Aneurysm Treatment in Acute SAH with Hydrophilic-Coated Flow Diverters under Single-Antiplatelet Therapy: A 3-Center Experience

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ABSTRACT

BACKGROUND AND PURPOSE: In certain clinical circumstances, dual-antiplatelet therapy can be problematic in patients with acute SAH. In some aneurysms, however, flow-diverting stents are the ideal therapeutic option. We report our experience with ruptured intracranial aneurysms treated with flow diverters with hydrophilic coating (p48 MW HPC and p64 MW HPC) under single-antiplatelet therapy.

MATERIALS AND METHODS: Patients were treated with either flow-divertor placement alone or a flow diverter and additional coil- ing. Due to the severity of the hemorrhage, the potential for periprocedural rehemorrhage, and the potential for additional surgical interventions, a single-antiplatelet regimen was used in all patients.

RESULTS: Thirteen aneurysms were treated in 10 patients. The median age was 62 years; 5 patients were male. All had acute SAH due to aneurysm rupture. Four blood-blister, 2 dissecting, and 7 berrylike aneurysms were treated. Seven aneurysms were adjunctively coiled. Eight of the 10 patients received a single-antiplatelet protocol of aspirin, 1 patient was treated with prasugrel only, and 1 patient was treated with tirofiban first and then switched to the aspirin single-antiplatelet protocol. One device-related complication occurred, a thrombosis of an overstented branch. All stents, however, remained open at DSA, CTA, or MRA follow-up.

CONCLUSIONS: The implantation of flow diverters with reduced thrombogenicity due to hydrophilic surface coating under single-antiplatelet therapy seems to be an option in carefully selected cases of SAH due to aneurysm rupture.

ABBREVIATION: PO = orally

The endovascular treatment of unruptured intracranial aneurysms with flow diverters has become a routine procedure. The use of flow diverters for the treatment of ruptured aneurysms is considerably more complex due to the requirement for dual-antiplatelet therapy. However, for selected ruptured aneurysms, flow diverters might still be considered the treatment of choice when other strategies are too risky or simply not possible. This scenario can occur in wide-neck sidewall, fusiform, or blister aneurysms. Therefore, a modified flow diverter that could be safely implanted with single-antiplatelet therapy would represent a major advance.

Three flow diverters with coatings or surface modifications designed to reduce thrombogenicity, the Pipeline Embolization Device with SHIELD technology (PED Shield, Medtronic) and the p48 MW HPC or p64 MW HPC with hydrophilic coating (phenox), currently have Conformité Européenne mark clearance. Although instructions for use recommend standard dual-antiplatelet therapy after the implantation of these devices, for the latter 2, the instructions for use indicate that single-antiplatelet therapy is on-label if justified by the clinical circumstances.

In the present study, we report our experience using the p48 MW HPC and the p64 MW HPC with single-antiplatelet therapy for the treatment of ruptured intracranial aneurysms in the setting of acute SAH.

MATERIALS AND METHODS

We retrospectively included patients from prospectively collected data bases from 3 different centers (Institute for diagnostic and interventional Neuroradiology, Helios Klinikum Erfurt, Erfurt...
Regimen 1. Six patients received 5000 IU of heparin IV and 250 or 500 mg of aspirin IV during the procedure after microcatheter positioning. After the procedure, the patients were given enoxaparin, 40 mg twice daily, and 250 mg of aspirin IV twice daily for the duration of the stay in the intensive care unit. Afterward, they were switched to 100 mg of aspirin orally (PO) per day, and the enoxaparin was withdrawn. SAH leads to an activated platelet aggregation, which explains the increased dosage of aspirin and IV application.9

Regimen 2. One of the patients received 5000 IU of heparin IV after microcatheter positioning and before flow-diverter placement. A body weight–adapted continuous IV infusion of tirofiban was started after stent deployment. The patient was kept on tirofiban for 24 hours and was then switched to prasugrel 10 mg PO per day after a loading dose of 60 mg PO with an overlap of 4 hours accompanied by enoxaparin, 40 mg twice a day, for the duration of the stay in the intensive care unit.

Regimen 3. One patient who received 2 flow diverters in 2 different locations received 5000 IU of heparin IV and 250 mg of aspirin IV before placement of the flow diverter. During the procedure, a body weight–adapted bolus of tirofiban was given due to suspected thrombus formation. Another 250 mg of aspirin IV and 2500 IU of heparin IV were given before placement of the second flow diverter.

Regimen 4. In 2 patients, the interventions were performed with aspirin, 250 mg IV, and 5000 IU of heparin IV before stent placement. After stent placement, a continuous body weight–adapted IV infusion of eptifibatide was started for 8 hours. This was changed to prasugrel starting with a loading dose of 60 mg orally with an overlap of 2 hours. In 1 patient, the prasugrel was switched to ticagrelor after 2 days.

Response testing was not performed and, therefore, not included in the analysis. Details of the medical regimen for each patient included in the study are listed in the Online Supplemental Data.

Follow-up
All patients were followed with CT with CTA or, alternatively, MR imaging with MRA or DSA to prove the patency of the flow diverters. The methods chosen depended on the condition of each patient and the clinical situation.

RESULTS
From August 2018 to June 2020, ten patients were included of 260 screened patients treated endovascularly in the setting of acute SAH due to rupture of an intracranial aneurysm at the 3 different centers. All patients were treated within 24 hours of diagnosis of acute hemorrhage and within 48 hours of the onset of acute SAH-like headache. The median age of patients was 62 years (range, 50–76 years); 5 patients were men. The median Hunt and Hess grade was 2 (range, 1–4). Two patients were treated with 1 p64 MW HPC each; 8 patients were treated with 9 p48 MW HCPs. In 1 patient, 2 p48 MW HPCs were placed in 2 different aneurysms. In 7 aneurysms, additional coiling was used. Altogether, 13 aneurysms were treated. Of these aneurysms, 2 were classified as dissecting aneurysms; 7, as berry aneurysms; and 4, as blood-blower aneurysms. Eight patients were treated with the aspirin regimen (regimen 1). 1 patient was treated with the prasugrel regime, 1 patient was treated with the tirofiban/aspirin regimen (regimens 2 and 3, as described above under Materials and Methods).
The median time on single-antiplatelet therapy until last available follow-up was 13.5 days (range, 3–194 days). Four patients were controlled with CT/MRA, 1 patient was controlled with CT/CTA, and 5 patients were controlled with DSA. One device-related complication occurred (explained in detail below).

There were 2 intraprocedural but not flow-diverter-related complications: 1 aneurysm rupture due to attempted placement of a Woven EndoBridge endovascular flow disruptor (MicroVention), which was then coiled and secured with a p48 MW HPC flow diverter afterward to cover an adjacent blood-blister-like aneurysm as well. This patient died 3 days later due to the sequelae of the SAH (patient 2, Online Supplemental Data). In 1 aneurysm, which was treated with a p48 MW HPC and adjunctive coiling, a coil dislocation occurred, which led to a superior cerebellar artery infarction. In both cases, the flow diverter remained open on control (patient 4, Online Supplemental Data). Further detailed results and patient characteristics are given in the Online Supplemental Data.

Four sample patients are detailed in Figs 1–4.

**Device-Related Complications**

One patient (patient 9, Online Supplemental Data) with a broad-based berry-type aneurysm sitting asymmetrically on the inferior trunk of the left MCA right after the bifurcation was treated with a p48 MW HPC, applying regimen 1 (mentioned above under Materials and Methods). The patient initially was Hunt and Hess grade 1 and therefore clinically well, other than a significant headache, with no neurologic deficits. The procedure was performed successfully, and the patient awoke from anesthesia with still no neurologic deficits. A scheduled angiogram 24 hours after the procedure showed the flow diverter perfectly patent. However, after removal of the arterial sheath, groin compression and application of the pressure dressing, the patient suddenly developed an aphasia and a right hemiparesis up to an NIHSS of about 15 during about 10 minutes. In an immediately performed angiogram of the left internal carotid artery, a thrombosis of the overstented superior branch of the left MCA was noted, with the flow-diverting device being perfectly patent. A body weight-adapted bolus of tirofiban with consecutive body weight–adapted continuous infusion of tirofiban accompanied by an elevation of the mean arterial blood pressure was initiated; and the thrombus was resolved, and the hemiparesis and aphasia recovered completely. The patient was then switched to a dual-antiplatelet therapy with aspirin, 100 mg PO, and prasugrel, 10 mg PO. The patient remained stable under this therapy for about 10 days when he began to develop severe vasoospasm in the left MCA territory, which was treated noninvasively as well as by an intra-arterial medical vasodilation treatment, but which finally led to significant infarction in the left MCA and anterior cerebral artery territory. The flow diverter remained patent throughout all of the controls. The reason for the initial acute thrombosis of the overstented superior trunk is not clear, but it was presumably due to a vaso-vagal reaction during the groin compression and a
subsequent drop of blood pressure, which led to an overshoot of
flow diversion and an initiation of the thrombosis in the superior
trunk (Fig 2).

DISCUSSION
In our retrospective 3-center study, we present 10 patients with
acute aneurysmal SAH treated with novel hydrophilic-coated
flow diverters and a postprocedural single-antiplatelet therapy.
The main observation is that all flow diverters remained patent
with no ischemic events attributable to in-stent thrombosis of
the flow diverters. However, 1 patient had a thrombotic complica-
tion in an overstented branch attributable to a blood pressure drop
and overshoot of the flow-diverting effect of the flow diverter.

The rationale for the above-mentioned treatments is that the
treatment of patients with acute aneurysmal SAH with flow
divers is complicated. Dual-antiplatelet therapy can result in
hemorrhagic complications, elevating the risk of any subsequent
surgical procedures and potentially increasing the risk and sever-
ity of aneurysm rupture.5,10,11

Several publications, however, have evaluated the safety of
flow-diverter treatment for ruptured intracranial aneurysms
(Table). Recently, Ten Brinck et al12 reported a series of 44
patients with acute SAH treated with standard flow diverters.
The mean time from SAH to treatment was 3 days. In 9 cases,
additional coiling was used. Dual-antiplatelet therapy was
used in all cases. Twenty-five (44%) periprocedural complica-
tions occurred in 20 different patients, 5 of which were intra-
procedural, including 6 ischemic strokes (not related to
vasospasm), 10 intracranial hemorrhages (2 ventricular shunt
hematomas, 1 subdural hematoma), and 4 other non-CNS
hemorrhages (gastrointestinal bleeds and retroperitoneal
hematomas). Periprocedural stroke resulted in permanent
neurologic deficits in 12 patients (27%). They concluded that
flow-diverter treatment of ruptured intracranial aneurysms is
associated with a high rate of periprocedural complications.12

A review by Cagnazzo et al,13 in 2018, evaluated the topic in a
meta-analysis that systemically reviewed studies from 2006 to
2018 addressing occlusion rates, complications, rebleeding, and
factors influencing the outcome. They included 223 patients from
20 studies in their analysis. The mean interval between SAH and
treatment was 6.7 days. Most patients were treated with a single
flow diverter (75%) and some without additional coiling (81%).
Most of the treatment targets were either blister, dissecting, or
 fusiform aneurysms; only 18% were saccular. A complete occlu-
sion rate of 88.9% was reported, with immediate angiographic
occlusion in 32%. The overall complication rate was 17.8%, with
the highest rate of complications observed with saccular (23%)
and posterior circulation aneurysms (27%). Ischemic complica-
tions occurred in 8%, and hemorrhagic events, in 7%. The rate of

FIG 2. A, SAH primarily in the left Sylvian fissure on NCCT. The patient was Hunt and Hess 1 at that time. B, Aneurysm on the inferior trunk of
the MCA, broad-based (white arrow). C, Implantation of a p48-MW-HPC flow-diverting stent from M1 into M2 (white arrows pointing to stent
endings). D, DSA control 24 hours later. The flow diverter is patent; some stasis in the aneurysm is seen (white arrow). E, DSA control about
15 minutes later. Acute thrombosis developed on the superior trunk (white arrow). The flow diverter is patent. The patient had acute aphasia
and hemiparesis after application of a pressure dressing in the groin. F, After therapy with IV tirofiban, the thrombosis disappeared (white
arrow). The neurologic deficits resolved completely. G, After approximately 10 days, severe vasospasm developed (white arrow). H, The vaso-
spasm, unfortunately, despite intense therapy, led to severe infarction of the left MCA and anterior cerebral artery territory (white arrow)(this is
patient 9, Online Supplemental Data).
acute in-stent thrombosis was 4%. They reported a treatment-related mortality of 4.5% and a good neurologic outcome in 83%. Aspirin and clopidogrel were used in most cases (67.7%), with tirofiban, prasugrel, and abciximab used less frequently. The aneurysm rebleeding rate was 3%. They concluded that in their study, flow-diversion treatment led to a high complete occlusion rate; however, with a relatively high complication rate, especially in the posterior circulation.

Overall, the existing literature demonstrates that the treatment of acutely ruptured intracranial aneurysms with flow diverters is feasible and effective in achieving aneurysm occlusion but carries a substantial risk of periprocedural hemorrhagic and thrombotic complications. Fewer thrombogenic devices may obviate the requirement for dual-antiplatelet therapy and reduce the risk of periprocedural ischemic events. To this end, several surface modifications have been proposed to reduce the thrombogenicity of flow diverters.

The PED Shield is covered with a 3-nm-thick layer of covalently bonded phosphorylcholine to reduce contact platelet activation. In a study by Girdhar et al, the PED Shield showed a lower thrombogenicity compared with other flow diverters. However, the PED Shield is supposed to be used under dual-antiplatelet therapy. The use of the PED Shield for recently ruptured aneurysms is off-label. To date, there are 1 case report and 1 case series that reported the use of the PED Shield under single-antiplatelet therapy. Hanel et al, in 2017, treated a patient with an acute SAH due to a fusiform aneurysm of the dominant vertebral artery with 2 overlapping flow diverters and additional coiling of the aneurysm. The patient was preloaded with 325 mg of aspirin 2 hours before treatment. After the treatment, the patient was maintained on 81 mg of aspirin per day. For 24 hours after the procedure, the flow-diverter construct remained open, as proved by angiography. A third angiography after 10 days, however, demonstrated an occlusion of the flow diverter. It can be argued that the aspirin dose was way too low; therefore, an insufficient effect was achieved.

In the retrospective multicenter study by Manning et al, in 2019, fourteen patients were treated with the PED with Shield Technology for intracranial aneurysms with acute SAH. In all patients a single antiplatelet therapy with aspirin was used, with dosage at the discretion of the operator as well as a single dose of glycoprotein IIb/IIIa inhibitors. The time to treatment was 1 day. PED Shield placement was successful in all patients. Twelve patients received additional coiling. Complete aneurysm occlusion was achieved in 86%. Three symptomatic complications (4 in total) occurred; treatment mortality and morbidity were 7.1% and 7.1%. All of the symptomatic complications (2 hemorrhagic) were associated with postinterventional heparin use. In the last 5 patients with a twice-daily aspirin dosing regimen (twice, 100–150 mg daily), no complications occurred.

The p48 MW HPC is coated with a 10-nm thick glycan-based pHPC. The pHPC aims to replicate the properties of carbohydrates on the endothelial surface ("surface coat"), thereby...
reducing the thrombogenicity of the device.\(^6,17\) To date, there are 2 case reports on single-antiplatelet regimens in pHPC-coated neuroendovascular devices, 1 in the setting of acute SAH.\(^6,18\) Henkes et al,\(^6\) in 2019, reported a ruptured MCA bifurcation aneurysm treated endovascularly with a pHPC-coated bifurcation stent (pCONUS; phenox) and subsequent coiling. Before treatment, the patient was preloaded with 500 mg of aspirin IV. For a postprocedural regimen, they

![A, NCCT depicts an acute basal SAH. B, DSA on the day of the SAH shows no aneurysm. C, SAH rebleeding on day 5 after the initial bleed. D, NCCT now demonstrates an unusual aneurysm interpreted as a dissecting aneurysm of a basilar artery perforator (arrow). E, Treatment of the aneurysm with a hydrophilic-coated flow diverter; unsubtracted image right after deployment (arrows indicate the ends of the flow diverter). F, Subtracted image from the treatment. Slow filling of the aneurysm can be still seen (late arterial phase, arrows at the ends of the flow diverter). G, Five days after the treatment, CTA demonstrates that the flow diverter is patent (arrows). H, T2-weighted axial MR imaging 11 days after treatment. A small infarction in the territory of the aneurysm carrying the perforator can be seen (arrow). No infarcts due to the flow diverter are noted (this is patient 5, Online Supplemental Data).]

**Recent studies of FD treatment in acute SAH in specific conditions**

| Authors            | Publication Date | Aneurysm Type                      | No. of Patients/ Mean Age | Treatments                                                                 | Results/Occlusion Rates | Complications                                                                 |
|--------------------|------------------|-----------------------------------|---------------------------|---------------------------------------------------------------------------|-------------------------|-------------------------------------------------------------------------------|
| Maus et al\(^24\)  | 2018             | Dissecting vertebrobasilar        | 1556 yr                   | 15 IAs, 22 FDSs, treatment within 12 h of SAH onset                       | 36% Directly occluded;  | 3 (Ischemia, vessel perforation, ongoing active bleeding)                     |
| Bhogal et al\(^22\) | 2018             | Small IA (1–4 mm)                 | 760 yr                    | 7 IAs, 8 FDSs, treatment within 6.3 days from SAH (median)               | 100% Occluded on FU     | None                                                                          |
| Lozupone et al\(^23\) | 2018            | 8 BBAs, 9 dissecting IAs          | 174 yr                    | 17 IAs, 21 FDs, treatment within 4.2 days (median)                       | 12 of 15 Patients      | 12% Mortality; 12% morbidity                                                  |
| AlMatter et al\(^21\) | 2019          | Saccular (18), fusiform (5), BBA (7), dissecting (15) | 4558. 8 yr                | 45 IAs, FDSs as sole or adjunct device, treatment within 30 days after SAH | 94.6% Complete occlusion on follow-up among survivors | 13.3%; 2.2% Morbidity; 4.4% mortality                                           |

**Note:** IA indicates intracranial aneurysm; FDS, flow-diverting stent; FU, follow-up; BBA, blood-blister-like aneurysm; FD, flow diverter.
chose to administer 500 mg of aspirin IV twice daily for the following days. On DSA after 13 days, the stent remained patent and the aneurysm was occluded. Clinically the condition of the patient improved to mild headaches and impaired short-term memory at a 3-month control.6

Schüngel et al14 treated a patient with recurrent astrocytoma and an incidental broad-based anterior cerebral artery aneurysm. Because the aneurysm was increasing in size, it was treated electively with a p48 MW HPC flow diverter with planned dual-antiplatelet therapy for 6 months. However, after discharge, the patient stopped taking the dual-antiplatelet medication and switched to a phytopharmaceutical medication he designed on his own (primarily consisting of garlic oil). On DSA 3 months after the intervention, the stent was open, with only a mild in stent stenosis.

Very recently Bhogal et al,19 in 2020, published a small retrospective series in which they reported their experience in aneurysm treatment with the p48 MW HPC and single-antiplatelet therapy. They treated 5 patients with 4 saccular aneurysms and 1 dissecting aneurysm. All patients were premedicated with 10 mg of prasugrel per day at least 5 days before the treatment and were kept on this medication afterward. One patient switched to 75 mg of aspirin per day after 2 weeks on her own volition. Angiographic follow-up was available in 4 patients at 8.5 months (range, 6–12 months). Three aneurysms were completely occluded. No thromboembolic complications occurred. One patient developed a localized hematoma from the treated dissecting aneurysm that was managed conservatively without any clinical sequelae.19

Also, very recently, Aguilar-Pérez et al,20 in 2020, reported their experience with the p48 MW HPC flow diverter in 8 patients with SAH due to ruptured intracranial aneurysms on single-antiplatelet therapy. They included patients up to 6 days after acute SAH. Mainly dissecting aneurysms were included. All stents could be successfully placed. They identified transient thrombus formation in 50% of their patients. In the follow-up period, 1 patient developed an in-stent thrombosis after 3 days, which resolved after a switch to dual-antiplatelet therapy. They recorded no rebleeding. Two of their patients died due to vasospasm. They used 2 single-antiplatelet regimens. They started with either 100 mg of aspirin or 10 mg of prasugrel PO 3 days before the procedure or with a loading dose of 500 mg of aspirin IV or 30 mg of prasugrel PO 3 hours before the procedure. They heparinized the patients during the procedure. After the procedure, they kept the patients on either 500 mg of aspirin IV or 10 mg of prasugrel PO. They concluded that their above-mentioned treatment is an option in selected cases but has to be applied with great caution because thromboembolic complications can be a problem.20

CONCLUSIONS

Hydrophilic-coated devices (like p48 MW HPC or the p46 MW HPC) may be used with single-antiplatelet therapy in selected clinical situations in which dual-antiplatelet therapy might be hazardous. This strategy is primarily relevant in the setting of ruptured aneurysms, which are unsuitable for standard endovascular or surgical treatments. Which drug should be used for single-antiplatelet therapy, however, remains to be determined. Aspirin is a possible option, but other drugs like prasugrel might have advantages. In any case, the proper dosage in the acute phase after SAH also remains an issue. Prospective studies are underway to define the safety and effectiveness of this strategy.

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