseline characteristics.

| Number of patients | *N* = 80 |
|---|---|
| **Sex** | |
| Male | 61 (76.25%) |
| Female | 19 (23.75%) |
| Age (years), median (IQR) | 53 (47–56) |
| **Symptoms** | |
| Headache | 34 (42.5%) |
| Dizziness | 29 (36.25%) |
| Nausea or vomiting | 15 (18.75%) |
| **Pretreatment mRS** | |
| 0 | 31 (38.75%) |
| 1 | 44 (55%) |
| 2 | 5 (6.25%) |
| Hypertension | 44 (55%) |
| Diabetes mellitus | 7 (8.75%) |
| Hyperlipidemia | 7 (8.75) |
| Smoking | 28 (35%) |
| Alcohol | 20 (25%) |
| Number of patients with a single aneurysm | 73 (91.25%) |
| Number of patients with two aneurysms | 7 (8.75%) |
| **Aneurysm size** | |
| Small (<10 mm) | 30 (34.48%) |
| Large (10–25 mm) | 50 (57.47%) |
| Giant (>25 mm) | 7 (8.04%) |
| **Aneurysm location** | |
| Vertebral artery | 75 (86.21%) |
| Basilar artery | 4 (4.6%) |
| Vertebrobasilar junction | 3 (3.45%) |
| Middle cerebral artery | 3 (3.45%) |
| Posterior cerebral artery | 1 (1.15%) |
| Carotid artery | 1 (1.15%) |
| **Procedure details for patients with a single aneurysm** | |
| PED alone | 61 |
| PED with adjunctive coiling | 12 |
| **Procedures details for patients with two aneurysms** | |
| Both aneurysms treated | 4 |
| One aneurysm treated | 3 |
| Ischemic complications | 4 (5%) |
| Hemorrhagic complications | 1 (1.25%) |
| Number of patients with radiological follow up | 29 (36.25%) |
| **Length of radiological follow-up (months), median (IQR)** | |
| **Complete occlusion of aneurysms** | |
| Length of clinical follow-up (months), median (IQR) | 26 (16–37) |
| **Follow-up mRS** | |
| 0 | 56 (70%) |
| 1 | 18 (22.5%) |
| 2 | 2 (2.5%) |
| 5 | 1 (1.25%) |
| 6 | 3 (3.75%) |

*IQR, interquartile range; PED, pipeline embolization device; mRS, modified Rankin Scale.*

(34, 42.5%), dizziness (29, 36.25%), and nausea or vomiting (15, 18.75%).

Most of those patients had IDAs that compromised the intradural segment of the vertebral artery (68, 85%), basilar artery (4, 5%), vertebrobasilar junction (3, 3.75%), middle cerebral artery (3, 3.75%), posterior cerebral artery (1, 1.25%), and carotid artery (1, 1.25%). Among these patients, seven had multiple aneurysms: one patient had two aneurysms on one vertebral artery, while six patients had an aneurysm on both vertebral arteries. Therefore, 80 patients harbored a total of 87 aneurysms. Fifty (57.47%, 50/87) aneurysms were classified as large (10–25 mm), 30 (34.48%, 30/87) as small (<10 mm), and seven (8.04%, 7/87) as giant (>25 mm).

None of the patients in our cohort were treated previously with other stents or coils. Of the 73 patients with a single aneurysm, 61 had PED placement alone and 12 had adjunctive coiling. A total of 80 devices were used to treat 73 IDAs. Four patients with multiple aneurysms had both aneurysms treated, and two of them had staged treatment. The other three patients with multiple aneurysms had only one aneurysm treated. Successful deployment of the PED was achieved for all patients, and only two of them required a second attempt. Two patients presenting with an aneurysm at the vertebrobasilar junction had PED deployment on one side and vertebral artery sacrifice on the other.

Six patients experienced intra- or peri-procedural complications, and one had perforator artery occlusion during the procedure. Tirofiban was administered after the exclusion of hemorrhage confirmed by DynaCT; this patient did not develop any new symptoms after treatment and recovered well. One encountered in-stent thrombosis during the procedure, and tirofiban was administered proximal to thrombus intra-arterially through a microcatheter; the patient recovered well at follow-up. Two patients suffered from thromboembolic complications within 2 days after the operation. One of these two patients underwent vertebral artery sacrifice, and they recovered well at discharge. However, that patient died due to in-stent thrombosis 10 months later. The other patient who experienced a thromboembolic event managed to have a full recovery at follow-up. One patient presented with intracranial hemorrhage 1 day after the operation and died at discharge. One patient had the stent fall into the aneurysm sac 4 days after the procedure, and basilar artery sacrifice was performed. The patient recovered well at a long-term follow-up with an mRS score of 2.

At least one DSA follow-up was available among 29 patients (37.18%, 29/78). The median follow-up duration was 6 months (range, 3–18 months). We selected the final DSA follow-up of every patient as the timepoint at which to evaluate the efficacy of PED. Only one patient had obvious aneurysm residual on follow-up, and the occlusion rate was 96.56%. Two patients were confirmed to have vertebral artery occlusion on the side of PED placement, and they presented with mild-to-moderate dizziness.

The median clinical follow-up was 26 months (range, 3–61 months) for patients who were alive at discharge. A favorable clinical outcome was achieved in 76 (95%) of patients. One patient with basilar artery IDAs had cerebellar infarction

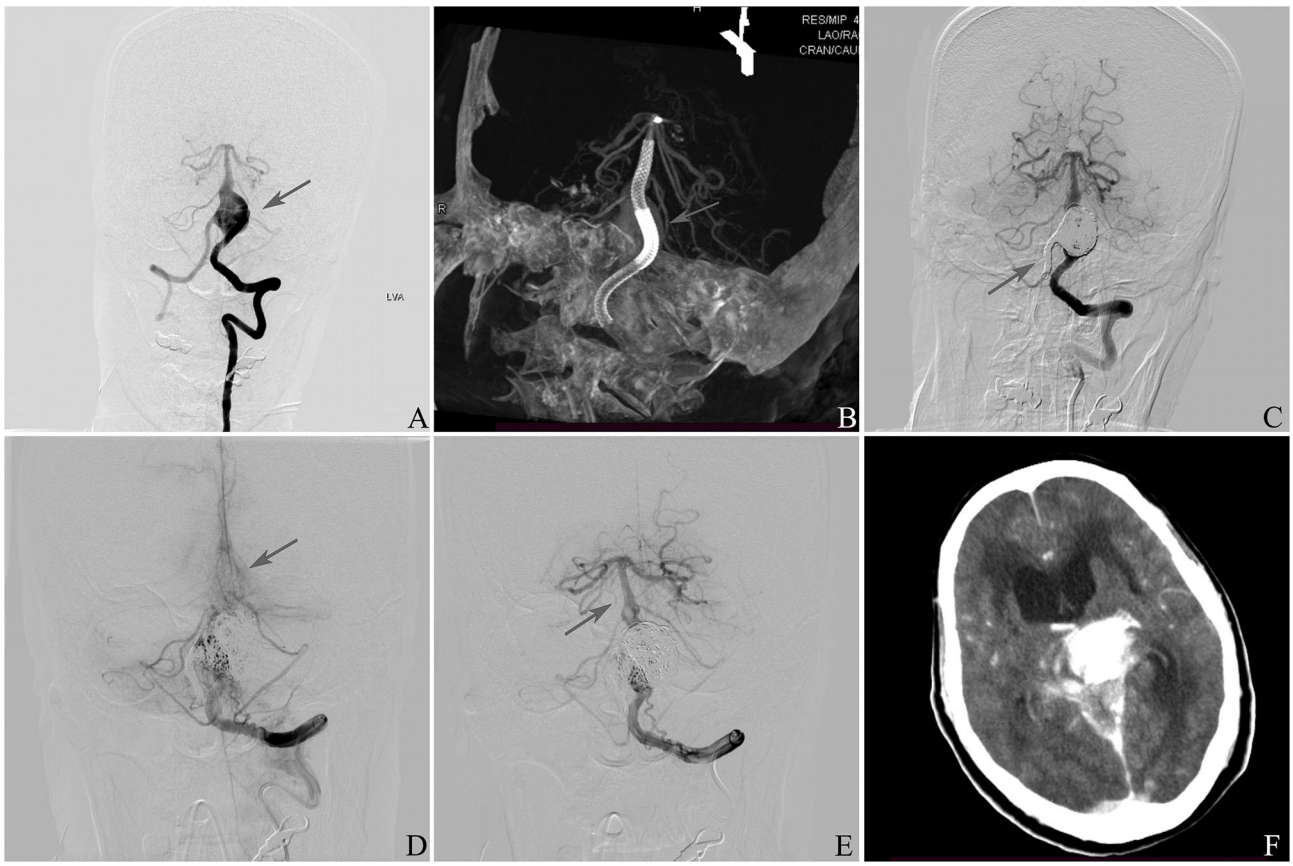


**FIGURE 1 | (A)** Frontal vertebral arteriograms showing a dissecting aneurysm at the vertebrobasilar junction (arrow). **(B)** Placement of pipeline embolization device (arrow). **(C)** Sacrifice of right vertebral artery (arrow). **(D)** Occlusion of basilar artery 10 months later after discharge (arrow). **(E)** Reopening of the basilar artery (arrow). **(F)** Computed tomography showing the brain stem, thalamus, and subarachnoid hemorrhage.

diagnosed at the local hospital 5 months after the treatment and was severely disabled (mRS 5). One patient died suddenly at the last follow-up due to unknown reasons 1 month after discharge. The overall unfavorable rate was 5%, and the mortality rate was 3.75%.

## Illustrative Case 1

This patient was a 61 year-old female in whom an IDA was accidentally discovered (**Figure 1**). On the initial diagnostic angiogram, the presence of an IDA at the vertebrobasilar junction was confirmed. She had a normal response to aspirin and clopidogrel. A PED was placed, and the right vertebral cerebral artery was sacrificed. She experienced a thromboembolic event 1 day after the procedure and recovered without any complications at discharge. The DSA follow-up 6 months later showed that the aneurysm was occluded completely. This patient had a sudden loss of consciousness 10 months later. DSA confirmed the occlusion of the basilar artery due to in-stent thrombosis, and intra-arterial thrombolysis was administered immediately. The basilar artery was reopened completely after the procedure, and computed tomography showed the brain stem, thalamus, and SAH. She died 1 day later.

## Illustrative Case 2

This was a 37-year-old female presenting with a right occipital headache (**Figure 2**). Angiography demonstrated a giant IDA involving the upper basilar trunk. Two PEDs were deployed in the right position. She developed a severe progressive headache and vomiting the next 4 days after the procedure. DSA showed the PEDs had fallen into the aneurysm sac, and basilar artery sacrifice was then performed. The patient had an uneventful recovery with mild disability (mRS 2) at discharge, and she remained the same at follow-up.

# DISCUSSION

Currently, the natural history of unruptured IDAs is still unclear, and their management remains a dilemma (15). Conservative treatment with anticoagulation therapy was initially adopted and resulted in a benign clinical outcome, suggesting that intervention is not always required and that close follow-up is reasonable (16, 17). However, the risk of bleeding from unruptured IDAs was proved to be higher than previously thought and has been an important source of SAH (5, 18). Symptoms due to mass effects or aneurysms with large size or

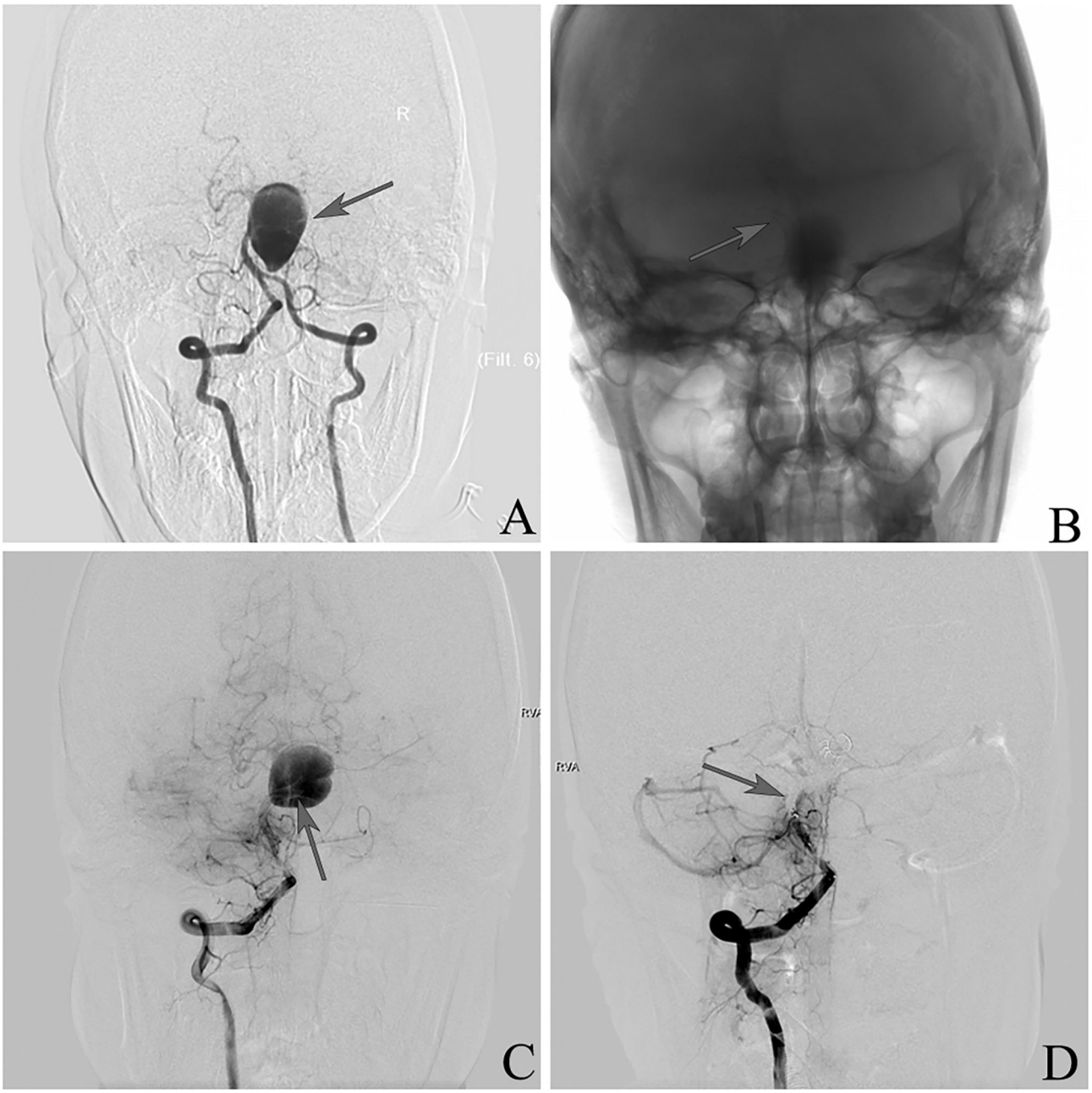


**FIGURE 2 | (A)** Frontal vertebral arteriograms showing a dissecting aneurysm at the upper basilar trunk (arrow). **(B)** Placement of pipeline embolization device (arrow). **(C)** Pipeline embolization device falling into aneurysm sac (arrow). **(D)** Sacrifice of the basilar artery (arrow).

persistent dilation further supported the argument for definitive treatment of unruptured IDAs.

Treatment of IDAs is regarded as a technical challenge due to their histopathological features and localization. There are several treatment strategies for IDAs including proximal occlusion, trapping with or without bypass, clipping or wrapping of the aneurysm sac, stent-assisted coil embolization, and stent monotherapy with flow diverters. Since its origin, flow diverters, especially the PED, have emerged as an attractive therapeutic option for these challenging lesions. The PED consists of a tightly braided alloy and has low porosity. It diverts blood flow and allows blood to cross the interstices. The metal surface area acts as a scaffold for intraluminal reconstruction. Therefore, the PED can facilitate aneurysm exclusion and also preserve important functional perforators (19).

The initial experience of using PED for the treatment of unruptured IDAs was shared by de Barros Faria et al. (13). Eleven patients with unruptured IDAs were treated in that study.

Though the complications after treatment were not reported specifically, all patients achieved a good clinical outcome at a short-term follow-up. Later, Yeung et al. reported the long-term outcome of four patients with unruptured IDAs of the vertebral artery receiving endovascular reconstruction using PEDs (14). No periprocedural complication was encountered, and no patient showed any recurrence, in-stent thrombosis, or side-branch occlusion at angiographic follow-up at a mean of 22 months after treatment. All of them had favorable outcomes with an mRS score of 0 at long-term clinical follow-up. Fischer et al. reported the largest number of cases using PEDs for the treatment of intra- and extracranial fusiform and dissecting aneurysms (8). In this case series, 69 aneurysms were treated, and 31 were classified as dissecting. The morbidity and mortality rates in this entire series were 5 and 8%, respectively. However, the outcomes for patients with unruptured IDAs were not reported. A few other studies with a small number of cases also investigated the efficacy and safety of the PED for the treatment of unruptured IDAs, and the results seem excellent (6, 7, 9–12).

According to our knowledge, we reported the largest number of cases, and 80 consecutive patients harboring 87 unruptured IDAs were included in this study. A total of 84 aneurysms were treated by a PED or a PED with an adjunctive coil. Technical success was achieved for all these patients. Twenty-nine patients had DSA follow-up, and 28 (96.56%) of them had aneurysm occlusion. A favorable clinical outcome was achieved in 76 (93.75%) of patients with a median follow-up of 26 months, and the mortality rate was 3.75%. Overall, the results of our cohort proved that using PEDs for the treatment of unruptured IDAs is effective and safe.

However, special attention should be paid to the complications of PED treatment for unruptured IDAs even though they were not reported previously. In-stent thrombosis, thromboembolic events, and hemorrhagic events are feared complications. In our cohort, six patients experienced intra- or peri-procedural complications. Intraprocedural events occurred in two patients. One had a perforator artery occlusion, and another had in-stent thrombosis. After the procedure, two patients suffered from thromboembolic events, and one from a severe hemorrhagic event. One had the stent fall into the aneurysm sac, and the basilar artery was ultimately sacrificed. One of these six patients died due to hemorrhage at discharge. These events prove that careful selection of patients appropriate for PED treatment and intensive care after the procedure are needed.

Late thrombosis is another complication that should be noted even though it is considered a rare event (20). In our study, two patients developed vertebral artery occlusion on the side of PED placement, and they had mild-to-moderate dizziness. Moreover, at the follow-up, one patient died due to basilar artery occlusion caused by in-stent thrombosis 10 months later, and one patient had a severe disability due to cerebellar infarction 5 months later after the PED placement at the basilar artery. All these patients were compliant with antiplatelet treatment. Therefore, late thrombosis after PED placement, especially in the posterior circulation, might not be rare as previously thought. Special attention should be paid to antiplatelet therapy, and it might need to be individualized.

This study has several major limitations. First, the DSA imaging follow-up was only available for 29 patients, making it difficult to evaluate the effectiveness of aneurysm occlusion after PED placement. Second, this was a single-center study, limited by its retrospective nature and by the inherent bias of this kind of study design.

## CONCLUSION

Reconstruction using a PED is safe and effective in the treatment of unruptured IDAs, showing favorable long-term clinical and angiographic outcomes. However, the complications of this treatment should be noted. Careful selection of appropriate patients and individualized antiplatelet therapy might be needed.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Tiantan Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

JC conducted the study design and prepared the manuscript. MT and JH collected the data and performed the clinical follow-up. XF, FP, XT, HN, and NM reviewed the data. AL reviewed and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CORRECTION
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# Corrigendum: Pipeline Embolization Device for the Treatment of Unruptured Intracranial Dissecting Aneurysms

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**Keywords: unruptured intracranial dissecting aneurysms, pipeline endovascular device, outcomes, complications, treatment**

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## A Corrigendum on

**Pipeline Embolization Device for the Treatment of Unruptured Intracranial Dissecting Aneurysms**

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In the published article, there was an error in affiliation 3, as published. Instead of "Department of Neurosurgery, Third Hospital of Shanxi Medical University, Taiyuan, China," it should be "Department of Neurosurgery, First Hospital of Shanxi Medical University, Taiyuan, China."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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ORIGINAL RESEARCH
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# Safety and Efficacy of the FRED Jr Flow Re-Direction Endoluminal Device for Intracranial Aneurysms: Retrospective Multicenter Experience With Emphasis on Midterm Results

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**Background and Purpose:** Flow diversion is increasingly used as an endovascular treatment for intracranial aneurysms. In this retrospective multicenter study, we analyzed the safety and efficacy of the treatment of intracranial, unruptured, or previously treated but recanalized aneurysms using Flow Re-Direction Endoluminal Device (FRED) Jr with emphasis on midterm results.

**Materials and Methods:** Clinical and radiological records of 150 patients harboring 159 aneurysms treated with FRED Jr at six centers between October 2014 and February 2020 were reviewed and consecutively included. Clinical outcome was measured by using the modified Rankin Scale (mRS). Anatomical results were assessed according to the O'Kelly-Marotta (OKM) scale and the Cekirge-Saatci Classification (CSC) scale.

**Results:** The overall complication rate was 24/159 (16%). Thrombotic-ischemic events occurred in 18/159 treatments (11%). These resulted in long-term neurological sequelae in two patients (1%) with worsening from pre-treatment mRS 0–2 and mRS 4 after treatment. Complete or near-complete occlusion of the treated aneurysm according to the OKM scale was reached in 54% (85/158) at 6-month, in 68% (90/133) at 1-year, and in 83% (77/93) at 2-year follow-up, respectively. The rates of narrowing or occlusion of a vessel branch originating from the treated aneurysm according to the CSC scale were 11% (12/108) at 6-month, 20% (17/87) at 1-year, and 23% (13/57) at 2-year follow-up, respectively, with all cases being asymptomatic.

**Conclusions:** In this retrospective multicenter study, FRED Jr was safe and effective in the midterm occlusion of cerebral aneurysms. Most importantly, it was associated with a high rate of good clinical outcome.

**Keywords: flow diversion, cerebral small vessels, FRED junior, low-profile flow diverter, intracranial aneurysm**

## INTRODUCTION

The treatment of intracranial aneurysms of complex morphology, such as aneurysms with a wide neck, irregular shape (e.g., daughter sac aneurysms), or aneurysms with incorporated branching vessels, may be unfavorable or even unsuitable for traditional endovascular or microsurgical treatments (1, 2). Also, recanalized aneurysms after endovascular or microsurgical treatment often show characteristics of complex morphology, limiting the options for successful retreatment (3, 4). In these cases, flow diversion stent treatment is an increasingly used alternative (1). The densely braided mesh of a flow diversion stent delivered at the aneurysm base decreases the blood flow into the aneurysm and induces thrombus formation within the aneurysm sac while maintaining adequate blood flow through the parent artery and the covered vessel branches (5). The development of smaller flow diverters like Flow Re-Direction Endoluminal Device Jr (FRED Jr; MicroVention, Tustin, California), which can be delivered into small-caliber (<3 mm diameter) vessels, enabled the expansion of indications for flow diversion stent treatment in smaller parent vessels (2, 6). However, there is only a limited number of studies evaluating flow diverter devices specifically developed for smaller arteries (2, 7).

In this study, we evaluate the applicability of flow diverter stent treatment using the FRED Jr for unruptured or previously treated but recanalized intracranial aneurysms in smaller vessels and examine the device's safety and efficacy.

## METHODS

### Patient and Case Selection

This retrospective study was approved by the local ethics committees. Treatment decisions were made by a multidisciplinary team (vascular neurosurgeons and interventional neuroradiologists) on a case-by-case basis. Clinical and radiological records of all patients with intracranial, unruptured, or recanalized aneurysms treated with FRED Jr at six centers between October 2014 and February 2020 were reviewed and consecutively included. Midterm follow-ups of these patients were added. Patients' demographics were assessed, including age, sex, clinical presentation, and modified Rankin Scale (mRS).

Regarding the treated aneurysms, we evaluated the type, size, location, vessel diameter, and existence of branching vessels from the aneurysm sac itself or from the parent artery adjacent to the aneurysm (distance of ≤2 mm to the aneurysm neck), which needed to be covered by the flow diverter.

**Abbreviations:** ACA, anterior cerebral artery; ACom, anterior communicating artery; ASA, acetylsalicylic acid; CSC, Cekirge-Saatci Classification; FRED Jr, FRED Junior; FDCTA, flat detector computed tomography angiography; NICE, non-ischemic cerebral enhancing; OKM, O'Kelly-Marotta Grading Scale; PCA, posterior cerebral artery; PCom, posterior communicating artery; SUCA, superior cerebellar artery.

### Antiplatelet and Anticoagulant Therapy

All patients were treated either with dual or mono antiplatelet therapy. Antiplatelet therapy used during each procedure is listed in the **Supplementary Material**. The dual therapy combined 100–300 mg of acetylsalicylic acid (ASA) with 75 mg of clopidogrel (loading dose 300 mg), starting no <5 days before the treatment. Platelet inhibition was tested prior to procedures. During all procedures at all centers, weight-adjusted heparinization with an activated clotting time >250 s was maintained. Depending on the case and the imaging results during the follow-up period, the initial antiplatelet therapy was maintained for a minimum of 6 months after the procedure followed by ASA monotherapy for at least 6 months or lifelong. At four centers, especially for patients younger than 65 years, an initial daily mono antiplatelet medication with prasugrel 10 mg (loading dose 40 mg) was maintained for 1 year and thereafter either discontinued or continued with reduced doses of prasugrel or ASA lifelong.

### Description of Technique

After determining the shape, size, and neck width of the aneurysm, a suitable flow diverter, fully covering the neck, and safety margins of at least 2 mm proximally and distally to the aneurysm, was chosen. To document the degree of expansion and vessel wall adherence of the flow diverter, a flat detector computed tomography angiography (FDCTA) was performed during and/or after the deployment. Additional coiling was performed in jailing technique in cases with high rupture risk or where complete occlusion with sole flow diverter treatment was deemed unlikely. Furthermore, data from retreatment procedures were collected.

### Clinical Evaluation

Clinical evaluation, including mRS, was documented by an experienced neurointerventionalist, neurologist, or neurosurgeon 1 day after the procedure, the following day, at discharge, and at follow-up examinations, respectively. Good clinical outcome at follow-up was defined either as mRS 0–2 at follow-up or an unchanged mRS prior unchanged to pre-treatment (8). Minor stroke was defined as NIHSS ≤3, and major stroke as NIHSS >3 (9).

### Anatomical Evaluation

Follow-up imaging, depending on the local standard of care, was performed either with contrast-enhanced MR-angiography, FDCTA, or DSA and interpreted by two senior neuroradiologists not involved in the treatment. The grade of aneurysm occlusion was rated according to the O'Kelly-Marotta (OKM) grading scale (10). The occlusion grade describes the degree of aneurysm filling after treatment (A = total, B = subtotal, C = entry remnant, and D = no filling). Adequate aneurysm occlusion was defined as OKM C and OKM D.

Furthermore, aneurysms were rated according to the Cekirge-Saatci Classification (CSC) (11). The CSC class describes not only the degree of aneurysm filling after treatment but also the patency of vessel branches arising from the treated aneurysm

(Class 1 = complete occlusion, 1A: with full patency of the integrated branch, 1B: with the branch reduced in caliber, and 1C: with no antegrade filling of the branch; Class 2 = neck filling; Class 3 = incomplete occlusion with aneurysm filling; Class 4 = reserved for an immediate post-operative result based on end-of-treatment DSA, 4A: contrast stagnation, and 4B: without contrast stagnation; and Class 5 = stable remodeling with flow modification, i.e., filling in the neck region).

## Statistics

Patient and aneurysm characteristics as well as patients' clinical status (mRS) and aneurysm occlusion at follow-up were summarized using descriptive statistics and are presented as mean ± standard deviation (minimum–maximum) or as absolute number (relative frequency in percentage). For the descriptive statistics of clinical and anatomical results at different time points of follow-up, missing data were replaced by the last observation carried forward method. These data are included in the **Supplementary Material**.

Differences in variable distribution for the subgroups with complete vs. incomplete aneurysm occlusion at the 6-month follow-up were compared using a multivariate binary logistic regression with a *p*-value of 0.05 as the threshold for statistical significance. The same variables were tested for association with thrombotic-ischemic complications. These analyses were performed with SPSS Version 24 (IBM, Armonk, New York). Further details about the analyses can be found in the **Supplementary Material**.

We assessed the influence of vessel branches originating from aneurysms on occlusion rates for cases with 2-year follow-up examinations, by conducting a Kaplan–Meier analysis using GraphPad Prism 7 (San Diego, CA, USA).

# RESULTS

## Patient and Aneurysm Characteristics

Overall, 150 patients (101 females and 49 males) and 159 aneurysms were treated between October 2014 and February 2020. In nine patients, two aneurysms in different locations were treated separately with one FRED Jr each. Mean patient age was 55 ± 12 years (15–81 years); 30/159 (19%) aneurysm cases were secondary treatments, due to residual aneurysm filling or regrowth after previous treatment with either clips (7 aneurysms), coils (19 aneurysms), woven endobridge (WEB) device (MicroVention, Aliso Viejo, USA) (1 aneurysm), or flow diverters other than FRED Jr (3 aneurysms). Aneurysms had a mean diameter of 6.7 ± 4.9 mm (1.0–36.0 mm) with a mean neck size of 4.0 ± 2.1 mm (1.1–14.5 mm). Proximal and distal mean diameters of the parent vessel were 2.4 ± 0.4 mm (1.4–3.6 mm) and 2.1 ± 0.4 mm (1.4–3.4 mm). One hundred eight (68%) of the treated aneurysms had a vessel arising either directly from the aneurysm or from the vicinity of the aneurysm sac, which was covered by the flow diverter. More characteristics and the locations of the treated aneurysms are given in **Table 1** and **Supplementary Material**.

**TABLE 1 |** Aneurysm characteristics.

| | % of total |
|---|---|
| **Location** | |
| Distal ICA and PCom | 2 (1%) |
| M1 of MCA | 21 (13%) |
| Bifurcation of MCA | 48 (30%) |
| Distal (to bifurcation) MCA | 6 (4%) |
| A1 of ACA and ACom | 34 (21%) |
| Distal (to ACom) ACA | 32 (20%) |
| VA | 3 (2%) |
| SUCA | 1 (1%) |
| BA | 1 (1%) |
| P1 of PCA | 2 (1%) |
| Distal (to P1) PCA | 9 (6%) |
| **Proximal vs. distal location** | |
| Proximal | 112 (70%) |
| Distal (to MCA bifurcation, to ACom, to P1 of PCA) | 47 (30%) |
| **Anterior vs. posterior circulation** | |
| Anterior | 143 (90%) |
| Posterior | 16 (10%) |
| **Aneurysm morphology** | |
| Blister | 4 (3%) |
| Fusiform | 12 (8%) |
| Dissecting | 14 (9%) |
| Saccular | 125 (79%) |
| Giant | 4 (3%) |
| **Aneurysm size** | |
| Large (>1 cm) | 27 (17%) |
| Small (<1 cm) | 132 (83%) |

*ACA, anterior cerebral artery; ACom, anterior communicating artery; BA, basilar artery; PCA, posterior cerebral artery; PCom, posterior communicating artery; SUCA, superior cerebellar artery; VA, vertebral artery.*

## Procedural Aspects and Complications

In all procedures, a single FRED Jr device could be successfully deployed across the aneurysm base to achieve complete coverage. Additional coiling was performed in six cases. In one case with a dysplastic bifurcation of the middle cerebral artery (MCA) with two associated aneurysms, a WEB device was placed into one of the aneurysms prior to deployment of a FRED Jr.

Overall, procedure-related complications were observed in 24/159 (16%) of treatments.

Technical complications occurred in 6/159 (3%) of the procedures. In five procedures, the chosen flow diverter was either too short or too long and had to be replaced. On one occasion, the distal portion of the FRED Jr opened insufficiently due to a stenosis of the parent artery distal to the aneurysm, and a balloon angioplasty was performed to achieve a satisfying result.

Thrombotic-ischemic complications occurred in 18/159 (11%) of the treatments. In 12/159 (7%) of the aneurysm treatments, in-stent thrombosis in the parent artery was seen during the procedure after deployment of the FRED Jr. In all of these cases, the administration of tirofiban could maintain or restore full vessel patency. Within the first 30 days after

treatment, 9/159 (6%) patients suffered from periprocedural ischemic events. Seven out of these nine patients had minor strokes with transient symptoms. Two patients had major strokes with remaining clinical sequelae, worsening from an initial mRS of 0 to mRS 2 and mRS 4, respectively. Three of these complications, including the two cases of major strokes, were related to thrombosis in the parent vessel. In one case, 10 days after the treatment of an MCA bifurcation aneurysm, we noted a minimal stent deformation with distal caliber reduction, which could be described as "fishmouthing," and the patient suffered from a transient mild paresis of the left hand.

In 1/159 (1%) procedures, a minor asymptomatic periprocedural subarachnoid hemorrhage occurred during flow diverter placement without clinical consequences.

No patient suffered from intraparenchymal hemorrhage after the treatment.

There was one patient (1/159; 1%) who developed a puncture site pseudoaneurysm and was successfully treated with surgery.

Regarding antiplatelet therapy, patients were medicated with ASA and clopidogrel in 69 treatments and with prasugrel in 90 treatments. Antiplatelet therapy with prasugrel was significantly predictive of fewer thrombotic-ischemic complications, according to a multivariate analysis (odds ratio 11.21, CI 2.93–42.86, *p*-value 0.0004; **Table 2**).

**TABLE 2 |** Multivariate analysis of predicting factors for treatment-related complications (thrombotic or ischemic events) and of predicting factors for aneurysm occlusion conducted on 158 cases at 6-month follow-up.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95% CI)** | ***p*-value** | **OR (95% CI)** | ***p*-value** |
| **Independent variables for adequate aneurysm occlusion** | | | | |
| Gender (Female vs. male) | 1.82 | 0.15 | 1.93 | 0.10 |
| Age (Continuous) | 0.98 | 0.20 | | |
| Antiplatelet therapy (ASA/clopi. vs. pras.) | 0.77 | 0.50 | | |
| Shape (Diss./Fusi. vs. Sacc.) | 0.93 | 0.92 | | |
| Diameter (Continuous) | 0.93 | 0.24 | | |
| Neck size (Continuous) | 1.18 | 0.37 | | |
| Branch from aneurysm (No vs. yes) | **4.80** (1.74–13.30) | **0.002** | **5.48** (2.05–14.66) | **0.001** |
| **Independent variables for thrombotic-ischemic complications** | | | | |
| Gender (Female vs. male) | 0.97 | 0.95 | | |
| Age (Continuous) | 0.95 (0.91–0.99) | 0.02 | 0.95 (0.91–0.99) | 0.09 |
| Antiplatelet therapy (ASA/clopi. vs. pras.) | **11.44** (2.88–45.40) | **0.001** | **11.21** (2.93–42.86) | **0.0004** |
| Shape (Diss./Fusi. vs. Sacc.) | 2.19 | 0.38 | | |
| Diameter (Continuous) | 1.08 | 0.42 | | |
| Neck size (Continuous) | 0.87 | 0.40 | | |
| Branch from aneurysm (No vs. yes) | 0.74 | 0.65 | | |

*CI, confidence interval; Diss., dissecting; Dist., distal; Fusi., fusiform; OR, odds ratio; Prox., proximal; Sacc., saccular, vs., versus.*
*Values that reached statistical significance in the multivariate analysis are printed in bold.*

## Clinical and Anatomical Results Over Time

Clinical and anatomical results at 6 months were evaluated for 158/159 aneurysm treatments. One patient treated in 2018 was lost to follow-up due to Alzheimer's disease. Flow diverter deformation was seen in one case at 5-month follow-up, causing an asymptomatic stenosis of <50% of the distal parent vessel. One patient developed asymptomatic parenchymal lesions seen at the 4-month follow-up MRI, which regressed under steroid medication without further sequelae and could be described as non-ischemic cerebral enhancing (NICE) lesions (12). Two patients still suffered from sequelae of a major stroke with an mRS of 2 and 4, respectively. One aneurysm (also mentioned below in the *Patients Requiring Retreatment* section) required retreatment with parent artery occlusion due to aneurysm growth 3 months after the initial treatment and then suffered from a major ischemic stroke with worsening from mRS 0 to mRS 2. Thus, the rate of good clinical outcome at the 6-month follow-up was 99% (157/158). Aneurysm occlusions according to the OKM scale were OKM C 11% (18/158), OKM D 42% (67/158), and OKM C + D 54% (85/158), respectively. In 108/158 cases with a vessel branch arising from the aneurysm sac or from the parent vessel adjacent to the neck of the aneurysm, aneurysm occlusion rates were CSC 1A 23% (25/108), CSC 1B 6% (7/108), CSC 1C 5% (5/108), and CSC 5 6% (7/108), respectively. The narrowing (CSC 1B) or occlusion (CSC 1C) of a vessel arising from the aneurysm was asymptomatic in all 12 cases.

Clinical and anatomical results at 12 months were available for evaluation in 133/134 cases. One hundred thirty-four cases were treated before February 2019 and therefore eligible for the 12-month follow-up. As mentioned above, one patient was lost to follow-up due to Alzheimer's disease. No patient reported new neurological symptoms at the 12-month follow-up visit. Aneurysm occlusions according to the OKM scale were OKM C 15% (20/133), OKM D 53% (70/133), and OKM C + D 68% (90/133), respectively. In 87/133 cases with a vessel branch arising from the aneurysm, occlusion was CSC 1A 27% (23/87), CSC 1B 9% (8/87), CSC 1C 10% (9/87), and CSC 5 12% (10/87), respectively. The narrowing (CSC 1B) or occlusion (CSC 1C) of a vessel branch arising from the aneurysm was asymptomatic in all 17 cases.

Clinical and anatomical results at 24 months were evaluated in 93 cases, all of which were treated before February 2018 and were therefore eligible for the 24-month follow-up. Twelve of these cases were not yet screened at the 24-month follow-up. For these cases, results from the last observation were carried forward for the evaluation of the 24-month follow-up. No new neurological symptoms were reported at the 24-month follow-up. Aneurysm occlusions according to the OKM scale were OKM C 19% (18/93), OKM D 63% (59/93), and OKM C + D 83% (77/93), respectively. In 57/93 cases with a vessel branch

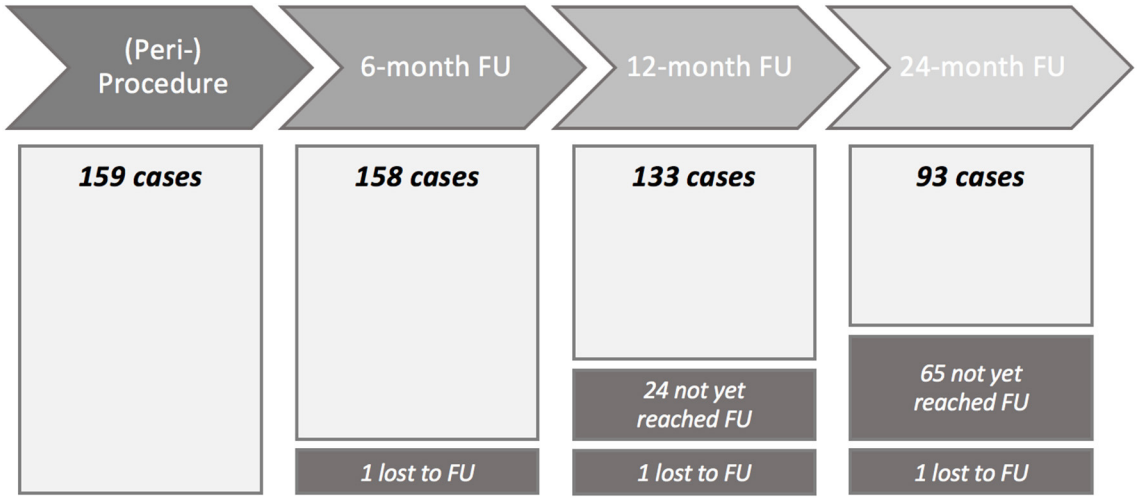


**FIGURE 1 |** Flowchart of cases included into the analysis at each time point. FU, follow-up.

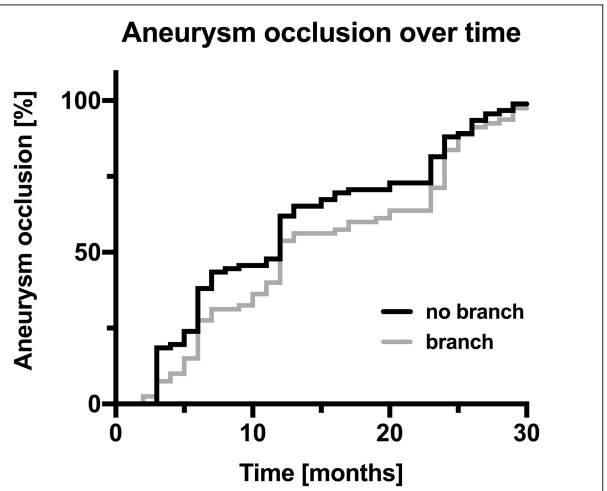


**FIGURE 2 |** Kaplan–Meier curves of the percentage of aneurysm occlusion over time; cases comprising a branch originating from the aneurysm covered by the flow diverter are displayed in gray, and cases without a branch originating from the aneurysm are displayed in black.

arising from the aneurysm, occlusions were CSC 1A 37% (21/57), CSC 1B 11% (6/57), CSC 1C 12% (7/57), and CSC 5 16% (9/57), respectively.

**Figure 1** shows the number of cases included in the analysis over time.

## Predictors of Aneurysm Occlusion

Predictive factors for adequate aneurysm occlusion (OKM C + D) at the 6-month follow-up identified by a multivariate analysis are presented in **Table 2**. A branch arising from the aneurysm sac or its immediate vicinity was an unfavorable factor for adequate aneurysm occlusion (odds ratio 5.48, CI 2.05–14.66, *p*-value 0.001).

When we compared occlusion rates in cases with vs. without incorporated vessel branches by a Kaplan–Meier analysis, we found a statistical trend (Gehan–Breslow–Wilcoxon test, chi square 2.905, *p*-value 0.088) for delayed occlusion of aneurysms with an incorporated vessel branch in the 93 cases available for analysis at 24-month follow-up (see **Figure 2** for corresponding Kaplan–Meier curves).

## Patients Requiring Retreatment

In total, retreatment was necessary for 6/159 (4%) aneurysms. A dissecting aneurysm located at the P2-segment of the posterior cerebral artery (PCA) showed enlargement 3 months after flow diverter treatment, requiring coil occlusion of the parent artery, which resulted in an ischemic infarction distal to the occluded artery with worsening of the mRS from 0 to 2. In another dissecting PCA-P3 aneurysm, parent artery occlusion was performed 29 months after the initial treatment due to further growth of the aneurysm sac. Four more patients showed insufficient occlusion of the treated aneurysm upon follow-up, and an additional flow diverter was placed coaxially within the FRED Jr (for more details see the **Supplementary Material**).

# DISCUSSION

In this retrospective multicenter study, the safety and efficacy of the FRED Jr for the treatment of intracranial aneurysms were investigated with emphasis on midterm results. The study represents a real-world scenario by including various types and locations of aneurysms treated in different international centers with variations in technical approaches, periprocedural management, and interventionalists' experience.

We demonstrated that aneurysm treatment with FRED Jr is overall safe in terms of neurological outcome. Although the overall complication rate of 16% is relatively high, it should be considered that many of the aneurysms featured a complex anatomy and also were associated with incorporated vessels

and abruptly changing vessel diameter, which makes them more challenging to treat. In aneurysm cases associated with complex vessel anatomy settings, FRED Jr has the advantage of allowing the usage of a smaller 0.021-in microcatheter, which can facilitate vessel probing. Nevertheless, in 3% of treatments, technical complications were encountered mainly due to the inappropriate choice of the flow diverter size. We suppose that in smaller vessels with changing vessel diameters, the shortening of the flow diverter in its final location was more difficult to predict. Most complications were, in line with other studies, related to thrombotic events (7%) and could be mitigated effectively by the application of tirofiban with low rates of severe neurological complications (13). Despite a 6% rate of periprocedural ischemic events, there were only two patients who suffered from ischemia-related long-term neurological complications with mRS 2 and mRS 4, respectively, resulting in a good clinical outcome rate (mRS 0–2) of 99% in our study. Cagnazzo et al. reports an overall complication rate of 20% comprising 16% of thrombotic-ischemic events in a meta-analysis of flow diverter treatment in MCA aneurysms (14). This result is comparable to our results, when considering that 48% of the aneurysms in our study were located in the MCA. In our multivariate analysis, we found lower thrombotic-ischemic complications in patients treated with prasugrel for antiplatelet therapy. Prasugrel is a promising antiplatelet agent, showing less drug–drug interactions than clopidogrel or ticagrelor and a faster onset of action (15). Nevertheless, when interpreting this result, it should be noted that this medication was not consistently used in every study center, and other factors in periprocedural management may influence thrombotic-ischemic complications. Further studies randomized for antiplatelet treatment will be needed to uncover the true potential of variations in antiplatelet therapy.

When judging occlusion rates, one must consider that 68% of the aneurysms treated in our cohort incorporated vessel branches. Therefore, occlusion results cannot be easily compared to studies examining treatments in proximal vessel locations (16). The aforementioned meta-analysis by Cagnazzo et al. about flow diversion in MCA aneurysms reports that complete/near-complete occlusion rates vary between 60 and 90% in the 12 studies they included into their analysis (14). Our results, showing complete/near-complete occlusion rates of 68% after 1 year and 83% after 2 years, can be found in that range. In line with previous studies, a vessel branch incorporated in the treated aneurysm was found to be predictive of occlusion failure at 6-month follow-up (17). However, a Kaplan–Meier analysis revealed that a vessel branch covered by the flow diverter only delays aneurysm occlusion. At the 2-year follow-up, aneurysm occlusion rates in aneurysms with vs. without incorporated vessels leveled out. The rate of occlusion or narrowing of a vessel branch covered by FRED Jr was 11% at the 6-month follow-up, 19% at the 1-year follow-up, and 23% at the 2-year follow-up. However, none of the patients in this cohort was symptomatic. A possible explanation is that the diminished flow in an aneurysmal vessel branch after flow diverter placement induces the development of a pial collateralization, slowly reducing the demand for antegrade blood supply, which then facilitates the occlusion of the aneurysm (18, 19). Our study results indicate that occlusion of aneurysms with incorporated vessel branches might take more time but can occur even years after the treatment.

Three of the six aneurysms, which needed retreatment, had a clearly dissecting morphology (20). In dissected vessels, the chronically diseased vessel wall is characterized by a disruption of the endothelium, which might result in an inadequate endothelial re-layering (21). Although flow diverter stent treatment might act as a reconstructive technique for dissected vessels by maintaining parent vessel patency and inducing vessel wall healing, further research will be needed to identify which cases are suitable for this technique. Hence, we should be alert in cases of suspected dissecting aneurysms treated with flow diverter stents, controlling for aneurysm recurrence or growth in shorter intervals (21).

## Limitations and Strengths

Patients for this study were recruited from multiple international centers, which allowed the inclusion of a large number of cases and a broad spectrum of applications for FRED Jr. The focus of this study was to analyze the applicability of FRED Jr, and therefore, aneurysm inclusion was not restricted to a specific aneurysm location or aneurysm shape or type. Nevertheless, the retrospective nature of the study comes with data inhomogeneity and limits the flexibility of statistical analysis of the aneurysm treatments. Furthermore, our study group was very heterogeneous with regard to shape, size, and location of the aneurysms, but most aneurysms were small (<1 cm maximum diameter) and located at the bifurcation of the middle cerebral artery or the A1/anterior communicating artery (ACom) complex. Fusiform and dissecting aneurysms as well as aneurysms from the posterior circulation are underrepresented, and results from our statistical analyses might not be easily applied to these subgroups.

# CONCLUSIONS

In this retrospective multicenter study of 159 unruptured or previously treated but recanalized aneurysms, flow diversion with the FRED Jr proved to be technically successful and clinically safe. Adequate aneurysm occlusion rate was 83% after 2 years. Most importantly, interventionalists should not be discouraged by early follow-up results after treatment of aneurysms with an incorporated vessel branch, since they often occlude later in time.

# DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

# ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Medizinischen Fakultät Heidelberg and Etik Kurulu of Cerrahpasa Tip FakIstanbul. Written informed consent to participate in this study was provided by the participants.

## AUTHOR CONTRIBUTIONS

NK and MM designed the study. NK, CI, MM, FB, IS, MK-O, and SC performed the interventions, were responsible for patient monitoring, and data acquisition of the post-interventional period. JJ, NA, and EÖ performed image analysis. EÖ, DV, and NA performed review of the clinical information. JJ wrote the paper. OK, NK, MB, DV, EÖ, and IS reviewed the paper. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.722183/full#supplementary-material

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# Virtual Flow-T Stenting for Two Patient-Specific Bifurcation Aneurysms

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The effective treatment of wide necked cerebral aneurysms located at vessel bifurcations (WNBAs) remains a significant challenge. Such aneurysm geometries have typically been approached with Y or T stenting configurations of stents and/or flow diverters, often with the addition of endovascular coils. In this study, two WNBAs were virtually treated by a novel T-stenting technique (Flow-T) with a number of braided stents and flow-diverter devices. Multiple possible device deployment configurations with varying device compression levels were tested, using fast-deployment algorithms, before a steady state computational hemodynamic simulation was conducted to examine the efficacy and performance of each scenario. The virtual fast deployment algorithm based on a linear and torsional spring analogy is used to accurately deploy nine stents in two WNBAs geometries. The devices expand from the distal to proximal side of the devices with respect to aneurysm sac. In the WNBAs modelled, all configurations of Flow-T device placement were shown to reduce factors linked with increased aneurysm rupture risk including aneurysm inflow jets and high aneurysm velocity, along with areas of flow impingement and elevated wall shear stress (WSS). The relative position of the flow-diverting device in the secondary daughter vessel in the Flow-T approach was found to have a negligible effect on overall effectiveness of the procedure in the two geometries considered. The level of interventionalist-applied compression in the braised stent that forms the other arm of the Flow-T approach was shown to impact the aneurysm inflow reduction and aneurysm flow pattern more substantially. In the Flow-T approach the relative position of the secondary daughter vessel flow-diverter device (the SVB) was found to have a negligible effect on inflow reduction, aneurysm flow pattern, or WSS distribution in both aneurysm geometries. This suggests that the device placement in this vessel may be of secondary importance. By contrast, substantially more variation in inflow reduction and aneurysm flow pattern was seen due to variations in braided stent (LVIS EVO or Baby Leo) compression at the aneurysm neck. As such we conclude that the success of a Flow-T procedure is primarily dictated by the level of compression that the interventionalist applies to the braided stent. Similar computationally predicted outcomes for both aneurysm geometries studied suggest that adjunct coiling approach taken in the clinical intervention of the second geometry may have been unnecessary for successful

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aneurysm isolation. Finally, the computational modelling framework proposed offers an effective planning platform for complex endovascular techniques, such as Flow-T, where the scope of device choice and combination is large and selecting the best strategy and device combination from several candidates is vital.

**Keywords: T-stenting technique (Flow-T), virtual fast deployment algorithm, hemodynamic simulation, inflow reduction, wide necked cerebral aneurysms**

## INTRODUCTION

Most cerebral aneurysms preferentially occur at vessel bifurcations (1, 2). With the major advancements in endovascular treatment over the last two decades, various of treatment strategies along with dedicated devices have been developed to deal with bifurcation aneurysms. When it comes to treating more difficult Wide neck bifurcation aneurysms (WNBAs), devices such as the pCONus and pCANvas devices (Phenox, Bochum, Germany), the Pulserider (Pulsar Vascular, Los Gatos, California, USA), and the eCLIPs devices (Evasc Medical Systems Corp.) are used to cover the neck of aneurysm and assist aneurysm coiling. Alternatively, devices such as the WEB (Microvention, Aliso Viejo, California, USA) and Luna/Artisse (Medtronic, Dublin, Ireland) are utilised to disturb intrasaccular flow and are deployed within the aneurysm dome (3).

Stent-assisted coiling has shown good clinical results in the treatment of WNBAs (4–6). During the treatment of WNBAs, a mechanical scaffold is provided by stents to stabilise the coils and prevent prolapse into the parent artery. To deal with geometrically complex bifurcation aneurysms involving both daughter branches of bifurcation, a single stent may not be sufficient (7, 8). As a result, implanting double stents in different configurations such as Y or T stenting are considered frequently as endovascular treatment of WNBAs (9–11). The conventional T-stenting technique, described as non-overlapping Y-stent technique originally, is a successful method that proven to stabilise aneurysm occlusion progressively (12, 13). Y-stenting is another eligible but challenging techniques to treat WNBAs (14), this approach uses large profile microcatheters to deliver stents which makes manipulate during navigation through sharply angled side branches difficult to operate. With the development of new dedicated low-profile devices such as the Baby Leo and LVIS EVO that can be deployed through low-profile 0.17 in microcatheters, Flow-T stenting technique merged as an advancement approach based on the conventional T-stenting (13).

In the treatment of WNBAs, the clinical use of different devices along with their detailed deployment strategy remains empirical and is amenable to optimisation. There is series of vital factors needed to be considered, such as the foreshortening of FDs after placement in the aneurysm neck, which may allow coil to prolapse into the parent vessel (15, 16), the local haemodynamic environment before and after endovascular treatment is complex (17, 18), the effect on the haemodynamics inside the aneurysm by selecting different FDs (19). In the Flow-T approach, whether coiling is necessary or not is left to be proven. Clearly, the response of WNBAs following treatment by FD is understudied. Therefore, patient-specific computational fluid dynamics (CFD) models can be utilised to evaluate the effectiveness of FD treatment in WNBAs (20).

In this study, two WNBAs were virtually treated by a novel T-stenting technique (Flow-T) with Silk Vista Baby, Baby Leo and LVIS EVO devices. Multiple possible device deployment configurations were tested, using fast-deployment algorithms, before a steady state computational hemodynamic simulations were conducted to examine the efficacy and performance of each scenario.

## MATERIALS AND METHODS

### Aneurysm Geometries and Clinical Approach

Two WNBA geometries located on the Middle Cerebral artery (MCA) that were identified for treatment were segmented from CT angiography imaging data in OsiriX (OsiriX v.4.1.1, Freeware) before being imported into Blender (Blender Foundation, Amsterdam, The Netherlands) as stereolithography (STL) format. As seen in **Figure 1**, the pre-intervention geometry was trimmed to produce vessel lengths of about six vessel diameters distal and proximal to the aneurysm site. Both aneurysm geometries were treated using Flow-T stenting, with the post-implantation 3D geometry and maximum intensity project (MIP) also shown in **Figure 1** for reference. In the clinical approach the WNBA I case was treated with a 3 × 24 mm LVIS EVO device deployed in the primary daughter vessel (left-hand in the figure) and a 2.25 × 15 mm Silk Vista Baby flow diverter in the secondary daughter vessel. In the WNBA II case a 2.5 × 25 mm Baby Leo device was deployed in the primary daughter vessel (also left-hand in the figure) and a 2.25 × 15 mm Silk Vista Baby flow diverter in the secondary daughter vessel.

### Virtual Deployment

In order to model the Flow-T approach virtually the three different types of devices used were reconstructed in simplified form, as shown in **Figure 2**. In total nine variants of the devices were created to quantify the effect of slightly different approaches to the procedure. Stent I mimics the SVB device (2.25 × 15 mm) deployed as per manufacturer instructions with a free expansion of up to 2.5 mm in diameter. Stents II-IX mimic both of the devices deployed in the primary daughter vessel with varying degrees of compression applied to the device, as these devices are compressed at the aneurysm neck during deployment to improve flow-diverting capacity. In both cases the middle third of the device (∼8 mm length) can be compressed; Stents II-V represent the LVIS EVO device compressed in length by 0, 33,

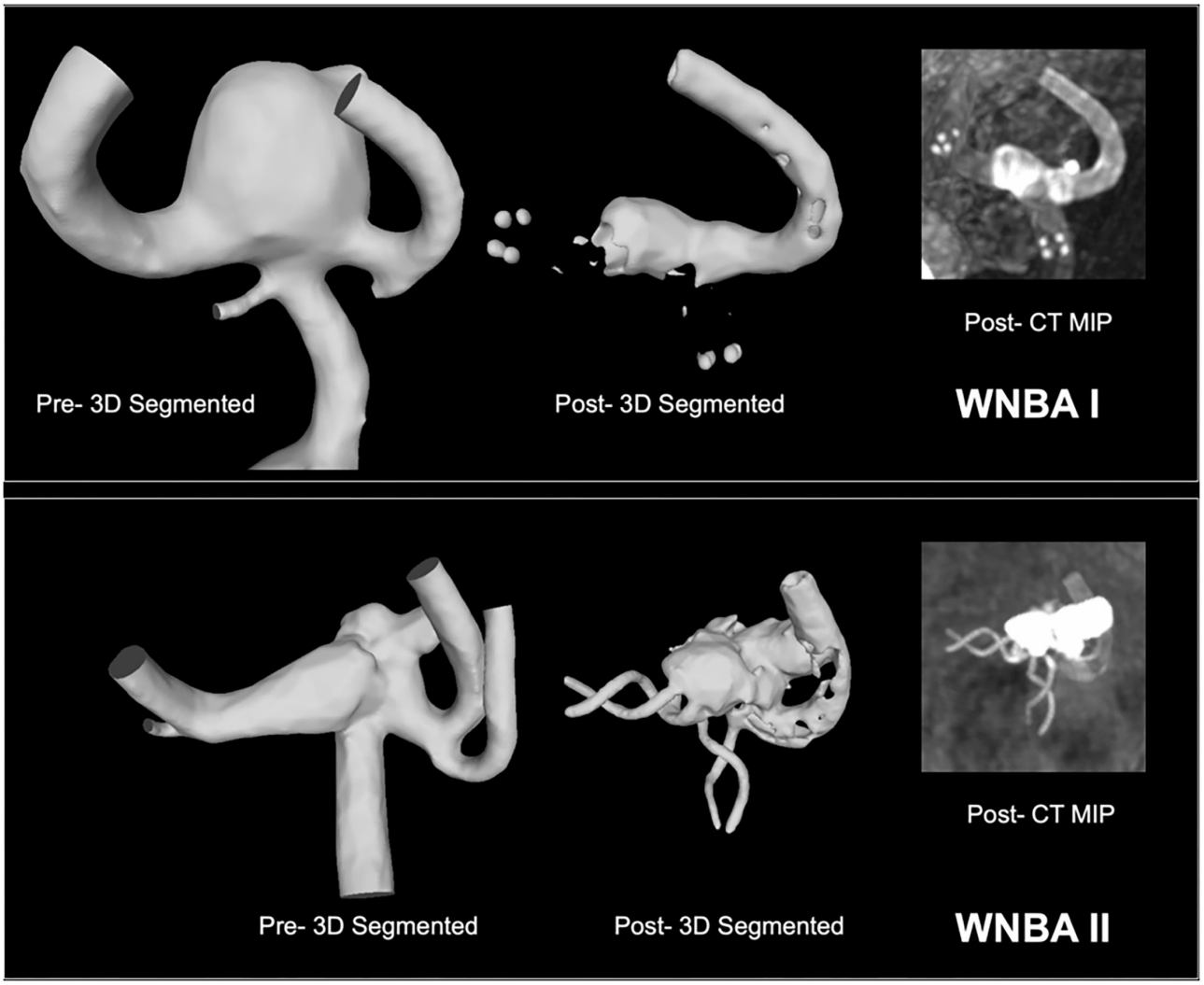


**FIGURE 1 |** WNBA geometries I and II reconstructed from CT angiography pre-intervention with Flow-T for virtual stenting (left) and post-intervention for reference (right). Flow diverters placed in the secondary daughter vessel (right-hand in both orientations) are fully visible while the stent placed in the primary daughter vessel is indicated with end (LVIS EVO) or helical (Baby Leo) markers.

50, and 67%, respectively, with an unconstrained diameter of 3.8 mm. Stents VI-IX represent the Baby Leo device compressed by length to the same degrees, with an unconstrained dimeter of 3.2 mm. Visual inspection of the post-intervention imaging confirmed in both clinical cases that the deployed configuration of the primary daughter vessel stent was most consistent with the 50% compression devices (Stent IV and Stent VIII for WNBA I and II, respectively).

The virtual deployment of devices is achieved using a fast-deployment algorithm implemented in Visual Studio 2019 (Microsoft, Albuquerque, New Mexico, USA) and Blender. Details of deployment algorithms were previously reported by the authors (21, 22). In summary, the mechanical system is discrete to a system with fictitious masses linked with springs, then the movement of such mechanical system obeys the equations of dynamic equilibrium. The contact between stent and vessel is defined to occur when the distance between the vertex of the vessel and any of the stent's vertices becomes smaller than a chosen parameter $\alpha$. After contact is detected, the vertex displacements in contact are still calculated in future iterations. However, its position can only change if it is located within the $\alpha$-boundary of the vessel inner surface. A wireframe representation of the device is compressed to reduce the radius and then aligned with the vessel centreline to simulate the sheltering of the device by the catheter. The unsheathing of devices is achieved by the relaxing of the device along its length progressively. The device expands to its stress-free shape (unconstrained diameter) within the limit of vessel wall. The three-dimensional device is created by adding thickness to the deployed device's wireframe, before being trimmed by removing the lengths in the parent and daughter vessels to improve the efficiency of CFD mesh generation subsequently. Device sizing, porosity and pore density

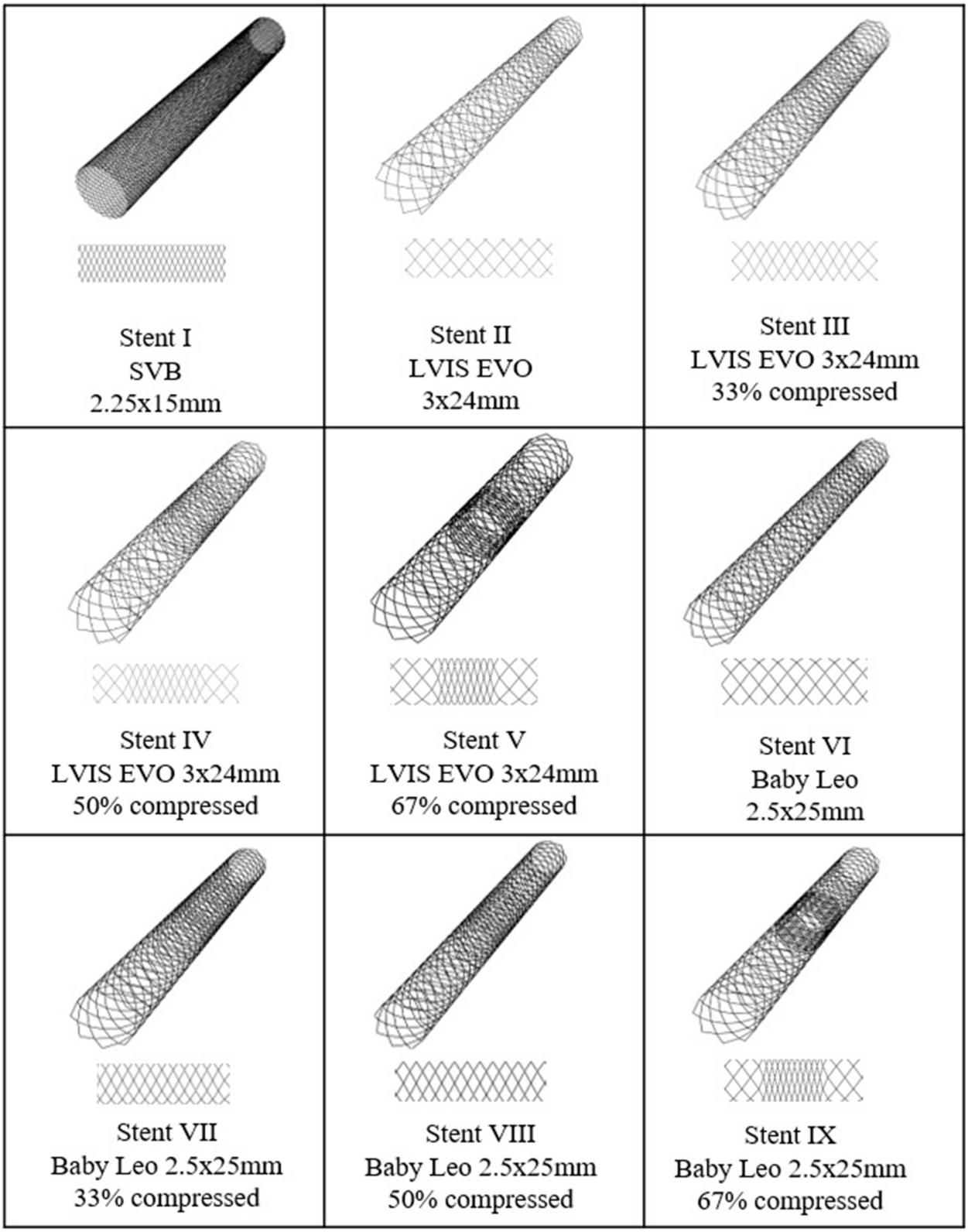


**FIGURE 2 |** SVB, LVIS EVO, and BABY LEO designs to be virtually deployed in each WNBA geometry. Stent I is flow-diverting stent whereas stent II–VIII are low-profile braided stents with different compression level at mid third part of the devices.

**TABLE 1 |** Stent porosity and construction.

| | Device | Compression [%] | Typical Porosity (compressed) [%] | Typical Pore Density (Compressed) [$mm^{-1}$] |
|---|---|---|---|---|
| Stent I | SVB | 0 | 60 (–) | 45 (–) |
| Stent II | LVIS EVO | 0 | 70 (–) | 2 (–) |
| Stent III | LVIS EVO | 33 | 70 (65) | 2 (3) |
| Stent IV | LVIS EVO | 50 | 70 (55) | 2 (4) |
| Stent V | LVIS EVO | 67 | 70 (35) | 2 (5) |
| Stent VI | Baby Leo | 0 | 80 (–) | 4 (–) |
| Stent VII | Baby Leo | 33 | 80 (70) | 4 (5) |
| Stent VIII | Baby Leo | 50 | 80 (65) | 4 (6) |
| Stent IX | Baby Leo | 67 | 80 (50) | 4 (10) |

is shown in **Table 1** as per the for the SVB, LVIS EVO, and Baby Leo as per manufacturers' guidance (23).

In addition to modelling the over- and under-compression of the stent placed in the primary daughter vessel, the relative position of the SVB flow-diverter deployed in the secondary daughter vessel was also varied. Three configurations of SVB were considered: the realistic positioning of the device inferred from visual inspection of the post-intervention angiography; an idealised positioning of the device where the SVB perfectly abuts the LVIS EVO or Baby Leo device creating a connected "T"; and finally, a poorly positioned device where a substantial gap between the SVB and primary daughter vessel device is present. These configurations are referred to generally as "real," "ideal," and "poor."

## CFD Methodology

The aneurysm geometries with and without devices deployed were meshed using CFD-VisCART (ESI Group, Paris, France) using a projected single domain non-conforming unstructured mesh, an Omnitree Cartesian tree type and three near-wall Cartesian layers to give a smooth and well-resolved boundary definition. The meshes were then imported into the multi physics suite CFD-ACE+ (ESI Group) and solved assuming steady flow conditions.

Blood was modelled as an incompressible fluid with steady 3D Navier–Stokes governing equations that were solved following the finite volume approach, with a central differencing scheme for spatial interpolations. The SIMPLE Consistent (SIMPLEC) pressure correction method (24, 25) and an algebraic multigrid method for convergence acceleration (26) were used. Given previous studies in the literature that confirmed the non-Newtonian effects of blood to be small in the cerebral circulation, (27, 28) blood is modelled as a Newtonian fluid with a density of 1,000 $kg/m^3$ and a dynamic viscosity of 0.004 Pa s. Arterial walls were modelled as rigid, with the effect of such an assumption on flow patterns having been shown to be negligible (29). A no-slip boundary condition was imposed on both the vessel walls and device struts.

A radially symmetric inlet velocity boundary condition was applied to each geometry scaling the corresponding velocity to a mean internal carotid artery (ICA) flow rate of 230 ml/min. A fixed pressure outlet boundary condition was applied to all geometry outlets; more complex outflow conditions incorporating Windkessel models were considered but rejected given very little variation in daughter vessel flowrates under a constant pressure condition when compared to physiological values (to within 5% of mean flow rates reported in the literature). Convergence criteria of absolute or relative residual reduction to $1 \times 10^{-8}$ and $1 \times 10^{-5}$ were employed.

Mesh independence to within 2% for both aneurysm inflow and wall shear stress (WSS) magnitude was assumed by meshing the geometries with a mesh density >5,000 elements per $mm^3$, as per similar studies by the authors (30, 31). This resulted in mesh sizes of 4.69–10.7 million elements across the cases. CFD simulation results are post processed by visualising the WSS distributions and velocity streamlines withing the aneurysm dome. A neck plane defining the boundary of the aneurysm is place proximal to the deployed devices and allows the inflow into the aneurysm to be monitored.

# RESULTS AND DISCUSSION

## Virtual Deployment

The fast virtual deployment algorithm was applied to each device (Stents I-IX) in two WNBA geometries as shown in **Table 1** and **Figure 1**. Similar to clinical intervention, the release of flow-diverter starts from the distal side of device to the proximal side of the device with respect to aneurysm sac. **Figure 3** demonstrates snapshots of the LVIS EVO at three stages of deployment process in the WNBA I.

The virtual deployment is developed in Visual Studio 2019 and executed on a single 2.60 GHz core without parallelization such as multi-threading. The deployed position of each device for each geometry was achieved after around 50 iterations, and in a computation time of <1 min per case. The deployed devices are in a good contact with the vessel wall, with the wall considered as fixed throughout the deformation. Different deployment configurations of the SVB are achieved by editing the centerline of the secondary daughter vessel as shown in **Figures 3A–C**, **4A–C**. The realistic deployment is validated with the post-intervention imaging, which give clear indication of device's position. **Figures 3D–F**, **4D–F** shows the deployment of LVIS EVO and BABY LEO with different compression levels for the primary daughter vessel device (Stents II-IX). These configurations of deployed devices in each geometry are summarised in **Tables 2**, **3**.

## Pre- and Post-intervention Haemodynamics

Calculations of inflow entering through the aneurysm neck in each case (WNBA I and II) are shown in **Tables 2**, **3** with values of 129.6 and 78.18 ml/min, respectively, representing ∼100 and 60%, respectively, of the parent vessel (MCA) average flowrate.

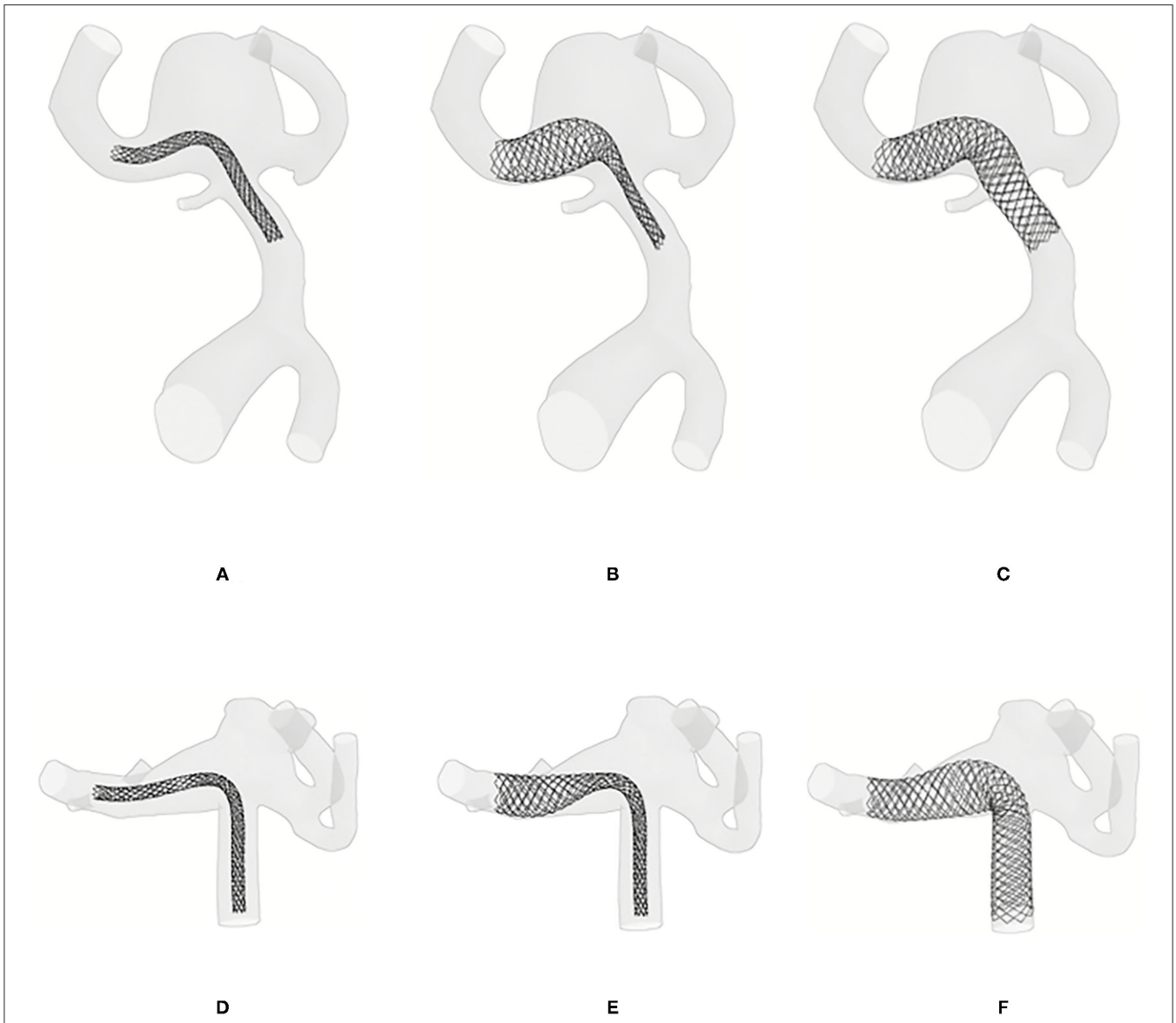


**FIGURE 3 |** Virtual deployment process. **(A)** Crimped LVIS EVO flow-diverter placed on the centerline of the target vessel. **(B)** Half way through the LVIS EVO expansion process, starting from the distal to proximal side of the device with respect to aneurysm sac. **(C)** Configuration of full expanded LVIS EVO. **(D–F)** The deployment of BABY LEO in WNBA II.

Velocity streamlines for both of these "No Device" cases are shown in the top rows of **Figures 6**, **7** below, where in both geometries relatively fast flow ($\sim$0.5 $ms^{-1}$) can be seen to enter deep into the aneurysm dome. These jets of flow, most prominent in the WNBA I case, lead to regions of elevated WSS magnitude within the aneurysm dome caused by both the impact of the jet on the vessel wall (at the aneurysm tip) and the impingement flow leaving the dome (at the neck). The high aneurysm inflow rates (as a percentage of parent vessel flow rate), concentrated jet inflow, and regions of flow impingement have all been correlated with increased aneurysm rupture risk (32–34) and confirm the fragile nature of the aneurysm cases prior to clinical intervention.

In WNBA I the deployment of both devices in a realistic configuration (Case A in **Table 2**) can be seen to dramatically reduce the inflow into the aneurysm dome by 64.3%. Closer inspection of the second row of **Figure 6** shows that this reduction has been achieved by eliminating the inflow jet almost entirely (very little flow enters the left-hand portion of the aneurysm) and by substantially reducing the velocity of the flow that does enter aneurysm. Additionally, it is clear from the velocity streamlines of WNBA I A that the vast majority of flow entering the aneurysm dome then exits via the right-hand daughter vessel through the SVB device. This change in flow pattern has eliminated much of the flow impingement visible

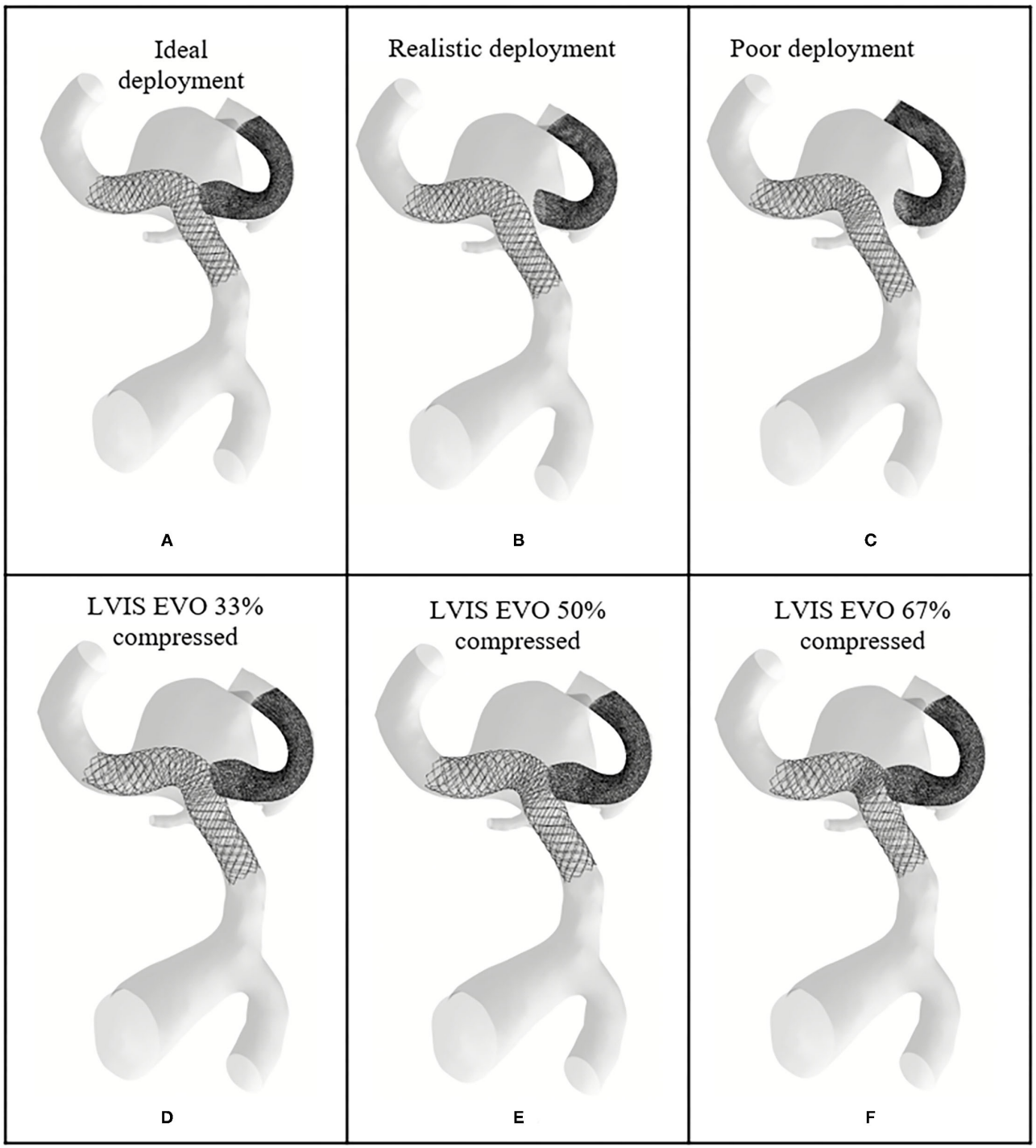


**FIGURE 4 |** Deployed device positions in WNBA I. **(A)** Ideal deployment of LVIS EVO in the side daughter vessel. **(B)** Realistic deployment of LVIS EVO in the side daughter vessel. **(C)** Poor deployment of LVIS EVO in the side daughter vessel. **(D–F)** The deployment of LVIS EVO with 33, 50, 67% compression rate in the mid third part of the devices.

in the No Device case, where some flow exits the aneurysm dome via the left-hand daughter vessel causing elevated WSS (∼8 Pa) at the aneurysm neck. The WSS magnitude plot for WNBA I A in **Figure 5** confirms the elimination of the flow jet and impingement zone with the entire aneurysm dome WSS remaining around 2 Pa—a value typical of healthy vasculature.

**TABLE 2 |** Percentage reductions of total flow entering the sac of WNBA I with different deployment strategies and different compression level.

| WNBA I | | | |
|---|---|---|---|
| **ID** | **Description** | **Qin (ml/min)** | **% Reduction** |
| ND | No devices | 129.6 | – |
| A | Real EVO (50%) and real SVB | 46.32 | 64.3 |
| B | Real EVO (50%) and ideal SVB | 44.22 | 65.9 |
| C | Real EVO (50%) and poor SVB | 48.93 | 62.3 |
| D | Uncompressed EVO (0%) and real SVB | 67.9 | 47.6 |
| E | Undercompressed EVO (33%) and real SVB | 54.45 | 58.0 |
| F | Overcompressed EVO (67%) and real SVB | 46.35 | 64.2 |

**TABLE 3 |** Percentage reductions of total flow entering the sac of WNBA II with different deployment strategies and different compression level.

| WNBA II | | | |
|---|---|---|---|
| **ID** | **Description** | **Qin (ml/min)** | **% Reduction** |
| ND | No devices | 78.18 | – |
| A | Real Baby Leo (50%) and real SVB | 22.93 | 70.7 |
| B | Real Baby Leo (50%) and ideal SVB | 23.87 | 69.5 |
| C | Real Baby Leo (50%) and poor SVB | 25.28 | 67.7 |
| D | Uncompressed Baby Leo (0%) and real SVB | 39.42 | 49.6 |
| E | Undercompressed Baby Leo (33%) and real SVB | 25.06 | 68.0 |
| F | Overcompressed Baby Leo (67%) and real SVB | 11.82 | 84.9 |

Variation in the deployment position of the SVB device in WNBA I cases B and C shown in **Table 2** indicate very little variation in inflow reduction with <5% difference in inflow reduction across the "real," "ideal," and "poor" configurations. This would suggest that the precise placement of the SVB device in the secondary daughter vessel does not substantially affect the overall flow-diverting effect of the Flow-T procedure in this geometry.

More variation in inflow reduction is seen by the level of compression of the LVIS EVO device in the WNBA I geometry as shown for cases D, E, and F in **Table 2**. With no compression of the EVO device (case D) the flow reduction drops by more than a quarter, compared to the realistic compression of 50%, to a flow reduction of 47.6%. The third row of **Figure 6** shows the corresponding velocity and WSS distributions for this uncompressed case (D). While little difference in WSS distribution is visible between cases A and D, the lack of EVO compression in case D has resulted in a more substantial aneurysm inflow jet visible in the velocity streamline plots. The aneurysm flow pattern, with flow entering in the centre of the aneurysm neck, is similar in case D compared to case A, with the more open device pores in case D creating a single jet with velocity magnitudes around 0.25 ms-1. Ver or under-compressing the LVIS EVO device compared to the 50% length reduction used in the clinical deployment has a much more modest effect on inflow reduction as cases E and F in **Table 2** illustrate. In these cases, the variation in inflow reduction of around 6% (or <10 ml/min) due to levels of compression appears to be dictated by the device pore size, and therefore the intensity of the aneurysm inflow jet. However, a slight shift in aneurysm flow pattern can be seen in the final row of **Figure 6** whereby the higher degree of compression in the mid third of the device (67%) has resulted in not all of the aneurysm neck being covered by a compressed portion of the device, hence the reemergence of flow entering the left-hand portion of the neck where uncompressed EVO device is exposed.

There are similarities in the performance of the different configurations of devices for the WNBA II geometry as summarised in **Table 3**. Deployment of both devices in the realistic configuration (case A) results in an inflow reduction of 70.7%. Comparing the first and second rows of **Figure 7**, the result of the Flow-T intervention is similar to before: jets of fast flow ($>0.5$ ms$^{-1}$) entering the aneurysm are reduced and the complex and impinged flow within the aneurysm dome is arrested to relatively simple circulating flow with blood entering the aneurysm on the right-hand side and exiting via the left. In particular, the concentrated region of high WSS magnitude ($>8$ Pa) seen close to the amorphous neck of the aneurysm in the No Device case is dramatically reduced following the device placements in all configurations (cases A–F). As before in the WNBA I case, the elimination of regions of elevated WSS and complex impinging flow would suggest that the Flow-T proceed substantially reduces the risk of aneurysm rupture and would promote thrombosis and aneurysm stabilisation.

Once again variation in positioning of the SVB device in the secondary daughter vessel in either the "poor," "real," or "ideal" configurations does little to affect the overall flow-diverting effect of the procedure. Less than 3% variation in inflow reduction is seen across the three cases (A–C) as shown in **Table 3**. Although it should be noted that the "ideal" SVB placement actually reduces the inflow reduction slightly when compared to the "real" position. This initially counter-intuitive effect results from the "ideal" SVB placement increasing the resistance to flow exiting the aneurysm dome compared to the "real" position, but the effect is small.

The variation in inflow reduction by Baby Leo device compression (cases D, E, and F in **Table 3**) is larger in the WNBA II geometry. A Flow-T configuration with compression applied to the Baby Leo stent results in an aneurysm inflow reduction of 49.6%—a figure similar to the first WNBA I geometry. Comparing the first and third row of **Figure 7** it is clear that some flow complexity in the aneurysm dome remains when the Leo stent is uncompressed, but the magnitude of aneurysm flow velocity is substantially reduced compared to the No Device case. Finally, the over-compressed Baby Leo device in case F with 67% length reduction resulted in a very large increase in aneurysm inflow reduction to 84.9%. From the bottom row of **Figure 7** it is clear that very little flow is entering the aneurysm dome in this case, and no coherent jet of flow is visible at all.

WNBA II is a complicated geometry to treat with any endovascular technique due to the extremely wide and

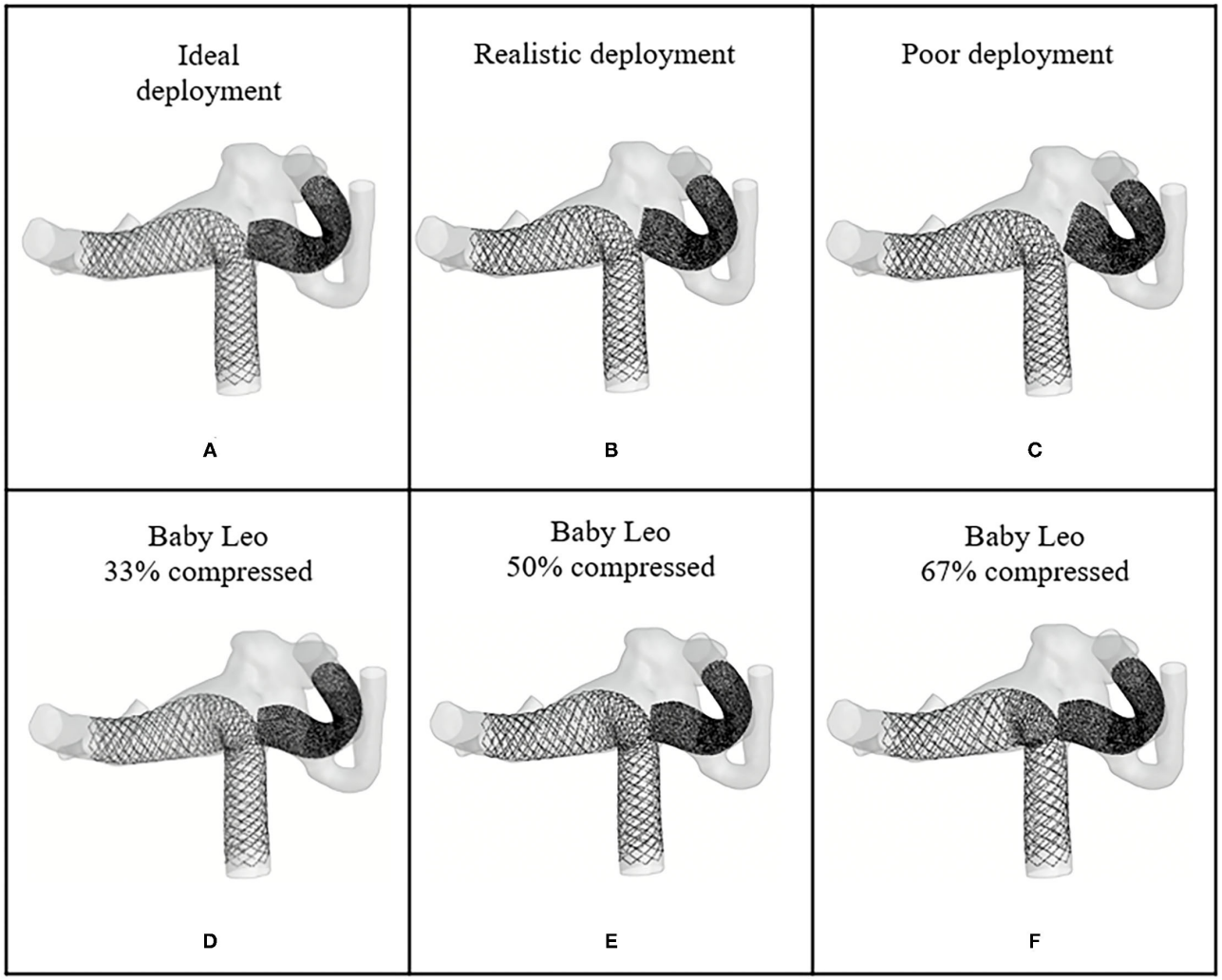


**FIGURE 5 |** Deployed device positions in WNBA II. **(A)** Ideal deployment of SVB in the side daughter vessel. **(B)** Realistic deployment of SVB in the side daughter vessel. **(C)** Poor deployment of SVB in the side daughter vessel. **(D–F)** The deployment of BABY LEO with 33, 50, 67% compression rate in the mid third part of the devices.

amorphous aneurysm neck, which creates additional problems when defining the measurement plane through which aneurysm inflow can be measured. In the clinical approach coils were also added to the aneurysm sac prior to aid aneurysm isolation, although the similarity in modelled response of both WNBA I and WCNA II to Flow-T in this study suggest that such an adjunct measure may have not been necessary.

## CONCLUSIONS

This study detailed a computational workflow for virtually modelling device deployment configurations and simulating the resultant aneurysm haemodynamics for the novel Flow-T technique. The results obtained illustrate the value of using such tools to plan endovascular interventions and strategies, especially in complex aneurysm geometries and with a choice of device types and configurations—both key features of when the Flow-T technique would be chosen.

In this study, a fast deployment algorithm was used to deploy numbers of minimally invasive devices into the patient-specific geometries. The algorithms provide fast and precise deployment of devices which allows for the real time interaction and positioning optimization.

In the two patient-specific wide-necked aneurysms considered regardless of device configuration and compression aneurysm inflow is reduced by at least ∼50% and regions of elevated WSS due to flow jetting and impingement are eliminated—all features associated with successful aneurysm isolation. These results reinforce the view that Flow-T represents a good endovascular option for hard-to-treat wide necked bifurcation aneurysms.

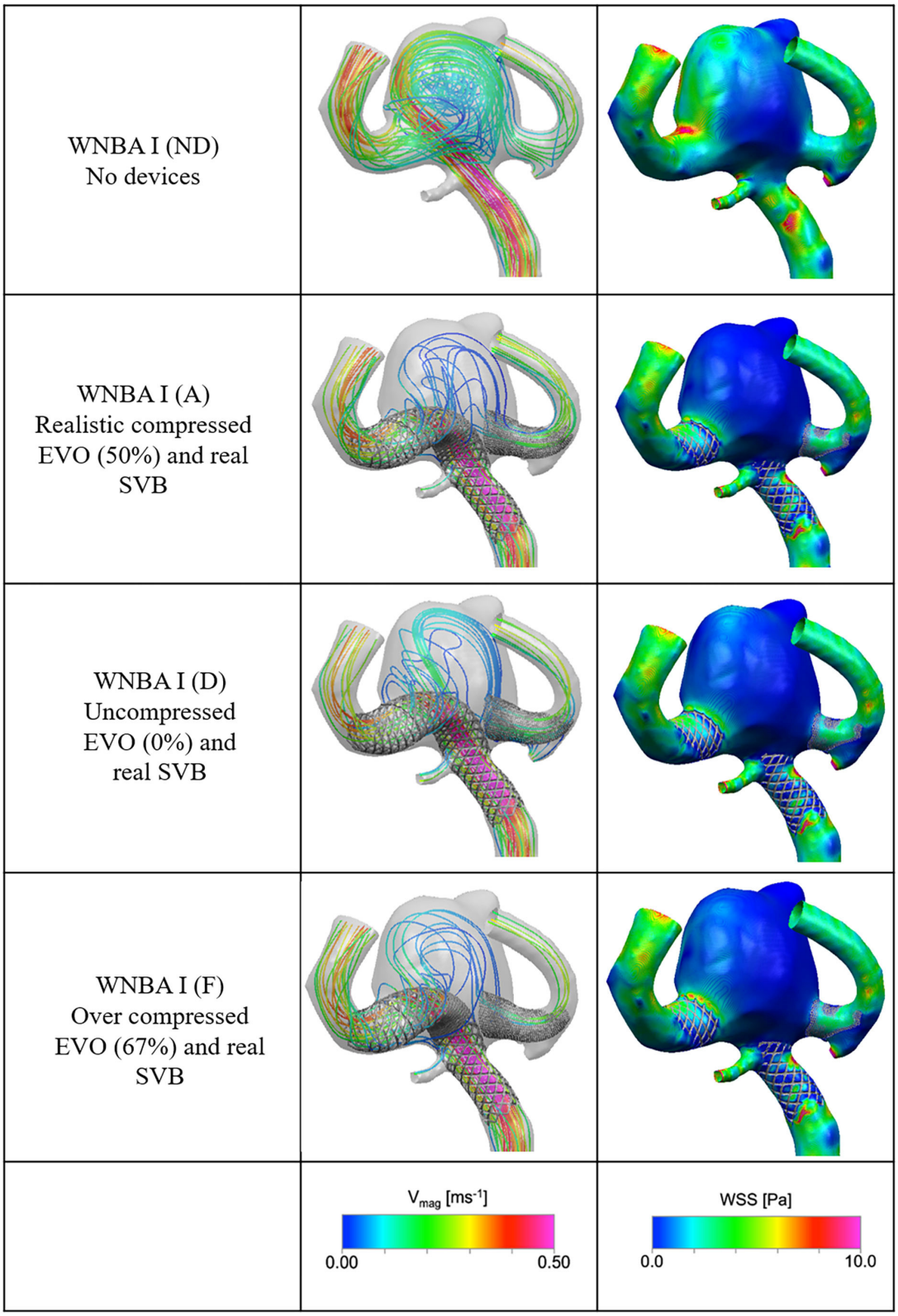


**FIGURE 6 |** Velocity streamlines and WSS distributions for the No Device (ND) and selected device configurations (cases A, D, and F) for the WNBA I geometry.

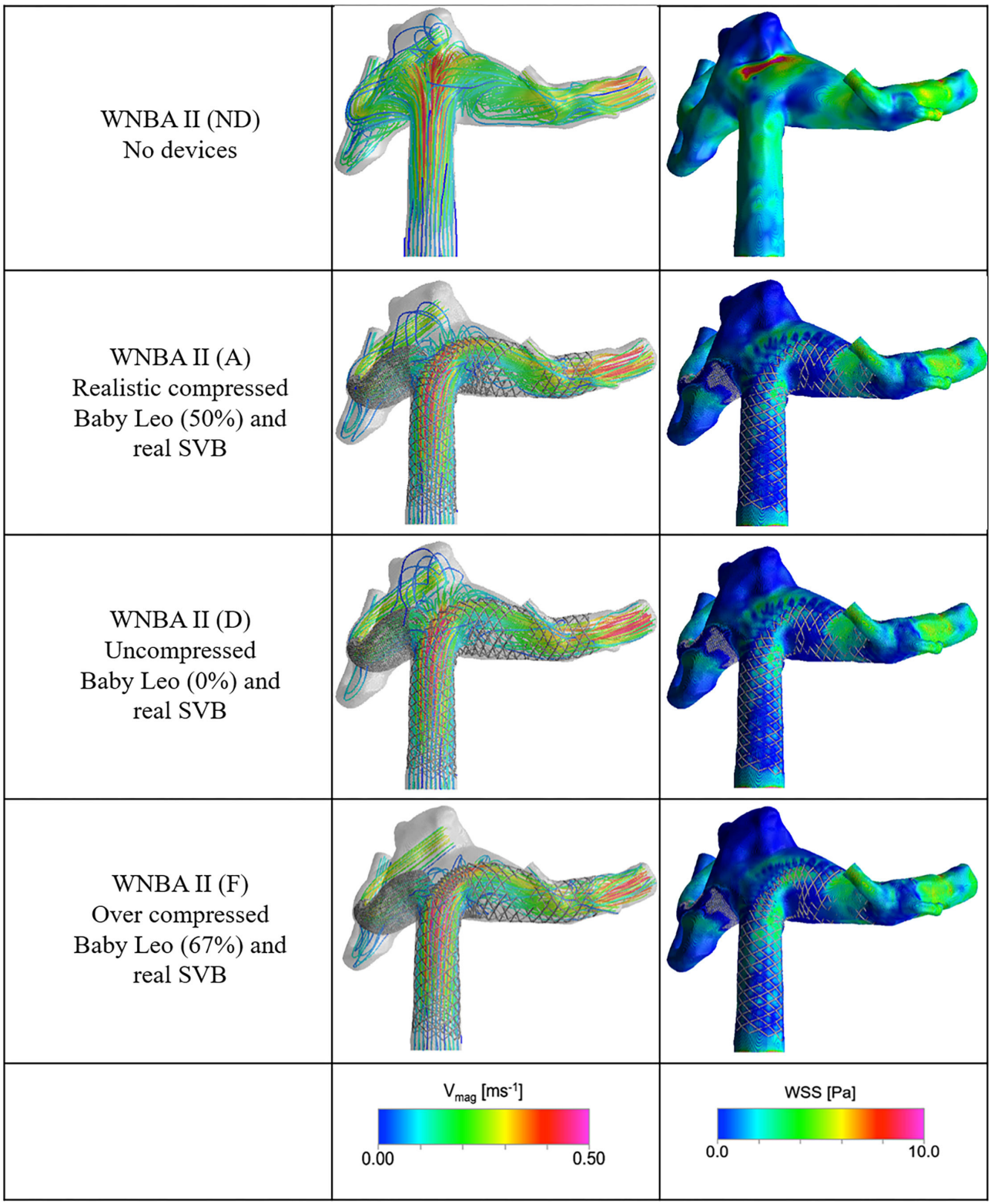


**FIGURE 7 |** Velocity streamlines and WSS distributions for the No Device (ND) and selected device configurations (cases A, D, and F) for the WNBA II geometry.

In the Flow-T approach the relative position of the secondary daughter vessel flow-diverter device (the SVB) was found to have a negligible effect on inflow reduction, aneurysm flow pattern, or WSS distribution in both aneurysm geometries. This suggests that the device placement in this vessel may be of secondary importance. By contrast, substantially more variation in inflow reduction and aneurysm flow pattern was seen due to variations in braided stent (LVIS EVO or Baby Leo) compression at the aneurysm neck. As such we conclude that the success of a Flow-T procedure is primarily dictated by the level of compression that the interventionalist applies to the braided stent. The similar positive results seen in both patient-specific geometries after virtually completing the Flow-T procedure suggest that the adjunct coiling that was utilised in the clinical approach to the second aneurysm geometry may have not been necessary for aneurysm stabilisation.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

ML virtual stenting algorithms development, literature research, manuscript preparation, and analysis statistical. TP CFD simulation and analysis CFD results and manuscript editing and preparation. YV manuscript editing and study design and data acquisition. PB clinical studies, provide essential data, and contribute in study concept and design. LM clinical studies and provide clinical data. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Indirect Flow Diversion for Off-Centered Bifurcation Aneurysms and Distant Small-Vessel Aneurysms, a Retrospective Proof of Concept Study From Five Neurovascular Centers

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**Background:** Treatment of cerebral aneurysms using hemodynamic implants such as endosaccular flow disruptors and endoluminal flow diverters has gained significant momentum during recent years. The intended target zone of those devices is the immediate interface between aneurysm and parent vessel. The therapeutic success is based on the reduction of aneurysmal perfusion and the subsequent formation of a neointima along the surface of the implant. However, a subset of aneurysms–off-centered bifurcation aneurysms involving the origin of efferent branches and aneurysms arising from peripheral segments of small cerebral vessels–oftentimes cannot be treated *via* coiling or implanting a hemodynamic implant at the neck level for technical reasons. In those cases, indirect flow diversion–a flow diverter deployed in the main artery proximal to the parent vessel of the aneurysm–can be a viable treatment strategy, but clinical evidence is lacking in this regard.

**Materials and Methods:** Five neurovascular centers contributed to this retrospective analysis of patients who were treated with indirect flow diversion. Clinical data, aneurysm characteristics, anti-platelet medication, and follow-up results, including procedural and post-procedural complications, were recorded.

**Results:** Seventeen patients (mean age: 60.5 years, range: 35–77 years) with 17 target aneurysms (vertebrobasilar: $n = 9$) were treated with indirect flow diversion. The average

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distance between the flow-diverting stent and the aneurysm was 1.65 mm (range: 0.4–2.4 mm). In 15/17 patients (88.2%), perfusion of the aneurysm was reduced immediately after implantation. Follow-ups were available for 12 cases. Delayed opacification (OKM A3: 11.8%), reduction in size (OKM B1-3: 29.4%) and occlusion (D1: 47.1%) were observable at the latest investigation. Clinically relevant procedural complications and adverse events in the early phase and in the late subacute phase were not observed in any case.

**Conclusion:** Our preliminary data suggest that indirect flow diversion is a safe, feasible, and effective approach to off-centered bifurcation aneurysms and distant small-vessel aneurysms. However, validation with larger studies, including long-term outcomes and optimized imaging, is warranted.

**Keywords: bifurcation aneurysms, indirect flow diverting, slipstream effect, distant small-vessel aneurysms, deconstruction over time**

## INTRODUCTION

Technical limitations of conventional endovascular aneurysm treatment, most importantly coiling with and without the help of assistive devices, have triggered the development and clinical use of flow-modulating implants, such as endosaccular flow disruptors and endoluminal flow-diverting stents (1–3). Both classes of devices are based on a dense mesh of braided wires that cover the aneurysm neck, whereby endosaccular flow disruptors act from within the aneurysm, and flow-diverting stents operate from within the parent artery (1). The common therapeutic tenets are (a) inducing thrombosis within the aneurysm and (b) creating complete remodeling of the parent artery *via* providing a solid scaffold for the development of a neointima at the aneurysm-parent artery interface (4–6). Each class of hemodynamic implant has a specific aptitude for certain types of aneurysms–endosaccular flow disruptors have proved to be especially valuable for the treatment of wide-necked bifurcation aneurysms at and distal to the Circle of Willis (3, 7), whereas flow-diverting stents are considered the treatment of choice for wide-necked sidewall aneurysms (8) and non-saccular aneurysms (9–11). Flow-diverting stents have also been used for off-label indications, such as the treatment of bifurcation aneurysms (12–14), but unsatisfactory aneurysm occlusion in a number of cases, together with ischemic and hemorrhagic complications, remains a concern according to some investigators (15, 16). In fact, hemodynamic aspects of bifurcation aneurysms differ substantially and must be evaluated carefully to select the most suitable therapeutic strategy for the individual patient. In case the aneurysm represents spatially distinct, broad-based outpouching of a bifurcating main stem and does not involve the smaller efferent branches of the bifurcation, an endosaccular flow disruptor is a viable and potentially preferable option, as it allows to functionally separate and occlude the aneurysm without affecting the afferent or efferent segments of the bifurcation. If the aneurysm is not centered at the bifurcation but arises slightly distal to it and involves the origin or even a more peripheral portion of a small efferent branch, endosaccular flow disruptors cannot be applied safely, because these dependent vessels are at risk of occlusion. The same applies for aneurysms arising from a peripheral segment of a small cerebral vessel, for example, the anterior communicating artery, M2–M3 branches of the middle cerebral artery, or the cerebellar arteries. In such cases, the concept of implanting a flow-diverting stent proximal to the aneurysm–indirect flow diversion–may represent the most suitable therapeutic option (17, 18). Currently, there is only anecdotal evidence on the application of indirect flow diversion. As a consequence, this study aims to report the experiences of five neurovascular centers, specifically focusing on the feasibility and efficacy of the approach, thromboembolic or hemorrhagic complications, and early aneurysm occlusion rates.

## MATERIALS AND METHODS

### Ethics Approval

This retrospective study was approved by the ethics committee of the University Hospital Halle/Saale, Germany (IRB00011721 Faculty of Medicine, Martin-Luther-University Halle-Wittenberg).

### Study Design

The study was designed as a multicenter, single arm retrospective analysis. The following neurovascular centers contributed to the study: University Hospital Halle ($n = 5$), Heinrich-Braun-Hospital Zwickau ($n = 1$), University Hospital Udine ($n = 7$), National University Hospital Singapore ($n = 1$), and the Charité Berlin ($n = 3$). Patient data, aneurysm properties, interventional details, and technical as well as clinical complications, together with early angiographic follow-ups, were reviewed. **Table 1** summarizes the relevant data.

### Endovascular Procedure and Antiplatelet Regimen

All treatments were performed in general anesthesia using biplane digital subtraction angiography (DSA) suite. Arterial access was gained via the right femoral artery. Dual antiplatelet treatment (DAPT) was used in all cases to prevent thromboembolic complications and was performed according to

**TABLE 1 |** Summary of all included cases.

| Patient-No. | Age | Aneurysm localization | Neck width in mm | Dome width in mm | Dome height in mm | Implanted flow diverter | Proximal landing zone | Distal landing zone | Distance from FD to aneurysm in mm | OKM immediately after FD | OKM last available |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | 57 | Left proximal PICA | 2.7 | 4.9 | 3.8 | FRED 4 × 12/18 mm | V4 proximal to the PICA | V4 distal to the PICA | 2.0 | A1 | A1 (no FU yet) |
| 2[b] | 72 | Right proximal AICA | 2 | 4.5 | 6.3 | Pipeline Flex Shield 4.75 × 14 mm | BA adjacent to V4 confluens | BA–middle third | 2.3 | A3 | A3 (no FU yet) |
| 3[b] | 75 | Left P1-P2-junction | 4.2 | 6.4 | 4.9 | FRED Jr. 2.5 × 13 mm | P1 segment | P2 segment | 1.5 | A3 | A1 (4 months & 5 months) |
| 4[c] | 53 | M2: superior trunk | 4 | 5.6 | 3.4 | P48MW_HPC 2 × 9 mm | Distal M1 segment | Proximal M3 segment | 1.0 | A2 | D1 (4 months) |
| 5[d] | 58 | Left proximal PICA | 4.2 | 4 | 3 | Surpass streamline 3 × 20 mm | V4 proximal to the PICA | V4 distal to the PICA | 2.0 | A1 | D1 (6months & 4years) |
| 6[c] | 43 | AcomA | 3.3 | 7 | 7 | Silk vista baby 2.5 × 15 mm | A1 | Proximal A2 | 2.4 | A3 | D1 (4 months) |
| 7[e] | 39 | MCA-M1 | 2.2 | 5.7 | 5 | PED3 vantage with shield technology 2.5 × 12 mm | Distal M1 | Distal M1 | 2.0 | B2 | B2 (no FU yet) |
| 8[c] | 63 | Right proximal A1 segment | 2.6 | 7.7 | 10.6 | Silk Vista Baby 2.75 × 15 mm | ICA communicating segment | Right M1 segment | 2.1 | A3 | D1 (3months) |
| 9[c] | 55 | Right posterior communicating artery | 1.3 | 1.9 | 1.3mm | Derivo 4.0 × 15 mm | ICA communicating segment | Right M1 segment | 1.6 | A3 | B3 (3months) |
| 10[f] | 68 | Left SUCA | 1.6 | 2.3 | 3.9 | PED 2 Shield 2.75 × 20 mm | BA: distal third | Left P1 segment | 1.1 | A2 | B3 (4months) |
| 11[g] | 63 | Right proximal PICA | 5.1 | 3.8 | 5.2 | FRED jr. 3.5 × 22 mm | V4 proximal to the PICA | V4 distal to the PICA | 2.1 | A2 | D1 (18 months) |
| 12[g] | 71 | Distal M1: origin of lateral fronto-orbital artery | 4.8 | 10.2 | 8.3 | FRED jr.3 × 19 mm | Middle M1 | Proximal M2 | 1.6 | A2 | D1 (6 months) |
| 13[g] | 70 | Left M2-M3-segment | 5 | 4.7 | 3.9 | Silk vista baby 2.75 × 15 mm | Inferior trunk: distal third | Parietal artery | 0.6 | A2 | D1 (16 months) |
| 14[g] | 66 | Right proximal AICA | 4.8 | 3.3 | 2.4 | Silk vista 4 × 15 mm | BA: proximal third | BA: middle third | 1.0 | A3 | D1 (4months) |
| 15[g] | 77 | Right M1-M2-segment | 6.7 | 10.7 | 6.7 | P48MW_HPC 3 × 15 mm | M1: middle third | M2: inferior trunk (dominant branch) | 2.4 | A2 | B2 (6 months) |
| 16[g] | 35 | Left proximal PICA | 4.3 | 9.2 | 4.5 | FRED X 4 × 18 mm | V4 proximal to the PICA | Distal V4 | 0.4 | A3 | A3 (no FU yet) |

*(Continued)*

**TABLE 1** | Continued

| Patient-No. | Age | Aneurysm localization | Neck width in mm | Dome width in mm | Dome height in mm | Implanted flow diverter | Proximal landing zone | Distal landing zone | Distance from FD to aneurysm in mm | OKM immediately after FD | OKM last available |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 17[g] | 63 | Right proximal A1 | 3 | 5.6 | 6.6 | Silk Vista 4 × 20 mm | Right C6 segment | Right M1 segment | 1.9 | B1 | B1 (no FU yet) |

*Dual anti-platelet therapy:*
*[a]9 months ASA 100 mg and Clopidogrel 75 mg daily, followed by ASA only lifelong.*
*[b]4 months ASA 100 mg and Clopidogrel 75 mg daily, followed by ASA only lifelong.*
*[c]6 months ASA 100 mg and Ticagrelor 90 mg twice a day, followed by ASA only lifelong.*
*[d]4 months ASA 100 mg and Ticagrelor 90 mg twice a day, followed by ASA only lifelong.*
*[e]12 months ASA 100 mg and Prasugrel 30 daily, followed by ASA lifelong.*
*[f]6 months ASA 100 mg and Clopidogrel 75 mg daily, followed by ASA only lifelong.*
*[g]3 months ASA 100 mg and Clopidogrel 75 mg, followed by ASA only lifelong.*
*Triaxial endovascular access in eleven cases (patients 1, 2, 4, 5, 6, 7, 8, 9, 10, 13, 14).*
*Guiding catheter: Neuron Max 088 (Penumbra) or the Benchmark 071 (Penumbra) or the Envoy 6F (Codman).*
*Distal access catheter: Sofia 5F (Microvention), Sofia EX (Microvention), CAT 5 (Stryker).*
*Biaxial endovascular access in six cases (patients 3, 11, 12, 15, 16, 17).*
*Guiding catheter: Envoy 6F or Envoy 7F (Codman).*

each center's individual regimen. The dosage and duration of the medication for each patient are shown in **Table 1**. Platelet function testing was not mandatory for our analysis.

## Procedure Assessment, Radiological, and Clinical Follow-Up

Post-procedurally, the patency of the jailed artery and the stented artery was assessed angiographically. Furthermore, the hemodynamic effect of the implant on aneurysm perfusion was evaluated according to the O'Kelly-Marotta scale [OKM,(19)]. Subsequently, after standardized surveillance on the intensive care unit overnight, cranial computed tomography (CCT) was performed within 24 h after the intervention as a post-interventional standard. Further follow-up examinations were performed in accordance with each center's follow-up regimen.

# RESULTS

## Patients, Aneurysms, and Devices

Overall, 17 patients (mean age: 60.5 years, range: 35–77 years) were included in our study. Slightly more than half of the aneurysms (9/17) were located in the posterior circulation. Two of the patients treated for aneurysms in the posterior circulation had a second aneurysm of the sidewall type, which was treated with the same flow-diverting stent as the aneurysm distant to the parent artery. The dimensions of each target aneurysm, its location, the distance to the remotely implanted flow-diverting stent, the immediate results after implantation of the flow-diverting stent, and the results of follow-up imaging are demonstrated in **Table 1**. On average, the closest distance between the distal end of the flow-diverting stent and the respective aneurysm neck was 1.65 mm, ranging from 0.4 to 2.4 mm.

## Treatments and Procedural Aspects

In total, 17 flow-diverting stents were successfully implanted. Procedural details, together with the applied DAPT regimen, are summarized in **Table 1**. **Figure 1** exemplifies indirect flow diversion in case of a broad based AcomA-aneurysm. **Figure 2** demonstrates indirect flow diversion for treatment of an MCA-bifurcation aneurysm. **Figure 3** shows indirect flow diversion for treatment of an AICA-aneurysm. None of the cases required more than one flow-diverting stent. Both aneurysms of the right-hand side proximal A1 segment had a claviform shape with a large fundus height and a significant uncoilable neck. To enhance the hemodynamic effect of the flow-diverting stent, the fundus was loosely coiled with a 3D coil. As mentioned above, the patient suffering from the left-hand side PCA aneurysm also had a distinct basilar tip aneurysm, which was treated with a WEB device in the same session. Otherwise, no additional devices or maneuvers including balloon-pta were required to achieve good technical results.

## Unexpected/Adverse Events

### Unexpected Events Without Clinical Sequelae

In the case of the posterior communicating artery aneurysm treated with a Derivo flow-diverting stent, the latter covered the

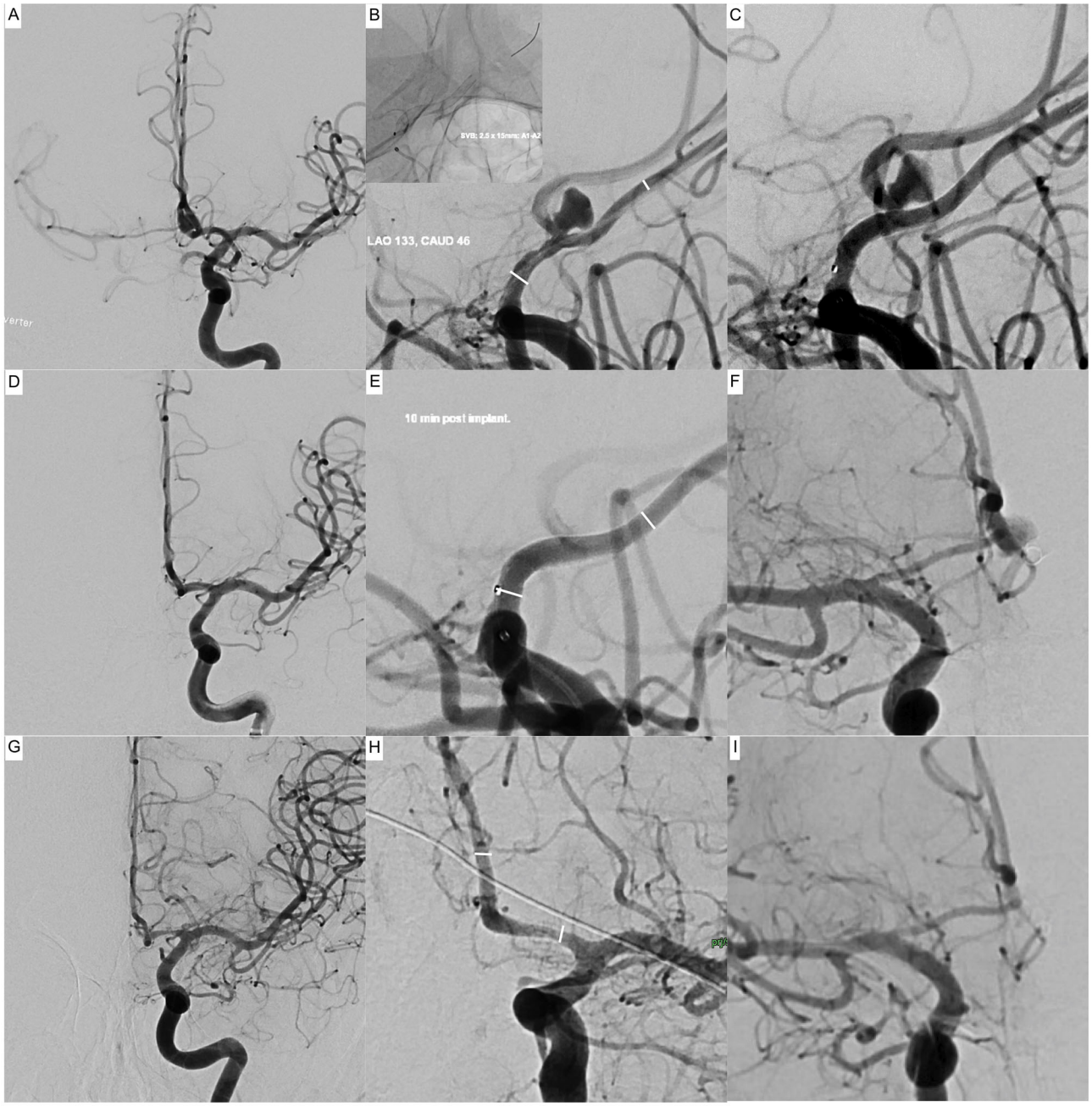


**FIGURE 1 |** Indirect flow diversion for treatment of an incidental broad-based aneurysm of the anterior communicating artery in a 44-year-old patient. The left A1 segment is dominant; the right A1 segment is hypoplastic (0.7 mm) but contributes significantly to the supply of the ipsilateral anterior cerebral artery territory. The aneurysm (7 × 7 mm fundus, 3.3-mm neck) arises from the middle of the anterior communicating artery (2 mm in diameter). The aneurysm is 2.4 mm distant to the origin of the anterior communicating artery at the A1–A2 junction of the left-hand side. Upper row **(A–C)**: Implantation of a Silk Vista Baby flow-diverting stent into the left A1–A2 segment. **(A)** Initial angiogram of the left-hand side internal carotid artery in posterior-anterior projection prior to implantation. Note the strong crossflow to the contralateral middle cerebral artery via the anterior communicating artery. **(B)** Working projection, prior implantation. The white lines indicate the intended proximal and distal landing zones. The upper left image shows the correspondingly implanted flow diverter. **(C)** Control injection after implantation. The aneurysm dome is already less opacified, indicating a good therapeutic effect. Middle row: **(D–F)** result, 10-min post implantation. **(D)** Despite a forceful injection, there is no more crossflow to the contralateral vessels. **(E)** The anterior communicating artery, including the aneurysm, is no longer opacified. The white lines indicate the proximal and distal endings of the implanted device. **(F)** Injection of the contralateral side: the aneurysm is slightly opacified from the right-hand side A1 segment. Inferior row **(G–I)**: Follow-up angiograms 3 months after treatment. **(G)** Angiogram of the left-hand side internal carotid artery in posterior-anterior projection comparable to **(A)**. The aneurysm is occluded, no crossflow to the contralateral side. **(H)** Magnified image in a slightly oblique projection to visualize the A1–A2 junction. Mild-moderate neointimal hyperplasia at the proximal landing zone. The white lines indicate the proximal and distal endings of the implanted device. **(I)** Angiogram of the right-hand side internal carotid artery in a projection matching. **(F)** The aneurysm is no longer opacified via the contralateral A1.

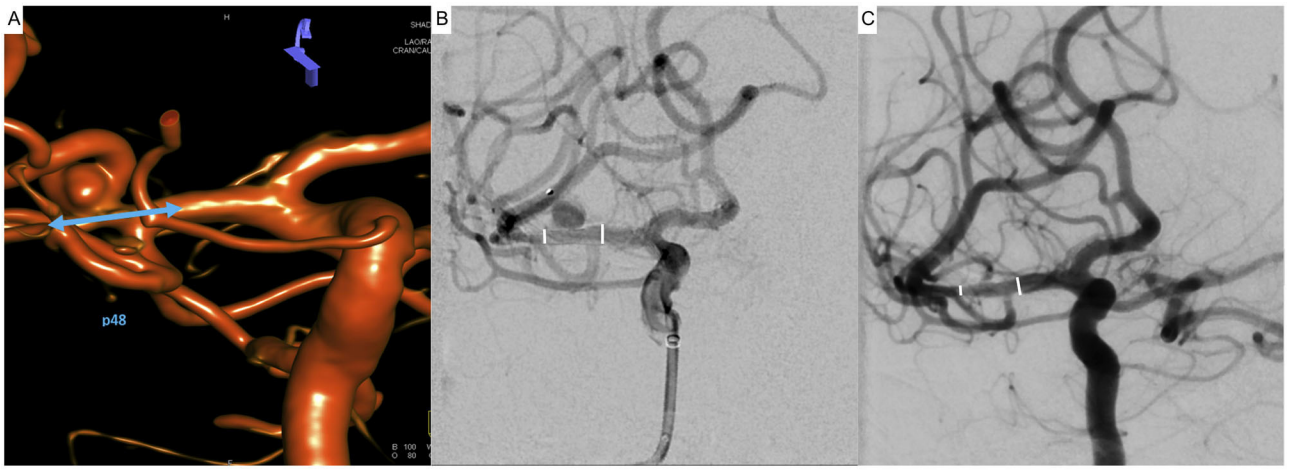


**FIGURE 2 |** Indirect flow diversion for treatment of an incidental broad-based aneurysm of the right-hand side middle cerebral artery in a 53-year-old patient. The aneurysm (5.6 × 3.4 mm fundus, 4-mm neck) arises from the superior trunk of the middle cerebral artery involving the bifurcation of the latter. The closest distance between aneurysm and outer wall of the treated vessel is 1 mm; however, the aneurysm-parent artery interface is significantly distal to the flow diverter. **(A)** Reconstruction of a 3D rotational angiogram demonstrating the spatial relationship of the aneurysm to the branches of the middle cerebral artery. The aneurysm involves the bifurcation but primarily arises from the superior trunk. The blue arrow indicates the intended proximal and distal landing zones; the goal is to jail the superior trunk and its aneurysm. **(B)** After implantation of the p48MW-HPC flow-diverter stent, jailing the superior trunk and the temporal branch, the control injection revealed prolonged stasis of the contrast agent within the aneurysm (O'Kelly-Marotta Grade A2). The white lines indicate the proximal and distal endings of the implanted device. **(C)** Four months later, the aneurysm is occluded; all branches of the middle cerebral artery, including the superior trunk, remained patent. The white lines indicate the proximal and distal endings of the implanted device.

origins of the posterior- and anterior-communicating arteries of the right-hand side internal carotid artery. After unremarkable implantation of the device, the flow within the covered A1 segment was reduced significantly, as expected. Subsequently, the relationship between the (conflicting) crossflow from the contralateral internal carotid artery *via* the anterior communicating artery and the antegrade flow within the covered right-hand side A1 segment changed toward the disadvantage of the A1 segment, and blood flow stagnated in the latter. Within a waiting period of 15 min, thrombus formed in the proximal A1 segment. A bolus of bodyweight adapted eptifibatide (Integrilin, GlaxoSmithKline) was given intravenously, according to the manufacturer's instructions. The thrombus resolved completely; there were no lesions in diffusion weighted imaging after 24 h. In follow-up imaging after 3 months, the A1 segment remained patent.

In the case of the left-hand side PCA aneurysm involving the atypically originating calcarine artery, an asymptomatic occlusion of the left-hand side ICA occurred at some point during the 4-month follow-up interval. As the left-hand side PcomA was now supplied from the vertebrobasilar territory, flow direction reversed and flow *via* the corresponding PCA increased; the initial hemodynamic effect (OKM Grade A3) was no longer visible in the follow-up after 4 months.

## Clinical Adverse Events

There were no clinically manifesting complications during or after the treatments.

## Angiographic Follow-Up

### *Hemodynamic Effect Immediately After Implantation*

From a total of 17 assessed aneurysms, the majority (13 lesions) revealed a marked delay in aneurysm perfusion, equivalent to OKM A2-A3 immediately post implantation. In 2 further cases, the aneurysm dome was only partially opacified, corresponding to OKM Grades B1 and B2. Unchanged aneurysm morphology (OKM A1) was observed in 2 cases.

In total, 15/17 aneurysms already showed a distinctly delayed perfusion or even a decrease in aneurysm size immediately after indirect flow diversion.

### *Hemodynamic Effect at the First Follow-Up Imaging*

The first angiographic follow-up was available for 12 aneurysms after a mean time of 5.4 months. Of those, one half (6 aneurysms) were already completely excluded from the intracranial circulation, corresponding to OKM D1. One quarter (3 aneurysms) was markedly reduced in size corresponding to OKM B2-B3. Two aneurysms showed significant stagnation within the aneurysm dome (OKM A2-A3). Only one lesion remained morphologically unaltered, equivalent to OKM A1.

In conclusion, after ∼5 months, the majority of the treated patients with available follow-ups (11/12 lesions) already showed a distinct delay in aneurysm opacification or even a decreased size of the residually perfused aneurysm dome.

### *Overall Hemodynamic Outcome at the Last Available Follow-Up Imaging*

Considering the last available angiographic follow-up of all patients included in this study ($n = 17$), complete aneurysm occlusion (OKM D1) was observed in eight patients. In five patients, the aneurysm dome was only residually perfused, corresponding to OKM B1-B3. Two lesions showed a distinct delay in perfusion with contrast stasis until the venous phase (OKM A3). However, two of the treated lesions remained

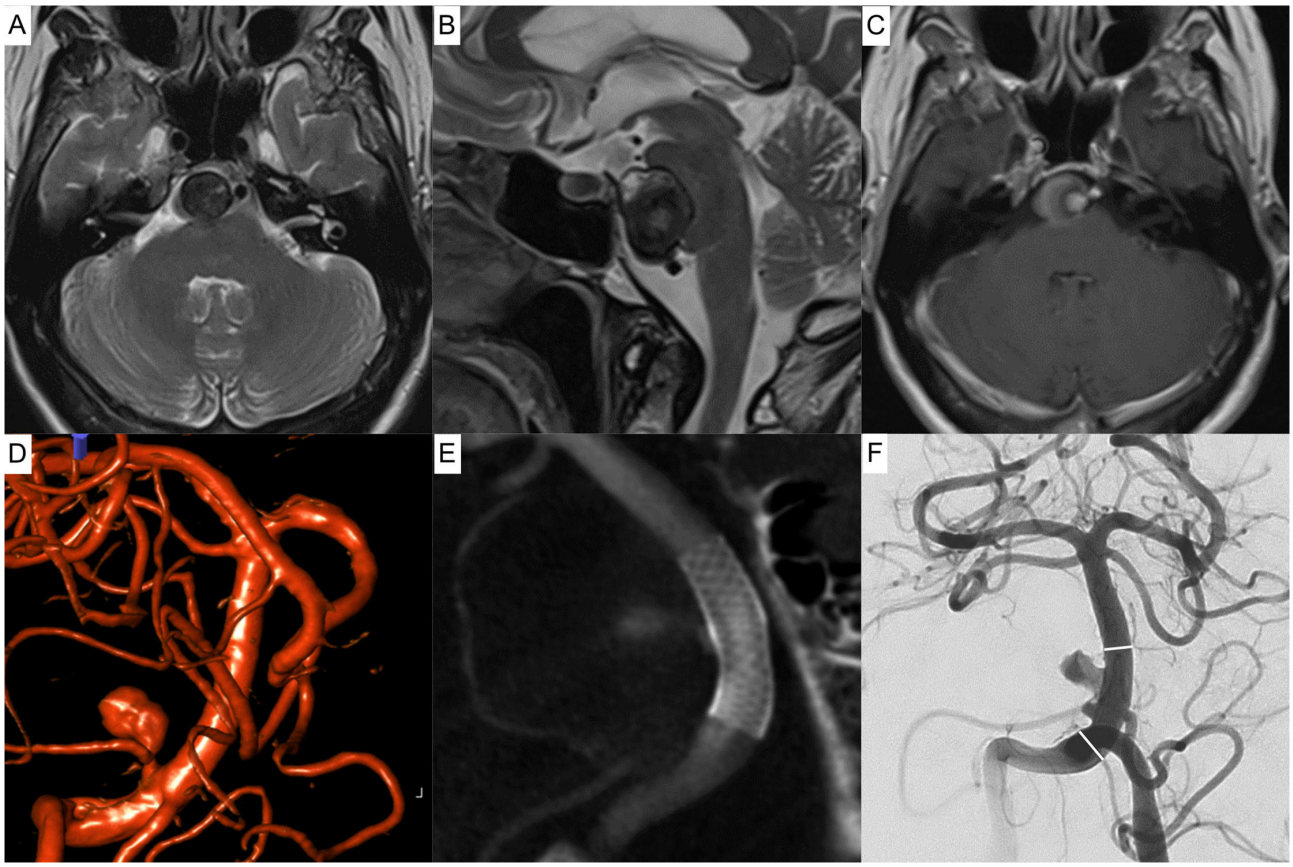


**FIGURE 3 |** Indirect flow diversion for treatment of a partially thrombosed dissecting aneurysm of the right-hand side anterior inferior cerebellar artery in a 73-year-old patient. The perfused aneurysm (4.5 × 6.3 mm fundus, 2.0-mm neck) is 2.4 mm distant to the basilar artery. Upper row **(A–C)** magnetic resonance imaging of the incidental aneurysm compressing the pons. **(A)** Axial T2 weighted image showing the partially thrombosed aneurysm of the pre-meatal segment of the anterior inferior cerebellar artery lateral to the basilar artery. **(B)** Corresponding sagittal T2 weighted image demonstrating the mass effect of the aneurysm. **(C)** Axial T1 weighted image post Gadolinium showing the basilar artery, the perfused part of the aneurysm and the thrombosed portion. Middle row **(D–F)**: Peri-interventional images. **(D)** Reconstruction of a 3D angiogram prior to treatment, showing the relationship between basilar artery, parent vessel, and aneurysm. **(E)** Contrast enhanced Xper-CT after implantation of a PED Flex Shield 4.75 × 14 mm into the basilar artery, jailing the aneurysm, bearing anterior-inferior cerebellar artery. **(F)** Postinterventional angiogram: aneurysmal perfusion is immediately altered (O'Kelly-Marotta Grade A3). The white lines indicate the proximal and distal endings of the implanted device. At the last available imaging study, 3 months post implantation, the aneurysm discretely decreased in size (not shown).

without appreciable changes in morphology and perfusion despite technically successful flow diversion.

### *Fate of Covered Branches*

At the last available follow-up, two of the jailed branches were occluded. The first occluded branch was the AcomA, 3 months after flow-diverter implantation into the dominant A1-A2 segments, as shown in **Figure 1**. The second occluded branch, also 3 months after the procedure, was the right-hand side A1 segment after implantation of the flow-diverting stent into the ipsilateral M1–communicating ICA. The remaining jailed branches were patent at the last imaging follow-up.

## DISCUSSION

As debated by Dmytriw et al. the uptake of flow-diverting technology in general is rapidly outpacing the availability of clinical evidence, and, especially, evidence on the suitability of flow-diverting technology for treatment of bifurcation aneurysms or anatomically complex lesions is currently insufficient (8). Nevertheless, as a consequence of the broad successful application of flow diversion, humanitarian off-label use has increased tremendously. For example, ruptured dissecting vertebrobasilar aneurysms and aneurysms arising from peripheral cerebral arteries have become recommendable targets for direct flow diversion (9, 10).

Great controversy exists regarding the application of flow-diverting stents for the treatment of bifurcation aneurysms, as the devices not only change the hemodynamic situation in the aneurysm but also alter the perfusion of necessarily covered dependent major branches or perforators (12–16). According to the meta-analysis of Cagnazzo et al. which focused on flow diversion for MCA aneurysms, procedural complications occurred in almost 21% of the cases with persisting deficits in almost 10% and were predominantly related to ischemic events (20). This is contrasted by significantly lower complication rates

reported by large-volume neurovascular centers (12–14, 21) and underlines the importance of proper patient selection, treatment technique, and a patient-tailored, appropriate DAPT regimen (18, 22). The results of the latter studies are in line with our experiences with the use of flow-diverting stents for treatment of bifurcation aneurysms, showing good safety and efficacy with low complication rates, especially when applying flow-diverting stents with anti-thrombotic coatings (11, 23).

Although the number of studies on direct flow diversion for treatment of bifurcation aneurysms and side wall-type aneurysms of small caliber cerebral vessels is substantial, comprehensive investigations specifically focusing on the feasibility of indirect flow diversion, i.e., employing flow-diverting stents in a main artery for the treatment of aneurysms arising remotely from small caliber parent arteries, are few. Wajnberg et al. for the first time suggested the approach of progressive deconstruction to treat cerebral aneurysms (24). In this report, a PED was placed across the parent artery of a giant MCA aneurysm, resulting in an asymptomatic occlusion of the aneurysm and its parent vessel over time, compensated by the development of leptomeningeal collaterals. Aguilar-Pérez et al. (18) reported the case of a patient successfully treated with flow-diverting stents for a PICA aneurysm and an aneurysm arising from the second temporal branch of the MCA, where the devices were implanted in the adjacent main arteries (the V4 segment of the vertebral artery and the M1 segment of the MCA) to reduce flow within and subsequently "reconstruct" the small caliber parent arteries. They coined the term "slipstream effect" for the main therapeutic mechanism behind the successful remodeling of the parent artery, despite the aneurysm itself is not covered by the flow-diverting stent. In line with those works, Wallace and coworkers demonstrated the general safety and efficacy of implanting a PED into the vertebral artery, jailing the PICA, for treatment of PICA aneurysms in a series of 14 cases (25). In addition, MacLean et al. demonstrated that implantation of a flow-diverting stent into the PcomA–P2 segment successfully treated two P1 aneurysms by changing the flow within the PcomA–PCA complex, coining the approach "competitive flow diversion" (26). Furthermore, Nossek et al. showed successful treatment of supraclinoid ICA aneurysms and ICA bifurcation aneurysms after disrupting flow in the ipsilateral A1 segments with endovascular techniques, such as flow diversion and coiling (27, 28). In accordance with those reports, the results of our study indicate that indirect flow diversion is a viable approach to aneurysms arising from bifurcations that involve small, efferent branches and aneurysms arising from a peripheral portion of small cerebral arteries as well. The therapeutic effect is based on the progressive deconstruction of the aneurysm and, potentially, its parent vessel (24). Regarding the fate of jailed branches, Iosif et al. demonstrated that the presence of an important collateral supply is decisive for immediate and long-term hemodynamic changes after flow-diverter implantation (29). More specifically, they were able to show that competitive flow from collaterals was associated with an immediate reduction of the flow rate within the covered arteries and, furthermore, led to significantly smaller ostia compared to the control group with absent collateral supply. This finding correlates well with the results in our study—early occlusion of jailed branches only manifested in the presence of competitive flow, for example, after jailing of the AcomA or the A1 segment. As a consequence, careful evaluation of the individual collateral situation at hand is important for treatment success and must be included in the pre-interventional workup. In the light of the aforementioned studies, disconnecting the Circle of Willis with flow-diverting technology, for example, at the ACA-AcomA complex, the PCA-PcomA complex, and the ICA bifurcation, should be considered a functionally significant strategy for aneurysm treatment (26–28).

Nevertheless, a number of uncertainties remain and must be clarified in further studies. First of all, it is important to learn whether there is an efficacy threshold regarding the distance between the flow diverter and the aneurysmal orifice, and other factors like the inflow angle as well as the ratio of diameters of the main artery vs. the parent vessel (30). Furthermore, the most appropriate DAPT combination and its optimal duration must be determined in context of indirect flow diversion. As reflected by recent reports, the choice of the anti-platelet medication is a crucial determinant of the rate of ischemic and hemorrhagic complications in flow diversion (26) and may influence the time point of aneurysm occlusion as well (11). From a current perspective, the combination of ASA and Ticagrelor appears to be superior to ASA and Clopidogrel (22), although single anti-platelet therapy (SAPT) with Prasugrel only has shown promising results in combination with anti-thrombotically covered flow-diverting stents (31). Contrary to that, SAPT using ASA as only anti-aggregant was associated with a significant number of ischemic complications despite the use of flow-diverting stents with anti-thrombotic coating (32). Therefore, a calculated and controlled anti-platelet medication (33), together with a proper selection of the flow-diverting stent with special regards to its hemocompatibility (34) and its flow-diverting potential, certainly influences the success of indirect flow diversion. However, the limited data of our retrospective study are not sufficient to make recommendations in this regard. In general, our study suffers from a number of limitations. The number of included patients is small, and the individual hemodynamic situation of the included cases differs substantially. Procedural and follow-up kinds of imaging were not performed with a specific focus on the aspect of indirect flow diversion; therefore, the relationship between the aneurysm-parent artery interface and the implanted flow diverter is not ideally displayed in a number of cases, underlining the need for an optimized imaging protocol for future studies in this regard. Furthermore, platelet-function testing was not available for most patients, and the occurrence of high on treatment platelet reactivity was, therefore, not evaluable. Also, long-term outcomes and follow-up imaging were not available for a number of included patients; therefore, our results remain preliminary, and validation in a greater patient cohort with long-term follow-ups is required.

## CONCLUSION

Our study indicates that indirect flow diversion is a safe and feasible approach to the treatment of aneurysms associated with

efferent branches of bifurcations and aneurysms arising distantly to the origin of small cerebral vessels. Further studies with long-term follow-ups are needed to validate the concept and to determine the limitations of the approach, especially with regard to the distance between aneurysm and the flow-diverting stent and other hemodynamically important factors like the inflow angle and the ratio of the diameters of the main artery and the parent vessel.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital Halle (Saale), Germany (IRB00011721 Faculty of Medicine, Martin-Luther-University Halle-Wittenberg). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

SS performed interventions, was responsible for data acquisition, designed the study, and wrote the paper. RB was responsible for data acquisition, wrote the paper, and performed image analysis. ES performed interventions, data acquisition, and follow-up imaging analysis. MSk and M-SS curated the data and were responsible for vascular analysis. WW and NG reviewed the paper and curated the data. DM, AG, and GB performed interventions, data acquisition, and image analysis. MSc and JP were responsible for data curation and reviewed the paper. VG and MSp performed interventions, image analysis, and reviewed the paper. All authors contributed to the article and approved the submitted.

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# Endovascular Treatment of Large or Giant Basilar Artery Aneurysms Using the Pipeline Embolization Device: Complications and Outcomes

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**Background:** This study aimed to investigate clinical and angiographic outcomes of Pipeline embolization device (PED) treatment of large or giant basilar artery (BA) aneurysms and examine associated factors.

**Methods:** Clinical and angiographic data of 29 patients (18 men, 11 women) with large or giant BA aneurysms were retrospectively examined. Mean age was 44.1 ± 21.2 years (range, 30–68). Mean aneurysm size was 22.2 ± 8.3 mm (range, 12.0–40.1).

**Results:** Mean angiographic follow-up was 18.3 ± 3.4 months (range, 4.5–60). The rate of adequate aneurysmal occlusion (O'Kelly–Marotta grade C–D) was 87%. The overall complication rate was 44.8%; most complications (84.6%) occurred in the periprocedural period. Univariable comparison of patients who did and did not develop complications showed significant differences in aneurysm size ($p < 0.01$), intra-aneurysmal thrombus ($p = 0.03$), and mean number of PEDs used ($p = 0.02$). Aneurysm size (odds ratio, 1.4; $p = 0.04$) was an independent risk factor for periprocedural complications in multivariable analysis. Mean clinical follow-up was 23.5 ± 3.2 months (range, 0.1–65). Nine patients (31%) had a poor clinical outcome (modified Rankin scale score ≥3) at last follow-up, including 7 patients who died. Univariable comparisons between patients with favorable and unfavorable clinical outcomes showed that aneurysm size ($p = 0.009$) and intra-aneurysmal thrombus ($p = 0.04$) significantly differed between the groups. Multivariable analysis showed that aneurysm size (odds ratio, 1.1; $p = 0.04$) was an independent risk factor for poor clinical outcome.

**Conclusion:** PED treatment of large or giant BA aneurysms is effective and can achieve a satisfactory long-term occlusion rate. However, the treatment complications are not negligible. Aneurysm size is the strongest predictor of perioperative complications and poor clinical outcome.

**Keywords: basilar artery, aneurysm, pipeline embolization device, large, giant**

## INTRODUCTION

Large (≥10 mm) or giant (>25 mm) basilar artery (BA) aneurysms have a particularly poor natural history. Frequently, they are clinically characterized by thrombosis or mass effect on the brainstem, which can cause death if left untreated (1, 2). Patients presenting with symptoms related to brainstem compression have a 5.9% annual risk of stroke and a 40% 5-year mortality (3). However, elective treatment of posterior circulation aneurysms using either surgical or traditional endovascular techniques can result in poor outcomes (4).

Conventional endovascular treatment for vertebrobasilar aneurysms is associated with a high recurrence rate and inadequate parent vascular remodeling (5). In the treatment of large or giant aneurysms, Pipeline embolization device (PED; Medtronic, Minneapolis, MN, USA) treatment has a much higher success rate than other endovascular techniques. In addition, the PED enables treatment of fusiform or complex aneurysms that were previously considered untreatable (6, 7). As experience with flow diverters (FDs) has increased, off-label use of the PED for treatment of posterior circulation aneurysms has become more common (7–9); however, safety and efficacy data for PED treatment of large or giant BA aneurysms are lacking. This study describes our experience using the PED to treat these aneurysms, reports our clinical outcomes, and examines factors that affect periprocedural complications and clinical outcomes.

## MATERIALS AND METHODS

### Study Population

We retrospectively collected the data of consecutive patients with large or giant BA aneurysms who were electively treated using the PED at our center from January 2016 to October 2020. Patient demographics, symptoms at presentation, aneurysm location, specific interventions, and immediate and follow-up clinical and angiographic outcomes were recorded. Aneurysm location on the BA was classified according to segment (proximal or distal) based on the origin of the anterior inferior cerebellar artery. Aneurysmal morphology was classified as saccular or fusiform. No vertebrobasilar dolichoectasia (VBD) were included in our study. All patients provided written informed consent and were informed that use of the PED to treat large or giant BA aneurysms was considered off-label.

### Endovascular Treatment

All patients received dual antiplatelet therapy (clopidogrel 75 mg/d and aspirin 100 mg/d) for at least 5 days before the procedure. Thromboelastography was used to identify patients with low response to clopidogrel: those with inhibition rate <30% were switched to ticagrelor.

Endovascular procedures were performed by experienced interventionalists. All patients underwent general anesthesia and systemic heparinization (3,000 IU bolus followed by infusion at 1,000 IU/h) for the procedure. A triaxial guide-catheter system using a 6-Fr Cook catheter (Cook Medical, Bloomington, IN, USA), 5-Fr or 6-Fr Navien guiding catheter (Medtronic, Minneapolis, MN, USA), and Marksman microcatheter (Medtronic) was used to deploy the PED. If necessary, another biaxial system was introduced into the contralateral vessels (i.e., vertebral artery) to navigate a microcatheter transporting coils or a balloon. PED device size was selected based on parent vessel measurements obtained on working angle views and three-dimensional angiography. Once the PED reached the position of optimal placement, it was released carefully by withdrawing the Marksman catheter and advancing the delivery wire. We preferred to deploy longer PEDs *in situ* and avoided using the push-pull technique with the microcatheter in the aneurysmal lumen. Bridging with an additional PED was performed if the aneurysmal neck was too broad to be covered entirely by a single stent. For complicated vertebrobasilar junction (VBJ) aneurysms that involved the V4 segments of both vertebral arteries, we sacrificed the distal V4 segment of the nondominant vertebral artery to prevent an inflow jet into the aneurysmal sac. After treatment, we recommend that blood pressure be maintained at the lower limit of normal values during the perioperative period. For patients with long segmental disease, prophylactic administration of tirofiban was usually administered. We routinely used methylprednisolone (80 mg, bid) for 3 days after PED treatment of large or giant basilar aneurysms to prevent delayed rupture and worsening mass effect. Dual antiplatelet therapy was continued for at least 6 months after the procedure. Aspirin monotherapy was continued for life.

### Complications and Outcomes

Migration, insufficient opening (<50%), and foreshortening of the PED were defined as technical complications. If neurological symptoms developed after the procedure, head computed tomography (CT) was performed to exclude hemorrhage and magnetic resonance imaging (MRI) was performed to identify any ischemic event. Periprocedural complications were defined as those that developed within 30 days of the procedure. Angiographic follow-up was generally recommended 3–6 months after treatment, preferably using conventional digital subtraction angiography (DSA). CT angiography (CTA) or magnetic resonance angiography (MRA) was performed in patients who refused conventional angiography. Clinical follow-up data were acquired via outpatient office visits and/or telephone. Clinical outcomes were evaluated using the modified Rankin scale (mRS). Favorable outcome was defined as mRS score ≤2; poor outcome was defined as score ≥3. Angiographic outcomes were evaluated using the O'Kelly–Marotta (OKM) scale (10): A, total filling; B, subtotal filling; C, entry remnant; and D, no filling.

### Statistical Analyses

Statistical analyses were performed using SPSS software version 25 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables are presented as means with standard deviation. Non-normally distributed continuous variables are presented as medians with range. Categorical variables are presented as numbers with frequency. Continuous variables were compared using the two-tailed Student's *t*-test or Mann-Whitney test as appropriate. Categorical variables were compared using the chi-square or Fisher's exact test as appropriate.

Variables identified in univariable analysis as potential predictors were included in multivariable logistic regression analysis to determine independent predictors of perioperative complications and clinical outcomes after adjusting for potential confounders. $P < 0.05$ was considered significant.

# RESULTS

Patient and aneurysm characteristics, procedural details, complications, and outcomes are summarized in **Table 1**.

## Patient Characteristics

Twenty-nine patients with a large or giant BA aneurysm were treated using the PED during the study period (18 men, 11 women). All had a single BA aneurysm and two had additional aneurysms in another location. Mean patient age was 44.1 ± 21.2 years (range, 8–76). Before treatment, 20 patients presented in excellent neurological condition (mRS score 0–1) and 4 had mild disability (mRS score 2). The most common presenting symptom was mass effect (13 patients, 44.8%). Nine patients (31.0%) presented with headache. One patient (3.4%) presented with ischemic. Five patients (17.2%) had a history of hypertension and three patients (10.3%) had a history of smoking. Five patients (17.2%) had both a history of hypertension and a history of smoking.

## Aneurysm Characteristics and Procedural Details

Seventeen BA aneurysms were large and 12 were giant. Mean aneurysm size was 22.2 ± 8.3 mm (range, 12.0–40.1). Fusiform aneurysms were more common (18 patients, 62.1%). Fifteen BA aneurysms (51.7%) were classified as distal and 14 as proximal. Eight aneurysms (25.8%) presented with intra-aneurysmal thrombus; two (cases 12 and 16) had been previously coiled and required retreatment because of recanalization.

Forty-one PEDs were implanted in the 29 patients. Mean number of PEDs used per patient was 1.4 ± 0.7 (range, 1–4). A single PED was placed in 20 patients (69.0%) and multiple PEDs were placed in nine (31.0%). Adjunctive coiling or balloon placement was performed in 12 patients (41.4%), including six who underwent contralateral vertebral artery sacrifice. Of the 10 VBJ aneurysm patients, six underwent PED placement along with coiling and vertebral artery sacrifice and four underwent placement of a single PED. The PED covered at least one-third of the BA in all patients. Sufficient PED opening was achieved in all patients.

## Angiographic Outcomes

Twenty-three patients (79%) received angiographic follow-up. Twenty-one patients received DSA follow-up, 1 patient received CTA follow-up, and 1 patient received MRA follow-up. Mean angiographic follow-up was 18.3 ± 3.4 months (range, 4.5–60). Complete occlusion (OKM D) was achieved in 17 aneurysms (74%) and near-complete occlusion (OKM C) in three (13%). Therefore, the rate of adequate occlusion (OKM C–D) was 87%. Incomplete occlusion (OKM B) occurred in three aneurysms (13%). The mean time to complete occlusion overall confirmed by the first imaging was 10.0 ± 1.1 months (range, 4.5–18). The mean time to complete occlusion confirmed by the first imaging was significantly longer in fusiform aneurysms than saccular aneurysms (12.1 ± 3.9 months vs. 7.1 ± 3.5 months; $p = 0.036$). In addition, the mean time to complete occlusion confirmed by the first imaging was significantly longer in aneurysms involving branches than in those not involving branches (12.5 ± 3.6 months vs. 6.4 ± 2.7 months; $p = 0.018$).

## Clinical Outcomes and Complications

Periprocedural complications included ischemic stroke in five patients, worsening mass effect in three, and delayed cerebral hemorrhage in four. Among the ischemic strokes, four were perforator strokes and one was embolic; all five were treated with telescopic PEDs (mean number of PEDs used, 2.4 [range, 2–4]). Case 7 experienced acute onset dysarthria and right hemiplegia 12 h after placement of four PEDs. CT and MRI showed a large brainstem infarct with no hemorrhage. After a 24-h tirofiban infusion, the patient's symptoms gradually resolved. However, on postprocedure day 3, headache and vomiting developed, which rapidly progressed to loss of consciousness, cardiorespiratory arrest, and death before CT could be performed. Relevant imaging studies are shown in **Figure 1**. Delayed aneurysmal rupture was the presumed cause of death. Other patients who developed neurological symptoms after the procedure also underwent CT to exclude hemorrhage and infusion of tirofiban for 24 h: cases 11 and 18 recovered completely but cases 8 and 21 had mild residual single-limb paresis (final mRS score 2).

Three patients with giant aneurysms experienced worsened mass effect after treatment; all presented with initial symptoms of brainstem compression. Cases 5 and 19 experienced abducens nerve palsy after the procedure; however, MRI did not show an infarction. At last follow-up, they had fully recovered. Case 17 developed dyspnea because of aneurysmal brainstem compression after treatment and maintained a tracheotomy until he died of severe pulmonary infection 11 months later (**Figure 2**).

In the perioperative period, four patients with aneurysm size ranging from 22 to 40 mm developed fatal subarachnoid hemorrhage. Three of the four SAHs occurred in patients with aneurysms located on the proximal segment of the BA, including two with a VBJ aneurysm who underwent placement of a single PED without coiling and contralateral vertebral sacrifice. **Figure 3** demonstrates an illustrative case (case 29).

Univariable comparison of patients who did and did not develop complications showed significant differences in aneurysm size (30.6 ± 6.3 mm vs. 18.5 ± 6.0 mm; $p < 0.01$), intra-aneurysmal thrombus (54.5 vs. 11.1%; $p = 0.03$), and mean number of PEDs used (1.9 ± 0.9 vs. 1.2 ± 0.5; $p = 0.02$). Aneurysm size (odds ratio, 1.4; 95% confidence interval, 1.0–1.8; $p = 0.04$) was an independent risk factor for periprocedural complications in multivariable analysis (**Table 2**).

In-stent thrombosis occurred in four patients (13.8%) during follow-up. All had a fusiform aneurysm. Cases 10, 21, and 18 developed in-stent thrombosis at 5, 6, and 11 months after the procedure, respectively; clopidogrel was discontinued in all three because of acute gastrointestinal bleeding. In case 25, in-stent thrombosis occurred 19 months after the procedure

**TABLE 1 |** Patient and aneurysm characteristics, procedural details, complications, and outcomes.

| No. | Age(yrs)/ Sex | Initial mRS /Presentation | Vascular risk factors and multiple aneurysms | Aneurysm Location | Aneurysm type | Largest Aneurysm Size(mm) | PED no. | Aneurysm involving side branches | Adjunct Coling | VA Sacrifice | Periprocedural complication (days) | Long- term adverse events(mos) | Last angiographic FU (time/OKM) | Last clinical FU (time/mRS) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 61,F | 0/None | No | Distal | Saccular | 15.0 | 1 | No | Yes | No | | | 12 mos/D | 24 mos/ 0 |
| 2 | 61,F | 1/ME | No | Distal | Saccular | 13.0 | 1 | Yes | No | No | | | 12 mos/A2 | 24 mos/0 |
| 3 | 28,F | 1/HA | No | Proximal | Saccular | 25.0 | 1 | Yes | Yes | Yes | | | 12 mos/D | 22 mos/ 0 |
| 4 | 17,M | 2/ME | PICA An | Proximal | Fusiform | 23.0 | 1 | Yes | No | No | | | 19 mos/D | 24 mos/0 |
| 5 | 72,M | 1/ME | PcomA An | Distal | Fusiform | 29.0 | 1 | No | No | Yes | WorseningME | | 6 mos/D | 22 mos/1 |
| 6 | 17,F | 1/HA | No | Proximal | Fusiform | 30.0 | 3 | Yes | No | Yes | | | 8 mos/D | 21 mos/0 |
| 7 | 12,M | 1/HA | No | Distal | Fusiform | 33.0 | 4 | Yes | No | No | IS, DRA, died | | None | 0.1 mos/6 |
| 8 | 56,M | 1/HA | HT | Proximal | Fusiform | 26.0 | 2 | Yes | Yes | Yes | IS | | 8mos/D | 31 mos/2 |
| 9 | 68,M | 1/ME | HT,SM | Distal | Saccular | 12.0 | 1 | No | Yes | No | | | 6 mos/D | 25 mos/0 |
| 10 | 56,M | 0/None | HT,SM | Distal | Fusiform | 18.0 | 1 | No | No | No | | IST (5) | 5 mos/B | 21 mos/4 |
| 11 | 37,F | 1/ME | No | Distal | Saccular | 34.0 | 2 | No | No | No | IS | | 6 mos/D | 15 mos/ 0 |
| 12 | 34,M | 1/HA | SM | Distal | Saccular | 20.0 | 1 | Yes | Yes | No | | | 4.5 mos/D | 23 mos/ 0 |
| 13 | 69,M | 2/ME | No | Proximal | Fusiform | 31.4 | 1 | No | No | No | DRA, died | | None | 0.1 mos/6 |
| 14 | 8,F | 1/HA | No | Proximal | Fusiform | 26.0 | 2 | Yes | Yes | Yes | | | 12 mos/D | 65 mos/0 |
| 15 | 34,F | 1/HA | No | Proximal | Fusiform | 16.2 | 2 | Yes | Yes | No | | | 14.5 mos/D | 65 mos/0 |
| 16 | 61,M | 2/ME | No | Distal | Saccular | 15.0 | 1 | Yes | Yes | No | | | 3 mos/D | 55 mos/2 |
| 17 | 49,F | 2/ME | No | Proximal | Saccular | 39.0 | 1 | Yes | Yes | Yes | WorseningME | Died (11) | None | 11 mos/6 |
| 18 | 61,F | 0/None | HT | Proximal | Fusiform | 22.0 | 2 | Yes | Yes | Yes | IS | IST (11), died | 11 mos/C | 11 mos/6 |
| 19 | 8,M | 1/ME | No | Proximal | Fusiform | 26.0 | 2 | No | Yes | Yes | WorseningME | | 6 mos/D※ | 40 mos/0 |
| 20 | 52,M | 1/HA | HT,SM | Proximal | Fusiform | 22.0 | 2 | Yes | No | No | DRA, died | | None | 1 mos/6 |
| 21 | 68,M | 1/ME | HT,SM | Proximal | Fusiform | 26.5 | 2 | Yes | No | No | IS | IST (6) | 7 mos/C1 | 13 mos/3 |
| 22 | 31,M | 0/None | SM | Distal | Fusiform | 13.0 | 1 | Yes | No | No | | | 8 mos/D | 29 mos/0 |
| 23 | 49,F | 0/None | HT | Distal | Fusiform | 13.0 | 1 | Yes | No | No | | | 15 mos;D | 38 mos/0 |
| 24 | 31,M | 1/ME | SM | Distal | Fusiform | 13.8 | 1 | Yes | No | No | | | 15 mos;D | 37 mos/0 |
| 25 | 50,M | 0/None | HT | Distal | Fusiform | 20.0 | 1 | Yes | No | No | | IST (19), died | 19 mons;B | 19 mos/6 |
| 26 | 76,M | 1/ME | SM | Distal | Saccular | 12.1 | 1 | No | No | No | | | 6 mos,D | 32 mos/0 |
| 27 | 67,F | 1/IS | HT | Proximal | Saccular | 13.5 | 1 | No | No | No | | | None | 6 mos/0 |
| 28 | 19,M | 1/ME | No | Distal | Fusiform | 17.0 | 1 | No | No | No | | | 7 mos;C | 8 mos/0 |
| 29 | 26,M | 0/None | No | Proximal | Saccular | 40.1 | 1 | Yes | Yes | No | DRA, died | | None | 0.1 mos/6 |

*Adjunct, adjunctive; BA, basilar artery; BT, basilar artery trunk; CN, cranial nerve; DAR, delayed aneurysmal rupture; FU, follow-up; HA, headache; HT, hypertension; IST, in-stent thrombosis; IS, ischemic stroke; ME, mass effect; Mos, months; mRS, modified Rankin Scale; PED, Pipelime embolization device; SM, smoking; VA, vertebral artery; Yrs, years.*

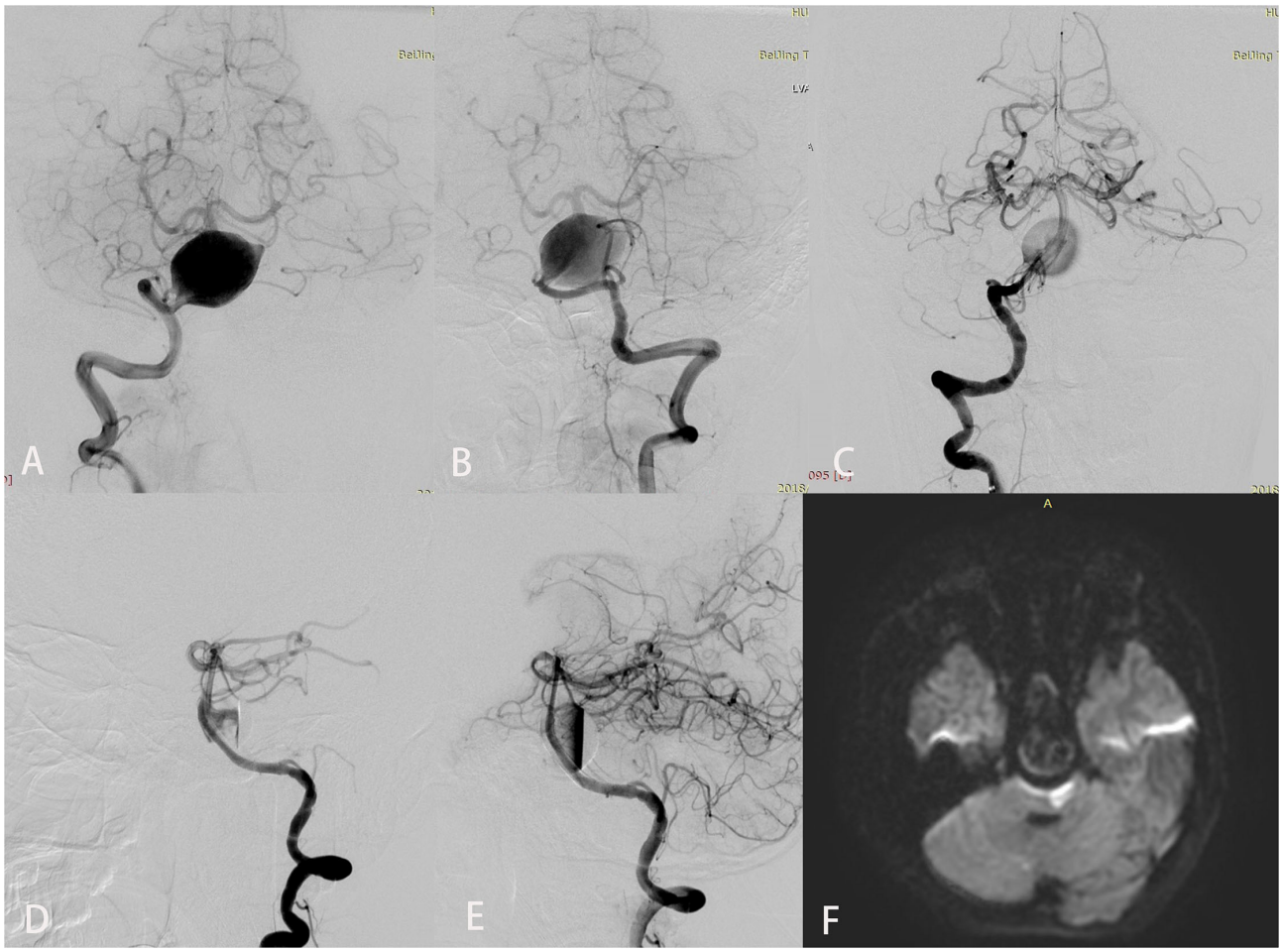


**FIGURE 1 |** Imaging studies for a 12-year-old boy (case 7) who presented with an 8-month history of chronic headaches and vertigo. Preoperative anteroposterior views of right **(A)** and left **(B)** vertebral angiography showed a giant fusiform basilar artery aneurysm. Anteroposterior **(C)** and lateral **(D)** views of right vertebral angiography immediately after treatment demonstrated excellent reconstruction of the basilar artery with 4 Pipeline embolization devices. An inflow jet is seen in the early arterial phase in **(D)**. **(E)** In the late arterial phase, contrast stasis is seen in the lumen of the aneurysm. Diffusion-weighted imaging **(F)** obtained to evaluate dysarthria and right hemiplegia that developed 12 h after the procedure showed a large brainstem infarct.

because antiplatelet therapy was stopped for an orthopedic surgical procedure. Although blood flow through the PED was restored in all four after emergency thrombolytic therapy and subsequent intra-arterial thrombectomy, the patients still experienced severe neurological deficits. Furthermore, angiography after thrombectomy revealed that these aneurysms were not completely occluded. At last follow-up, cases 10 and 21 had mRS scores of 4 and 3, respectively, while cases 18 and 25 died a short time after thrombectomy.

Overall, mean clinical follow-up was 23.5 ± 3.2 months (range, 0.1–65) and the complication rate was 44.8%. Twenty-one patients (72.4%) achieved a favorable clinical outcome (mRS score ≤2) or experienced clinical improvement at last follow-up. Nine patients (31%) experienced a poor clinical outcome (mRS score ≥3), including two patients with severe disability and seven patients who died. Overall rates of morbidity and mortality were 10.3 and 24.2%, respectively. The main causes of death were delayed aneurysmal rupture ($n = 4$), in-stent thrombosis ($n = 2$) and worsened mass effect ($n = 1$). Univariable comparisons between patients with favorable and unfavorable clinical outcomes showed that aneurysm size (28.0 ± 8.2 mm vs. 19.6 ± 7.0 mm; $p = 0.009$) and intra-aneurysmal thrombus (55.6 vs. 15%, $p = 0.04$) significantly differed between the groups. Multivariable regression analysis showed that aneurysm size (odds ratio, 1.1; 95% confidence interval, 1.0–1.3; $p = 0.04$) was an independent risk factor for poor clinical outcome (**Table 3**).

## DISCUSSION

Large or giant aneurysms involving the BA are less common than those involving the vertebral artery. Despite advances in endovascular and surgical treatment, complex vertebrobasilar artery aneurysms remain difficult to treat (11). In a series of 21 surgically treated patients, Nakatomi et al. (2) reported early postoperative morbidity and mortality rates of 47.6 and 14.3%, respectively; at last follow-up, the respective rates were 71.4

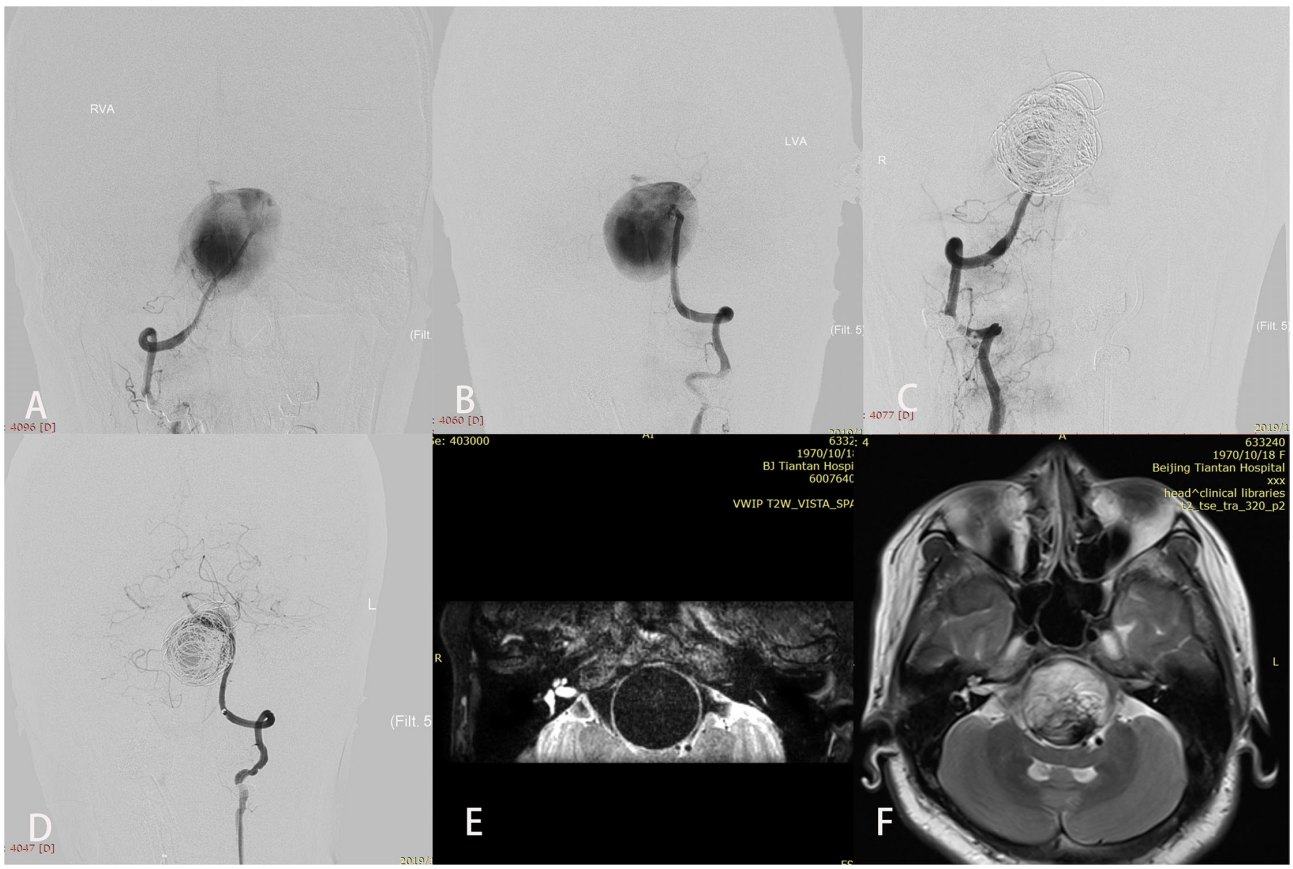


**FIGURE 2 |** A patient (case 17) with symptoms of mass effect from a giant vertebrobasilar junction aneurysm underwent placement of a single Pipeline embolization device along with coiling and right vertebral artery sacrifice. After treatment, disturbed consciousness and dyspnea developed. Preoperative anteroposterior views of right **(A)** and left **(B)** vertebral angiography showed the aneurysm. **(C,D)** Angiography immediately after the procedure showed successful sacrifice of the right vertebral artery, excellent reconstruction of the basilar artery, and contrast stasis in the lumen of the aneurysm. **(E)** T2-weighted imaging before the intervention demonstrated a complete flow void within the aneurysm. **(F)** T2-weighted imaging after treatment showed aneurysmal enlargement and signal inhomogeneity within the aneurysm consistent with thrombosis.

and 57.1%. In another study of 19 patients with large or giant BA aneurysms who were treated with stenting or stent-assisted coiling, Mu et al. (5) reported postoperative complications or poor neurologic outcome in five (26.3%); overall mortality was 15.8% and complete occlusion was achieved in only 20% at last angiographic follow-up.

The PED is another treatment option in patients with complex posterior circulation aneurysms. Use of the PED can achieve better outcomes than surgical or other endovascular techniques (6, 7). To our knowledge, our study is the largest one to date that has examined PED treatment of large or giant BA aneurysms. Our angiographic results are encouraging, as 87% of aneurysms achieved adequate occlusion (OKM C–D). **Table 4** summarizes the findings of 10 previous studies comprising five or more patients that reported FD treatment of large or giant BA aneurysms. When pooling these studies' data, the calculated rate of complete occlusion is 75.6%, which is in line with our complete occlusion rate (74%) and far superior to rates achieved by conventional endovascular treatment (5, 22).

This superiority may be related to our long angiographic follow-up period. Studies have shown that aneurysms treated using the PED are more likely to achieve complete occlusion over time compared with aneurysms treated using conventional endovascular treatment (23, 24). Complete exclusion of an aneurysm from the circulation requires formation of neointima (25), which begins at the site of contact between the FD and the parent artery. For fusiform aneurysms involving the BA, neoendothelialization requires a longer time in arteries with longer segments of disease, as shown in a histopathological study that reported that thrombosis and endothelial coverage of the FD may not occur before 1 year (18, 26). Complete aneurysm occlusion is also limited in aneurysms involving branches. Continued inflow from a side branch may affect the ability of the FD to reduce aneurysmal inflow and may limit the degree of stasis within the aneurysm, which negatively affects the ultimate outcome of treatment (23, 27). Our observations were similar: fusiform aneurysms and aneurysms involving branches took longer to completely occlude

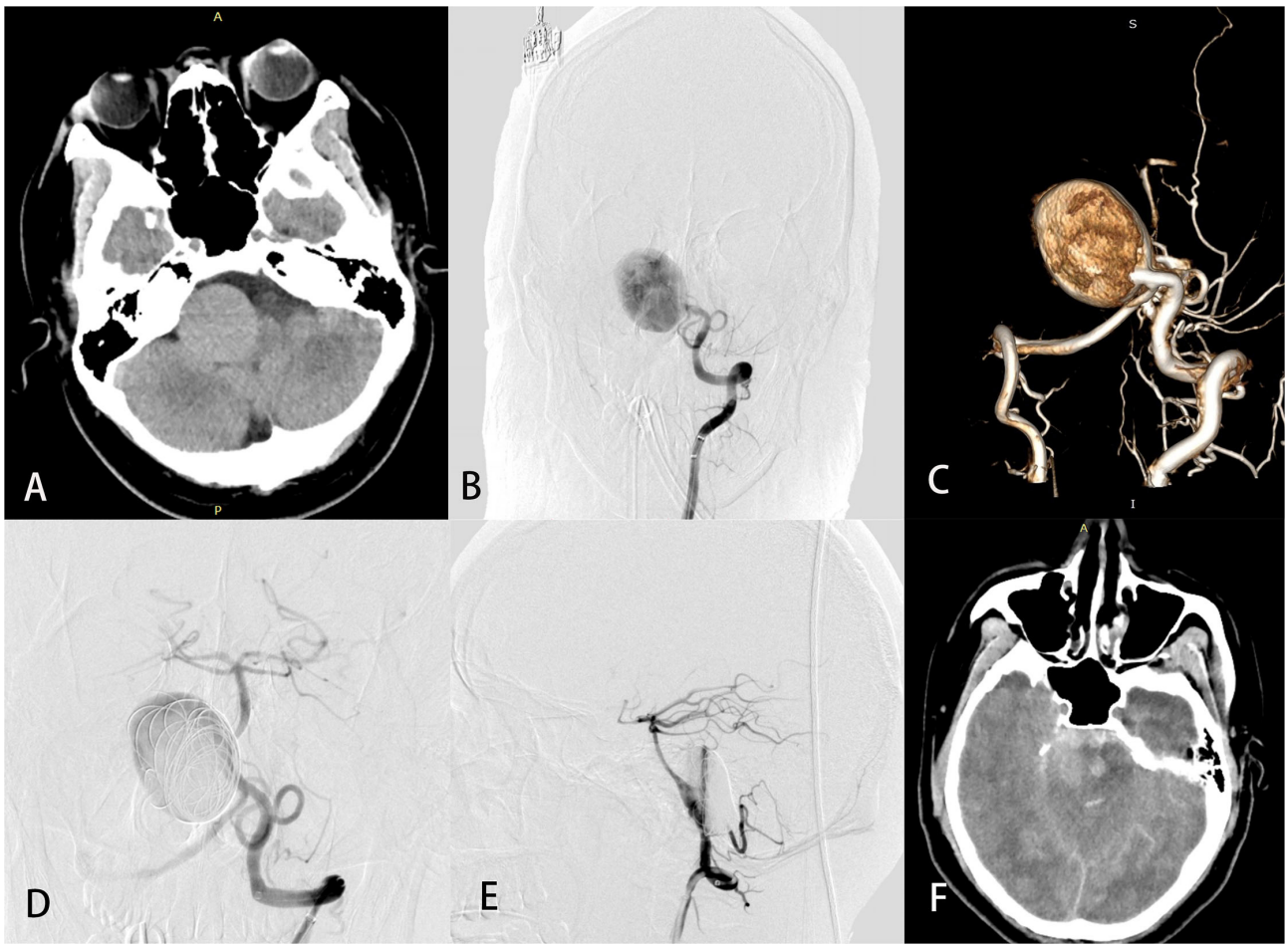


**FIGURE 3 |** A 26-year-old man (case 29) with a giant basilar artery aneurysm presented with tinnitus. Preoperative computed tomography **(A)** showed a large mass in the right anterior brainstem. Preoperative angiography **(B)** with 3-dimensional reconstruction **(C)** showed a giant side wall saccular aneurysm of the proximal basilar artery. Anteroposterior **(D)** and lateral **(E)** views of left vertebral angiography demonstrated excellent reconstruction of the basilar artery and contrast stasis in the lumen of the aneurysm. Computed tomography **(F)** on postprocedure day 3 was obtained to evaluate headache, vomiting, and disturbed consciousness and revealed massive subarachnoid hemorrhage. The patient later died.

compared with saccular and aneurysms that did not involve branches, respectively.

A recent systematic review of posterior circulation aneurysm patients reported a 22% rate of major complications after flow diversion, with VBJ and BA aneurysms having the worst outcomes (28). As shown in **Table 4,** the pooled complication rate, morbidity, and mortality among 101 patients with large or giant BA aneurysms treated with FDs was 40, 12.7, and 20.7%, respectively; the overall incidence of adverse outcome was 33.4%.

Our overall complication rate (44.8%) and mortality (24.2%) were slightly higher. Most complications (84.6%) occurred perioperatively. Aneurysm size was an independent risk factor for periprocedural complications and poor clinical outcome. Mean aneurysm size in our study was 22.2 ± 8.3 mm, which is larger than the mean size reported in other series and may explain our higher complication rate. Liang et al. (24) suggested that giant posterior circulation aneurysms (>25 mm) are associated with a high incidence of periprocedural complications. Kiyofuji et al. (9) also reported that large or giant posterior circulation aneurysms are associated with an unfavorable safety profile and poor outcome. Our findings are consistent with previous studies.

Large, partially thrombosed aneurysms in the posterior circulation are prone to thrombus propagation, which can lead to perforator infarction or in-stent thrombosis (29, 30). The most common complication in our study was ischemia, including four perioperative perforator strokes, one perioperative embolic stroke, and four cases of in-stent thrombosis owing to discontinuation of antiplatelet therapy. This result was also similar to a previously reported meta-analysis on FD treatment of posterior circulation non-saccular aneurysms (31). Circumferential involvement of the vessel wall and presence of vital perforating arteries are frequently encountered problems when treating large or giant BA aneurysms. Moreover, the larger the aneurysm and the longer the segment of the BA involved, the more perforator arteries that are damaged. Lesions that involve a great length require the deployment of multiple

**TABLE 2 |** Univariable and multivariable analyses of factors associated with perioperative complications.

| Parameter | Univariable Analysis | | | Multivariable Analysis; OR (95% CI), *p*-Value |
|---|---|---|---|---|
| | Perioperative complications (*n* = 11) | No-perioperative complications (*n* = 18) | *p*-Value | |
| Age | 46.4 ± 22.7 | 42.7 ± 20.8 | 0.66 | |
| Sex (Male) | 8/11 (72.7%) | 10/18 (55.6%) | 0.45 | |
| Smoking | 2/11 (18.2%) | 6/18 (33.3%) | 0.67 | |
| Hypertension | 4/11 (36.4%) | 5/18 (27.8%) | 0.69 | |
| Initial presention | 8/11 (72.7%) | 6/18 (33.3%) | 0.06 | |
| Intra-aneurysmal thrombus | 6/11 (54.5%) | 2/18 (11.1%) | 0.03 | 17.1 (0.8–360.4), $p = 0.07$ |
| **Aneurysm location** | | | | |
| Proximal BA | 9/11 (81.8%) | 10/18 (55.6%) | | |
| Distal BA | 2/11 (18.2%) | 8/18 (44.4%) | | |
| Aneurysm involving side branches | 7/11 (63.6%) | 11/18 (61.1%) | 0.60 | |
| Largest aneurysm size (mm) | 29.9 ± 6.2 | 17.5 ± 5.4 | <0.01 | 1.4 (1.0–1.8), $p = 0.04$ |
| **Aneurysm type** | | | | |
| Fusiform | 8/11 (72.7%) | 8/18 (44.4%) | 0.25 | |
| Saccular | 3/11 (27.2%) | 10/18 (55.6%) | | |
| Median no. of PEDs (range) | 1 (1–3) | 2 (2–4) | 0.02 | 2.3 (0.2–23.6), $p = 0.49$ |
| Adjunct Coling | 7/11 (63.6%) | 5/18 (27.8%) | 0.51 | |

*BA, basilar artery; CI, confidence interval; no., number; OR, odds ratio; PEDs, Pipeline embolization devices.*

**TABLE 3 |** Univariate and multivariate analyses of factors associated with unfavorable clinical outcome.

| Parameter | Univariable Analysis | | | Multivariable Analysis; OR (95% CI), *p*-Value |
|---|---|---|---|---|
| | Favorable clinical outcomes (*n* = 20) | Unfavorable clinical outcomes (*n* = 9) | *p*-Value | |
| Age | 49.2 ± 18.9 | 41.8 ± 22.2 | 0.39 | |
| Sex (Male) | 11/20 (55%) | 7/9 (77.8%) | 0.41 | |
| Smoking | 5/20 (25%) | 3/9 (33.3%) | 0.68 | |
| Hypertension | 4/9 (44.4%) | 5/9 (55.6%) | 0.09 | |
| Initial presention | 9/20 (45%) | 5/9 (55.6%) | 0.70 | |
| Intra-aneurysmal thrombus | 3/20 (15%) | 5/9 (55.6%) | 0.04 | 5.5 (0.8–40.1), $p = 0.09$ |
| **Aneurysm location** | | | | |
| Proximal BA | 11/20 (55%) | 8/9 (88.9%) | 0.11 | |
| Distal BA | 9/20 (45%) | 1/9 (11.1%) | | |
| Aneurysm involving side branches | 11/20 (55%) | 7/9 (77.8%) | 0.41 | |
| Largest aneurysm size (mm) | 28.0 ± 8.2 | 19.6 ± 7.0 | 0.009 | 1.1 (1.0–1.3), $p = 0.04$ |
| **Aneurysm type** | | | | |
| Fusiform | 9/20 (45%) | 7/9 (77.8%) | 0.13 | |
| Saccular | 11/20 (55%) | 2/9 (22.2%) | | |
| Median no. of PEDs (range) | 1 (1–3) | 1 (1–4) | 0.93 | |
| Adjunct Coling | 9/20 (45%) | 3/9 (33.3%) | 0.69 | |

*BA, basilar artery; CI, confidence interval; no., number; OR, odds ratio; PEDs, Pipeline embolization devices.*

devices to reconstruct the parent artery. Placement of multiple overlapping PEDs may increase resistance to perforator artery filling caused by the increased surface coverage area (7), which further compounds the perforator injury. Multiple PEDs may also cover more perforators. In our study, perioperative ischemic stroke was associated with greater aneurysm size and the use of multiple PEDs. Siddiqui et al. (12) reported two brain stem ischemic events in seven patients with large or giant fusiform BA aneurysms treated using FDs; the mean number of stents placed per patient was 4.8. Lopes et al. (11) indicated that use of ≥3 PEDs is a strong predictor of major neurological morbidity and mortality. Phillips et al. (32) reported three perforator strokes that occurred in patients treated using a single PED partially or entirely within the BA, which indicates that coverage of a perforating artery ostium may not be the only etiology of stroke in this subset of patients. Heterogeneity in aneurysm size and type between the studies may explain the discrepancy. Although use of multiple PEDs was not an independent risk factor for periprocedural complications in our multivariable analysis, we preferentially deployed a single longer and larger PED *in situ* and avoided using the push/pull technique with the microcatheter in the lumen of aneurysm to reduce perforator coverage and intra-aneurysmal thrombus propagation. We also administered tirofiban prophylactically within 24 h of embolization in patients with long segmental lesions who underwent placement of multiple PEDs, which may explain the absence of serious neurological complications in our patients who experienced perioperative ischemia.

Another more troublesome ischemic complication in our study was in-stent thrombosis. Four patients developed in-stent thrombosis at 5, 6, 11, and 19 months after treatment, respectively. Two experienced severe neurological deficits and two died. Klisch et al. (33) reported two patients with large fusiform basilar trunk aneurysms who developed in-stent thrombosis after clopidogrel was stopped; follow-up angiography at 12 months still demonstrated minimal residual filling of both aneurysms. The authors speculated that PEDs within the thrombosed portion of these fusiform aneurysms may endothelialize at a rate far slower than that observed when a similarly sized PED was placed across a non-fusiform aneurysm.

**TABLE 4 |** Summary of large series (>5 patients) reporting flow diverter treatment of basilar artery aneurysms.

| Reference | FD type | All BA cases | Mean size (mm) | No. of FD | Complication (%) | Ischemic complications (%) | Hemorrhagic complications (%) | Mass effect (%) | Morbidity (%) | Mortality (%) | CO at FU (total FU cases,%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhou et al. (13) | PED | 7 | 25.4 | 13 | 3 (42.9) | 2 (28.6) | 0 (0) | 0 (0) | 1 (14.2) | 1 (14.2) | 5 (6,83.3) |
| Dmytriw et al. (8) | PED/FRED | 16 | 20.2 | 16 | 3 (18.8) | 0 (0) | 2 (12.5) | 1 (6.3) | 2 (12.5) | 1 (6.3) | 11 (14,71.7) |
| Tascher et al. (14) | Surpass | 26 | 17.7 | 46 | NA | NA | 1 (3.8) | NA | NA | 8 (30.6) | NA |
| Da Ros et al. (15) | PED/SILK/ FRED | 5 | 20 | 5 | 2 (40) | 1 (20) | 1 (20) | 0 (0) | 1 (20) | 1 (20) | 5 (5,100) |
| Natarajan et al. (17) | PED | 8 | 14.5 | 14 | 2 (25) | 1 (12.5) | 0 (0) | 0 (0) | 1 (12.5) | 0 (0) | 8 (8,100) |
| Monteith et al. (19) | PED | 5 | 26.2 | 10 | 2 (40) | 1 (20) | 1 (20) | 0 (0) | 1 (20) | 1 (20) | 1 (4,25) |
| Toma et al. (20) | PED/SILK | 8 | >10 | NA | 5 (62.5) | 2 (25) | 1 (12.5) | 1 (12.5) | 2 (25) | 3 (37.5) | NA |
| Siddiqui et al. (12) | PED/SILK | 7 | 20.8 | 34 | 5 (71.4) | 3 (42.9) | 2 (28.6) | 0 (0) | 1 (14.3) | 4 (57.1) | NA |
| Kulcsar et al. (16) | SILK | 12 | 11.5 | 12 | 5 (41.7) | 5 (41.7) | 0 (0) | 0 (0) | 3 (25) | 0 (0) | 7 (12,58.3) |
| Byrne et al. (21) | SILK | 7 | >10 | NA | 3 (37.5) | 1 (12.5) | 0 (0) | 2 (25) | 1 (12.5) | 2 (25) | NA |
| Total | | 101 | | 150/86 | 30/75 | 16/75 | 8/101 | 4/86 | 11/86 | 21/101 | 37/49 |
| Total (mean) | | | | 1.7 | 30 (40) | 16 (21.3) | 8 (7.9) | 4 (4.6) | 11 (12.7) | 21 (20.7) | 37 (49,75.6) |

*BA, basilar artery; CO, complete occlusion; FD, flow diverter; FRED, flow redirection endoluminal device; FU, follow-up; NA, data not available; PED, pipeline embolization device.*

Similar results were observed in our study, in which the mean time to complete occlusion of fusiform aneurysms confirmed by first angiographic exceeded 12 months, which was significantly longer than the time to occlusion for saccular aneurysms. The four patients with fusiform aneurysms who experienced in-stent thrombosis in our study showed residual aneurysm filling at the final angiographic follow-up. Antiplatelet agents were discontinued in these patients because of gastrointestinal bleeding or planned surgery. Therefore, discontinuation of antiplatelet therapy may never be safe after flow diversion in patients with large or giant BA fusiform aneurysms with residual filling. When persistent residual filling is encountered months after PED reconstruction, Klisch et al. (33) suggested that placement of additional devices is preferable to altering the antiplatelet regimen.

Delayed aneurysmal rupture is another potentially serious complication of FD treatment that can have a devastating outcome. Hou et al. (34) performed a systematic review of patients who experienced delayed rupture after FD placement and concluded that increased intra-aneurysmal pressure, destabilization of the aneurysm wall by intra-aneurysmal thrombus, persistent residual intra-aneurysmal flow, large or giant size, presence of symptoms, and FD-induced mechanical injury might contribute to delayed rupture. In our series, four patients with aneurysm sizes ranging from 22 to 40 mm developed delayed rupture; three occurred from aneurysms located in the proximal segment, including two with a VBJ aneurysm that was treated with a single PED without coiling and contralateral vertebral sacrifice. For VBJ aneurysms treated using the PED, coil occlusion of the contralateral vertebral artery is required to prevent disease progression (35). Coiling can also provide protection from hemorrhagic complications by changing intra-aneurysmal flow dynamics and controlling intra-aneurysmal thrombosis (17); however, coiling may worsen mass effect in some cases (36). Our pooled analysis demonstrated a 4.6% rate (range, 0–25) of worsening mass effect after FD treatment of BA aneurysms (**Table 4**). Worsening of mass effect after treatment may be associated with aneurysm thrombosis, increase in maximal aneurysm diameter, and new adjacent edema (37). Several studies (12, 35, 38) have shown that early management before compressive symptoms develop is important to achieve a good clinical outcome. In our study, three patients who experienced mass effect symptoms postoperatively had symptoms of brainstem compression before PED treatment. Two of these patients had intermittent episodic symptoms for less than 2 months before treatment and ultimately had a favorable clinical outcome. Another patient had severe brainstem compression symptoms for 6 months prior to treatment and experienced worsened mass effect after treatment with a single PED and adjunctive coiling. She eventually died of mass effect-related brainstem failure. Although initial clinical presentation was not associated with complications or poor outcome in our study, we believe that early management of patients with symptomatic mass effect can achieve favorable clinical outcomes.

## LIMITATIONS

Our study is limited by its single-center retrospective design and relatively small sample size, which may have introduced statistical bias.

## CONCLUSION

The results of this small series suggest that PED treatment of large or giant BA aneurysms is effective and can achieve a satisfactory long-term occlusion rate. However, the treatment complications are not negligible. Aneurysm size is the strongest predictor of perioperative complications and poor clinical outcome.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

YL and ML: conception and design. KL, LZ, YZ, YJ, PL, and HH: analysis and interpretation of data. XC and HG: drafting the article. YL: approved the final version of the manuscript on behalf of all authors. All authors critically revised the article. All authors contributed to the article and approved the submitted version.

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# Safety and Efficacy of Cangrelor Among Three Antiplatelet Regimens During Stent-Assisted Endovascular Treatment of Unruptured Intracranial Aneurysm: A Single-Center Retrospective Study

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**Introduction:** Thromboembolic events represent the most frequent complications of endovascular treatment of unruptured intracranial aneurysm using stent-assisted coilling or flow diverter stents. Dual antiplatelet therapy has become the standard to prevent these but remains unstandardized. We present here a single center experience of 3 standardized antiplatelet regimens during brain aneurysm treatment, while emphasizing the use of the Cangrelor.

**Method:** We retrospectively reviewed data from patients treated using stent-assisted coilling or flow diverter stents from 2016 to 2021. We collected and compared safety and efficacy data within 6 months of three groups of patients corresponding to three antiplatelet standardized regimens: group T with Ticagrelor, with preprocedural preparation; group E with Eptifibatide, injected during procedure; group C with Cangrelor, injected during procedure.

**Results:** Data of 112 patients were analyzed and 76 belonged to group T, 21 to group E, and 15 to group C. Eleven events over the 14 recorded were adjudicated to be related to antiplatelets, their repartition did not differ between the 3 groups ($p = 0.43$). All symptomatic events ($N = 8$) were not distributed significantly differently between the 3 groups ($p = 0.11$) and asymptomatic events were also balanced ($p = 1.00$). Of these, 6 subjects had a change in the mRS score at 3–6 months. Thrombo-embolic events represented the most encountered events in the sample: 2 acute ischemic strokes were recorded in group E and 1 in group T; 1 transient ischemic stroke was noted in group E; 4 silent infarcts were found on control MRI (2 belonged to group T, 1 to group E and 1 to group C). Among 3 intracranial bleeding events, 1 was symptomatic in group C, 2 were asymptomatic in group T. On the control evaluation performed at 6 months, there was no significant difference on aneurysmal occlusion ($p = 0.67$).

**Conclusion:** This single-center retrospective study compared 3 antiplatelet regimens, finding no significant difference in the safety and efficacy in the context of endovascular treatments of unruptured aneurysm using stent or flow diverters. This study adds data for the Cangrelor use and suggests its usefulness in the field of neuro-endovascular intervention. Randomized controlled studies are warranted to confirm these results.

**Keywords: aneurysm, unruptured, Cangrelor, antiplatelets, stent-assisted coilling, flow diverter**

# INTRODUCTION

Stent-assisted endovascular therapies of intracranial aneurysms may be complicated by thromboembolic events (1, 2). Dual antiplatelet therapy (DAPT) has become a standard regimen to prevent them (3). Actually, there is no standardized DAPT protocol in interventional neuroradiology, which leads to divergent drugs use (4). The use of aspirin and a $P2Y_{12}$ receptor antagonist is inferred from the cardiology literature (5). Historically, Clopidogrel was the first $P2Y_{12}$ inhibitor to be used. Clopidogrel has the disadvantage of a wide response variability (6) and a duration of effect of more than 5 days (7). Ticagrelor and Prasugrel are faster acting (30 min−4 h) than Clopidogrel [2–8 h (8)] and they also present less interpatient response variability (7). These three $P2Y_{12}$ inhibitors can only be administered orally. According to the cardiology literature (9–11), Eptifibatide has the advantage of being used intravenously, with a short onset (15 min) and offset of action (within 4–8 h) (12). Quite similar in structure to Ticagrelor, Cangrelor also allows intravenous administration (13) and short on/offsets (1 min) with a half-life of 3–5 min. **Table 1** summarizes the pharmacokinetic and pharmacodynamic properties of these antiplatelet agents. In 2015, Cangrelor was approved by the U.S. Food and Drug Administration as adjunctive therapy for percutaneous coronary intervention as it was effective in reducing intra-stent thrombosis and the risk of peri-procedural myocardial infarction (14). **Table 2** summarizes primary studies that investigated the use of Cangrelor in interventional neuroradiology (15–19). These studies used different doses of Cangrelor either for bolus (15–30 μg/kg) or maintenance (0.75–4 μg/kg/min), furthermore these studies reported various procedures from mechanical thrombectomy to ruptured aneurysm treatment.

In this study, we aimed to analyse the clinical safety and efficacy of three standardized antiplatelet regimens used during scheduled endovascular procedures for unruptured aneurysms using stent-assisted coilling (SAC) or flow diverter stents (FD), while emphasizing the place of Cangrelor.

# METHOD

## Population

Data from all patients treated for intracranial aneurysm from February 2016 to March 2021 at the University Hospital were retrospectively collected. Patients treated by simple coilling and ruptured aneurysms were excluded. Three groups of patients were constituted according to their initial antiplatelet regimen that included Ticagrelor, Eptifibatide or Cangrelor. Patients for which another molecule was used were not considered.

We retrospectively collected basic patient demographics, comorbidity, diagnosis, target aneurysm characteristics and procedure-related outcomes and complications from patient medical records included in a prospectively maintained database of all the interventional neuroradiology procedures performed in the center.

## Procedures

Every indication for endovascular treatment was previously validated during a multidisciplinary meeting. The initial treatment strategy was recorded. According to the center habits, antiplatelet regimen was decided before the procedure. For the treatments with anticipated high risk of bleeding (as turning inside the aneurysm, difficult catheterization of recurrent branches, associated microaneurysms, etc.), intravenous antiplatelets were preferred (without $P2Y_{12}$ loading dose before the procedure). Treatment related details were recorded.

## Anti-platelet Regimen Groups

No platelet aggregation test was performed. All patients received a dose of 75 mg Aspirin 1 day prior to the procedure and on the day of the procedure. Systemic anticoagulation was achieved using an intravenous bolus injection of heparin (50 IU/kg, 3,000–5,000 IU, range) after the femoral/radial artery access followed by an additional 1,000–2,000 IU/h according to the results of the activated clotting time.

Group T used a loading dose of 180 mg Ticagrelor 1 day prior to the procedure, and 90 mg Ticagrelor on the day of the procedure.

Group E used a loading dose of 180 μg/kg Eptifibatide during the procedure. If used, the maintenance dose of Eptifibatide was administered at 2 μg/kg/min, within 2 h.

Group C used a loading dose of 30 μg/kg Cangrelor during the procedure, followed by a maintenance dose at 4 μg/kg/min.

Decision of an oral maintenance therapy of 90 mg Ticagrelor twice a day for group T was made after the procedure as soon as a clinical evaluation was possible. Decision of an oral switching for group E and C was made after the procedure as soon as a clinical evaluation was possible, via a loading dose of an oral $P2Y_{12}$ receptor inhibitor (180 mg Ticagrelor or 60 mg Prasugrel), administered 2 h after discontinuation of Eptifibatide, or 30 min before Cangrelor infusion was stopped. All patients received a

**Abbreviations:** SAC, stent-assisted coiling; FD, flow diverter stents; DAPT, Dual antiplatelet therapy; MRI, Magnetic Resonance Imaging; mRS, modified Rankin Scale.

**TABLE 1 |** Pharmacokinetic and pharmacodynamic properties of antiplatelet agents.

| | Clopidogrel | Prasugrel | Ticagrelor | Eptifibatide | Cangrelor |
|---|---|---|---|---|---|
| Class | Thienopyridine | Thienopyridine | Triazolopyrimidine | GPIIb/IIIa | ATP analog |
| Administration | Oral | Oral | Oral | Intravenous | Intravenous |
| Reversibity | Irreversible | Irreversible | Reversible | Irreversible | Reversible |
| Loading dose | 300 mg | 60 mg | 180 mg | 90–180 μg/kg | 15–30 μg/kg |
| Maintenance dose | 75 mg (once daily) | 10 mg (once daily) | 90 mg (twice daily) | 0.5–2 μg/kg/min | 2–4 μg/kg/min |
| Onset of effect | 2–8 h | 30 min−4 h | 30 min−4 h | 5–15 min | 0–2 min |
| Half-Life | 6 h | 7 h | 8 h | 1–3 h | 2–5 min |
| Duration of effect | 5–7 days | 7–10 days | 3–5 days | 4–8 h | 30–60 min |

**TABLE 2 |** Review of the literature on the use of Cangrelor in aneurysm treatments.

| Author | Journal | Year | Unruptured aneurysm (*N*) | Ruptured aneurysm (*N*) | Use of Cangrelor during intracranial stenting | Loading dose | Maintenance dose |
|---|---|---|---|---|---|---|---|
| Linfante et al. | J NeuroIntervent Surg | 2021 | 1 | 4 | Yes | 30 μg/kg | 4 μg/kg/min |
| Godier et al. | British Journal of Anaesthesia | 2019 | 2 | 5 | No | No | 0,75 μg/kg/min |
| Abdennour et al. | Clin Neuroradiol | 2020 | 2 | 5 | Yes | 30 μg/kg | 4 μg/kg/min |
| Aguilar et al. | J NeuroIntervent Surg | 2019 | 1 | - | Yes | 15 μg/kg | 2 μg/kg/min |
| Cortez et al. | Neuroradiology | 2021 | 8 | 16 | Yes | 15–30 μg/kg | 2–4 μg/kg/min |
| Cheddad El Aouni et al. | Frontiers in Neurology | 2021 | 15 | - | Yes | 30 μg/kg | 4 μg/kg/min |

daily dose of 75 mg Aspirin as a maintenance therapy after the decision of oral DAPT.

## Safety and Efficacy

Main outcome of interest was the presence of an event directly related to DAPT. Adjudication of such accountability was consensually made (by all investigators) on the standardized WHO-UMC system for case causality assessment by taking into account the events which corresponded to the terms "Certain" and "Probable / Likely" (20), with access to all data.

Other secondary items of safety were recorded mainly as symptomatic/asymptomatic hemorrhage/ischemic or other procedure-related events.

Symptomatic events included: intracranial hemorrhage, ischemic stroke, other neurologic symptoms unrelated to ischemia nor hemorrhage, arterial access site complication requiring surgical management and death from any cause within 3 months. Neurological symptoms were also classified as permanent or transient.

Asymptomatic events included transient ischemic attack and silent ischemia/hemorrhage were assessed on the basis of the control MRI at 3–4 months.

Additional relevant outcomes were shift and description of functional conditions from baseline to 3–6 months using the modified Rankin Scale (mRS) (21).

Endovascular treatment efficacy was passed on the basis of both control catheter angiography and MRI at 3–6 months. Eventual intrastent stenosis was recorded in three categories: unsignificant (<20% of the lumen), moderate (20–39%) and substantial (>40%); and aneurysmal occlusion using the Raymond Roy classification (22). The review of all imaging points were made consensually by the neuro-interventionists, JCG – JO – MA – MCEA, blinded to the clinical data.

## Average Cost of Antiplatelets Regimen

The cost of antiplatelet drugs was reported using the following actual hospital market price: 50 mg Cangrelor powder for concentrate for solution for injection/infusion preparation USD 403.3; 10cc vial (2 mg/ml) Eptifibatide USD 36.87; 100cc vial (0.75 mg/ml) Eptifibatide USD 76.48; 90 mg Ticagrelor USD 1.15; 75 mg Aspegic USD 0.045.

The calculation of the cost was based on the actual consumption of antiplatelet drugs for each patient, extracted from the anesthetic record, taking into account the antiplatelet preparation before the procedure and during the procedure, and without taking into account the cost of the maintenance dose. If an infusion was maintained after the procedure without immediate oral switch, this was also taken into account in the cost. This global cost was then given by the average of this consumption for each regimen group.

## Statistics

Data were analyzed using STATA/MP 16 (Statacorp LP, USA) with the aim to compare the safety and efficacy endpoints between the three groups of antiplatelet regimens. A parsimonious analysis was carried out: when they were more adequate, descriptive statistics were preferred. Quantitative variables were described by median an interquartile range (IQR)

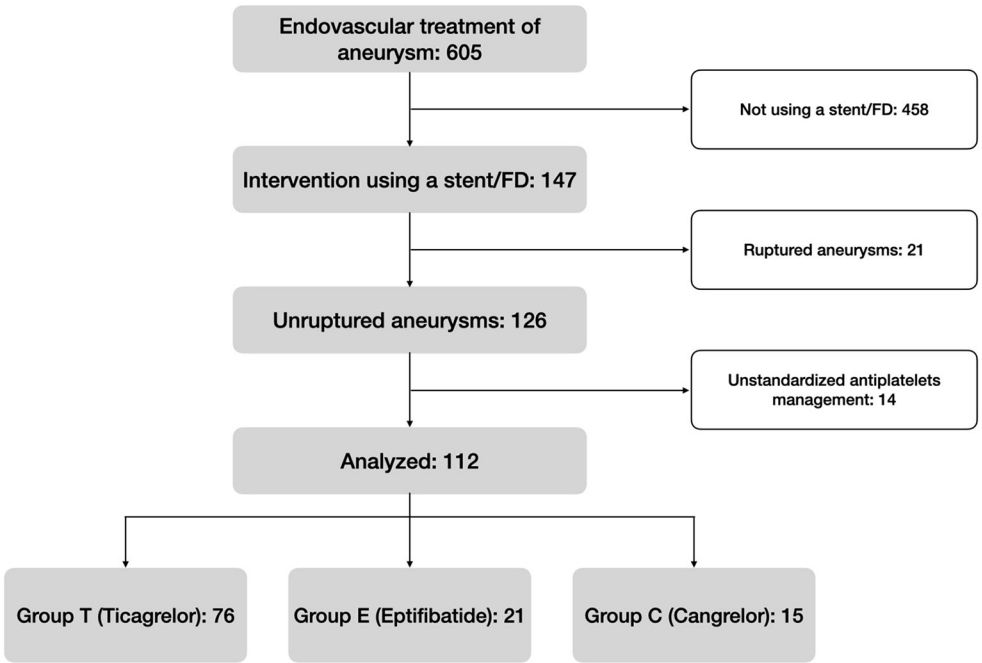


**FIGURE 1 |** Flowchart of the study.

and compared using a Kruskal-Wallis test. A Chi-squared or Fisher's exact test was used when comparing frequencies between groups for qualitative variables. A value of $p < 0.05$ was considered significant.

## Ethical Statement

The use of Cangrelor was off-label in this study. In all cases no final alternative was found to intracranial stenting and the choice to treat these patients under Cangrelor was made multidisciplinary. Patients were informed before each treatment of the initial strategy and possible alternatives and gave verbal consent. The study and need for patient informed consent was conducted in accordance with actual laws and ethics and with the Helsinki Declaration and its revisions: as a non-interventional retrospective study, a commitment to compliance (Reference Methodology MR-3) was declared to the French national information science and liberties commission (CNIL), in respect to the General Data Protection Regulation. NCT04504695.

# RESULTS

## Population and Procedure

From February 2016 to March 2021, 605 patients who underwent endovascular intervention for the treatment of an aneurysm were screened. One hundred and forty seven of these were treated by SAC or FD, and 126 were scheduled. Fourteen cases were finally ruled out because the patients did not initially receive neither Ticagrelor, Eptifibatide, nor Cangrelor. **Figure 1** summarizes the flow chart.

A total of 112 patients were retrospectively analyzed and 76 belonged to group T (68%), 21 to group E (19%), and 15 to group C (13%). Eighty-one (72%) were women and the median age was 55 years (45–63 years, IQR). No patients had renal failure. Only one stent was used for each procedure. There were no significant differences between the three groups concerning the patients' baseline-characteristics ($p>0.05$), neither regarding aneurysm shape ($p = 0.494$) or size ($p = 0.970$). **Table 3** summarizes the general characteristics of the population.

Half ($N = 57$) of the intervention consisted in SAC and there were significantly less SAC in group T ($p < 0.001$; 37 vs. 76% in group E and 87% in group C). Seven stent placements (6%) were not initially planned. Considering the type of stents used, 20 (18%) were open-cell stents (Neuroform Atlas, Stryker, USA), 23 (20%) were braided stents (Leo+ and Leo+ baby, Balt, USA; Lvis Evo, Microvention, USA), and 69 (62%) were FD (Pipeline Embolization Device, Medtronic, USA; Silk Vista and Silk Vista Baby, Balt, USA; Surpass Evolve, Stryker, USA). More use of FD were significantly depicted in group T ($p < 0.001$; 78 vs. 24% in group E and 33% in group C). In group T, stents were preferentially placed in the internal carotid artery (51%, $p = 0.001$), in group E indifferently ($p = 0.125$), in group C in the middle cerebral artery (60%, $p < 0.001$).

## Safety and Efficacy

All the patients' DAPT were switched to oral DAPT maintenance regimen; except for one of the patients in the group C for which antiplatelets were definitely stopped after a vessel

**TABLE 3 |** General characteristics of the population.

| Characteristics | Group T | | Group E | | Group C | | *p*-value |
|---|---|---|---|---|---|---|---|
| Antiplatelet regimen (*n*, %) | 76 | 68% | 21 | 19% | 15 | 13% | |
| Age in years (median, IQR) | 55 | 46–60 | 59 | 43–63 | 61 | 45–63 | 0.559 |
| Gender (female, %) | 58 | 76% | 13 | 62% | 10 | 67% | 0.344 |
| Smoking (yes, %) | 14 | 18% | 6 | 29% | 4 | 26% | 0.467 |
| Hypertension (yes, %) | 21 | 28% | 8 | 38% | 2 | 13% | 0.275 |
| Previous treatment (yes, %) | 34 | 45% | 10 | 48% | 9 | 60% | 0.601 |
| Aneurysm type (sacciform, %) | 70 | 92% | 21 | 100% | 15 | 100% | 0.494 |
| Aneurysm location | | | | | | | <0.001 |
| Internal carotid artery (*n*, %) | *49* | *64%* | *7* | *33%* | *1* | 7% | <0.001 |
| Anterior cerebral artery (*n*, %) | *10* | *14%* | *6* | *29%* | *4* | 26% | 0.156 |
| Middle ceerebral artery (*n*, %) | *9* | *12%* | *5* | *24%* | *9* | 60% | <0.001 |
| Posterior circulation (*n*, %) | *8* | *10%* | *3* | *14%* | *1* | 7% | 0.804 |
| Size of the aneurysm | | | | | | | 0.970 |
| <5 mm (*n*, %) | 24 | 32% | 6 | 29% | 5 | 33% | |
| 5–7 mm (*n*, %) | 14 | 18% | 5 | 24% | 4 | 27% | |
| 7–15 mm (*n*, %) | 24 | 32% | 6 | 29% | 3 | 20% | |
| >15 mm (*n*, %) | 14 | 18% | 4 | 18% | 3 | 20% | |
| Treatment modality | | | | | | | <0.001 |
| Flow diverter stent (*n*, %) | 59 | 78% | 5 | 24% | 5 | 33% | <0.001 |
| Laser cut stent (*n*, %) | 9 | 12% | 10 | 48% | 1 | 7% | 0.001 |
| Braided stent (*n*, %) | 8 | 10% | 6 | 28% | 9 | 60% | <0.001 |
| Assisted coiling (*n*, %) | 28 | 37% | 16 | 76% | 13 | 87% | <0.001 |
| Unplanned stenting (*n*, %) | 0 | 0% | 5 | 24% | 1 | 7% | |

*n: number; %: percentage.*

rupture. All patients in groups T and E had a relay with Ticagrelor as a maintenance regimen. In group C, 13 patients were switched to Ticagrelor, and 1 to Prasugrel because of respiratory insufficiency.

The overall results concerning safety and efficacy are summarized in **Table 4**.

Eleven events over the 14 recorded were adjudicated (i.e., certainly or likely) to be related to DAPT (10% of events related to DAPT in the total sample), their repartition did not differ between the 3 groups ($p = 0.432$; 7% in group T, 15% in group E, 13% in group C).

All symptomatic events ($N = 8$) were not distributed significantly differently between the 3 groups ($p = 0.106$; 4% of the group T, 14% in group E and 13% in group C) and asymptomatic events were also balanced ($p = 1.000$; 5% in group T, 4% in group E and 7% in group C). Of these 8 symptomatic events, 6 subjects had a change in the mRS score at 3–6 months: 2 in group T (from 5 to 6 and from 0 to 2), 2 in group E (from 1 to 3 and from 0 to 1), 2 in group C (from 0 to 1 and from 3 to 4).

Death occurred in one patient in group T 2 months after the intervention and was related to aspiration pneumonia linked to general condition deterioration caused by a mass effect of a giant carotid aneurysm.

Thrombo-embolic events represented the most encountered events in the sample (8/14). Two acute ischemic strokes were recorded in group E and one in group T. One transient ischemic stroke was noted in group E. Four silent infarcts were found on control MRI (two belonged to group T, one to group E and one to group C). No delayed acute ischemic presentations were reported.

Among three intracranial hemorrhage events, one was symptomatic and occurred in group C (vessel rupture), two were asymptomatic and occurred in group T. These cases are illustrated in the **Figure 2**.

Two other miscellaneous events were recorded: one pseudo-aneurysm of the superficial femoral artery that required surgical intervention in the group C, and one contrast-induced encephalopathy that occurred in group T.

One hundred and one patients (90%) underwent a follow-up catheter angiography. There was no significant difference in the repartition of intra-stent stenosis between the 3 groups ($p = 0.246$), neither considering the aneurysmal occlusion rates ($p = 0.670$). The occlusion of the target aneurysm was complete at the control imaging (3–6 months) according to Raymond Roy's classification in 69% in group T, 76% in group E and 80% in group C.

## Average Cost

In the group T, all the patients were given previously describe medication, for an average cost of USD 3.54 per patient.

In the group C, two patients required an additional vial of cangrelor due to their weight, for an average cost of USD 457.16 per patient.

**TABLE 4 |** Safety and efficacy evaluation.

| Description (*n*, %) | Group T (*N* = 76) | | Group E (*N* = 21) | | Group C (*N* = 15) | | *p*-value |
|---|---|---|---|---|---|---|---|
| Events | 7 | 9% | 4 | 19% | 3 | 20% | *0.279* |
| Events adjudicated to be related to DAPT | 5 | 7% | 4 | 19% | 2 | 10% | *0.148* |
| Symptomatic events | 3 | 4% | 3 | 14% | 2 | 13% | *0.106* |
| Acute ischemic stroke | 1 | 1% | 2 | 10% | 0 | 0% | |
| Transient ischemic stroke | 0 | 0% | 1 | 4% | 0 | 0% | |
| Intracranial hemorrhage | 0 | 0% | 0 | 0% | 1 | 7% | |
| Others | 1 | 1% | 0 | 0% | 1 | 7% | |
| Death | 1 | 1% | 0 | 0% | 0 | 0% | |
| Change in mRS score at 3–6 months | 2 | 3% | 2 | 10% | 2 | 13% | |
| Asymptomatic events | 4 | 5% | 1 | 4% | 1 | 7% | *1.000* |
| Silent infarcts | 2 | 2.6% | 1 | 4% | 1 | 7% | |
| Intracranial hemorrhage | 2 | 2.6% | 0 | 0% | 0 | 0% | |
| Intra-stent stenosis at 6 months | | | | | | | *0.246* |
| Number of catheter angiography performed at 6 months | 73 | 96% | 19 | 90% | 9 | 60% | |
| No significant intra-stent stenosis | 63 | 87% | 15 | 79% | 8 | 89% | |
| Moderate intra-stent stenosis | 9 | 12% | 3 | 16% | 0 | 0% | |
| Major intra-stent stenosis | 1 | 1% | 1 | 5% | 1 | 11% | |
| Aneurysmal occlusion score at 3–4 months | | | | | | | *0.670* |
| Raymond-Roy 1 | 52 | 69% | 16 | 76% | 12 | 80% | |
| Raymond-Roy 2 | 15 | 20% | 2 | 10% | 1 | 7% | |
| Raymond-Roy 3 | 8 | 11% | 3 | 14% | 2 | 13% | |

*n: number; %: percentage.*

In group E, two patients were continued on Eptifibatide for 24 h and one patient for 72 h due to three declared ischemic events, for a mean cost of USD 217.77 per patient.

# DISCUSSION

## Safety and Efficacy

Facing the heterogeneity of practices and studies, the optimal DAPT regimen(s) for interventional neuroradiology cases remain unclear. This study did not depict a significant difference in the repartition of DAPT related events between the three groups of antiplatelet regimens, neither in the rate of all symptomatic (or a symptomatic) events. Thus, our study support the growing literature on the pending demonstration that Cangrelor could be an effective antiplatelet agent for preventing thromboembolic events in situation of stenting, and a safe agent regarding bleeding risk and possibility to reverse its effect rapidly.

The only event that occurred in the group that used Cangrelor that was considered as a thromboembolic complication was a silent infarction on the control MRI. This event did not modify the functional outcome of the patient nor the latter management of DAPT. Cangrelor was found to be useful when decision was made to proceed without DAPT regimen upfront because the need of stenting was not anticipated (6% of the sample), and these results are encouraging in terms of efficacy of the chosen antiplatelet management. Also, the percentage of symptomatic ischemic complications (3%) found in this study is in agreement with the literature: a meta-analysis of symptomatic ischemic complications with the use of a flow diverter by O'Kelly et al.found a rate of 4% (23) and a second meta-analysis with the use of a stent-assisted coiling by Phan et al. found a rate of symptomatic ischemia of 4.5% (1).

The only bleeding event using Cangrelor was symptomatic (**Figure 2**), and occurred while treating a previously ruptured P2-P3 aneurysm by a low profile FD. The operator decided to inflate the balloon in the stent and experienced an arterial rupture. The heparin was immediately reversed and the infusion of Cangrelor stopped, followed by an occlusion the posterior communicating axis. The neurosurgery team was immediately notified and an external ventricular derivation was performed within 30 min. At 3 months persisted a left hemiparesis, with a mRS score of 4 (for an initial mRS of 3). This case perfectly emphasizes that the rapid offset of Cangrelor allows prompt management during per procedural bleeding complications (i.e., aneurysm rupture, vessel perforation), or need of a surgical intervention (8).

The last event that occurred in patients under Cangrelor was a femoral puncture site false aneurysm, requiring surgical management. The mRS score of this patient was modified at 3 months (from 0 to 1).

The DAPT regimen did not affect aneurysm occlusion at 3–4 months and intra-stent stenosis on arteriography at 6 months.

## Cangrelor Use

A loading dose of Cangrelor of 30 μg/kg and a maintenance dose of 4 μg/kg/min were used in our study. This dosage was derived from the cardiology literature (24). Preliminary studies have investigated Cangrelor at half dose, with a loading dose of 15 μg/kg and a maintenance dose of 2 μg/kg/min (18, 19). These studies did not show an increased ischemic risk. In our center, the choice of Cangrelor was preferred to Ticagrelor when there was a

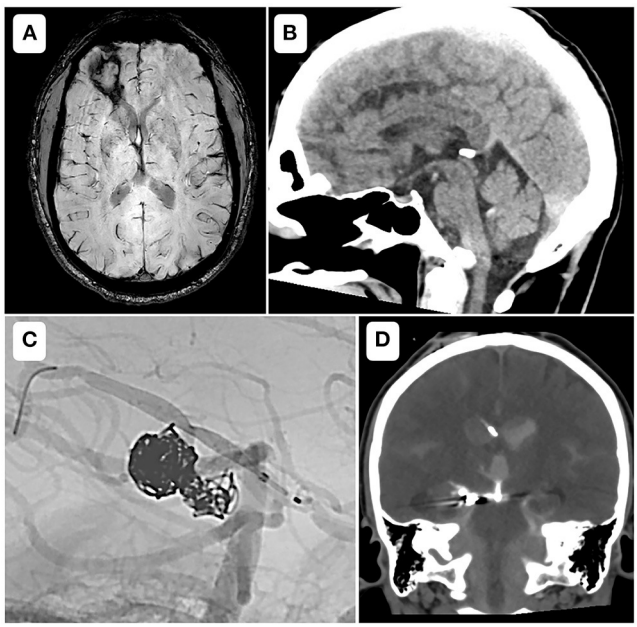


**FIGURE 2 |** Bleeding events. **(A)** Axial susceptibility weighted imaging, showing a parenchymal bleeding sequelae at 4 months of a stent assisted coiling of the recanalization of a previously ruptured anterior communicating artery aneurysm. The patient belonged to group T and did not present any neurologic deficit. **(B)** Sagittal reformat of a day 1 control CT-scanner, after a placement of a flow diverter to treat an unruptured fusiform aneurysm of the right vertebral artery, showing an isolated intraventricular hemorrhage in the fourth ventricle. The patient belonged to group T and did not present any neurologic deficit. **(C)** Case of a 33-year-old female, modified Rankin Scale 3, with a history of aneurysmal rupture, who underwent a scheduled treatment for an early recanalization of a right posterior cerebral artery aneurysm. After coilling through a microcatheter from the right vertebral artery, a low profile flow diverter was placed through a microcatheter from the right posterior communicating artery. An intra-stent balloon angioplasty provoked a vessel rupture that was jugulated with glue. Heparin was reversed and Cangrelor infusion was stopped. The neurosurgeon was immediately notified and a ventricular derivation was performed within 30 min **(D)**. The patient kept left hemiparesis, with a modified Rankin Scale of 4.

risk of bleeding during the procedure. Further studies are needed to assess the optimal dosage of Cangrelor for endovascular neuro-interventions regarding its safety and efficacy.

The use of Cangrelor requires careful planning with the anesthesia team. The maintenance infusion should be delivered immediately after the loading bolus. We prepared at the same time all syringes and operators had to wait 10 min after the bolus to place the stent and had to paid attention to the injection site patency until the oral relay.

Ticagrelor is the best choice for oral relay because it binds to the $P2Y_{12}$ receptor in a different way than Cangrelor (25). In our study one subject in Group C was given Prasugrel as a relay because of pre-existing respiratory failure, limiting the theoretical use Ticagrelor.

According to the cardiologic literature, Ticagrelor can be given at any time during the infusion of Cangrelor (25). *In vitro* studies have shown interaction of Cangrelor with Prasugrel and Clopidogrel (26). In order to limit these interactions, it is recommended for the relay with Prasugrel to be performed 30 min before the end of the Cangrelor infusion (27). Clopidogrel should only be delivered after the end of the Cangrelor infusion (28). In our practice, we favor a relay with Ticagrelor because of less drug-drug interaction with Cangrelor, and less interpatient response variability.

One should not forget that Cangrelor is still an expensive drug and that cost-effectiveness analysis may be welcome in further studies, similar to that made with Ticagrelor (29).

## Limitation

This was a retrospective, non-randomized, single-center study. Authors acknowledge an obvious selection bias: patients with anticipated procedure-related hemorrhage risk were preferentially treated using Eptifibatide or Cangrelor. Furthermore, the group using a Ticagrelor preparation used more FD without coiling. Similarly, at-risk locations, such as the middle cerebral artery because of the presence of recurrent divisions, were more represented in the groups that received intravenous antiplatelets. These groups (E and C) also included a greater proportion of patients for whom stenting was not initially planned, secondary to coil protrusion or, conversely, to avoid protrusion of a risky coil. Another limitation could be the relative diversity of procedures and devices used, as new medical implant devices with surface modifications are currently being developed and the safety and efficacy profiles of antiplatelets management in these cases should be studied (30, 31).

Our study included 15 patients treated using Cangrelor. To our knowledge, this is the largest current cohort of unruptured aneurysms with the use of Cangrelor (**Table 2**). Results of safety profile of Cangrelor was compared to two other standardized DAPT regiment in our center, but not compared to a proper control group. Also, different dosing protocols are described in the literature and have not been compared. Further prospective comparative studies with larger cohorts are needed to confirm our results and clarify the best protocols and real comparative safety profiles. Studies of Cangrelor in interventional neuroradiology are still rare. This medication has a rapid onset and offset of action, owing to its short half-life, that fit the demand for neuro-intervention procedures. This preliminary study paves the way for a randomized analysis to confirm its potential for routine use.

# CONCLUSION

This single-center, retrospective study over 4 years and 3 months compared three DAPT regimens in the context of aneurysm treatment requiring a stent/FD, through the report of their safety and efficacy. From the results, Cangrelor allows for a secure transition to long-term DAPT and secured surgery in cases of unexpected complications. The studies on Cangrelor are still rare with few patients. Randomized controlled studies are warranted to confirm the results of our study.

# DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

MN, JG, and EM contributed to conception and design of the study. MC and MA organized the database. JO and MC performed the statistical analysis. MC, JO, and MA wrote the first draft of the manuscript. MC, EM, MA, MN, JG, and JO wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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# Critical Angiographic and Sonographic Analysis of Intra Aneurysmal and Downstream Hemodynamic Changes After Flow Diversion

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**Introduction:** Successful treatment of intracranial aneurysms after flow diversion (FD) is dependent on the flow modulating effect of the device. We aimed to investigate the intra-aneurysmal and parent vessel hemodynamic changes, as well as the incidence of silent emboli following treatment with various FD devices.

**Methods:** We evaluated the appearance of the eclipse sign in nine distinct phases of cerebral angiography before and immediately after FD placement in correlation with aneurysm occlusion. Angiographic and clinical data of consecutive procedures were analyzed retrospectively. Patients who had successful FD procedure without adjunctive coiling, visible eclipse sign on post embolization angiography, and reliable follow-up angiographic data were included in the analysis. Detailed analysis of hemodynamic data from transcranial doppler after FD was performed in selected patients, such as monitoring for silent emboli.

**Results:** Among all patients ($N = 65$) who met inclusion criteria, complete aneurysm occlusion at 12 months was achieved in 89% (58/65). Eclipse sign prior to FD was observed in 42% (27/65) with unchanged appearance in 4.6% (3/65) of the treated patients. None of these three patients achieved complete aneurysm occlusion. Among all analyzed variables, such as aneurysm size, device type used, age, and appearance of the eclipse sign pre- and post-FD, the most reliable predictor of permanent aneurysm occlusion at 12 months was earlier, prolonged, and sustained eclipse sign visibility in more than three angiographic phases in comparison to the baseline ($p < 0.001$). Elevation in flow velocities within the ipsilateral vascular territory was noted in 70% (9/13), and bilaterally in 54% (7/13) of the treated patients. None of the patients had silent emboli.

**Conclusions:** Intra-aneurysmal and parent vessel hemodynamic changes after FD can be reliably assessed by the cerebral angiography and transcranial doppler with important implications for the prediction of successful treatment.

**Keywords: cerebral aneurysm, flow diversion, cerebral hemodynamics, cerebral angiogram, cerebral embolization, transcranial doppler**

## INTRODUCTION

Flow diversion (FD) has emerged as **one** of the main methodologies for treatment of wide neck aneurysms, aimed to achieve aneurysm thrombosis by the reduction of intra-aneurysmal flow. Multiple studies utilizing various quantification methods, such as computation fluid dynamics (CFD) (1), optical flow maps (2), and angiographic parameters (3) have defined intra aneurysmal hemodynamic changes as the principal physiologic mechanism associated with treatment success after placement of FD stents. However, to this date, no specific qualitative angiographic parameters following FD have been established as a uniform predictor of successful aneurysm thrombosis. The "eclipse" sign is a characteristic angiographic finding of contrast stagnation in large and giant aneurysms after FD, historically associated with successful aneurysm thrombosis. The eclipse sign was **first** described by Lylyk et al. in the setting of FD with Pipeline Embolization Device (PED) (4). The authors demonstrated cases of contrast layering within the dependent portion of larger aneurysms typically persisting through the venous phase after embolization with PED and likely related to the marked disruption of aneurysm inflow. The appearance of eclipse sign was postulated to predict the progression to complete angiographic occlusion of the treated aneurysms. However, this hypothesis has not been fully investigated.

Another important physiologic factor associated with FD treatment of intracranial aneurysm that remains poorly investigated is the downstream hemodynamic effect on the parent vessel. The alteration of distal hemodynamics may play a pivotal role in the pathophysiology of intraparenchymal hemorrhage (IPH) and hyper-perfusion syndrome after endovascular and surgical treatment of large intracranial aneurysms (5, 6). Furthermore, the periprocedural thromboembolic risk remains a serious concern as it has been reported to occur in nearly 50% of the cases (7), yet the exact timing of this unfavorable event remains unclear. Transcranial doppler (TCD) is a readily available and easily accessible modality for bedside evaluation of intracranial hemodynamics and detection of silent emboli.

In this study, we investigated all aforementioned factors, such as qualitative and semi-quantitative comparative assessment of intra-aneurysmal hemodynamic changes by detailed appraisal of the eclipse sign in different phases of cerebral angiography, as well as the effect on downstream hemodynamics and the risk of silent emboli by critical evaluation of available TCD data in patients who underwent FD.

## MATERIALS AND METHODS

This was a multi-center retrospective analysis of 63 patients who underwent 65 embolization procedures with various FD devices. Patients were included in the study if (a) the FD procedure was completed successfully without adjunctive or prior coiling, (b) there was visible eclipse sign on post embolization angiography, (c) reliable follow-up diagnostic cerebral angiogram (DSA) data were available within 12 months after initial treatment. TCD was obtained in 13 patients. The approval of institutional review board (IRB) to conduct the study was obtained at each institution. A prospectively collected database of 133 patients who underwent FD was reviewed retrospectively. All patients who did not meet the above indicated study criteria were excluded from the analyses (adjunctive/prior coiling = 44; absence of eclipse sign = 24). Pertinent clinical and procedural characteristics, such as age, gender, aneurysm size and location, type of device used, periprocedural complications, and long-term clinical and angiographic outcome were collected through retrospective review of prospectively collected data.

### Comparative Angiographic Assessment of Intra-Aneurysmal Flow Changes Using the Eclipse Sign as a Marker for Flow Stagnation Pre- and Post-FD Treatment

We evaluated all angiographic data before and immediately after FD treatment for eclipse sign appearance in nine distinct phases of cerebral angiography as follows: (1) early arterial, (2) mid arterial, (3) late arterial, (4) early capillary, (5) mid capillary, (6) late capillary, (7) early venous, (8) mid venous, and (9) late venous. All patients underwent follow-up cerebral angiography at 12 months. Retrospective evaluation of all angiographic data was conducted by two experienced neurointerventionalists, followed by consensus adjudication. Complete occlusion was defined as no residual filling (D) according to the O'Kelly–Marotta scale (8). We conducted the univariate analysis comparing five separate angiographic eclipse sign appearance patterns (presence pretreatment, presence posttreatment, unchanged appearance, earlier appearance, and prolonged appearance in more than three phases) with complete aneurysm thrombosis at 12 months, followed by multivariate regression analysis including pertinent baseline variables (age, aneurysm size, device type used, and separate angiographic eclipse sign patterns) to identify the most significant predictor of complete aneurysm occlusion at 12 months.

### Transcranial Doppler Evaluation

Complete TCD evaluation was conducted in 13 consecutive patients within 24 h post FD, of whom three patients also had pretreatment TCD. All post procedural TCD examinations were performed at the bedside in the intensive care unit (ICU). The average systolic blood pressure (SBP) was closely monitored, and it ranged between 100 and 140 during examination. Mean flow velocities and pulsatility indices (PIs) were evaluated in all vascular territories of the treated aneurysm. All 13 patients underwent 30 min of continuous monitoring of the bilateral middle cerebral artery (MCA) (11/13) and bilateral posterior cerebral artery (PCA) (2/13) territories for silent emboli. Mean flow velocities (MFV) exceeding 70 cm/s in the middle cerebral artery (MCA) and 50 cm/s in the posterior cerebral artery (PCA), and PIs $\geq$ 1.2 were considered increased (9, 10).

## RESULTS

Among all patients who met inclusion criteria, 25% (16/65) were men, the mean age was 55 ($\pm$15.6), and the average aneurysm size

**TABLE 1 |** Clinical and procedural characteristics.

| Clinical and procedural characteristics | |
|---|---|
| Male % | 25% (16/65) |
| Age, mean (±SD) | 55 (±15.6) |
| Aneurysm size in mm, mean (±SD), median (range) | 16.3 (±8.17) 14 (4–38) |
| Device type–PED* | 33.8% (2/65) |
| Device type–P64 | 58.5% (38/65) |
| Device type–Surpass Evolve | 4.6% (3/65) |
| Device type–Fred | 30% (2/65) |
| Occlusion rate at 12 months | 89% (58/65) |
| Eclipse sign present prior to FD | 42% (27/65) |
| New Eclipse sign after FD | 58% (38/65) |
| Unchanged Eclipse Sign appearance after FD | 4.6% (3/65) |
| Prolonged Eclipse Sign appearance in ≥ 3 angiographic phases post FD | 89% (58/65) |
| Delayed Rupture | 3% (2/65) |
| Thromboembolic complications | 6% (4/65) |
| Intraparenchymal hematoma | 3% (2/65) |
| Mortality | 0% |
| Morbidity affecting mRS at 90 days | 3% (2/65) |

**PED, Pipeline embolization device; FD, flow diversion.*

was 16.3 (±8.17) ranging from 4 to 38 mm (**Table 1**). The most used FD device was P64 (Phenox, Bochum, Germany), followed by PED (Medtronic Neurovascular, Dublin, Ireland), Surpass Evolve (Stryker Neurovascular, Kalamazoo, MI, USA, and Fred (Microvention, Aliso Viejo, CA, USA). Combined ischemic and hemorrhagic complication rate was 6%, with 0% mortality, and 3% (2/65) morbidity due to delayed aneurysm rupture. About 89% (58/65) of the treated patients achieved complete aneurysm occlusion at 12 months.

Eclipse sign prior to FD was observed in 42% (27/65) with unchanged appearance in 4.6% (3/65) of the treated patients. None of these three patients achieved complete aneurysm occlusion. *De novo* eclipse sign appearance post FD implantation was noted in 58% (38/65) of the treated patients with only limited appearance in $< 3$ angiographic phases in four patients. None of these patients achieved complete aneurysm occlusion at 12 months.

Multivariate regression analysis revealed that among all analyzed variables, such as aneurysm size ($p = 0.99$), device type used ($p = 0.69$), age ($p = 0.87$), appearance of the eclipse sign pre-and post-FD (0.93), the most reliable predictor of permanent aneurysm occlusion at 12 months was prolonged and sustained eclipse sign visibility in more than three angiographic phases ($p < 0.001$). An example of a patient with a successfully treated large aneurysm and visible pre-intervention eclipse sign with significantly prolonged and delayed appearance post-FD embolization is depicted in **Figure 1**.

Among the 13 patients who underwent TCD evaluation, 11 had FD treatment in the anterior circulation aneurysm (**Table 2**). Elevation in MFV within the ipsilateral vascular territory was noted in 70% (9/13), and bilaterally in 54% (7/13) of the treated patients. All patients who had bilaterally increased MFVs also had robust flow into the contralateral MCA across the anterior communicating artery (A-Comm). Interval elevation in the PIs within the ipsilateral vascular territory was noted in 2/3 patients who underwent pre- and post-FD treatment TCD evaluation (**Table 3**). Detailed review of the TCD waveforms in those patients demonstrated changes in the systolic waves, accounting for the PIs elevation after FD (**Figure 2**). None of the patients had silent emboli or IPHs.

## DISCUSSION

Despite the proven beneficial effect and increasing utilization of FD devices for endovascular treatment of intracranial aneurysms, small percentage of the treated patients fail to achieve complete curative aneurysm obliteration and may require additional procedures (11–13). The basic mechanism of successful FD is the reduction of intra-aneurysmal flow leading to progressive thrombosis and gradual exclusion of the aneurysm from the intracranial circulation, while remodeling of the parent artery occurs around the endoluminal implant (14, 15). Following the inception of these fundamental principles and continued technological evolution, multiple FD devices with proven safety and efficacy have emerged over the past decades (16). Although seemingly different, all FD devices share a common mechanism, aimed to alter the hemodynamic interaction between the aneurysm and the parent vessel (14). Prediction of aneurysm occlusion following FD treatment is important to plan the optimal management and follow-up strategy for each individual patient. Intra-procedurally, it could help support decisions about using multiple devices to achieve the desired hemodynamic effect to maximize the aneurysm occlusion or to have closer monitoring for patients who are at a lower likelihood of aneurysm thrombosis.

As evidenced by the exhaustive literature involving CFD simulation, several key hemodynamic parameters have been identified as important predictors of successful thrombosis (17). However, despite the plethora of studies demonstrating the relationship between simulated hemodynamics and outcome, the CFD methodology remains utilized mostly in the research domain with little implications in routine clinical practice. The findings of our study provide a standardized approach for the prediction of successful FD treatment of intracranial aneurysms using readily available angiographic information. The combination of the qualitative and semi-quantitative methodology of visualization of eclipse sign presence in distinct angiographic phases used in our study is easily reproducible and widely applicable. Moreover, we established that the presence of the eclipse sign as a hallmark of aneurysmal flow stagnation can be often observed even prior to the FD treatment. In addition, we found that the presence of an eclipse sign after FD is not a reliable predictor of successful thrombosis. Instead, earlier and prolonged eclipse sign appearance is a highly predictive angiographic indicator of FD treatment success. This phenomenon can be explained by the increased intra-aneurysmal contrast residence time due to substantially decreased arterial

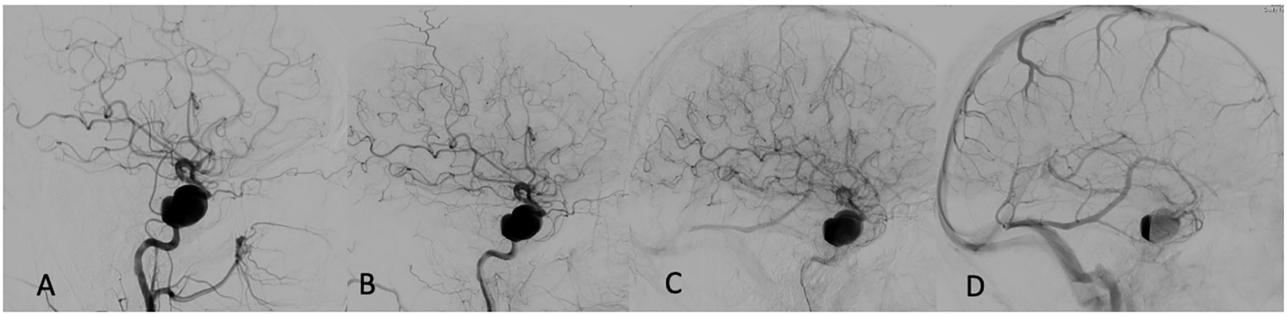


**FIGURE 1 |** Pre-embolization angiogram: **(A)** Early arterial phase. **(B)** Late arterial phase. **(C)** Capillary phase. **(D)** Venous phase—first appearance of eclipse sign prior to flow diversion (FD).

**TABLE 2 |** Summary of TCD results post FD treatment.

| Aneurysm/FD device location | Robust contralateral flow through COW | MFV R MCA | MFV L MCA | PI R MCA | PI L MCA |
|---|---|---|---|---|---|
| R ICA | No | **85** | 50 | **1.2** | **1.2** |
| R ICA | Yes | **75** | 68 | 0.78 | 0.78 |
| R ICA | Yes | **156** | **151** | 0.82 | 0.8 |
| L ICA | Yes | **90** | **101** | 0.8 | 0.8 |
| R ICA | Yes | **92** | **78** | 0.8 | 1 |
| R ICA | Yes | **159** | **101** | 1 | 0.57 |
| R MCA | Yes | **94** | **100** | 0.57 | 0.73 |
| L ICA | No | 69 | 56 | **1.2** | **1.2** |
| R ICA | Yes | **86** | **93** | 0.9 | 0.82 |
| L ICA | No | 128 | 92 | 0.82 | 0.94 |
| L ICA | Yes | **95** | **105** | 0.8 | 1.1 |
| Posterior circulation | **MFV R PCA** | **MFV L PCA** | **PI R PCA** | **PI L PCA** | |
| BA | No | 20 | 38 | 1 | 1 |
| R VA | Yes | 33 | 30 | **1.2** | 0.83 |

*Abbreviations: COW, circle of Willis; MFV, mean flow velocity; ICA, internal carotid artery; BA, basilar artery; VA, vertebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PI, pulsatility index. The bold values are used to indicate abnormally elevated values.*

**TABLE 3 |** Comparison of TCD results pre- and post-FD treatment in three patients.

| Aneurysm/FD device location | MCA MFV PRE | MCA MFV POST | PI RE | PI POST |
|---|---|---|---|---|
| R ICA | 82 | 85 | 0.9 | 1.2 |
| R ICA | 65 | 92 | 1.1 | 1.0 |
| L ICA | 95 | 93 | 0.9 | 1.2 |

inflow. The detailed comparative angiographic analysis between pre- and post-FD treatment presented in this study supports the aforementioned physiologic mechanisms and provides a reliable, practical, and widely applicable methodology for predicting successful aneurysm occlusion.

Aside from the significant intra-aneurysmal hemodynamic effect, it is logical to postulate that the FD treatment is associated with the downstream hemodynamic alteration. As detailed above, the well-known flow modulating effect on the aneurysm level has been a subject of extensive research. However, little is known about the parent vessel hemodynamic changes following endoluminal reconstruction with FD. Two small studies have demonstrated disrupted hemodynamics after PED placement (18, 19). The authors used quantitative magnetic resonance angiography (QMRA) to demonstrate lower MCA flows rates ipsilaterally to the treated aneurysm and attributed this phenomenon to delayed IPH—a rare and poorly understood complication of FD (20). The causal relationship between IPH and altered downstream hemodynamics was revealed by TCD examination in two patients in another small study by the same group (19). However, a substantial limitation of this study is that all TCD examinations after FD were performed

under general anesthesia immediately post-procedure. General anesthesia is associated with significant alterations of cerebral blood flow (CBF) through multiple physiologic mechanisms, such as the direct effect of anesthetic agents and ventilation parameters/end-tidal $pCO_2$ on cerebral vasomotor reactivity (VMR) (21). All TCD evaluations in our study were performed in an awake- and resting-state without significant alteration of normal physiologic state, except for BP control. Similar to prior studies, we established elevation of mean flow velocities in the ipsilateral vascular tree post-procedure. Furthermore, we demonstrated that contralateral MFV can be increased in patients with patent circle of Willis (COW), highlighting the FD effect on all involved vascular territories and potentially accounting for previously reported contralateral IPH (22). Another important finding in our study is the changes in PIs with more prominent peaked systolic waves (**Figure 3**). These findings confirm the hypothesis that the FD could alter the elasticity of the stented ICA segment, subsequently changing the blood pressure waveform propagated to the distal intracranial circulation (20, 23). Thus, it is logical to conclude that IPH after FD can be attributed to several factors, such as increased downstream hemodynamics, hemorrhagic transformation of thromboembolic events during the procedure, and dual antiplatelet-related coagulopathy.

In addition to the important pathophysiologic insights involving the parent vessel hemodynamic changes after FD, the results of our study have important practical implications. TCD is an easily accessible and widely available bedside tool, used in routine clinical practice. Patients with increased MFV and PI after FD may benefit from the more strict BP control and prolonged ICU observation, minimizing the postprocedural risk of reperfusion syndrome and IPH. Furthermore, our study demonstrates that thrombotic complications and distal embolization in the setting of FD are likely intraprocedural phenomenon.

## LIMITATIONS

There are several important limitations of this study. Given the strict inclusion criteria of absence of adjunctive coiling, we excluded many patients from our database. In addition, we excluded patients with no visible eclipse sign. Thus, our

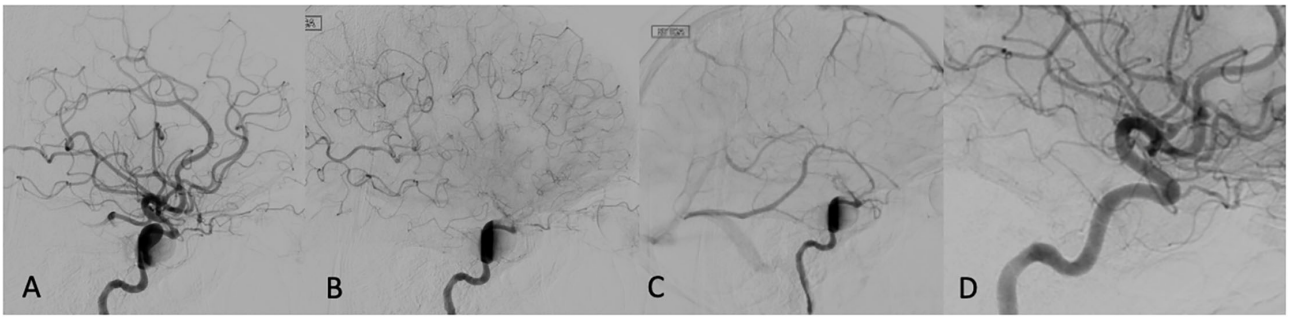


**FIGURE 2 |** Immediate post FD angiogram: first appearance of eclipse sign in late arterial phase **(A)** persisting through capillary **(B)**, and venous phases **(C)**. A 12-months follow-up showing complete aneurysm disappearance **(D)**.

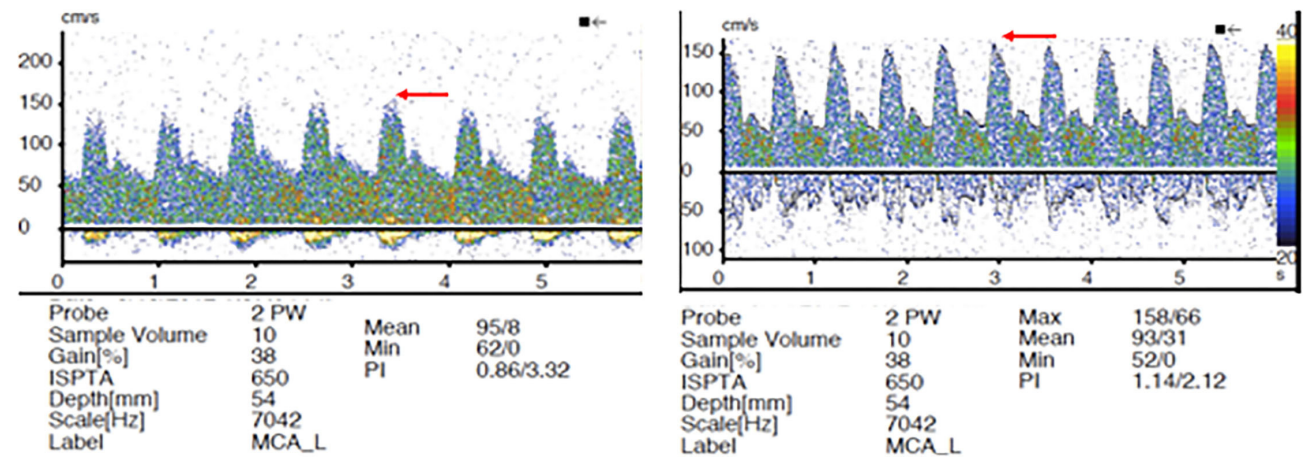


**FIGURE 3 |** Transcranial doppler (TCD) pre- and post-FD. Elevation of pulsatility indices (PIs) post-FD device placement with more spiked appearance in the peak systolic waves (red arrows).

findings cannot be applied in all patients treated with FD. Another limitation is the retrospective design of the study, as well as the relatively small sample size, especially in the TCD cohort.

## CONCLUSIONS

The sole presence of the eclipse sign does not correlate with subsequent aneurysm thrombosis, and it can be often observed even prior to FD. Instead, a comparative analysis of eclipse sign pre- and post-FD with earlier, prolonged, and sustained appearance in more than three angiographic phases provides a reliable prediction of aneurysm thrombosis, irrelevant of the aneurysm size, and type of device used. FD can also be associated with substantial downstream hemodynamic changes as evidenced by the frequently observed elevation of flow velocities and changes in pulsatility indices on TCD. Distal embolization after FD is a rare phenomenon. Further studies are needed to validate these results.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UCLA IRB. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

RR and ST contributed to conception and design of the study. RR, SS, and AS organized the database. HS performed the statistical analysis. RR wrote the first draft of the manuscript. SS, AS, HS, and ST wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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# Comparison of Pipeline Embolization Device and Traditional Endovascular Therapeutic Approaches in Distal Cerebral Circulation Aneurysms Using Propensity Score Matching Analysis

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**Background:** Coiling and stent-assisted coiling remain the first-line treatments for distal cerebral circulation aneurysms (DCCAs). The off-label use of the pipeline embolization device (PED) for these aneurysms has been explored recently but remains controversial.

**Objective:** To compare traditional endovascular therapeutic approaches (coiling and stent-assisted coiling) and PED for DCCAs in a multicenter cohort of patients.

**Methods:** A multicenter, retrospective cohort comparison study was conducted that included consecutive patients with unruptured DCCAs treated with either traditional endovascular therapeutic approaches or PED placement at three centers between 2016 and 2020. Propensity score matching analysis was applied to adjust for baseline risk factors between the PED and TET groups. Matching was based on age, sex, aneurysm size, location, morphology, adjunctive coiling, treatment history, and preoperative mRS score.

**Results:** In total, 209 patients with DCCAs treated with PED or traditional endovascular therapeutic approaches were identified. Thirty-seven patients underwent PED treatment, and 172 patients underwent traditional endovascular therapeutic approaches. After propensity score matching, 37 aneurysm pairs were matched, and the baseline characteristics of the patients were balanced between the groups. The complete occlusion rate between PED and traditional endovascular therapeutic approach in both matched cohorts (91.7 vs. 92.3%, $p > 0.78$) was similar. The rate of periprocedural treatment-related complications in both the PED and traditional endovascular therapeutic groups was 13.5%. Univariate analysis identified average parent vessel diameter as the only predictor of complete occlusion ($p = 0.038$).

**Conclusions:** PED is a viable option for treating DCCAs by providing occlusion and complication rates similar to those of traditional endovascular therapeutic approaches.

A rigid patient selection procedure and proper planning should be undertaken to reduce treatment-related complications.

**Keywords: aneurysm, complication, flow diversion, coiling, embolization**

## INTRODUCTION

The pipeline embolization device (PED; Covidien, Irvine, California) is a flow-diverting stent approved for treating large or giant wide-neck proximal carotid aneurysms (1). Recently, the off-label use of PED has been extended to almost all types of cerebral aneurysms, including distal cerebral circulation aneurysms (DCCAs) located at or beyond the M1 middle cerebral artery (MCA), P1 posterior cerebral artery, and A1 anterior cerebral artery (ACA) (2). Coiling and stent-assisted coiling as traditional endovascular therapeutic approaches remain the first-line treatment for DCCAs, wherein aneurysms at these locations remain a challenge for both microsurgical and traditional endovascular therapeutic approaches (3, 4). The promising performance of PED demonstrated earlier for anatomically complex abnormalities offers a new treatment option for refractory lesions (5). The luminal reconstruction ability and avoidance of PED in jailing a microcatheter to coil the aneurysmal sac further justifies its use (6). However, PED application in these settings has particular concerns, such as the narrow parent artery diameter and the mismatch in the distal–proximal artery diameters complicating the placement of PED, which may hamper the flow diversion effect of the stent.

Although several studies have compared the safety and efficacy of the PED and traditional endovascular therapeutic approaches, this study is the first to compare PED and traditional endovascular therapeutic approaches in matched groups of patients with DCCAs (7).

## MATERIALS AND METHODS

### Patient Selection

The studies involving human participants were reviewed and approved by the ethical committee of Beijing Tiantan Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Consecutive series of patients with unruptured DCCAs who underwent PED or traditional endovascular therapeutic approaches at three Chinese centers between March 2016 and November 2020 were included in this study. The indications for flow-diverting endovascular therapy or traditional endovascular therapeutic approaches in each case were based on medical comorbidities, complex geometrical morphology, and patient preferences. Data regarding the patients' general information, presentation, aneurysm morphology, procedural details, treatment outcomes, postoperative complications, and aneurysm occlusion at follow-up imaging were collected. Based on the outcome, every patient treated with PED was matched in a 1:1 fashion with a patient treated with traditional endovascular therapeutic approaches.

**Abbreviations:** ACA, anterior cerebral artery; MCA, middle cerebral artery; PED, pipeline embolization device; DCCAs, distal cerebral circulation aneurysms; IQR, interquartile range; mRS, modified Rankin Scale; FD, flow diversion; TET, traditional endovascular therapeutic.

### Procedural Details

All patients were premedicated with dual antiplatelet drugs that consisted of a daily dose of 100 mg aspirin and 75 mg clopidogrel, both administered at least 7 days before the procedure. We used thromboelastography to discriminate hyporesponders to clopidogrel. The subjects who displayed an inhibition rate under 30% were deemed hyporesponsive to clopidogrel. These patients were administered a booster dose of 300 mg clopidogrel. Aspirin was continued for 12 months, and clopidogrel was discontinued 6 months after the procedure if no other coronary or cerebral comorbidities necessitated the use of antiplatelet drugs.

### Clinical and Imaging Follow-Up

Modified Rankin scores (mRS) were evaluated before treatment, on discharge, and at the last follow-up. Patient and aneurysm characteristics, procedural details, and treatment-related complications were recorded. All patients were followed up with digital subtraction angiography or computed tomography angiography, and aneurysm occlusion was graded using the 3-point modified Raymond scale.

### Statistical Analyses

Continuous variables were expressed as the mean ± standard deviation and compared using the *t*-test or Mann–Whitney *U*-test. Categorical variables were compared using the $\chi^2$ test or Fisher's exact test. Statistical significance was set at $p < 0.05$. Additionally, propensity score matching (PSM) was used to balance the patients' backgrounds between the PED and traditional endovascular therapeutic groups. PSM was based on age, sex, aneurysm size, location, morphology, adjunctive coiling, previous treatment history, and preoperative mRS. We conducted a one-to-one matched analysis without replacement based on the estimated propensity score. One-to-one matched analysis used the nearest-neighbor method without replacement with the closest estimated propensity score. According to PED use and traditional endovascular therapeutic approaches followed, baseline characteristics, and operative outcomes were compared in both propensity score-matched and unmatched cohorts, respectively. Univariate analysis was used to test covariates predictive of the following dependent variables: periprocedural treatment-related complications and complete occlusion. Predictive factors found in the univariate analysis ($p < 0.05$) were entered into a multivariate conditional logistic regression analysis. Statistical analyses were performed using R 3.6.1 (Vienna, Austria; http://www.R-project.org/).

# RESULTS

## Baseline Characteristics

The baseline characteristics and operative data for patients undergoing PED or traditional endovascular therapeutic approaches are summarized in **Table 1**. In all, 299 patients with 209 unruptured aneurysms were included in our study. The baseline sample included 37 consecutive patients in the PED group and 172 cases in the unmatched traditional endovascular therapeutic group.

In the PED group, most aneurysms (29/37, 78.4%) were non-saccular. MCA aneurysms were the most commonly treated lesions (27/37, 72.9%), 22 of them located on the M1 segment and five on the M2 segment. ACA and PCA aneurysms were the second most common type (5/37, 13.5%). Two were located in segment A1 and three in segment A2 for ACA aneurysms. As for PCA aneurysms, three were located in the P1 segment and two in the P2 segment. Six (16.2%) patients had recurrent aneurysms, of whom four were previously treated with primary coil embolization and two were treated with clip reconstruction. The mean maximal aneurysm diameter was 12.3 mm (± 5.5). The majority of aneurysms found had a maximum diameter of 5.0–14.9 mm (25/37, 67.5%); more giant aneurysms (15.0–24.5 mm) comprised the second largest group at 21.6%. The average parent vessel diameter was 2.3 mm (± 0.4).

In the unmatched traditional endovascular therapeutic group, most aneurysms (126/181, 69.6%) had non-saccular morphology and a maximum diameter of 5.0–14.9 mm (101/172, 57.8%). Smaller aneurysms (<5 mm) comprised the second largest group at 34.3%. Most of the aneurysms (106/172, 61.6%) were located in the MCA segment. Three (1.7%) patients had recurrent aneurysms, of whom one was previously treated with primary coil embolization and two were treated with clip reconstruction.

In the unmatched cohort, most of the baseline characteristic variables were significantly different. Aneurysms treated with PED occurred in younger patients [53 years (interquartile range, IQR 39–59) vs. 57 years (IQR 49–63), $p = 0.004$] and were larger in maximum diameter (12.3 ± 5.5 mm vs. 7.6 ± 4.8 mm, $p < 0.001$). No significant difference was found in non-saccular aneurysm morphology between the PED and traditional endovascular therapeutic groups (29/37, 78.4% vs. 119/172, 69.2%). No significant differences were observed for patients' sex, aneurysm location, and pretreatment-mRS.

After PSM, 37 aneurysm pairs were matched, and the baseline characteristics were well-balanced between the two groups. The average diameter of proximal and distal parent vessel showed a significant difference in the unmatched cohort (2.3 ± 0.4 mm with PED vs. 2.6 ± 0.6 mm with traditional endovascular therapeutic approaches, $p = 0.025$); however, after PSM, there was no significant difference in the matched cohort (2.3 ± 0.4 mm with PED vs. 2.3 ± 0.4 mm with traditional endovascular therapeutic approaches, $p = 0.936$). The aneurysm diameters of the PED and matched traditional endovascular therapeutic groups were still different (12.3 ± 5.5 mm vs. 9.2 ± 6.3 mm, respectively; $p < 0.005$); however, there was no statistical difference between the subgroups.

## Procedural Results and Angiographic Follow-Up

The applied procedures were successful in all patients in both the PED and traditional endovascular therapeutic groups, and the operative outcomes are summarized in **Table 2**. In the PED group, treatment with a single PED was performed in 30 cases (81.1%). Multiple devices were used in 7 cases (18.9%). Adjunctive coil placement was performed in 9 cases (24.3%). In the matched traditional endovascular therapeutic group, treatment with simple coiling was performed in 28 cases (75.7%). Stent-assisted coiling was performed in 9 cases (24.4%), and in 1 case (2.7%) two stents were used in one aneurysm. In the unmatched cohort, patients who underwent traditional endovascular therapeutic approaches experienced more adjunctive coiling treatment than those in the PED group (24.3% vs. 56.4%, $p < 0.001$) and had more previously treated aneurysms (16.2% vs. 1.7%, $p = 0.001$).

In the unmatched cohort, the proportion of patients undergoing imaging follow-up in the PED group was significantly higher than in the traditional endovascular therapeutic group (36/37, 97.4% vs. 132/172, 76.7%, $p = 0.004$), while after PSM, there was a significant difference in the matched cohort (36/37, 97.4% vs. 26/37, 70.3%, $p = 0.002$). In both the unmatched and matched cohorts, there was no difference in median angiographic follow-up time between the PED and traditional endovascular therapeutic groups [median (IQR): 12 (6–12) vs. 8 (6–15) months, $p = 0.692$; and median (IQR): 12 (6–12) vs. 8 (6–28) months, respectively; $p = 0.586$]. In the PED group, 33 cases (91.7%) showed complete obliteration with O'Kelly–Marotta scale D, and 3 out of 33 (8.3%) showed near-complete occlusion with O'Kelly–Marotta scale C. In the matched traditional endovascular therapeutic group, 32/33 (92.3%) showed complete occlusion, 1/26 (3.8%) showed near-complete occlusion, and 3.8% of cases showed incomplete occlusion at the last follow-up. The complete occlusion status was similar between PED and traditional endovascular therapeutic groups in both the matched ($p > 0.777$) and unmatched cohorts ($p = 1$).

## Treatment-Related Complications and Clinical Follow-Up

Clinical data were available for all patients in both the matched groups. Treatment-related complication rates in the unmatched cohort were similar between the PED and traditional endovascular therapeutic groups (5/37, 13.5% vs. 20/172, 11.6%, $p = 0.967$), while after PSM, the complication rate was more similar (5/37, 13.5% vs. 5/37, 13.5%). Good clinical outcome (mRS = 0–2) rate at the latest follow-up did not differ between the cohorts.

In the PED group, 91.9% of patients (34/37) had good clinical outcomes at the last follow-up. Three patients experienced immediate post-procedural complications associated with a perforation infarction. The first patient experienced Heubner's perforator-territory stroke with an infarct in the left basal ganglia and centrum semiovale, presenting with mixed aphasia and right limb movement disorder. The symptoms slightly

**TABLE 1 |** Baseline characteristics and operative data for patients undergoing PED or TET approaches.

| | Unmatched cohort | | *p*-value | Matched cohort | | *p*-value |
|---|---|---|---|---|---|---|
| | **PED (*n* = 37)** | **TET (*n* = 172)** | | **PED (*n* = 37)** | **TET (*n* = 37)** | |
| Age in years (IQR)$^+$ | 53 (39–59) | 57 (49–63) | 0.004* | 53 (39–59) | 56 (50–61) | 0.108 |
| Male sex$^+$ | 21 (56.7%) | 69 (40.1%) | 0.064 | 21 (56.7%) | 18 (48.6%) | 0.485 |
| **Location of aneurysm$^+$** | | | | | | |
| ACA | 5 (13.5%) | 40 (23.3%) | 0.191 | 5 (13.5%) | 6 (16.2%) | 0.744 |
| MCA | 27 (72.9%) | 106 (61.6%) | 0.193 | 27 (72.9%) | 24 (64.9%) | 0.451 |
| PCA | 5 (13.5%) | 26 (15.1%) | 0.804 | 5 (13.5%) | 7 (18.9%) | 0.528 |
| **Maximal AN diameter$^+$ (mean ± SD)** | 12.3 (± 5.5) | 7.6 (± 4.8) | <0.001* | 12.3 (± 5.5) | 9.2 (± 6.3) | 0.005* |
| <5 mm | 3 (8.1%) | 59 (34.3%) | 0.002* | 3 (8.1%) | 9 (24.3%) | 0.058 |
| 5–14.9 mm | 25 (67.5%) | 101 (58.7%) | 0.318 | 25 (67.5%) | 22 (59.5%) | 0.469 |
| 15–24.9 mm | 8 (21.6%) | 11 (6.4%) | 0.009* | 8 (21.6%) | 5 (13.5%) | 0.359 |
| ≥25 mm | 1 (2.7%) | 1 (0.6%) | 0.323 | 1 (2.7%) | 1 (2.7%) | 1 |
| **Previous treatment$^+$** | 6 (16.2%) | 3 (1.7%) | <0.001* | 6 (16.2%) | 3 (8.1%) | 0.477 |
| Endovascular | 4 (66.7%) | 1 (33.3%) | 0.524 | 4 (66.7%) | 1 (33.3%) | 0.524 |
| Microsurgical clipping | 2 (33.3%) | 2 (66.7%) | 0.524 | 2 (33.3%) | 2 (66.7%) | 0.524 |
| **Morphology$^+$** | | | | | | |
| Non-saccular | 29 (78.4%) | 119 (69.2%) | 0.265 | 29 (78.4%) | 27 (73%) | 0.588 |
| Saccular | 8 (21.6%) | 53 (30.8%) | 0.265 | 8 (21.6%) | 10 (27%) | 0.588 |
| **Pretreatment-mRS$^+$** | | | | | | |
| Good (mRS = 0–2) | 37 (100.0%) | 170 (98.8%) | 1 | 37 (100.0%) | 37 (100.0%) | 1 |
| Poor (mRS = 3–5) | 0 (0%) | 2 (1.2%) | 1 | 0 (0%) | 0 (0%) | 1 |
| **Average parent vessel diameter (mean ± SD)** | 2.3 (± 0.4) | 2.6 (± 0.6) | 0.025* | 2.3 (± 0.4) | 2.3 (± 0.4) | 0.936 |
| **Adjunctive coil placement$^+$** | 9 (24.3%) | 97 (56.4%) | <0.001* | 9 (24.3%) | 9 (24.3%) | 1 |
| **Multiple stent placement** | 7 (18.9%) | 9 (5.2%) | 0.012* | 7 (18.9%) | 1 (2.7%) | 0.061 |

*Data are reported for the overall series and the propensity score-matched groups. PED, pipeline embolization device; TET, traditional endovascular therapeutic; IQR, interquartile range; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; mRS, modified Rankin Scale; SD, standard deviation; *, significant result; $^+$, baseline factors used for propensity score matching.*

**TABLE 2 |** Operative outcomes for patients undergoing PED or TET approaches.

| | Unmatched cohort | | *p*-value | Matched cohort | | *p*-value |
|---|---|---|---|---|---|---|
| | **PED (*n* = 37)** | **TET (*n* = 172)** | | **PED (*n* = 37)** | **TET (*n* = 37)** | |
| **Last angiographic follow-up** | 36 (97.4%) | 132 (76.7%) | 0.004* | 36 (97.4%) | 26 (70.3%) | 0.002* |
| Follow-up in months, median (IQR) | 12.0 (6.0–12.0) | 8.0 (6.0–15.0) | 0.692 | 12.0 (6.0–12.0) | 8.0 (6.0–28.0) | 0.586 |
| **Occlusion status in last follow-up** | | | | - | | |
| Completely occluded | 33 (91.7%) | 125 (94.7%) | 0.777 | 33 (91.7%) | 24 (92.3%) | 1 |
| Near completely occluded with neck remnant | 3 (8.3%) | 5 (3.8%) | 0.488 | 3 (8.3%) | 1 (3.8%) | 0.853 |
| Incompletely occluded | 0 (0%) | 2 (1.5%) | 1 | 0 | 1 (3.8%) | 0.419 |
| **Treatment-related complications** | 5 (13.5%) | 20 (11.6%) | 0.967 | 5 (13.5%) | 5 (13.5%) | 1 |
| **Clinical follow-up** | - | | | - | | |
| Good (mRS = 0–2) | 35 (94.6%) | 167 (97.1%) | 0.306 | 35 (94.6%) | 36 (97.3%) | 0.607 |
| Poor (mRS = 3–5) | 2 (5.4%) | 5 (2.9%) | 0.793 | 2 (5.4%) | 1 (2.7%) | 1 |
| Death (mRS = 6) | 0 (0%) | 0 (0%) | 1 | 0 (0%) | 0 (0%) | 1 |

*Data are reported for the overall series and the propensity score-matched groups. PED, pipeline embolization device; TET, traditional endovascular therapeutic; *, significant result; IQR, interquartile range; mRS, modified Rankin Scale.*

improved with intravenous administration of tirofiban; however, residual symptoms with mRS of 3 were observed at 6 months follow-up. The second patient, who had a right MCA M1 aneurysm, presented with aphasia, left central facial paralysis, and left limb hemiplegia. Digital subtraction angiography showed a diminished internal lenticulostriate artery, and computed tomography revealed new infarct in the right temporal island and basal ganglia 3 days after the procedure.

**TABLE 3 |** Treatment-related complications in the propensity score-matched groups.

| | PED | TET | *p*-value |
|---|---|---|---|
| Perforation | 3 (8.1%) | 1 (2.7%) | 0.607 |
| Thrombus formation | 1 (2.7%) | 4 (10.8%) | 0.354 |
| In-stent stenosis | 1 (2.7%) | 0 | 0.419 |
| SAH | 0 | 0 | 1 |

*PED, pipeline embolization device; TET, traditional endovascular therapeutic; SAH, subarachnoid hemorrhage.*

The patient was discharged with central facial paralysis and severe hemiparesis (mRS 4). The third patient presented with aphasia and hemiparesis; symptoms improved with intravenous administration of tirofiban, and mRS was 1 at follow-up. One patient developed severe right hemiplegia due to acute in-stent stenosis, and the blood flow recovered after tirofiban treatment. One patient developed severe right hemiparesis due to acute parent artery thrombosis that completely recanalized after systemic tirofiban injection. The patient was discharged with mild right limb weakness and a mRS of 1 at the 6-month follow-up.

In the matched traditional endovascular therapeutic group, 97.4% of patients (36/37) had good clinical outcomes (mRS 0–2) at the last follow-up. Overall, five patients (13.5%) experienced immediate postprocedural treatment-related complications associated with cerebral infarction. Four patients experienced thrombus formation, resulting in aphasia and hemiparesis. One patient presented with small perforator occlusion that manifested as severe hemiplegia and aphasia and was left with severe dysfunction with an mRS of 3 at the 8-month follow-up. Complications in both matched groups are listed in **Table 3**.

## Predictors of Aneurysm Occlusion Status and Complications

The following factors were tested as predictors of periprocedural treatment-related complications or complete occlusion: age, aneurysm size, aneurysm location, previous treatment, adjunctive coil placement, multiple stent placement, and average parent artery diameter. In the PED group, the univariate analysis revealed the average parent artery diameter as the only predictor of complete occlusion (odds ratio, 0.02; 95% CI, 0–0.79; $p = 0.038$). Multivariate logistic regression analysis did not reveal any significant factors.

# DISCUSSION

In this retrospective matched-pair analysis, we found no significant differences in complete occlusion at follow-up and treatment-related complication rates between PED and traditional endovascular therapeutic approaches in the treatment of unruptured DCCAs.

## Angiographic Outcome

Our study demonstrated a complete occlusion rate of 89.7% and a near-complete occlusion rate of 100%, which was comparable with the results of a meta-analysis of distal anterior circulation aneurysms with a median follow-up of 6 months by Cagnazzo et al. (8). This rate also appears higher than the general occlusion rate of 80% that was reported in other studies and a meta-analysis of flow diversion (FD) (9). Extensive studies have shown a high complete occlusion rate in patients with DCCAs after off-label use of PED (9). Atallah et al. (10), retrospectively reviewed 23 DCCAs treated with PED. At the last follow-up, 78.3% of patients manifested complete occlusion, and 95% had a good clinical outcome (mRS 0–2). Bender et al. (11) reviewed 67 patients with DCCAs treated with PED and reported a complete occlusion rate of 88% at 6 months, and almost 94% of patients showed a good clinical outcome. Similarly, Primiani et al. (12) found 83% complete aneurysm occlusion and 95% of patients achieving good clinical outcomes after treating 65 aneurysms at or beyond the A2, M2, and P2 segments using PED. Although traditional endovascular therapeutic approaches and PED achieved similar rates of complete occlusion in this study, there were limitations to the treatment with traditional endovascular therapeutic approaches in distal vessels. Regardless of whether simple coiling or stent-assisted coiling is used, it is not easy to deploy a catheter in a stable position at such a distal location (13). In most cases, PED avoids manipulation of the aneurysmal lumen. For example, in this study, there was an ACA segment A2 aneurysm treated with PED, which avoided unstable manipulation in the aneursymal lumen (**Figures 1A,B**). We also had an aneurysm in the A1 segment of the ACA that was treated with stent assisted coiling due to its relatively ideal location for catheter placement (**Figures 1C,D**).

As for predictors of aneurysm occlusion, Cagnazzo et al. (8) demonstrated different occlusion rates depending on the artery involved. MCA location was an independent factor for incomplete occlusion. Similarly, of the three aneurysms that were not completely occluded in our series, all were located in the M1 segment. The diameter of the MCA M1 segment was relatively larger than that of the distal artery, which may explain why only a smaller average parent artery diameter was associated with a higher complete occlusion rate in our univariate analysis.

The significant rate of recurrence treated with traditional endovascular therapeutic approaches justifies the implementation of PED for the treatment of DCCAs (14). Lin et al. (15), reviewed nine recurrent aneurysms that were subsequently retreated with PED and showed 83% complete aneurysm occlusion. Our study demonstrated comparable results, wherein 83% (5/6) of recurrent aneurysms achieved satisfactory results in the PED group. Henkes et al. (16), reported that complete occlusion was achieved in only 46.9% of retreated aneurysms after the first recoiling attempt and 35.2% after the second retreatment. Tahtinen et al. (17), focusing on the role of stent-assisted coil embolization for recurrent aneurysms, found that only 59% of aneurysms achieved complete occlusion, and 16% of patients required additional endovascular treatment. In a study by Daou et al. (18) of PED for previously coiled

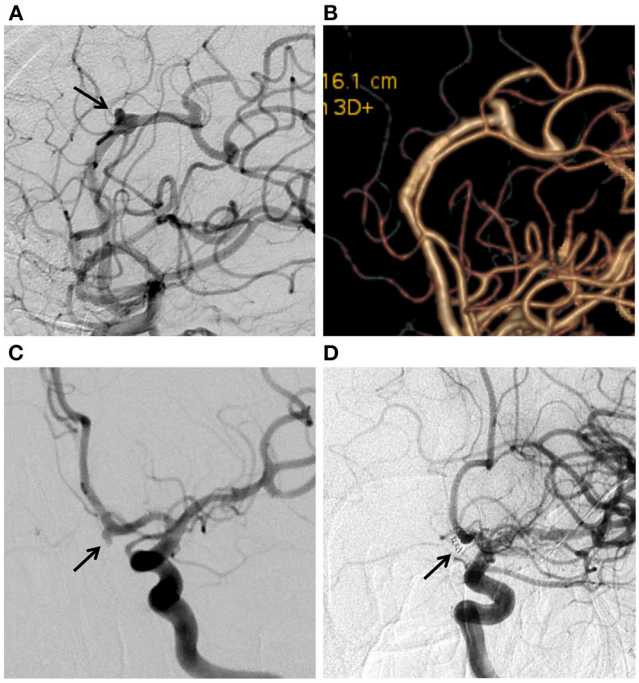


**FIGURE 1 | (A)** Digital subtraction angiogram (DSA) in working position views immediately after flow diversion shows diminished filling of the aneurysms (arrow) on the ACA A2 segment. **(B)** Twelve-month DSA follow-up shows aneurysm complete occlusion. **(C)** DSA showing the ACA A1 aneurysm (arrow). **(D)** 6-month DSA follow-up shows aneurysm complete occlusion after Stent assisted coiling treatment.

aneurysms, in 25% of patients, coiling was attempted twice before resorting to PED placement, which was the definitive and final treatment. The complication rates observed in these studies were comparable to those observed with the recoiling of previously coiled aneurysms. Renowden et al. (19) reported a complication rate of 3% after recoiling of recurrent aneurysms. Ringer et al. (20) reported that the total risk of retreatment mortality was 1.28% per patient. These complication rates are similar and even lower with coiling than with PED; however, in cases with multiple retreatments, the complication risk of conventional endovascular techniques may heighten with the number of reinterventions required. Overall, higher recurrence rates for previously coiled aneurysms are found with recoiling than with PED treatment, which justifies PED implementation for the treatment of previously coiled aneurysms. FD *via* PED can be positively considered as a management alternative for recurrent distal cerebral aneurysms.

The risk of in-stent stenosis (acute or chronic) must be considered when using PED in DCCAs. Two patients (7.1%, 2/28) were found to have chronic asymptomatic in-stent stenosis in our study, with 50% and 100% in-stent stenosis, respectively, at the imaging follow-up. This is comparable to the 5–10% risk in the general PED population and the 4.8% chronic in-stent stenosis rate reported by Cagnazzo et al. (8), Ravindran et al. (21) reported a rate of chronic in-stent stenosis of 7.1% after reviewing 162 intracranial aneurysms, and all these patients remained asymptomatic. Selecting a proper PED size is essential to ensure adequate FD and to limit the risk of ischemic complications. This phenomenon is common in the basilar and posterior cerebral arteries because the significant change in vascular diameter from the basilar artery to the posterior cerebral artery makes it challenging to completely open the distal end of the PED. To resolve this problem, we suggest using two PEDs of different sizes to treat fusiform or dissecting aneurysms with a wide aneurysm sac neck. However, multiple stents increase the metal coverage, which mitigates FD while also increasing the risk of in-stent stenosis (22). Therefore, it is imperative to recognize the native anatomy of the distal vessel to select an appropriately sized PED.

## Treatment-Related Complications

The effectiveness of PED must be weighed against the risk. Our study showed relatively higher treatment-related complication rates of 13.5% (5/37) compared with other reports of DCCAs, with 5.4% (2/37) morbidity. Five patients presented with immediate post-procedural cerebral infarction. Most symptoms had improved at discharge or clinical follow-up, with mRS scores of 0–1. In both the matched groups, we did not observe any new permanent neurological deficits at follow-up.

Regarding potential ischemic complications for ACA A1 segment aneurysms, we should consider the perforating medial lenticulostriate vessels. We found one ACA A1 aneurysm in which the recurrent artery of Heubner was jailed, and the patient experienced permanent symptomatic perforator-territory ischemia. However, some studies have indicated that the diameter of the recurrent artery of Heubner approximates to that of the ophthalmic artery and anterior choroidal artery, vessels that can be safely jailed when PED is used in patients with distal ICA aneurysms (22). PED used in ACA aneurysms may also induce perforator occlusion, especially at the A1-A2 junction (23, 24).

Our study, which included 27 MCA aneurysms, demonstrated a perforator-territory ischemia rate of 7.4% (2/27 patients) after the coverage of lenticulostriate vessels in the M1 segments. Kathryn et al. (25) reported a similar rate of 9.6% (5/52 patients) after the coverage of MCA M1 segments by flow diverters, but none had radiographic infarcts in the lenticulostriate territory. A study also focused on the covered perforator vessels of circle of Willis aneurysms treated by a flow diverter and showed a rate of temporary ischemic complications of 17.6% (3/17 patients) (26). Branching vessels and perforators arising from aneurysms are abundant at the level of the A1 segment and the M1 segment of the ACA and MCA, respectively, thereby increasing the risk of perforator stroke when they are covered with PED (27). Regarding non-perforator areas, Primiani et al. (12) analyzed 65 patients with A2, M2, P2, and distal aneurysms treated with PED. In their study, the overall complication rate was 7.7%, which was significantly lower than that found in our study. Furthermore, only one patient (1.5%) with an M2 aneurysm showed ischemic stroke and slow filling of the side branch, which resolved after administration of a IIb/IIIa inhibitor.

Asymptomatic occlusion of covered cortical branches appears universal, yet, ischemic complications are preferably linked to lenticulostriate territory occlusions. The fact that in our study,

three of these events led to patient neurological deficits highlights the importance of awareness that these complications can occur at any time during the endovascular procedure, especially in the MCA M1 and ACA A1 segments. It is important to know how to respond in every possible situation and to be prepared. The overall complication rates with PED were similar to those found in the traditional endovascular therapeutic group. However, there were some differences in the types of complications between the two groups. Perforator-territory ischemic events were more common in the PED group, whereas thrombus formation was more common in the traditional endovascular therapeutic group (**Table 3**).

Several studies have also reported low hemorrhagic complication rates in PED for intracranial aneurysms (28). However, delayed aneurysm rupture has been reported after treatment with PED, and this is one of the major concerns. Brinjikji et al. (29) reported that the incidence of delayed aneurysmal subarachnoid hemorrhage after PED was ∼4%. Some hemodynamic studies have attempted to explore the mechanism of delayed aneurysm rupture. Hassan et al. (30) found that a slow blood flow jet still exists inside the aneurysm at the end of the procedure. Cebral et al. (31) reported that PED placement could increase intra-aneurysmal pressure. Similarly, Li et al. (32) found that the luminal flow velocity was decreased in aneurysms with delayed rupture, while the pressure was increased. These factors may be related to delayed aneurysm rupture after treatment. For some large or huge aneurysms, a combination treatment of PED placement and coil embolization of the aneurysm has been recommended to promote intraluminal thrombosis and the transition from an unstable thrombus to a stabilized, organized thrombus (33).

### Limitations

This study has several limitations, including those inherent to a retrospective observational series, such as the limited number of cases and the relatively short follow-up period. While both PED and traditional endovascular therapeutic cohorts constituted consecutive cases, data collection and analysis were performed retrospectively and, as such, were subject to incomplete datasets. Extensive studies with long-term follow-up are needed to confirm the safety and efficacy of PED in DCCAs.

## CONCLUSIONS

PED treatment is a reliable and safe alternative for the treatment of DCCAs, especially in the case of recurrent aneurysms or those that are not amenable to traditional surgical or endovascular modalities. Proper planning and stringent patient selection may lead to better clinical outcomes.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

CM and HZ acquired most of the data, analyzed and interpreted the data, and drafted the article. SL, FL, and JS participated in the interventional procedures as assistants and helped to analyze the data. CJ and YZ participated in the interventional procedures as primary surgeons and made substantial contributions to the design of the work. All authors contributed to the article and approved the submitted version.

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# Flow Diversion for the Management of Ruptured Intracranial Arterial Infudibular Dilatation: Proof of Principle and Therapeutic Protocol

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Thought to be benign anatomical variants, cerebral infundibular dilatations (ID) are most commonly encountered at the junction of the internal carotid artery (ICA) and the posterior communicating artery (PcomA). The true nature of this entity remains controversial, as some literature reports suggest they should be considered preaneurysmal lesions and a potential source of devastating subarachnoid hemorrhage. This report describes cases of presumably ruptured IDs and their therapeutic endovascular management. We retrospectively reviewed and analyzed patients with isolated subarachnoid hemorrhage (SAH) where the only potential cause was ruptured cerebral IDs, treated or not, between January 2012 and June 2021. Morphological and radiological features, treatment and procedural considerations, clinical and angiographic outcomes were also reviewed. Natural history of the ID is poorly understood, and its relation to SAH remains controversial. Ruptured cerebral IDs can be the suspected cause of bleeding if no other vascular lesion is present during multimodal examinations. Endovascular flow diversion stenting is safe and effective for the proper treatment of ruptured IDs. Pending further validations with longitudinal data are needed to legitimate the natural course of these mysterious lesions.

**Keywords: infundibular dilatation, posterior communicating arteries, subarachnoid hemorrhage, flow diverter, anterior choroidal artery**

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## INTRODUCTION

The clinical significance of an infundibular dilatation (ID) at the origin of an intracranial artery remains a matter of debate. Those junctional dilatations have been postulated to have specific radiological characteristics with qualitative parameters including a maximum diameter of 3 mm, teardrop bulging or funnel-like shapes, and a lack of an aneurysmal-like neck (1). An infundibulum usually can be seen at branching sites within the intracranial circulation, typically at the internal carotid artery (ICA) and the posterior communicating artery orifice (2). However, IDs can less frequently occur at the level of the anterior choroidal artery, ophthalmic artery, anterior communicating artery, or superior cerebellar artery, or across the middle cerebral artery (**Figure 1**) (3, 4).

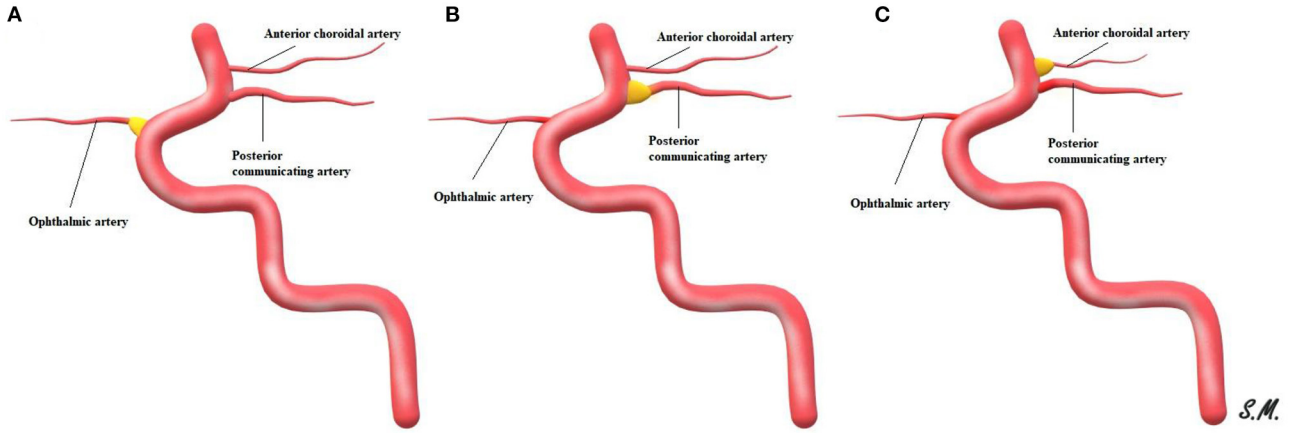


**FIGURE 1 |** Schematic representation of ID with the adjacent origin of an intracranial artery, ophthalmic artery ID **(A)**, posterior communicating artery ID **(B)** and ID at anterior choroidal artery **(C)**.

Although little is known regarding the actual natural courses of these entities, intracranial arterial infundibulums are commonly encountered during neurovascular clinical examinations (5). The reported incidence varies between 2.2 and 24.6% at the population level, and these entities may be misdiagnosed as aneurysms on non-invasive imaging (6, 7). IDs are commonly accepted to be benign lesions or normal anatomic variations whose clinical significance is unclear or non-existent (8). However, multiple reports have described ruptures with clinical sequelae and aneurysmal transformations of an ID (9–12). A diagnostic and therapeutic dilemma may occur only after a junctional dilatation is identified in the setting of unexplained subarachnoid hemorrhage (SAH) (13). The available literature is scarce and insufficiently consistent to entirely resolve the clinical uncertainties of IDs. Herein, we aim to emphasize and report the experience of a moderate-volume single center regarding the diagnosis and treatment management of ruptured IDs in the setting of otherwise unexplained SAH.

# METHODS

## Patients

An institutional review board-approved retrospective review was performed to identify and analyze patients with isolated and non-aneurysmal SAH. The only objective cause was ruptured cranial IDs, either treated or untreated, between January 2012 and June 2021. A search of the institutional medical record database revealed eight patients with IDs as a potential source of SAH. Among them, we treated six patients whose cases had not been previously published or reported.

IDs were defined as lesions meeting the following explicit morphological criteria: symmetrical cone-like outpouching at the level of the arterial ostium, with no distinct neck and a maximum diameter <3 mm. SAH due to ruptured ID was considered a diagnosis if no other vascular lesions were present during multimodal radiological examinations and delayed (7 days after onset) angiographic imaging. Three-dimensional rotational angiography (3DRA) was used to rule out blister aneurysms or dissecting aneurysms involving the PcomA origin that might mimic an ID.

The infundibulum's geometric ratios and morphological characteristics, and the involved parent artery were assessed during diagnosis, treatment, and radiological follow-up.

The patients' demographics, clinical and neurological status, and radiological records were obtained and reviewed. The clinical outcomes were measured and evaluated with the modified Rankin Scale at discharge. The parents' arterial vascular remodeling and ID occlusion were assessed according to the O'Kelly-Marotta scale during the endovascular procedure and 3–12 months after flow diversion (14).

## Treatment Considerations

According to our local institutional policy for all patients diagnosed with an acute SAH due to a possible ID rupture, all cases were discussed in neurovascular multidisciplinary team meetings. Concerns regarding the diagnosis itself, treatment indications, and modalities were fundamental aspects of each case analysis. The treatment decisions were based on all the aforementioned medical criteria, including the anticipated rebleeding prevention.

In general, the medical management of these patients did not significantly diverge from commonly accepted therapeutic protocols (15, 16). The only protocol deviation was the mandatory antiplatelet therapy on the conducted flow diverter stent (FD) implantation. The deployment of the flow modulation stent was aimed to fully cover IDs and the ostium of the involved parent artery.

## Management of Antiplatelet Therapy

All patients undergoing endovascular intervention received either a loading dose (per os) of aspirin (300 mg) and prasugrel (40 mg) 7 h before the procedure or an intraprocedural bolus

dosage of glycoprotein IIb/IIIa inhibitor. In the post-treatment phase, a standard daily dose of 1× 10 mg of prasugrel and 100 mg of aspirin were maintained for at least 6 months. Adequate therapy response was measured with VerifyNow assays (Accumetrics, San Diego, CA, USA) with a desired PRU < 120.

# RESULTS

## Patients' Baseline and Clinical Characteristics

The demographics and clinical details of the reviewed patients are summarized and presented in **Table 1**. We identified eight patients (six of whom were women), whose mean age was 44.5 years (range 19–60). Most IDs were located at the level of the PcomA ($n = 7$), and only one was located on the arterial orifice of the ophthalmic artery (OA). All patients reported in our series presented with radiologically confirmed acute SAH. Only one (12.5%) patient experienced SAH after a re-rupture earlier in life. Pretreatment Hunt and Hess (H&H) grade I and II were observed in five (62.5%) patients. However, two (25%) patients experienced severe and diffuse SAH resulting in H&H grade III, and one had an H&H score of IV.

In all cases, the initial computed tomography angiography (CTA) did not indicate that the presence of an aneurysm or any other vascular lesion was responsible for the SAH. However, in four cases, unilateral PcomA IDs were noted. In those cases, the SAH distribution from the non-contrast-enhanced CT scan was located predominantly near the anatomical location of the observed PcomA IDs into the origin of the ipsilateral suprasellar cistern and Sylvian fissure. One patient, patient No. 7, had a prior history of aneurysmal negative SAH 5 years prior.

The four IDs detected in the CTA were verified through subsequent digitally subtracted angiography (DSA). In general, DSA and preoperative 3DRA detected all IDs and indicated an absence of any other vascular pathology associated with the SAH. Delayed DSA examinations 7 days after onset confirmed the above findings in all eight patients. Endovascular therapy (EVT) of the ruptured ID was performed in six (75%) patients. Two patients (25%) rejected the therapeutic intervention because of their individual beliefs.

## Treatment Modality and Feasibility

The technical, procedural, and clinical results are summarized in **Table 2**.

Of the eight patients with SAH due to a ruptured ID, six underwent EVT in the acute phase of SAH. For the patients undergoing EVT, treatment of the ruptured ID was performed *via* implantation of an FD across the documented focal lesion. In all patients, only one FD was used; of the FDs used, two (33.3%) had additional antithrombotic surface coating. In all procedures, the attempted implantation of the FD was feasible. No unexpected procedure-related complications were encountered. No cases of recurrent bleeding resulted from the endovascular intervention or the mandatory antiplatelet medication. SAH related complications were observed, and all six patients demonstrated favorable outcomes, with modified Rankin Scale scores of 0 or 1 at discharge.

**TABLE 1** | Patients' baseline characteristics.

| Case | Age | Sex | Location | Hunt-Hess grade | Fisher scale | ID size and features | Similar previous symptoms | Confirmed on initial imaging (modality) | EVT treatment and used stent | Clinical outcome at discharge (mRS) | Clinical outcome at 12-month FU (mRS) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40s | F | L PcomA | Grade I | II | 2.7 mm cone | No | CTA/DSA | FD (p64) | 0 | 0 |
| 2 | 40s | F | L PcomA | Grade II | II | <3 mm cone | No | DSA/3D RA | FD (PED-S) | 0 | 0 |
| 3 | 60s | M | L PcomA | Grade II | III | <3 mm cone | No | DSA/3D RA | FD (p64) | 0 | 0 |
| 4 | 50s | F | L PcomA | Grade I | II | <3 mm cone | No | DSA/3D RA | Refused | N/A | N/A |
| 5 | 40s | M | R PcomA | Grade III | III | <3 mm cone | No | CTA/DSA | Refused | N/A | N/A |
| 6 | 40s | F | R PcomA | Grade IV | IV | <3 mm cone | No | CTA/DSA | FD (PED-S) | 1 | 0 |
| 7 | 40s | F | L PcomA | Grade III | III | <3 mm bleb (1 mm) | Yes 5 years ago | CTA/DSA | Failed coil/FD(p64) | 1 | 0 |
| 8 | ≥19 | F | L OA | Grade I | III | 2.5 mm cone | No | DSA/3D RA | FD (p64) | 0 | 0 |

*SAH, subarachnoid hemorrhage; F, female; FU, follow up; M, male; mRS, modified Rankin Scale; NA, not applicable; L/R, left or right; PcomA, posterior communicating artery; OA, ophthalmic artery; FD, flow diverter stent; CTA, computed tomography angiography; DSA, digital subtraction angiography; 3D RA, three- dimensional rotational angiography; p46, the p64 Flow diverter stent; PED-S, Pipeline Embolization Device with Shield Technology.*

**TABLE 2 |** Procedural, clinical, and follow-up angiographic results after the endovascular intervention.

| Patient number | Time to treatment since ictus | PRU results | EVT result | Clinical sequelae of complications | Observed rebleeding or retreatment | First angiographic follow-up, ID occlusion—OKM scale | First clinical follow-up |
|---|---|---|---|---|---|---|---|
| 1 | 12 days | 28 PRU | Stagnation | None | No | 3 months OKM D | No symp |
| 2 | 11 days | 17 PRU | Stagnation | None | No | 3 months OKM D | No symp |
| 3 | 7 days | 56 PRU | No filling | None | No | 4 months OKM D | No symp |
| 4 | 7 days | 44 PRU | Stagnation | None | No | 4 months OKM D | No symp |
| 5 | 10 days | 35 PRU | No filling | None | No | 4 months OKM D | No symp |
| 6 | 7 days | 25 PRU | Stagnation | None | No | 3 months OKM D | Headaches |

*EVT, endovascular therapy; N/A, not available; PRU, platelet Response Unit; ID, infundibular dilatation; OKM, O'kelly Marotta Scale.*

## Angiographic and Clinical Follow-Up

At least two cross-sectional radiological and clinical follow-ups were available for all patients who underwent EVT. The two patients who refused treatment were lost to follow-up after the initial presentation and discharge. The initial angiographic follow-up was conducted after a median of 3 months (range 3–4 months) after the intervention. No patients reported any post-treatment clinical and neurological symptoms associated with ID rerupture during the follow-up examinations. No mortality or morbidity was observed in this group.

## Illustrative Cases

### Case 1

A 46-year-old woman was admitted to another hospital for a sudden thunderclap headache (**Figure 2**). CT revealed diffuse SAH with increased blood collection in the left suprasellar cistern and left-sided Sylvian fissure. Subsequent CTA did not confirm the presence of any cerebrovascular findings that could be responsible for the acute SAH. DSA did not detect any intracranial aneurysms but revealed an ID at the origin of the left PcomA. The delayed 3DRA/DSA 7 days after onset identified a possible rupture bleb on the lateral side of the left PcomA ID. The patient had a history of an identical episode occurring 5 years earlier, but the radiological examinations did not confirm any intracranial hemorrhage. The patient's medical records included trombangiitis obliterans (Buerger disease), idiopathic thrombocytopenic purpura, and uncontrolled hypertonia. On the basis of the above findings, we concluded that the tiny bleb on the PcomA ID was responsible for the intracranial hemorrhage. Endovascular coil embolization of the ruptured infundibular bleb was performed but was unsuccessful. Coiling of the ruptured dilatation was not possible because the coils protruded toward the parent artery's lumen. Bailout flow diversion was considered appropriate for this case. The patient received a bolus dosage of glycoprotein IIb/IIIa–tirofiban and received a p64 (phenox, Bochum, Germany) FD. Contrast stagnation inside the ruptured bleb was observed on the final angiograph. The patient was discharged after 14 days with no new neurological deficits detected.

### Case 2

A 19-year-old woman was found unconscious at home (**Figure 3**). Her last memory was of an extreme burning sensation engulfing her neck and scalp. CT revealed a thin SAH mainly distributed in the left suprasellar cistern and left hemispheral subarachnoid spaces. CT cranial angiography and initial DSA did not indicate any aneurysmal dilatations or other vascular findings. Subsequently, 3DRA revealed the presence of an ID at the level of the orifice of the left ophthalmic artery. The secondary delayed DSA indicated the presence of a focal irregularity adjacent to the OA ID. The patient repeatedly reported having observed increasing flashes of light and bright spots in her left eye during this period. A ruptured OA ID was hypothesized to have been responsible for the cerebral hemorrhage, and the patient was scheduled for EVT with an FD stent. The patient was premedicated with a loading dose of DAP, and the implantation of the endoluminal flow modulation device was performed uneventfully. The patient was discharged without any related procedural complications. Follow-up angiography demonstrated no infundibular widening and the complete preservation of the OA.

### Case 3

A 60-year-old man was admitted to the hospital with severe headache, nausea, vomiting, and prominent neck stiffness (**Figure 4**). He reported that the headache intensity had worsened in the prior 7 days and did not respond to analgesics. CT demonstrated the presence of a diffuse SAH with a focal distribution mainly into the chiasmatic, interpeduncular, and left crural cisterns. CTA did not reveal any cerebrovascular pathology but confirmed the presence of an ID at the level of the left PcomA. The patient underwent catheter angiography, which yielded similar observations to those of the initial and delayed DSA examinations. Considering the above findings, we assumed that the most probable cause of the SAH was the rupture of the PcomA ID on the left. A loading dose of DAP was administered, and the patient underwent uneventful FD placement across the C7 segment of the left ICA. Noticeable contrast stagnation was found in the PcomA ID after stent implantation. The patient was discharged after 2 weeks of conservative management with no neurological deficits. Both mid- and long-term follow-up radiological examinations confirmed the complete remodeling of the PcomA with total obliteration of the treated ID.

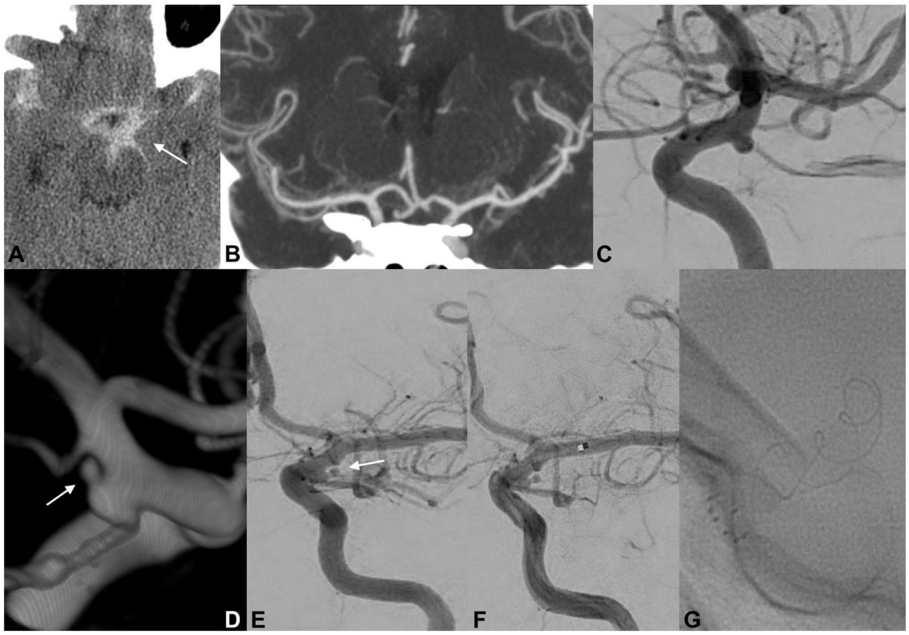


**FIGURE 2 |** EVT of a ruptured PcomA ID. An initial CT scan demonstrated the presence of SAH predominantly distributed across the left basal cisterns (**A**; white arrow). Cranial CTA did not document any cerebrovascular findings that could have caused the SAH **(B)**. At 6 h after onset, catheter angiography confirmed the absence of a ruptured aneurysm but revealed a typical ID at the origin of the left PcomA **(C)**. Delayed 3DRA/DSA (**D,E**; white arrows) 7 days after onset identified a possible rupture bleb on the lateral side of the left PcomA ID. Endovascular coil embolization of the ruptured bleb was unsuccessful, and a p64 FD was carefully deployed across the C7 segment of the left ICA **(F,G)**. Contrast stagnation inside the ruptured ID bleb was seen on the delayed angiographic phase (not provided).

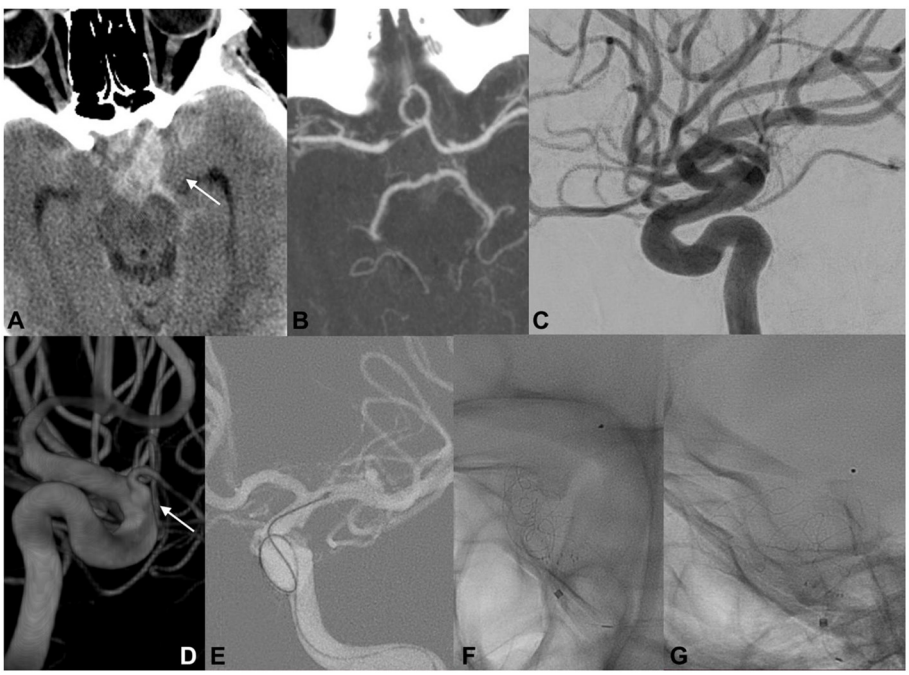


**FIGURE 3 |** EVT of ruptured OA ID in a young woman. The initial radiological work-up indicated intracranial hemorrhage, suggesting the rupture of an intracranial aneurysm (**A**; white arrow). Cranial CTA and initial DSA did not reveal any cerebrovascular pathologies that could be associated with the hemorrhage **(B,C)**. Three-dimensional rotational angiography demonstrated the presence of an ID at the level of the orifice of the left ophthalmic artery (**D**; white arrow). Endovascular FD deployment was performed with complete coverage of the OA infundibular orifice **(E–G)**.

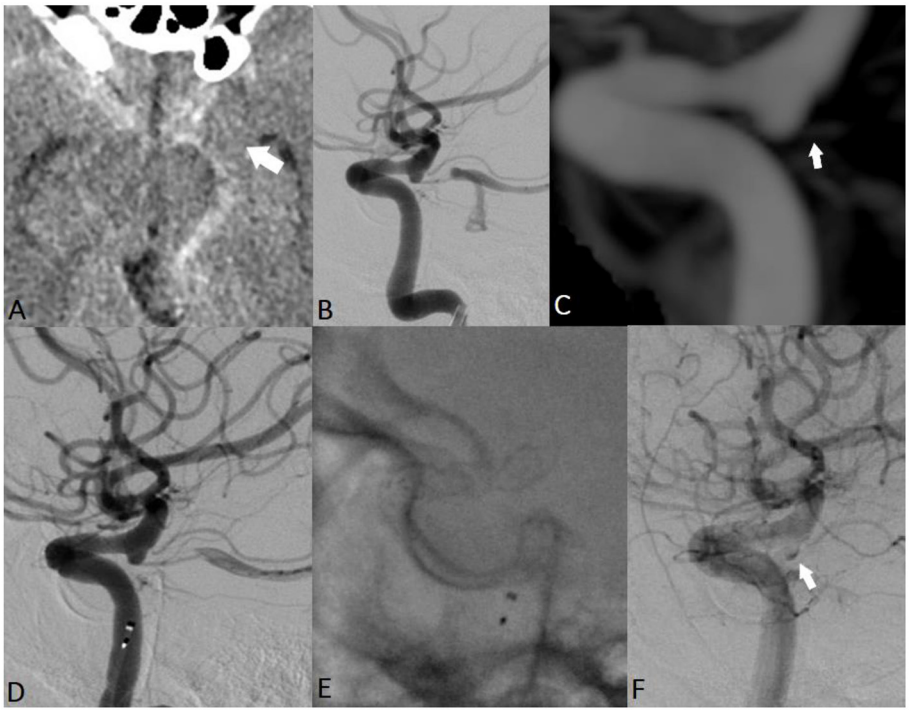


**FIGURE 4 |** EVT of a ruptured PcomA ID in a 60-year-old man. Non-contrast cranial CT revealed a thin hemorrhage in the chiasmatic, interpeduncular, and left crural cisterns (**A**; white arrow). Subsequent repeated radiological examinations did not reveal any cerebrovascular pathology but confirmed the presence of an ID at the level of the left PcomA (**B,C**; white arrow). The assumed rupture site was the observed ID, and the patient received EVT **(D,E)**. Noticeable contrast stagnation was observed in the PcomA ID after stent implantation **(F)**.

# DISCUSSION

## Pathogenesis and Histological Considerations

Arterial IDs are benign lesions commonly believed to be present in as many as one-quarter of cerebral angiograms (7, 13). Although these findings are considered normal vascular variants, whether they should be considered aneurysmal precursors, and candidates for clinical surveillance and potential treatment, remains a matter of debate (8, 17). We cannot fully determine whether this paradoxical understanding of IDs was initially derived from a divergence among published histological findings. Histologically, one of the first assumptions promoted by Hassler and Saltzmann was that cerebral infundibulum might resemble an aneurysm (18). Degenerative changes and arterial wall alterations were also noted in later studies histologically examining ID samples (19, 20). However, neither abnormalities nor structural arterial defects were observed in patients with junctional dilatations in the histological studies performed by Epstein et al. (21), who proposed that these conical dilatations might merely be developmental vessel remnants with non-conditional clinical significance.

Regardless of whether IDs exhibit degenerative changes in the internal elastic lamina, the lytic process of elastase has been demonstrated to play a role in the degenerative changes directly leading to aneurismal development (22). Small defects and structural anomalies within the internal elastic lamina have been documented in post-mortem analyses of ruptured ID (23). These biological events might result from focal disruption of the homeostatic balance in the affected arterial vessel wall, as a result of increased circumferential wall stress (24). Coupe et al. (25) have reported a surgically treated case of a ruptured ID with a macroscopically evident perforation site, thus suggesting that the ID bleeding might have resulted from wall weakness without prerequired aneurysmal transformation. The very geometrical definition of arterial infundibulum or funnel-shaped widenings at the branching sites of major cerebral arteries may lead to local fluid dynamics that result in further ID dilatation (26). Marshman et al. (27) have suggested that these hydraulic distentions, conditioned by Bernoulli's principle, might be directly associated with later aneurysmal transformation of an ID.

## Clinical Significance

Although arterial IDs are present in up to 25% of cranial angiographs, fully distinguishing them from their aneurysmal counterparts remains difficult. Currently, non-invasive radiological imaging modalities, i.e., CTA and magnetic resonance angiography, have become the primary screening techniques used to detect, differentiate, and evaluate cerebral aneurysms. Superioinferior projections of cerebral CTA can sometimes aid in revealing the horizontal direction of the infundibulum. CTA has a considerably lower spatial resolution than DSA, thus resulting in poor and limited visualization of small vessels. In the case of hypoplastic but present PcomA, CTA may not aid in differentiating ID from an aneurysm, particularly at the ICA-PComA junction. According to Min et al., the

sensitivity, specificity, and accuracy of CTA in differentiating cerebral aneurysms from IDs remain considerably high (28). Magnetic resonance imaging techniques with time-of-flight and volume rendering have been reported to have similarly high sensitivity and accuracy in detecting cerebral IDs (29). Furthermore, geometric parameters on magnetic resonance angiography axial source images can provide added value in the diagnostic process. Magnetic resonance imaging enables easy visualization of silhouettes of tiny or hypoplastic vessels adjacent to the infundibulum with fast spin-echo and fast imaging by using steady-state acquisition sequences. With fusion imaging, Satoh et al. have viewed the outer wall configuration of the ipsilateral ICA-PcomA junction to distinguish and differentiate both lesions successfully (30).

Despite being promoted as the "gold standard," DSA has several diagnostic and technical limitations in flow alterations and poor contrast filling of the PcomA during cerebrovascular catheter examinations. Recent technological improvements and software implementations with sophisticated smoothing and visualization algorithms have indicated the value of 3DRA, whose superior diagnostic properties to those of two-dimensional DSA imaging for evaluating cerebral IDs have been described (31).

Anecdotally, differentiating an aneurysm from an ID might not be the only dilemma faced by physicians. Labeling a "negative" radiological result as SAH in cases in which cerebral ID is present might be an equally difficult decision. The incidence of "normal" radiological findings in patients with SAH has been frequently reported in the literature. However, case reports are providing increasing evidence suggesting that these entities are not necessarily benign in nature (1, 29, 32–35). Particular radiological patterns, such as predominantly distributed SAH close to the observed infundibulum, may suggest the rupture site and the cause of the hemorrhage. For example, Yu et al. have found concentrated blood clots on CT located across the ipsilateral suprasellar cistern, interhemispheric cistern, and ipsilateral Sylvian fissure (33). Post-mortem reports have confirmed diagnoses of SAH associated with ID ruptures, thus underscoring the diagnostic challenges. Therefore, the question remains as to how often cerebral ID related hemorrhages are being neglected and misdiagnosed.

No defined guidelines or established clinical protocols exist regarding radiological follow-up of IDs in young patients. Because arterial IDs appear to be active lesions, radiological surveillance might be justified in these patients. In the literature, isolated case reports and case series have described progressive aneurysmal formation from ID (21, 26, 36, 37). Recently, Lee et al. have reported seven patients with ruptured PcomA IDs: two patients experienced directly ruptured IDs, whereas the other five experienced ruptured aneurysms originating from IDs. Only IDs of the PcomA had been incidentally identified during previous aneurysm treatment. However, the mean time between the identification of a PcomA ID and the rupture event was $9.2 \pm 4.8$ years. Fischer et al. have documented the objective transformation of a PcomA ID to a saccular aneurysm during follow-up angiography 7 years after the initial identification of the conical dilatation (38). Donauer et al. (39) have described a tiny acutely ruptured aneurysm (<2 mm fundus diameter) located on the infundibulum surface in a 62-year-old woman—an exemplary case demonstrating the feasibility and limitations of microvascular and endovascular approaches in managing these lesions.

In the present study, we reported our experience in diagnostic and endovascular management of ruptured cerebral IDs. Over more than 9 years, we identified eight patients with direct rupture of a cerebral ID. Multimodality imaging and specific radiological patterns drawn from the available literature allowed us to carefully conclude that an ID was the cause of the SAH in each case. In our experience, 3DRA remains the best diagnostic tool to successfully resolve any diagnostic discrepancies. Using post-processing reconstructions, we identified 0.5–0.7 mm blebs suspected to be ruptured sites. We strongly recommend performing at least one delayed radiological examination before planning any further action. Careful neuroprotection and blood pressure monitoring can meanwhile be successfully maintained.

Our experience in managing acutely ruptured complex and wide-necked aneurysms allowed us to successfully address these lesions. We consider endoluminal flow diversion to be an excellent stand-alone treatment candidate with high efficacy and a good safety profile (40). We acknowledge that acute SAH poses specific challenges to the safe use of FDs. Nevertheless, we suggest that careful analyses and strict selection of patients who could benefit from this integrated treatment are critical for its success.

It is essential to highlight that this study builds up around the SAH hypothesis due to ruptured IDs. The study case examples could only demonstrate that rupture can occur from an ID, but the inherent limitations of the design and the small sample size are not enough to the true nature of these lesions. Last but not least, with the more advanced FD technology, the available arsenal of stents, and the increased operator experience, we prove that such entities could be successfully adressed with a good safety profile. Tailoring a patient-specific approach with preoperative planning, adequate platelet inhibition and PRU testing, and competent operator experience should yield successful treatment results.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

SM, KS, KC, MP, and DM creating and writing the manuscript. MK, KM, KN, and VK participating in cases and review of the manuscript. SS performing the cases and final review. All authors contributed to the article and approved the submitted version.

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# Progressive volume reduction and long-term aneurysmal collapse following flow diversion treatment of giant and symptomatic cerebral aneurysms

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**Background:** The primary goal of conventional endovascular and microvascular approaches is the clinical and radiological resolution of the symptomatic aneurysm-induced mass effect. This study assessed the volume changes and mass effect reduction due to sac shrinkage after treatment with flow diverter stents (FD) for unruptured cerebral aneurysms.

**Methods:** We analyzed retrospectively 36 symptomatic aneurysms that were larger or equal to 25 mm in diameter in patients treated at our center from January 2016 to April 2022. Radiological and clinical outcomes were analyzed, including aneurysmal volume changes and resolution of aneurysm-related symptoms.

**Results:** At 6 months, 25 aneurysms decreased in size, 2 remained unchanged, and 9 aneurysms demonstrated a post-treatment dimensional increase. At 12 months, 30 aneurysms showed a progressive radiological volume reduction. Either no change or negligible shrinkage was observed in the remaining six aneurysms. At 24 months, 32 aneurysms showed aneurysmal shrinkage by a mean 47% volume loss with respect to baseline. At the last follow-up, all 13 patients who had presented with third cranial nerve palsy showed improvements. Complete reversal of the pretreatment edematous changes was confirmed in all cases. The overall post-treatment complication rate was 8.3%, as 3 patients experienced non-fatal delayed rupture of their aneurysm. There was no mortality in this study.

**Conclusion:** Flow diversion could effectively induce progressive aneurysmal shrinkage and resolution of the mass effect associated with giant symptomatic cerebral aneurysms.

KEYWORDS

**aneurysm, flow diversion, shrinkage, embolization, giant**

# Introduction

Giant (≥25 mm) intracranial aneurysms are a unique subcategory of cerebral aneurysms with poor natural history and technically demanding treatment options (1, 2).

If left untreated, patients with such aneurysms have a dismal prognosis, with an increased risk of rupture and poor long-term clinical outcomes (3, 4). Beyond the poor prognosis and increased risk of rupture, these aneurysms have other clinical consequences. Peri-aneurysmal edemic changes in adjacent brain structures are typically associated with these aneurysms (5). Depending on their distribution across the cerebral circulation, the functional integrity of some cranial nerves may be compromised (6, 7). Treatment strategies for these uncommon intracranial aneurysms remain a matter of substantial debate, because evidence from large clinical trials remains lacking (8). Therefore, a compelling biological rationale supports early treatment for medically suitable patients.

The microvascular clipping of large or giant cerebral aneurysms carries favorable chances for a definitive and durable cure (9). However, this treatment method still carries substantial risks (10, 11). Primary endovascular coil embolization with or without adjunctive devices has yielded varying angiographic and treatment results (12, 13). More recently, endoluminal flow diverter stents have been associated with high rates of complete aneurysm occlusion and an acceptable safety profile (14, 15). After endovascular flow diversion for large or giant aneurysms, the best possible outcome is significant shrinkage of the sac and complete aneurysmal obliteration (16, 17).

A combined study of long term radiological and clinical data on flow diverter treatment of large or giant symptomatic and unruptured cerebral aneurysms would be valuable but had not been reported. Therefore, this study analyzed the clinical and radiological outcomes of patients treated with flow diversion, and specifically evaluated the treatment effects on aneurysmal sac shrinkage and volume reduction.

# Materials and methods

## Adherence to ethical standards and legal requirements

This retrospective study was approved by the local institutional ethical committee, and was designed and performed in accordance with its policies and guidelines. Patient consent was not required, given the study's retrospective nature and the lack of identifying information.

## Data collection and study design

The strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines were followed to collect and report data (18).

## Study design and population

We examined the local electronic health database by using a unified code (I67.1) from the International Classification of Diseases, ver. 10 to identify patients with unruptured intracranial aneurysms diagnosed and treated in our center. A total of 51 cerebral aneurysms ≥25 mm in diameter were identified. This cohort represented ∼1.9% of all aneurysms treated in our center. To evaluate the effect of flow diversion on progressive aneurysmal shrinkage and focal neurological recovery, we did not include patients with asymptomatic, previously ruptured or treated giant cerebral aneurysms. Fusiform or serpentine-like morphology was also an exclusion criterion. A summary of the study's design is illustrated in Figure 1.

For the selected patients, we analyzed the demographics, neurological status, radiological characteristics and localization of the aneurysms, and the relevant medical history.

## Pre- and peri-procedural evaluation and endovascular procedure

The allocation of the treatment modality and the specifics of endovascular embolization were determined by a multidisciplinary working group consisting of two competent and experienced interventional radiologists and two microvascular neurosurgeons.

Neurologic and neuro-ophthalmologic evaluation was performed before treatment and at follow-up cross-sectional imaging. The modified Rankin scale was used to assess patient clinical pretreatment status and outcomes.

All patients underwent pretreatment cranial magnetic resonance imaging (MRI) and conventional digital subtraction angiography (DSA). Periprocedural three-dimensional rotational angiography (3D RA) was performed in all cases. Target aneurysm features were carefully examined, including dimensional characteristics, morphology, focal irregularities, adjacent lobulations and localization. Aneurysm volumes in $mm^3$ were measured with semi-automated 3D post-processing software (MR Vessel IQ Express) in all patients. The presence of intra-aneurysmal thrombosis, parent artery luminal characteristics and their relation to the aneurysm were also considered.

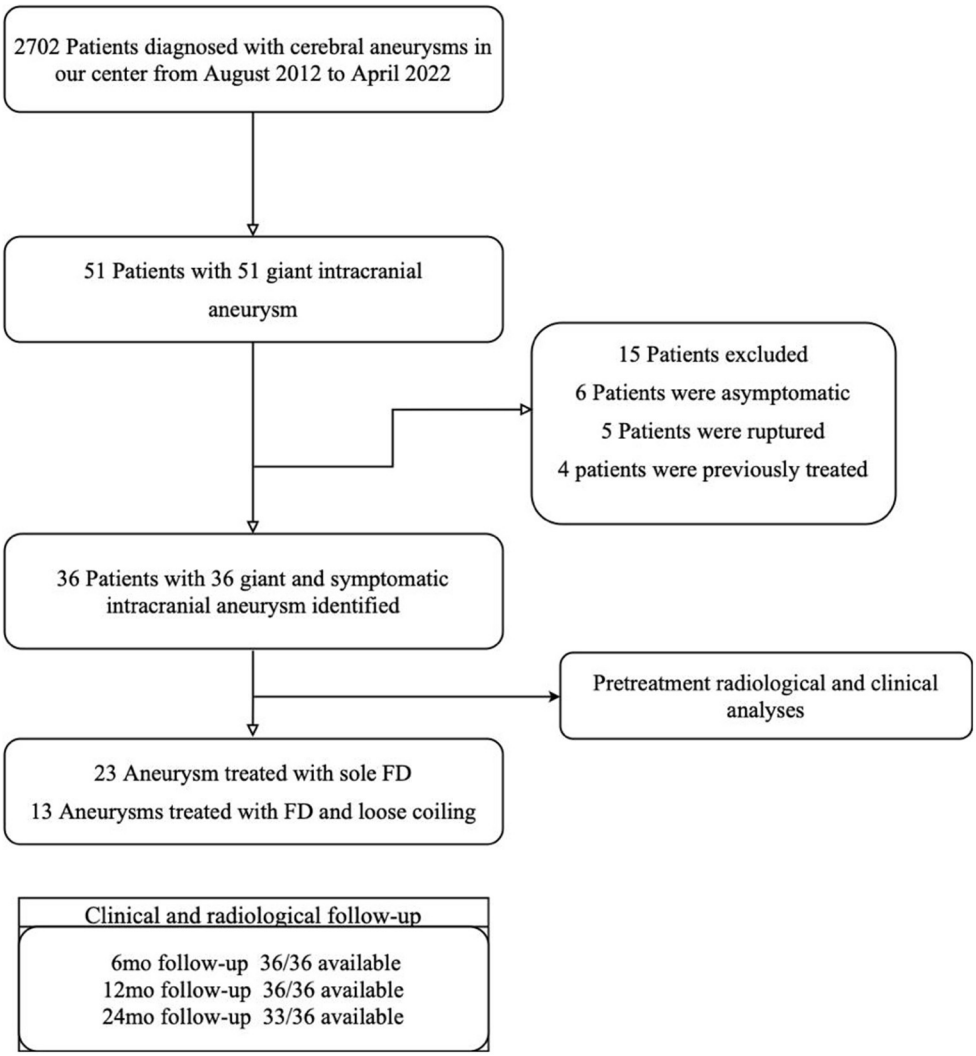


FIGURE 1
Illustrative flow chart of study design and population.

Endovascular procedures were performed in patients under general anesthesia with the commercially available FD devices—the p64 flow modulation device (Phenox, Bochum, Germany) and the Pipeline embolization device (PED; Medtronic, Minneapolis, MN, USA). Technical and procedural data associated with the embolization process were gathered and analyzed. The angiographic results were evaluated with the O'Kelly-Marotta (OKM) filling grade system (19).

## Antiplatelet, anticoagulation, and anti-inflammatory medications

As part of a routine medication protocol, all patients received dual antiplatelet therapy either 75 mg clopidogrel, 2×90 mg ticagrelor or 10 mg prasugrel, and 100 mg acetylsalicylic acid daily for at least 7 days before the treatment. Every patient received a responsiveness test to clopidogrel with the VerifyNow (Accumetrics) P2Y12 assay. Levels of <70 P2Y12 response units were defined as sufficient platelet inhibition. Patients with non-response to clopidogrel or results above 70 P2Y12 response units received a substitution therapy of either 1 × 10 mg prasugrel or 2 × 90 mg ticagrelor daily. No aneurysms were treated unless substantial platelet inhibition was confirmed (20, 21). All patients received intravenous heparin intraprocedurally with an activated clotting time of >200 s. Additionally, dabigatran, 150 mg twice per day, was prescribed to every patient postoperatively to avoid rapid and severe thrombosis of the target voluminous aneurysms. Oral anticoagulation *via* dabigatran was prescribed for 8 weeks in

patients with anterior circulation aneurysms and 12 weeks in patients with posterior circulation aneurysms. Intravenous application of corticosteroids was started in every patient to prevent post-therapeutic perianeurysm inflammation. Eight milligrams of dexamethasone was administered i.v. immediately after flow diverter stent placement and continued orally for the following week. Gradually, the dose was decreased by 2 mg each week. Concomitant non-steroidal anti-inflammatory drugs were prescribed for 3 weeks to maximize the prevention of aneurysmal inflammation and delayed ruptures.

## Clinical and radiological follow-up examinations

Follow-up clinical and angiographic examinations were routinely performed at 6, 12, and 24 months. Only MRI was used to evaluate the aneurysmal volume changes during follow-up. Radiological analyses and comparative studies with each prior assessment were determined on the basis of time of flight pre-contrast, 3D T1-weighted pre-contrast, time of flight (TOF) post-contrast, T2-weighted 3D CUBE, T2-weighted FLAIR 3D CUBE and 3D T1-weighted post-contrast sequences on either 1.5 or 3 Tesla scanners. Post-treatment perifocal brain parenchymal changes were assessed on T2-weighted 3D CUBE and T2-weighted FLAIR 3D CUBE sequences. All aneurysms were manually segmented by a single rater on a post-processing work station. Manual segmentation was used for 3D reconstruction, thus yielding the maximum diameter and semi-automated volume calculations for each aneurysm in each radiological examination. A decrease in aneurysmal dimensions and volume was defined as aneurysmal shrinkage.

## Statistical analysis

Data collection was performed with IBM SPSS Statistics, version 22 (Armonk, New York). The descriptive analysis presents categorical variables as percentages and absolute numbers, and continuous variables as mean and range.

# Results

## Patients' baseline characteristics

The patients' characteristics are summarized in Table 1.

A total of 51 cerebral aneurysms ≥25 mm in diameter were treated in our center. Among them, 36 giant, symptomatic and previously untreated aneurysms were identified in 36 patients, 28 of whom were women (77.7%). The mean age was 58.5 years (range 22–76 years). The most common clinical presentation was impaired third cranial nerve function, which was present in 13 patients (36.1%). Hydrocephalus and cranial nerve symptoms associated with vision were documented in 8.3 and 16.6% of patients. Headache with the radiological presence of peri-aneurysmal edemic changes in adjacent brain structures was observed in 11 patients. The cohort included 36 intracranial aneurysms, 30 internal carotid aneurysms (83.3%), 4 basilar aneurysms and 2 middle cerebral artery aneurysms. Of the aneurysms across the internal carotid artery, 13 were intradural, and the remaining 17 were extradural within the proximal cavernous sinus segment of the artery. The mean maximal diameter of the treated aneurysms was 26.6 mm (range 25–62 mm), with an average neck diameter of 8 mm (range 5–14 mm). The mean luminal diameter of the target parent artery was 4.28 mm (range 3.1–5.7 mm). The mean pretreatment volume of the aneurysms was 7,660 $mm^3$ (range: 2,225–80,822 $mm^3$). Seventeen aneurysms showed radiological evidence of thrombus formation inside the aneurysm, defined as a >10% difference between outer and luminal volume. A total of 23 aneurysms (63.8%) were treated with sole flow diversion, and the remaining 13 were treated with loose coil packing and flow diversion in the same procedure. More extradural aneurysms were treated with sole flow diversion than with adjacent coiling. The mean maximum size of the aneurysms treated with only flow diversion appeared slightly larger (27.02 mm) than that (25.9 mm) in patients with additional coiling and flow diverter stenting.

TABLE 1 Baseline patient demographics and clinical presentation of the study population.

| Patients characteristic | Value ($n = 36$) |
|---|---|
| Age | 58.5 (range 22–76) |
| **Sex** | |
| Female (*n*) | 28 (77.7%) |
| **Aneurysm characteristics** | |
| Neck (mean, mm) | 8 (range 5–14 mm) |
| Maximal diameter (mean, mm) | 26.6 (range 25–62 mm) |
| Pre-treatment volume (mean, $mm^3$) | 7,600 (range 2,225–80,822 $mm^3$) |
| Partially thrombosed (*n*) | 17 |
| **Aneurysm localization** | |
| Internal carotid artery (*n*) | 30 |
| Intradural ICA | 13/30 |
| Extradural ICA | 17/30 |
| Basilar artery | 4 |
| Middle cerebral artery | 2 |
| **Clinical presentation** | |
| Cranial nerve III palsy | 13 (36.1%) |
| Hydrocephaly | 3 (8.3%) |
| Optic/chiasmal compression | 6 (16.6%) |
| Peri-aneurysmal edema | 11 (30.5%) |
| Other | 3 (8.3%) |

TABLE 2 Procedural and angiographic results.

| Radiological outcome | Early follow-up (*n*, %) | Intermediate 12 month | Long-Term 24 month |
|---|---|---|---|
| Complete occlusion (OKM D) | 23 (63.8%) | 32 (89%) | 31 (86.1%) |
| Partial occlusion or residual aneurysm (OKM B) | 4 (11.2%) | – | – |
| Neck remnant (OKM C) | 9 (25%) | 4 (11%) | 2 (5.5%) |
| Diminishing aneurysms | 25 (69.4%) | 30 (83.3%) | 32 (88.8%) |
| Average volume reduction | 2,108 $mm^3$ | 3,662 $mm^3$ | 3,917 $mm^3$ |
| Stationary aneurysms | 2 (5.5%) | 6 (16.6%) | 1 (2.7%) |
| Enlarging aneurysms | 9 (25%) | 0 | 0 |
| Complications at the point of follow-up | 3 (8.3%) | 0 | 0 |
| Lost to follow-up | 0 | 0 | 3 (8.3%) |

## Radiological outcomes

Procedural and angiographic results are summarized in Table 2.

A total of 23 patients were treated with a single flow diverter stent covering the ostium of the target aneurysm, and 13 patients required implantation of a second stent in a telescopic fashion to reconstruct the aneurysmal neck/parent vessel interface. The telescopic stenting was performed to provide the best technical execution of the embolization.

To ensure complete wall apposition and maximal coverage of the aneurysmal neck, balloon dilatation of the stent was performed in five cases. The most commonly applied stent was 5/30 mm, given the mean luminal diameter of the parent artery of 4.28 mm. We did not observe any procedural-associated technical complications regarding device migration or foreshortening of the implanted stents. The curative mechanism of flow diversion requires weeks to months to occur; therefore, the initial aneurysm occlusion rates were not substantial, as expected. Subtotal filling or OKM grade B were observed in most of the aneurysms (27; 75%); reduced perfusion with only entry remnant or OKM grade C was noted in eight (22.2%) of the aneurysms; and complete occlusion or OKM grade D was documented in only one case.

## Early radiological results

Data from the 6 month radiological follow-up were available for all patients. Radiologically confirmed shrinkage of the treated aneurysms was confirmed in 25 cases (69.4%). The detected average volumetric reduction was 2,108 $mm^3$ (mean 30.6% of the pretreatment aneurysmal volume). Negligible or no radiological changes were observed in two cases. However, post-treatment growth of the aneurysms was found in nine cases or 25% (Figure 2). The mean volumetric increase in these aneurysms was ∼2,311 $mm^3$. Among the extradurally located ICA aneurysms, 14 showed an average volumetric reduction of 2,080 $mm^3$, whereas one remained unchanged, and two became enlarged. Six of the ICA aneurysms with intra-dural localization showed a mean 2,857 $mm^3$ decrease with respect to the pretreatment volume, one remained the same, and six demonstrated an aneurysmal increase. Furthermore, during the first follow-up, aneurysms with thrombotic material present inside the lumen tended to have a slightly greater mean volume loss (2,255 $mm^3$) than aneurysms without thrombi (1,972 $mm^3$). Aneurysm occlusion, evaluated with catheter angiography, confirmed complete aneurysm obliteration or OKM D grade in 23 aneurysms. A progressive reduction of aneurysm perfusion in OKM grade B and grade C was observed in four and nine patients, respectively.

## Intermediate radiological results

Data for the 12 month radiological follow-up were available for all 36 patients.

Complete occlusion was found in 32 patients (89%), and a neck remnant persisted (OKM C) in four patients (11%). No signs of aneurysmal reperfusion and recanalization were confirmed. Thirty of the aneurysms showed a progressive radiological volume reduction with an average 3,662 $mm^3$ loss with respect to the pretreatment volume. Either no change or negligible shrinkage was observed in the remaining six aneurysms. During this radiological follow-up, no increases in aneurysmal volume and dimensional characteristics were found.

## Long-term radiological results

Data for the 24 month follow-up were available for 33 patients. At that point, 31 of the aneurysms had become entirely obliterated, and entry filling of the aneurysms (OKM grade C) was observed in only two cases. The MRI examinations revealed that 32 of the aneurysms demonstrated aneurysmal shrinkage, by a mean of 3,917 $mm^3$ with respect to baseline (mean 47% volume loss). A comparison of results between the second and third follow-ups demonstrated that only 16 aneurysms continued to diminish (Figures 3, 4). No aneurysmal regrowth or adverse changes were found in their morphology at that point.

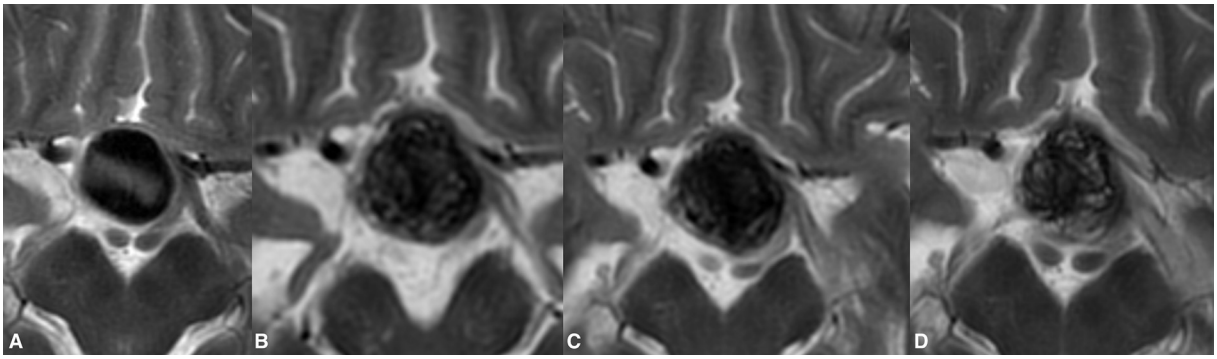


FIGURE 2
Post-treatment enlargement of a giant paraophthalmic ICA aneurysm **(A)**. During routine clinical examinations, the patient showed temporary aggravation of the presenting visual symptoms due to increase chiasmal compression. The first radiological follow-up demonstrated the treatment-related volume increase of the treated aneurysm **(B)**. Following prolonged steroid and NSID therapy, the patient's visual status improved notably. Twelve months after the treatment, the observed growth of the aneurysm was seized with documented aneurysmal shrinkage **(C)**. Lack of signal void within the aneurysm on T2WI in the same patient at 24 months indicates the ongoing aneurysm thrombosis **(D)**. The last follow-up also noted the collapse of the previous growing aneurysm.

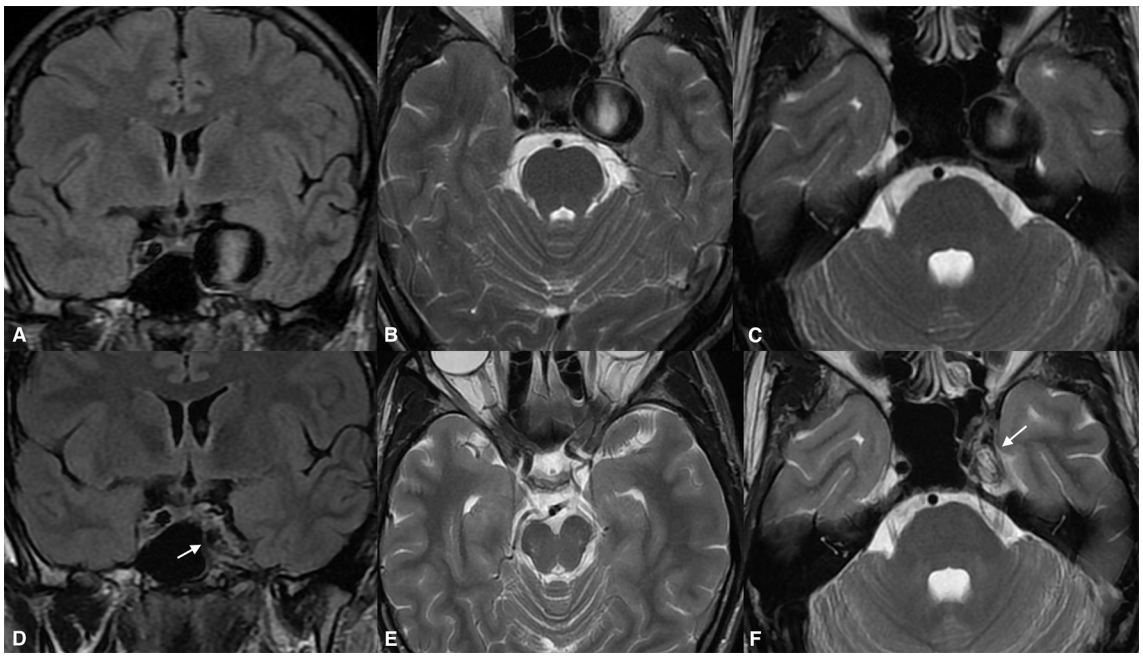


FIGURE 3
Giant cavernous internal carotid artery aneurysm causing diplopia from oculomotor nerve involvement **(A)**. The same aneurysm was causing a slight mass effect over the left temporal lobe and the adjacent brain tissue **(B,C)**. Twenty-four months after the treatment, the magnetic resonance imaging [**(D)**, arrow] demonstrated aneurysmal collapse **(E)** and elimination of the mass effect. Note the absolute shrinkage of the aneurysm with a volume reduction of up to 70% of its previous volume, as seen on the long-term follow-up [**(F)**, arrow].

## Clinical outcomes

Most of the patients demonstrated clinically significant improvements in their presenting symptoms after treatment. At the last follow-up, all 13 patients who had presented with third cranial nerve palsy showed improvements. Symptoms had resolved entirely in nine patients; one patient had minor diplopia due to persistent misalignment of the affected eye; and two had mild but ameliorated ptosis. Complete reversal of the pretreatment edematous changes was confirmed in all cases showing substantial mitigation of headaches. Quadriparesis in one patient presenting with brain stem compression and

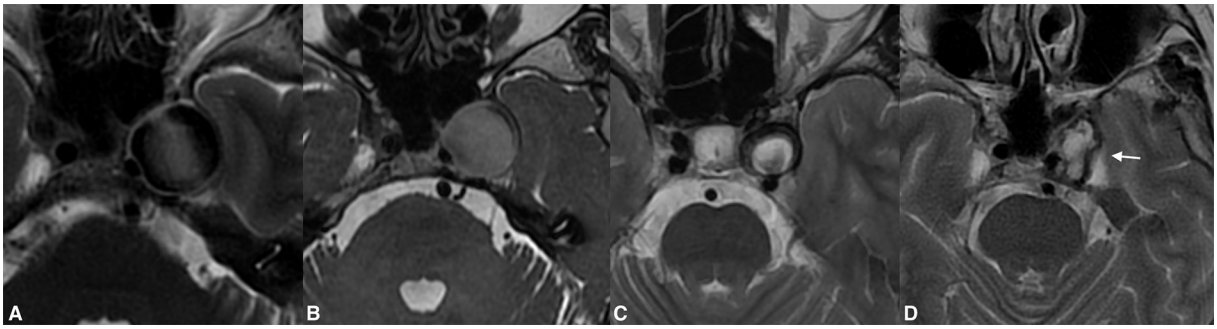


FIGURE 4
Giant extradural ICA **(A)** aneurysm demonstrating significant shrinkage following flow diversion. Despite the complete thrombosis of the aneurysm found on the first radiological follow-up, there were neglectable changes in the aneurysmal volume **(B)**. One year post-treatment, the aneurysm shrinkage was visible on the MRI **(C)**. The complete resolution of the aneurysm-induced compression of the left temporal lobe and the significantly diminished volume were present on long-term follow-up [**(D)**, arrow].

obstructive hydrocephalus was entirely resolved by the first clinical follow-up. Figure 5 provides the radiological data of the aforementioned case. Unfortunately, only two patients completely recovered from visual deficits due to optic or chiasmal compression. Among the remaining patients with presenting visual symptoms in two, vision improved from as low as finger counting to vision of 0.6.

## Treatment-related complications

Despite the aggressive corticosteroid and anti-inflammatory therapy, three patients experienced intracranial hemorrhage due to delayed rupture of their aneurysms between 1 and 4 weeks post procedurally. All three of these patients had treated aneurysms in the intra-dural segments of the internal carotid artery. Sole flow diversion was used in two of the ruptured aneurysms with loose coiling and FD stent in the remaining one. None of these complications resulted in death; however, gradual aggravation of their presenting symptoms was observed. Complete blindness was documented in the patient with the more severely ruptured aneurysm and adjacent brain hematoma. During the first clinical follow-up, two of the six patients with radiologically confirmed enlarging aneurysms showed temporary aggravation of their symptoms, thus requiring prolonged steroid and NSID therapy.

# Discussion

Cerebral aneurysms that reach a giant size (≥25 mm) without rupturing may act as space-occupying lesions (22). Compression syndromes over the locoregional neuronal tissue, dislocation or cranial nerve palsies are common clinical manifestation of these challenging lesions. The goal of the treatment is not only to prevent future hemorrhagic events but also to alleviate the associated mass effect and compression symptoms (23). Endoluminal implants that reduce and redirect the blood flow away from the aneurysm sac can diminish the pulsating phenomenon and induce steady intrasaccular thrombosis (24). Similarly to the wound healing mechanism, the biotransformation and organization of the intrasaccular thrombus to fibrous scar tissue allows the aneurysmal structure to reduce and eventually be resorbed to some extent (25). Studies have shown that this strategy effectively alleviates the compression symptoms of large and giant cerebral aneurysms (26, 27). According to Szikora et al. volume reduction and shrinkage of the aneurysm sac can be expected in most aneurysms treated with flow diversion (17). The findings of Pianto et al. are consistent with those of the abovementioned authors, and have confirmed the amelioration of mass effect symptoms after flow diversion for space-occupying aneurysms (28).

Healing and shrinkage may be preceded by acute and uncontrollable inflammatory changes inside the aneurysm that cause aggravation of compression-associated symptoms (29). Such circumstances can trigger widespread changes and potentially result in treatment-induced rupture (30). The phenomenon of delayed rupture and the triggering mechanism after endoluminal flow diversion is poorly understood. Specific conditions, i.e., hemodynamic alterations, larger sizes, complex geometry and pre-existing intrasaccular thrombosis, may trigger uncontrollable autolysis, which may overload the biologic defense mechanisms of the vessel wall and result in aneurysm rupture (31, 32). Kuzmik et al. have described the unpredictable nature of the endoluminal flow diversion, demonstrating substantially different treatment outcomes for aneurysms with the same morphology and location (33). Such complications often predispose patients to unfavorable or even fatal outcomes, because of the need for dual antithrombotic therapy with this technique (34).

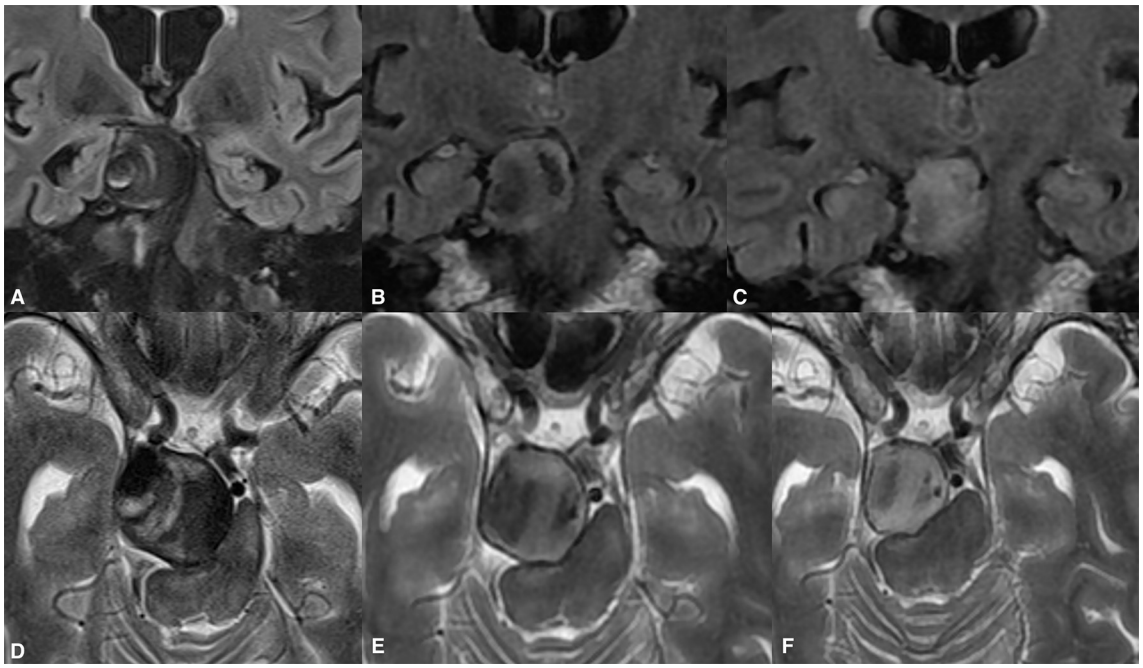


FIGURE 5
Giant partially thrombosed cerebral aneurysm causing quadriparesis and obstructive hydrocephalus due to brain stem compression **(A,D)**. Significant post-treatment clinical improvement was confirmed due to alleviation of the brain stem compression **(B,C)**. The ongoing collapse of the aneurysmal sac with progressive intrasaccular T2WI signal changes was noted during the long-term follow-up **(E,F)**.

This study retrospectively analyzed the volumetric changes in mass effect reduction after endoluminal flow diversion for giant cerebral aneurysms. We focused on the long-term effects of flow diversion in inducing clinical symptoms recovery and promoting aneurysmal sac collapse. Clinical improvements in impaired neurological functions are expected after the cessation of the aneurysmal pulsations followed by positive volumetric changes in the giant sac. According to Szicora et al. weeks to months are usually required before any improvement can be seen (17). In this study, at the first clinical follow-up at 6 months, 13 of 36 (36.1%) patients with CN III palsy who underwent treatment for their giant aneurysms demonstrated significant amelioration of their presenting symptoms. First, MRI radiological follow-up surveillance at 6 months confirmed shrinkage of the treated aneurysms in 25 cases (69.4%). The average volume mass reduction of 2,108 $mm^3$ induced by the treatment clearly facilitated the clinical recovery of the analyzed patients. Our mid- and long term results suggest that this method induces a steady but progressive disintegrative volume effect. The available MRI follow-up imaging revealed that aneurysmal collapse and mass effect resolution continued up to 24 months after the treatment. Importantly, we emphasize that, in our cohort, the greatest decrease in mass occurred within the first 6 months and in aneurysms with thrombotic changes inside the sac. Although the comparison was not statistically proven, in our study, aneurysms treated with sole flow diversion tend to have a better shrinkage rate than aneurysms that underwent coil implantation.

Moreover, we demonstrated that the locations of target giant aneurysms might predict the posttreatment behavior. The extradural ICA aneurysms treated in our cohort were more likely to decrease in size than intradurally located aneurysms. Similar findings and expectations have been suggested by Carneiro et al., according to their experience with FD and extremely large and giant intracranial aneurysms (35). Transient sac increase after flow-diversion for giant aneurysms is a well-recognized scenario (17, 27, 36, 37). Post-treatment, substantial aneurysmal enlargement in our cohort occurred in nine patients. At the second follow-up at 12 months, all the previously enlarging aneurysms demonstrated a slow collapse with mixed T1WI-T2WI signal intensity. Because these changes were observed only during the early follow-up, we believe they are probably part of the rapid evolution of the blood clots (38).

Although our study conceptualization and applied methods were not aimed at analyzing and discussing the angiographic occlusion results, the observed obliteration rates were consistent with those reported in the available FD literature (39–43). Our angiographic results suggested the unequivocal effect of flow diversion on giant aneurysms; however, the complications associated with this approach should not be overlooked. Although no patients died in this study, we documented unfavorable outcomes due to post-procedural

aneurysmal rupture or worsened clinical symptoms due to aneurysmal enlargement. The post-procedural aneurysmal rupture documented in our series occurred in three patients, in the first month after the conduced stent implantation, thus resulting in an 8.3% procedural-associated hemorrhagic complication rate. A similar rate of 7% early rupture of aneurysms treated with FDs has been found by Cagnazzo et al. who have highlighted that such events might be more likely to occur with sole flow-diversion than flow-diversion and adjacent coiling of the target aneurysm (2). Similarly, Lee et al. have suggested that sole flow diversion in large cerebral aneurysms might be associated with increased hemorrhagic rates (27). Interestingly, in our series, two of the three patients that experienced delayed rupture of their aneurysm were treated with sole flow diversion. However, we stray further from conclusions about whether coiling can mitigate delayed complications or induce them. This is mainly because the decision to use coils or not is based on the main operator discrepancy, resulting in a reliable source of bias.

To date, no consensus or specific guidelines have been published regarding the therapeutic management of these patients. The unpredictable and uncontrollable post-treatment inflammatory process inside aneurysms is likely to be associated with both the curative and the harmful mechanisms (44). Published neuro-interventional data regarding corticosteroid and anti-inflammatory drug management are inconsistent (45, 46). Corticosteroids are well-known to play an essential role in the modulation of the inflammatory response. These medications are effective in controlling cerebral vasogenic edema. Corticosteroids specifically inhibit platelet adhesion, thrombus formation and platelets' interactions with monocytes. In combination with the anti-inflammatory effects of non-steroidal anti-inflammatory drugs and the oral anticoagulant treatment, this therapy was our post-procedural management protocol for every patient (47). We believe that it could theoretically alleviate the autolysis of the aneurysm by controlling the thrombotic transformation and the ongoing inflammation. Therefore, we believe that the mitigation of the processes associated with aneurysmal thrombosis was responsible for the diminished volume at the first follow-up.

This study has several limitations, mainly due to its retrospective nature and small cohort. Our individual experience limited tailoring of the technical results and strategy. Furthermore, the lack of blinding might be interpreted as a source of bias. Therefore, our study results should be interpreted with caution and may not be widely applicable. Furthermore, we acknowledge that most of the aneurysms were located across similar locations, thus potentially influencing our results and observations.

## Conclusion

In this small series, we demonstrated that favorable volumetric reduction and aneurysmal sac shrinkage were obtained with endovascular flow diversion. Thus, radiologically confirmed reversal of the mass effect and subsequent clinical improvement can be expected in most cases. Progressive aneurysmal collapse is a time-consuming process requiring long-term follow-up. Finally, treatment-associated complications should be considered for flow diversion in patients with giant cerebral aneurysms.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

KS and SS: writing. KS, SM, and MP: verifying and secondary data analysis. KM, KN, AH, II, and VK: conceptualization of the study and critical review. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Case report: Covered stent placement to treat delayed aneurysmal rupture after flow diverter-assisted coil embolization

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**Introduction:** Flow diverter (FD) placement is widely accepted as a treatment for large saccular intracranial aneurysms. Delayed aneurysmal rupture (DAR) after FD placement is potentially catastrophic and difficult to treat. To our knowledge, using a Willis covered stent (WCS) to treat DAR after placement of a Pipeline Flex embolization device (PFED) combined with coiling has not been previously reported.

**Case presentation:** A 49-year-old woman with an incidental asymptomatic large right supraclinoid internal carotid artery aneurysm was treated with PFED placement and adjunctive coiling. DAR causing subarachnoid hemorrhage occurred 11 hours after the procedure. Treatment using a WCS was successful and resulted in a favorable clinical outcome (modified Rankin scale score 2).

**Conclusion:** DAR after FD implantation requires isolation of the aneurysm from the cerebral circulation as soon as possible. WCS placement can achieve this immediately and occlude the aneurysm. We hope our case could provide new idea for similar cases in the future.

KEYWORDS

**intracranial aneurysm, flow diverter, delayed aneurysm rupture, subarachnoid hemorrhage, case report**

## Introduction

Intracranial aneurysms are common and affect between 1 and 5% of the population, irrespective of ethnicity or geographical location (1). Flow diverter (FD) is an essential tool in endovascular treatment of large and giant intracranial aneurysms that can achieve satisfactory clinical and angiographic outcomes (2). However, it is associated with several complications, particularly delayed aneurysm rupture (DAR), which may cause severe neurological dysfunction or death (3). The mechanism of DAR after FD placement is not known. To our knowledge,

no effective means of prevention has been established. Surgical and endovascular treatments of subarachnoid hemorrhage (SAH) and/or intracerebral hemorrhage (ICH) resulting from DAR are unsatisfactory and treatment guidelines are lacking.

In contrast to the immediate effect of surgical clipping or endovascular coiling, the treatment effect of FD placement involves parent vessel remodeling and occurs over time. In the interim, any residual filling within an aneurysm treated is theoretically associated with risk of rupture. Complete aneurysm thrombosis and early isolation from the cerebral circulation can prevent late rupture after FD placement (4). The Willis covered stent (WCS; MicroPort, Shanghai, China) was designed for parent vessel reconstruction and has been approved for treatment of intracranial aneurysms. This device can exclude aneurysms from the circulation and promote their immediate occlusion. Moreover, its efficacy and safety have been established for treatment of distal internal carotid artery (ICA) aneurysms,

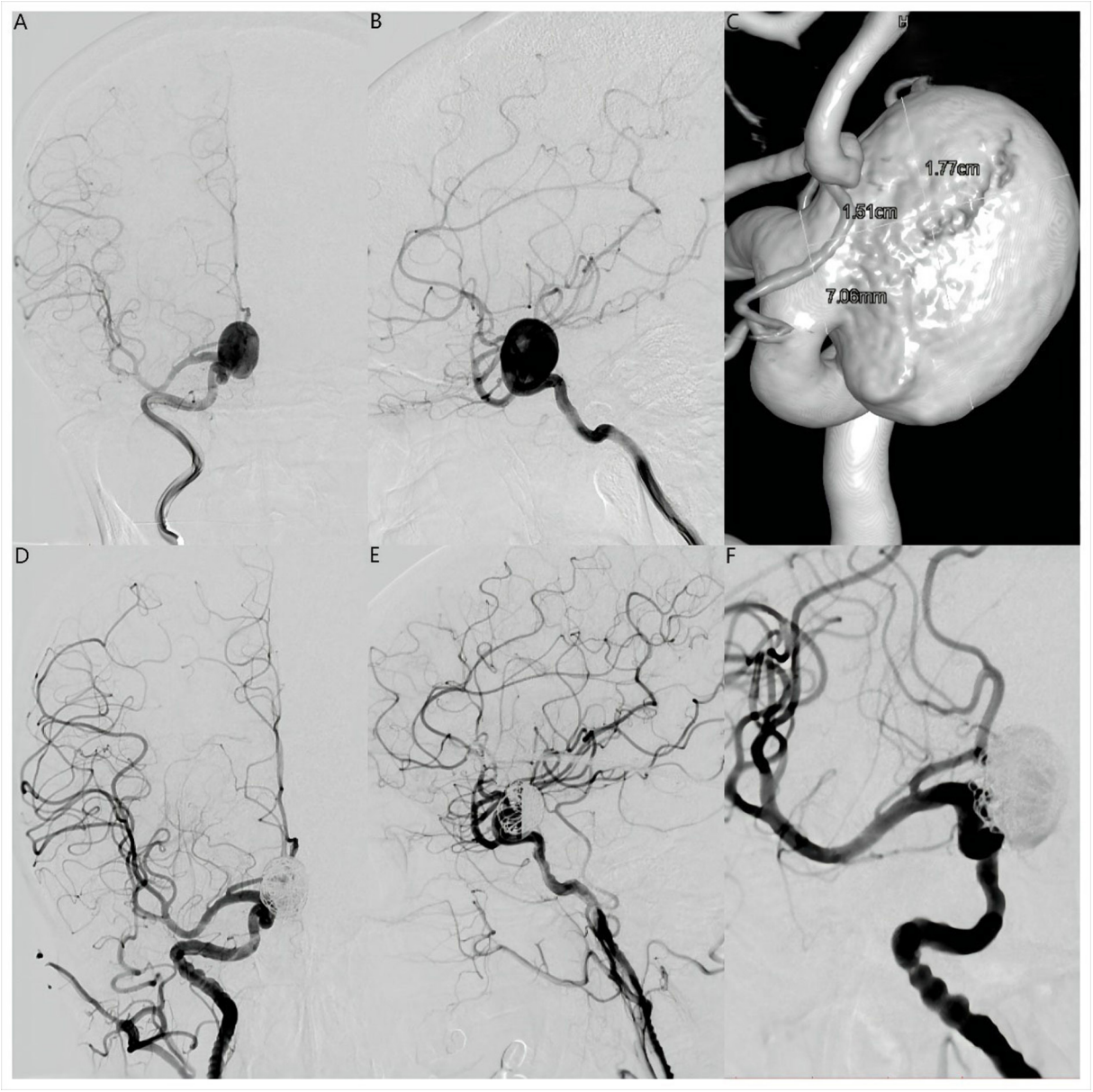


FIGURE 1
Anteroposterior **(A)** and lateral **(B)** digital subtraction angiography views and three-dimensional reconstruction angiography **(C)** revealed a large saccular right supraclinoid internal carotid artery aneurysm. Maximum diameter was 17.7 mm and the aneurysm neck was 7.06 mm. Anteroposterior **(D)**, lateral **(E)**, and operating position **(F)** angiographic views immediately after placement of a Pipeline Flex embolization device (Medtronic, Dublin, Ireland) showed contrast filling in the aneurysm lumen with entry remnant (O'Kelly-Marotta Grade C).

recurrent intracranial aneurysms after coiling, and large or giant aneurysms (5, 6).

We report a case of delayed rupture in a large supraclinoid ICA aneurysm that had been previously treated with placement of a Pipeline Flex embolization device (PFED; Medtronic, Dublin, Ireland) combined with adjunctive coiling. Treatment using a WCS during the acute rupture period successfully isolated the aneurysm from the cerebral circulation.

## Case presentation

A 49-year-old woman was found to have an incidental asymptomatic large saccular right supraclinoid ICA aneurysm on computed tomography angiography (CTA) of the head at an outside hospital and was transferred to our center for further treatment. Cerebral angiography confirmed a large right supraclinoid ICA aneurysm (Figures 1A–C). Management options were discussed within our multidisciplinary team of neurosurgeons and interventional neuroradiologists. Flow diversion with adjunctive coiling was selected.

Dual antiplatelet treatment (aspirin 100 mg daily and clopidogrel 75 mg daily) was initiated 5 days before the endovascular procedure. Platelet function was assessed by standard light transmittance aggregometry to measure platelet aggregation. Light transmittance aggregometry was conducted using platelet-rich plasma by the turbidimetric method in a 4-channel aggregometer (AG800; Techlink Biomedical, Inc, Beijing, China). Maximal platelet aggregation (MPA) was defined as the percentage change in light transmittance. The testing results showed that the MPA of ADP and arachidonic acid (AA) was 43.8 and 6.7%, respectively, suggesting that the platelet function of this patient was in a safe interval before therapeutic procedure. Under general anesthesia, a 6F 115 cm Navien (Covidien, Irvine, California, USA) intracranial support catheter assisted by a 6F 90 cm Neuron Max 088 sheath (Penumbra, Alameda, California, USA) was advanced into the right ICA. Under roadmap guidance, a 0.027-inch 150 cm Phenom 27 (Medtronic, MN, USA) microcatheter was navigated far into the middle cerebral artery (MCA) assisted by a 0.014-inch 200 cm Synchro-14 microwire (Stryker Neurovascular, Fremont, CA). A 0.017-inch 150 cm Echelon-10 (Medtronic, MN, USA) microcatheter was advanced into the aneurysmal sac for coiling. The PFED (4.5 mm × 25 mm) was then deployed from the M1 segment of the MCA to the C6 segment of the ICA. Two coils (25 × 50 mm, 22 × 50 mm, Axium Prime (Medtronic, Irvine, CA)) were deployed through the Echelon-10 microcatheter. Immediately after coiling, angiography showed near-complete occlusion with entry remnant (O'Kelly–Marotta grade C) (7) and Dyna-computed tomography (Dyna CT) showed no SAH or ICH (Figures 1D–F, 2A).

Eleven hours after the procedure, the patient was found unresponsive. Emergency head CT showed SAH in the right Sylvian cistern, anterior interhemispheric fissure, and lateral ventricle (Hunt–Hess grade IV; modified Fisher grade 2; Figure 2B). Delayed aneurysm rupture was considered as the cause, and digital subtraction angiography showed that there was still a small amount of blood flow into the lumen of the aneurysm, suggesting the location of delayed aneurysm

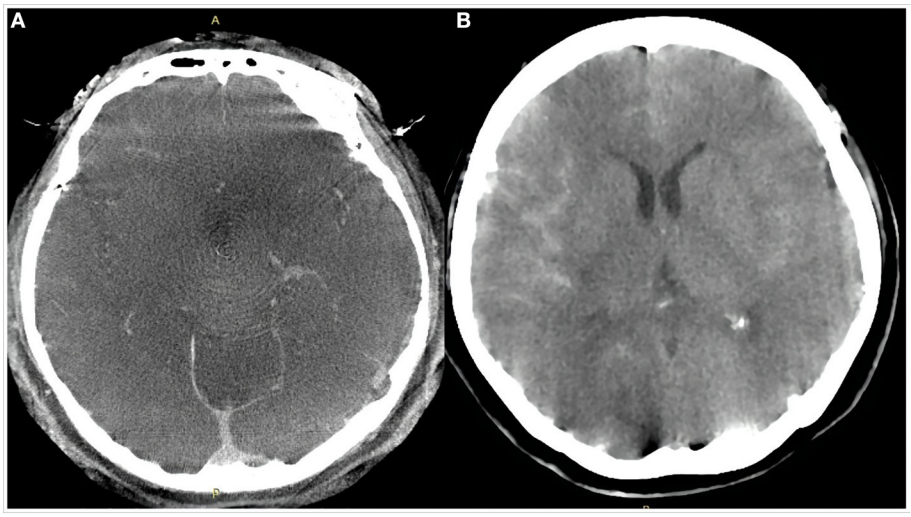


FIGURE 2
Dyna computed tomography immediately after the procedure **(A)** showed no subarachnoid hemorrhage or intracerebral hemorrhage. Emergency head computed tomography 11 h after the procedure **(B)** showed a small amount of hemorrhage in the Sylvian cistern, anterior interhemispheric cistern, and lateral ventricle.

rupture here (Figures 3A,B). After a rapid discussion, the multidisciplinary team elected to proceed with endovascular placement of a WCS to completely isolate the aneurysm from the cerebral circulation.

## Therapeutic intervention

The procedure was performed under general anesthesia. A 5F 115 cm Navien intracranial support catheter assisted by a 6F 90 cm Neuron Max 088 sheath was passed into the right ICA through the right femoral artery and a 0.014-inch 205 cm Transcend EX (Boston Scientific/Target Therapeutics) microwire was advanced carefully through the PFED into the M2 segment of the right MCA through a 0.027-inch 150 cm Excelsior XT-27 (Stryker, Fremont, California, USA) microcatheter. After retrieval of the microcatheter, a 4.0 × 10 mm WCS was pushed slowly over the microwire and anchored in the aneurysmal neck without covering the ipsilateral anterior choroidal artery. Cerebral angiography was performed to confirm stent location before it was slowly inflated with 6 atm of pressure under fluoroscopic visualization. Angiography immediately after deflation of the balloon showed no aneurysmal filling and parent artery patency (Figures 3C,D). The patient was transferred to the intensive care unit after the procedure.

## Outcome

The patient was extubated on the subsequent day after repeat head CT showed no progression of SAH (Figure 4A). Patients were asked to continue dual antiplatelet therapy (clopidogrel 75 mg/day and aspirin 100 mg/day) for at least 6 months after it was determined that the bleeding had stopped. Aspirin monotherapy

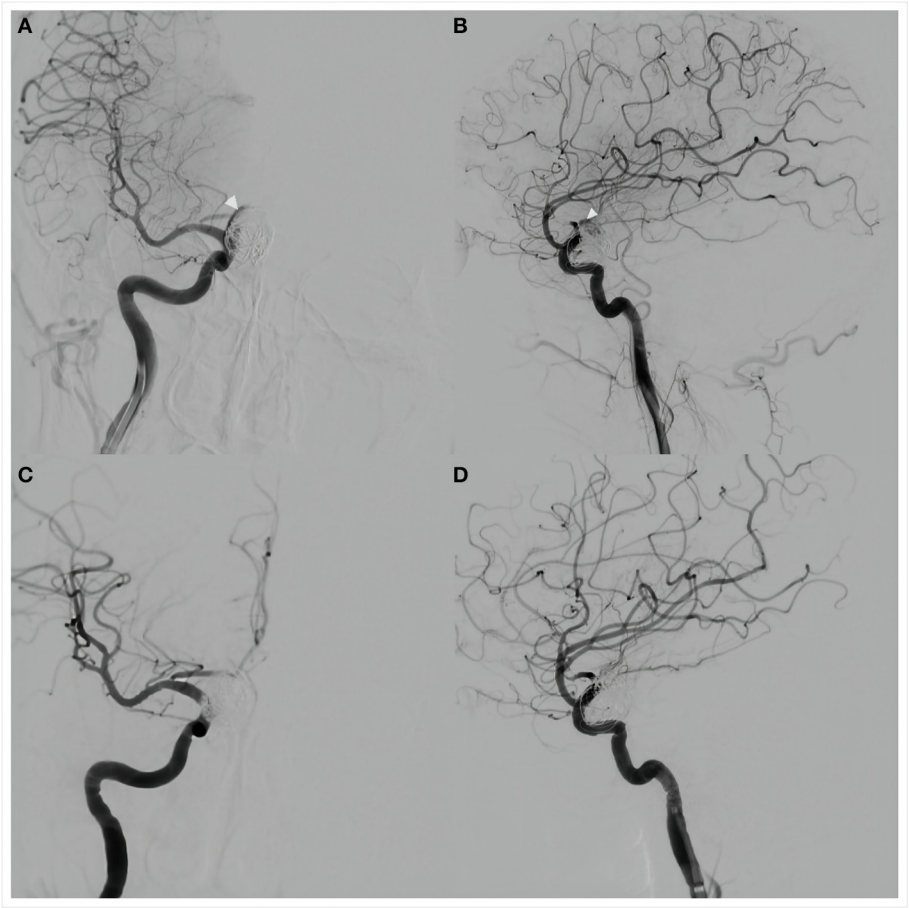


FIGURE 3
Anteroposterior **(A)** and lateral **(B)** views of cerebral angiography showed a small amount of blood flow into the aneurysm lumen (white arrows), suggesting delayed aneurysm rupture. Placement of a Willis covered stent (MicroPort, Shanghai, China) was then performed. Anteroposterior **(C)** and lateral **(D)** views of angiography performed immediately after the procedure showed no residual blood flow in the aneurysm lumen. The internal carotid and anterior choroidal arteries were patent.

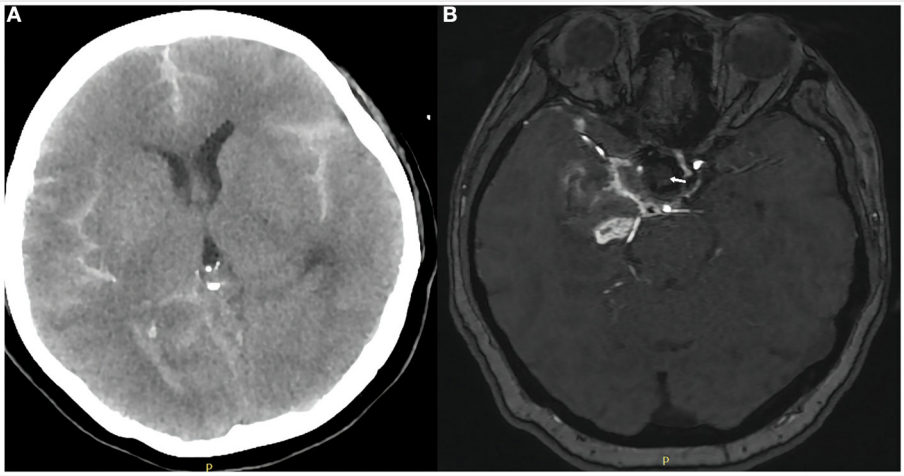


FIGURE 4
Computed tomography of the head on day 1 after covered stent placement **(A)** showed no progression of subarachnoid hemorrhage or other obvious abnormality. Magnetic resonance angiography of the brain on day 6 **(B)** showed the aneurysm was completely occluded (white arrow) and the parent artery was patent.

was continued for life. Magnetic resonance angiography 6 days after treatment demonstrated parent artery patency and no aneurysmal filling (Figure 4B). The patient's left limb strength was grade 3 on manual muscle testing. She was transferred to a rehabilitation facility 1 week after WCS placement with modified Rankin scale score 2. However, we followed up with her by phone after 1 month and there were no new symptoms and the mRS score was 1, which was an improvement from the time of discharge.

## Discussion

Flow diversion is widely used to treat large and giant intracranial aneurysms. However, delayed aneurysmal rupture (DAR) is a potentially devastating complication (8). In previous studies, reported incidence rates of DAR after FD placement ranged between 0.6 and 4% (9). The multicenter Chinese PLUS study reported an incidence of 2.1% (3). Approximately 80% of DARs occur within 30 days of the procedure. DAR results in poor clinical outcome or death in 70 to 80% of cases (9). Although the mechanism underlying DAR is unknown, computational fluid dynamic studies have demonstrated that flow modifications after stent placement can result in intra-aneurysmal pressure increases that may lead to rupture, especially in large and giant aneurysms (10). Other studies have suggested a potential role of intra-aneurysmal thrombus, as the thrombus is a source of various proteases with high proteolytic activity that can degrade the arterial wall (11, 12). Hou et al. (13) reported that 88.8% of the aneurysms that experienced delayed rupture after FD placement were large or giant; moreover, 97.8% were symptomatic. Saccular aneurysms with aspect ratio >1.6 also have a higher risk of DAR (11). Intra-thrombus proteases may play a role in the delayed rupture of these aneurysms, as they are more likely to have intraluminal thrombus (4, 9, 13–15). In large or giant aneurysms, adjunctive coiling or placement of multiple FDs to achieve complete aneurysm thrombosis and early isolation from the circulation have been suggested because of the higher risk of delayed rupture (16, 17). However, these strategies are not a panacea: in one study of patients presenting with DAR, multiple FDs were placed in 38.3% of patients (13); in another, adjunctive coiling was used in 20% (9, 13).

DAR can present with acute intracranial bleeding or carotid–cavernous sinus fistula (CCF). Rupture of ICA aneurysms located above the ophthalmic segment (C6) cause intracranial hemorrhage, while rupture of those located below the clinoid segment (C5) usually cause CCF. Patients presenting with CCF after FD placement tend to experience a relatively more favorable outcome; in contrast, those who present with hemorrhage almost always die because they deteriorate rapidly before further treatment can be rendered (13). Even with aggressive management, most patients experience inevitable deterioration and death. To the best of our knowledge, a standard treatment of DAR after FD placement has not been established. However, all patients are at risk because the treatment effect of flow diversion is not immediate but occurs over time. Mazur et al. (18) reported attempted implantation of a second FD in a patient who experienced DAR after placement of a single FD, but unfortunately failed. Hence, if rupture occurs during the latency period, the aneurysm must be isolated from the circulation as soon as possible to avoid rehemorrhage.

The WCS is a parent vessel reconstruction tool that can exclude an aneurysm from the circulation and achieve immediate occlusion. In theory, the WCS is the best treatment for intracranial aneurysms by preventing blood flow into the aneurysm sac and preserving the parent artery, thereby restoring normal vascular morphology. The use of WCS also avoids direct manipulation in the aneurysm sac, reducing the risk of aneurysm rupture (19). Willis covered stents have been proven to be safe and effective in the treatment of ruptured or unruptured ICA siphon aneurysms, distal ICA aneurysms, recurrent intracranial aneurysms after coiling, and large or giant aneurysms (5, 20–22). However, Zhu et al. (23) also noted that it is not recommended for patients with a tortuous parent artery or critical side branches, particularly the anterior choroidal artery, associated with the aneurysm. In view of this, PFED treatment was chosen instead of WCS treatment in our patient first. However, in our patients with DAR after PFED placement resulting in subarachnoid hemorrhage, we used WCS in addition to the original PFED in order to isolate the ruptured aneurysm as soon as possible. This occluded the aneurysm, prevented further hemorrhage, and resulted in a favorable clinical outcome. Covered stent placement is a feasible treatment option for patients with DAR after FD placement. However, its long-term outcome remains to be further followed up.

## Author's note

This work originated from the Beijing Neurosurgical Institute and Beijing Tian Tan Hospital, South Fourth Ring Road West 119, Fengtai District, Beijing.

## Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author/s.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Tian Tan Hospital. Written informed consent to participate in this study was provided by the patients/participants. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

XC and SG wrote the first draft of the manuscript and acquired the data. LZ and LD analyzed and interpreted the data. HG and PL edited the figures of the article. YL and ML conceived and designed the research. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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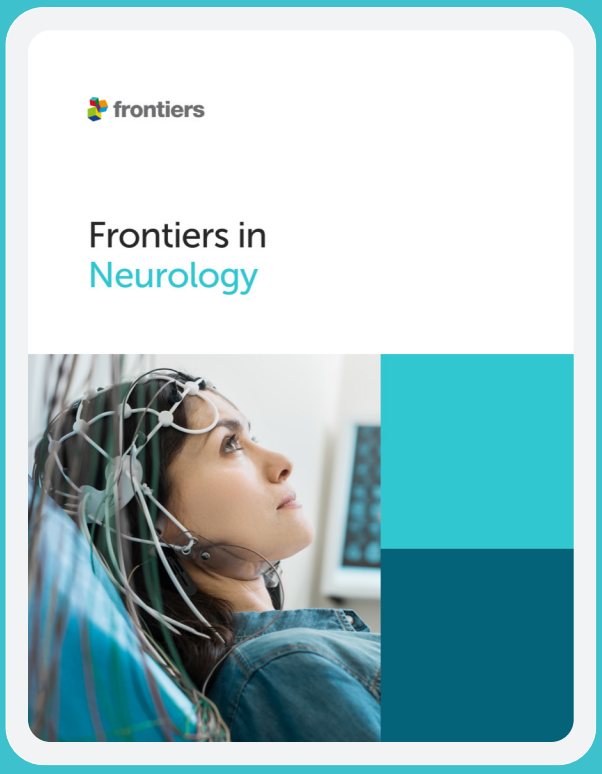


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