The p48 flow diverter: First clinical results in 25 aneurysms in three centers

Citation for published version (APA):

Document status and date:
Published: 01/06/2021

DOI:
10.1177/1591019920972213

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain.
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:
repository@maastrichtuniversity.nl
providing details and we will investigate your claim.

Download date: 27 Oct. 2023
The p48 flow diverter: First clinical results in 25 aneurysms in three centers

FRA Van den Bergh¹, T De Beule², WJ van Rooij³, MH Voormolen⁴, T Van der Zijden⁴, L Stockx², WH van Zwan⁵ and H Fransen¹

Abstract
Background: The novel low-profile p48 flow diverter has been designed to treat aneurysms on small vessels of 1.75–3mm. We report our first clinical experiences.

Methods: Between March 2018–January 2020, 22 patients with 25 aneurysms were treated with the p48 in 3 centers. One patient had 3 aneurysms covered by one p48 and one patient had 2 aneurysms. There were 5 men, 17 women, with a mean age of 55 years (median 59, range 29–73 years).

Results: In 25 aneurysms, 24 p48 flow diverters were placed. In 1 patient additional coils were placed in the aneurysm. Procedural vessel rupture by the micro guidewire occurred in 2 patients and vessel rupture during p48 balloon dilatation occurred in 1 patient. Overall, the permanent morbidity rate was 13.6% (3 of 22, 95%CI 3.9–34.2%) and mortality was 4.5% (1 of 22, 95%CI <0.01–23.5%). Most complications were procedure-related and not device-specific. Of 22 patients with 25 aneurysms treated with p48, 18 patients with 20 aneurysms had angiographic follow-up after 5–18 months. Of 19 aneurysms, 10 were occluded and 7 showed a remnant. Two aneurysms were open after 6 months. Three aneurysms were still not occluded after 12, 14, and 18 months and these 3 were retreated. Retreatment rate was 16% (3 of 19) and the adequate occlusion rate was 90% (17 of 19).

Conclusions: Treatment of aneurysms in small-caliber vessels with the p48 is feasible and effective but is not without complications. More data is needed to establish indications, safety, and efficacy more accurately.

Keywords
Flow diverter, flow diversion, intracranial aneurysms, complications, interventional radiology, p48, p48 MW, endovascular treatment

Received 10 August 2020; revised 13 October 2020; accepted 18 October 2020

Introduction
The introduction of flow-diverting stent technology expanded the armamentarium for the endovascular treatment of intracranial aneurysms. These new stents provide flow diversion, a mechanical redirection of blood flow, which allows for intra-aneurysmal stagnation of blood, clot formation, remodeling, and, ultimately, endothelial growth. The flow diverter has become a separate entity of the stent with a different purpose and set of indications. Indications include fusiform aneurysms, wide-necked aneurysms, and dissecting aneurysms in both anterior and posterior circulation.¹–⁶ A variety of different flow diverting stents are currently available: the Pipeline Embolization Device (PED) (Medtronic, Dublin, Ireland), Silk (Balt Extrusion, Montmorency, France), Surpass (Stryker Neurovascular, Fremont, CA, USA), p64 (PhenoX, Bochum, Germany) and the Flow Re-direction Endoluminal Device (FRED, MicroVention, Tustin, CA, USA). These high-profile devices are compatible with microcatheters of 0.027-inch or larger and are intended to treat aneurysms on (proximal) vessels from 3–5 mm. However, these devices also have successfully been used in smaller vessels down to 1.3 mm.⁷–⁹ Recently, lower-profile flow diverters have been introduced compatible with 0.021-inch microcatheters for treatment of

¹Department of Radiology, Algemeen Ziekenhuis St Lucas, Gent, Belgium
²Department of Radiology, Ziekenhuis Oost-Limburg, Genk, Belgium
³Department of Radiology, Algemeen Ziekenhuis Turnhout, Turnhout, Belgium
⁴Department of Radiology, Universitair Ziekenhuis Antwerpen, Edegem, Belgium
⁵Department of Radiology, Maastricht Universiteit Medisch Centrum, Maastricht, the Netherlands

Corresponding author:
FRA Van den Bergh, AZ St Lucas Gent, Groenevriel 1, 9000 Gent, Belgium.
Email: fransvandenbergh@gmail.com
aneurysms on more distal vessels from 1.5–3 mm: FRED Jr, (MicroVention), Silk Vista Baby, (BALT), and p48, (Phenox). The use of lower profile microcatheters and more flexible flow diverters makes navigation in tortuous vessels easier expanding the applicability of the device.

In this paper, we report the first clinical experiences in three centers with the novel low-profile p48 flow diverter, that has been designed to treat aneurysms on vessels of 1.75–3 mm.

Materials and methods

p48 flow diverter

The low-profile p48 flow diverter (Phenox, Bochum, Germany) comprises 48 braided drawn filled tubes. Each strand is made of platinum-filled nitinol tubing. The device is mounted on a central, independently movable stainless steel insertion wire. This wire has an atraumatic distal nitinol tip (the ‘olive’) to prevent the perforation of small distal vessels. A proximal radio-opaque marker on the insertion wire identifies the point at which the device can still be re-sheathed. The device is compatible with 0.021-inch microcatheters and is available in nominal diameters of 2 mm and 3 mm, intended to treat vessels of 1.75–3 mm diameter. The low-profile p48 shares the platinum filled wires and the movable wire with the p64, but, unlike the p64, it is not mechanically detached.

The p48 HPC (Hydrophilic Polymer Coating) became recently available. The surface is coated with a glycan-based multilayer hydrophilic polymer coating. It is claimed that HPC prevents the triggering of the clotting cascade and reduces the risk of thrombus formation. Thus, the p48 HPC is intended for use with single instead of dual anti-platelet medication.

Patients and aneurysms

Each patient was discussed in a multidisciplinary neurovascular team. Patients were informed about the nature of their disease and the intended treatment and potential alternatives, with informed consent obtained at least 24 hours before the procedure. The selection of the flow diverter was based on operator preference and the size of the parent vessel.

General indication for p48 treatment were unruptured intradural wide-necked or fusiform aneurysms and aneurysm remnants or recurrences after previous endovascular or surgical treatment. Ruptured supraclinoid carotid or vertebrobasilar dissection aneurysms were considered for p48 treatment if alternative treatment (for example, vertebral occlusion) was not possible.

Endovascular procedure

Procedures were performed with the patient under general anesthesia on a biplane or a single plane angiographic system (Philips Allura or Azurion, Philips Healthcare, Best, the Netherlands, and Siemens Zee, Siemens, Erlangen, Germany). Either a 6F guide catheter alone or triaxial access was used. A suitable working projection was identified from 3D angiographic imaging. The selection of diameter and length of the p48 was made with the aid of computer simulation on the Philips 3D workstation or with dedicated software (Sim & Cure, Grabels, France). A 0.021-inch microcatheter (Prowler Select Plus, Codman Neurovascular Raynham MA, or Headway 21 (MicroVention)) was placed over a 0.014-inch micro guidewire in a straight segment of the parent artery distal to the aneurysm neck. Slight under-sizing was allowed since the diameter of the unconstrained device is approximately 0.3 mm larger than the nominal diameter. Since under-sizing results in shortening and a denser metal coverage of the implant, this was avoided if side branches were covered. The device was then advanced to the desired position via the microcatheter. Deployment was performed by a combination of slow withdrawal of the microcatheter, with a continuous counterpressure on the delivery wire. After the distal end of the device was deployed and anchored in the target vessel, the microcatheter was no longer pulled back. Pushing the delivery wire of the p48 resulted in a progressive deployment of the device with a passive proximal movement of the microcatheter. If the wall apposition of the detached p48 was not as desired, a compliant micro balloon was inserted and gently inflated to obtain complete wall apposition.

Antiplatelet regimen and anticoagulation protocol

Patients were preloaded with 600 mg clopidogrel and 100 mg acetylsalicylic acid at least 1 day before the procedure. Platelet aggregation inhibition was tested before the procedure using different tests. In patients with clopidogrel resistance, medication was changed to ticagrelor or prasugrel. The dual antiplatelet medication was continued for six months, followed by acetylsalicylic acid only for life. When p48-HPC was used, the decision to use single antiplatelet medication was left to the discretion of the operator.

Periprocedural medication included systemic heparinization with ACT values aimed at 250. Additionally, all flushing solutions, including the guiding catheters and microcatheters, were heparinized (5000 IU unfractionated heparin/L).

If thrombus formation occurred during the procedure, a body weight-adapted bolus of 180 mcg/kg eptifibatide IV (Integrilin, GlaxoSmithKline, Munich, Germany) was administered.
Follow-up

Patients were scheduled for clinical and angiographic follow-up at 6 months and 2 years. Sometimes other follow-up intervals were used for clinical or logistic reasons. Clinical assessment at follow-up was performed according to the modified Rankin Scale. Angiographic results were graded as complete occlusion, neck remnant, or persistent flow. In-stent stenosis was graded as absent, mild (<25% diameter reduction), moderate (25–75% diameter reduction), severe (75–90% diameter reduction), and occlusion. If in-stent stenosis was present, on later angiographic follow-up, this was qualified as unchanged, decreased, resolved, or increased.

Results

Patient-and aneurysm characteristics are summarized in the Online Table.

Patients

We retrospectively reviewed the medical records and imaging studies of all patients treated with a p48 in three institutions. Between March 2018 – January 2020, 22 patients with 25 aneurysms were treated with the p48 and included in this analysis. One patient (#15) had 3 aneurysms on the same pericallosal artery and one patient (#16) had 2 aneurysms. There were 5 men and 17 women, with a mean age of 55 years (median 59, range 29-73 years). Of the 24 aneurysms, 11 had been discovered incidentally, 7 were additional to another ruptured aneurysm, 4 had reopened after previous endovascular coil treatment, 2 were acutely ruptured M1 dissection aneurysms, and 1 PCA dissection aneurysm presented with mass effect. Aneurysm location was anterior communication artery 5, middle cerebral artery 11, pericallosal artery 7, posterior communicating artery 1, and dissection aneurysm of the posterior cerebral artery 1.

Aneurysm size was defined as fundus size or lumen size in reopened aneurysms. The mean size was 6 mm (median 4, range 2–20 mm).

Procedural events and complications

In 25 aneurysms, 24 p48 flow diverters were placed. Nine p48s were coated with HPC. The p48 HPC was used in all centers from the moment it became available on the market. One p48 covered 3 pericallosal artery aneurysms (patient #15, Figure 1). Dislocation of the p48 immediately after placement occurred in a 59-year-old woman (#6) with a 5 mm recurrent middle cerebral artery aneurysm after coiling, probably because of inappropriate sizing. A second p48 was placed to completely cover the aneurysm neck. In another patient (#7) 2 p48 were needed to completely cover the neck. In 1 patient (#12), additional coils were placed in the aneurysm.

Figure 1. A 72-year-old woman with three aneurysms on the distal anterior cerebral artery additional to a previously treated ruptured middle cerebral artery aneurysm. Oblique angiogram (a) and 3D angiogram (b) showing the three aneurysms (black arrow). The largest is located on the proximal pericallosal artery and the two tiny aneurysms on the calloso-marginal artery. Note coiled left middle cerebral artery aneurysm (thick arrow). (c) Angiography immediately after placement of the p48, covering the largest aneurysm. The 2 tiny aneurysms are not in contact with the surface of the p48. There is an immediate effect on the largest aneurysm. D and E: Native (A) and subtracted (B) angiogram after three months. The largest aneurysm is occluded. Some in-stent stenosis in the p48. F: At 6 months the in-stent stenosis has resolved and all arterial branches are patent. The two tiny aneurysms are unchanged.
One patient (#13) had a retroperitoneal hematoma. One patient (#20) with an incidental 3 mm middle cerebral artery aneurysm had a postoperative seizure. MRI showed a small focus of recent ischemia anteriorly in the left insula without neurological deficit. On follow-up, she did well (mRS 0).

A 31-year-old woman (#16) with multiple aneurysms had pericallosal artery mirror aneurysms additional to a ruptured aneurysm. One of these 2 aneurysms was treated with a p48 without complications. During treatment of the second pericallosal artery aneurysm 9 months later a thrombo-embolic complication occurred resulting in a small frontal infarction. This patient recovered well without remaining symptoms (mRS 0).

A 52-year-old man (#12) presenting with a mass effect of a 20 mm dissection aneurysm of the posterior cerebral artery was treated with coils and a p48. The patient developed a partial posterior cerebral artery infarction with remaining quadrant hemianopsia (mRS 1) (Figure 2).

Procedural vessel rupture by the micro guidewire during placement of the microcatheter occurred in 2 patients. The first patient was a 45-year-old woman (#11) with a recanalized 12 mm anterior communicating artery aneurysm. Perforation occurred during passing the aneurysm to the A2 segment with the wire for placement of the microcatheter. She remained dependant (mRS 4-5). The second patient was a 59-year-old woman (#14) with a 4 mm incidental pericallosal artery aneurysm. The tip of the guidewire punctured a distal side branch during the placement of the microcatheter. This resulted in massive bleeding that later proved fatal (mRS 6). Both ruptures were procedure-related but not device-related.

In a 59-year-old woman (#17) with a 5 mm, anterior communicating artery aneurysm additional to another ruptured aneurysm, the expansion of the p48 was not complete. Dilatation with a compliant balloon resulted in rupture of the A1 and this vessel was subsequently occluded with coils. She remained dependent (mRS 3).

Overall, the permanent morbidity rate was 13.6% (3 of 22, 95%CI 3.9–34.2%) and mortality was 4.5% (1 of 22, 95%CI <0.01–23.5%). The 3 hemorrhagic complications were not device-related.

**Angiographic and clinical follow-up**

Of 22 patients with 25 aneurysms treated with p48, 16 patients with 18 aneurysms had angiographic follow-up after 5–18 months. One patient had MRI follow-up after 9 months. One patient died in the hospital from a complication. Three patients refused follow-up angiography and for 1 patients follow-up angiography is scheduled. There were no rebleeds in the 2 patients treated in the acute setting with a ruptured aneurysm during follow-up.

Of 19 aneurysms, 10 were occluded and 7 showed a remnant. Two aneurysms were open after 6 months. Three aneurysms were still not occluded after 12, 14, and 18 months and these 3 were retreated. The

---

**Figure 2.** 52-year-old man presenting with mass effect of a dissecting aneurysm of the posterior cerebral artery. (a) MRI shows aneurysm with mass effect on the brain stem. (b) 3D angiogram with large dissecting aneurysm of the left posterior cerebral artery. (c) and (d): situation after coiling and p48 placement across the neck of the aneurysm on radiograph (c) and lateral vertebral angiogram. Complete occlusion with patent posterior cerebral artery. MRI (e) and MRA (f) after treatment demonstrate partial infarction of the posterior cerebral artery with patency of the vessel. Note signal loss in parent vessel by the p48.
retreatment rate was 16% (3 of 19) and the adequate occlusion rate was 90% (17 of 19).

A middle cerebral artery aneurysm in a 69-year-old man (#3) that was still open after 14 months because of a retracted and luxated p48, was additionally treated. A Neuroform Atlas stent (Stryker, Fremont, CA) was placed as an intended scaffold for a second p48 and to correct the kinking between the M1 and the M2 with the p48. After placement of the stent, the p48 regained its original position obviating the need for a second p48. An anterior communicating artery aneurysm in a 64-year-old woman (#2) that remained open, was additionally treated with a Pipeline Embolization Device (Medtronic Fridley MN) through the p48 after 18 months. One wide-necked 3 mm middle cerebral artery aneurysm in a 65-year-old woman (#20) that was still not occluded at 12 months, was additionally clipped.

Of 19 aneurysms with angiographic follow-up, intimal hyperplasia was moderate in 2, mild in 3 (one p48 covering 3 aneurysms, pt #15), and absent in 14 aneurysms. Distal tapering (‘fish mouthing’) or side branch occlusion did not occur. In one patient (#6) with moderate hyperplasia at 6 months, this had disappeared after 12 months. The other patients with intimal hyperplasia had no further follow-up yet.

**Discussion**

In this small multicenter study of the treatment of 25 aneurysms with the p48 flow diverter, the permanent complication rate was 18% (4 of 22). At angiographic follow-up beyond the 6 months interval, 3 of 19 aneurysms (16%) were still open and were retreated. At first glance, these results seem somewhat disappointing, both in terms of complications as in aneurysm occlusion rate. However, most complications were not device-related and probably reflect a steep learning curve of this new device in the 3 centers involved. Clinical data of the recently introduced low-profile flow diverters are theoretically targeted to smaller caliber vessels. The first clinical results of low-profile flow diverters are encouraging with a favorable safety and efficacy profile flow diverters for cerebral aneurysms comprising 2493 treated aneurysms; none was occluded completely.

Complication rates in studies using high profile flow diverters for aneurysms in small cerebral vessels tend to be higher: in a meta-analysis comprising 572 aneurysms, procedural permanent morbidity was 9% and mortality was 4% with narrow confidence intervals.

The complication rates for high profile flow diverters in small vessels may be higher than reported complication rates in meta-analyses comprising aneurysms in all locations, although results vary: In a study by Zhou et al. of 3125 patients, complication rates were relatively low with permanent morbidity 4.5% and mortality 2.8%. On the other hand, in an earlier review covering 1018 aneurysms in 897 patients, morbidity was 9.9% and mortality was 4.1% in the same range as for small vessels.

In a large meta-analysis concerning the efficacy of flow diverters for cerebral aneurysms comprising 2493 treated aneurysms, occlusion rates at last follow-up varied considerably with an overall complete occlusion rate of 82.5% (95% CI, 78.8%-86%) across studies. Efficacy of aneurysm occlusion for the new low profile flow diverters appears to be in the same range or lower in the few available studies.

Because of the braided design of flow diverters, oversizing results in lengthening of the device. Inappropriate sizing results in uncertain final length of the flow diverter in turn making accurate positioning in the proximal landing zone uncertain. Also, inappropriate sizing affects the porosity of the devices. The metal coverage varies as a parabolic function of the ratio between the vessel and the device diameters. Oversizing of a flow diverter results in reduced metal coverage and increased porosity that could theoretically result in a reduced aneurysm occlusion rate. Hence, the inherent oversizing when using high profile flow diverters in small vessels may negatively affect occlusion rates at follow-up. Similarly, inappropriate sizing may affect the patency of covered side branches which is more likely to occur when these devices are used in small vessels in the distal circulation. These factors form a rationale for the development of flow diverters that are specifically targeted to smaller caliber vessels. The first clinical results of low-profile flow diverters are encouraging with a favorable safety and efficacy
profiles and very infrequent in-stent stenosis and side branch occlusions, especially important in small cerebral vessels.

Because of imperative double antiplatelet therapy, the primary indication for flow diverters are unruptured aneurysms. For some ruptured dissection aneurysms, flow diversion may be the only available option. In clinical practice, the approach of patients with ruptured and unruptured aneurysms should be tailored to the specific patient- and aneurysm characteristics.

In unruptured aneurysms, flow diversion has become a powerful tool. In patients with a ruptured aneurysm, double antiplatelet medication is generally contra-indicated and endovascular techniques without the need for antiplatelet medication, such as simple coiling, balloon-assisted coiling or WEB treatment\textsuperscript{26} are preferred.

Our study has several limitations and reflects the first experience in 3 centers with the p48 flow diverter. The included aneurysm population was inhomogeneous with small and large, ruptured and unruptured aneurysms. Follow-up duration was limited and some patients were lost to follow-up. Most complications were procedure-related and not device-specific, with 2 distal wire perforations during positioning of the microcatheter. Quaeschling et al.\textsuperscript{27} introduced a novel technique to reduce the risk of this complication by use of a low-profile stent-retriever as a railway for introduction of the required microcatheter to deliver the flow diverter.

In conclusion, the new low profile flow diverters such as the p48 are specifically designed for use in small-caliber vessels through 0.021-inch microcatheters. Treatment with these flow diverters is feasible and effective but is not without complications. More data is needed to establish indications, safety, and efficacy more accurately.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval
This retrospective study is in compliance with national law with a waiver for ethical approval.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs
T De Beule \( \text{https://orcid.org/0000-0002-2987-5818} \)
WJ van Rooij \( \text{https://orcid.org/0000-0001-5931-1186} \)
WH van Zwam \( \text{https://orcid.org/0000-0003-1631-7056} \)

Supplemental Material
Supplemental material for this article is available online.

References


