

Extending the Indications of Flow Diversion to Small, Unruptured, Saccular Aneurysms of the Anterior Circulation

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Background and Purpose—Flow diverters are currently indicated for treatment of large and complex intracranial aneurysms. The purpose of this study was to determine whether the indications of flow diversion can be safely extended to unruptured, small, saccular aneurysms (<10 mm) of the anterior circulation.

Methods—Forty patients treated with the pipeline embolization device (PED) were matched in a 1:4 fashion with 160 patients treated with stent-assisted coiling based on patient age, sex, aneurysm location, and aneurysm size. Procedural complications, angiographic results, and clinical outcomes were analyzed and compared.

Results—The rate of periprocedural complications was 5% in the PED group and 3% in the stent-coil group ($P=0.7$). In multivariable analysis, increasing age was the only predictor of complications. At follow-up, a higher proportion of aneurysms treated with PED (80%) achieved complete obliteration compared with stent-coiled aneurysms (70%) but the difference did not reach statistical significance ($P=0.2$). In multivariable analysis, increasing aneurysm size and aneurysm location were predictors of nonocclusion. The rate of favorable outcome (modified Rankin Scale, 0–2 and modified Rankin Scale, 0–1) was similar in the PED group and the coil group.

Conclusions—The PED was associated with similar periprocedural risks, clinical outcomes, and angiographic results compared with stent-assisted coiling. These findings suggest that the indications of PED can be safely extended to small intracranial aneurysms that are amenable to conventional endovascular techniques. Larger studies with long-term follow-up are necessary to determine the optimal treatment that leads to the highest rate of obliteration and best clinical outcomes. (*Stroke*. 2014;45:54-58.)

Key Words: aneurysm ■ stents

Flow diverters have become an important tool in the management of intracranial aneurysms.¹⁻⁴ The pipeline embolization device (PED) is a flow diverter that has received significant attention in the recent literature.^{2,3,5} The device was approved by the Food and Drug Administration (FDA) in 2011 for treatment of large and giant wide-necked aneurysms arising from the cavernous segment to the superior hypophyseal segment of the internal carotid artery. In most series, flow diverters including the PED were used for the treatment of complex aneurysms not amenable to conventional endovascular techniques, such as large and giant aneurysms, wide-necked aneurysms and fusiform aneurysms.⁶⁻¹⁰ Whether the indications for flow diversion can be expanded to small aneurysms in which conventional endovascular techniques are usually safe and effective remains uncertain.

Stent-assisted coiling is now a well-established technique for the treatment of intracranial aneurysms with an excellent safety–efficacy profile.^{11,12} Studies have assessed the safety and efficacy of the PED unilaterally without comparison with a control group treated with coiling or stent-assisted coiling.^{7,13-16}

These studies also included a heterogeneous population of patients (small versus large, ruptured versus unruptured, fusiform versus saccular, anterior circulation versus vertebrobasilar aneurysms), which precluded any confident conclusion as to the safety profile of flow diverters in specific subgroups of patients. We present the results of the first study comparing PED and stent-assisted coiling in patients with unruptured, small (<10 mm) saccular aneurysms.

Methods

The University Institutional Review Board approved the study protocol. Forty consecutive patients with unruptured, previously untreated, small (<10 mm) aneurysms treated with PED (2011–2013) at our institution were identified from a prospectively maintained database. Patients treated with PED and adjunctive coiling were not included in the analysis. Every patient treated with the PED was matched to 4 control patients treated with stent-assisted coiling (2004–2011) based on patient age, sex, aneurysm location, and aneurysm size. Patients were excluded from this study if the aneurysm had previously ruptured, was located in the posterior circulation, or was fusiform in morphology.

Patients undergoing PED therapy received 75 mg/d of clopidogrel and 81 mg/d of aspirin for 10 days before the intervention. Platelet

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function tests were routinely performed using aspirin assay and P2Y12 assay (VerifyNow; Accumetrics, San Diego, CA) to ascertain that the level of platelet inhibition was between 30% and 90%. Patients with inhibition <30% were reloaded and the assay rechecked. Poor responders to clopidogrel were then switched to prasugrel (brand name Effient, Eli Lilly and Company, Indianapolis, IN). Patients with inhibition >90% were admitted to the hospital, their procedure was canceled, and Plavix was held until platelet inhibition level fell <90%. An initial 100 U/kg of heparin bolus was administered and activated clotting time was maintained at 2× the patient's baseline intraoperatively. Heparin was discontinued but not reversed at the conclusion of the procedure. Dual antiplatelet therapy was continued for ≥6 months after the procedure. Procedures were performed under general endotracheal anesthesia and continuous neurophysiologic monitoring, including electroencephalography and somatosensory-evoked potentials. PEDs were deployed through a Marksman microcatheter (ev3, Irvine, CA) using a triaxial guide-catheter system. The number of stents deployed was left to the operator's discretion but, in general, when stasis was seen in the aneurysm dome no further devices were deployed. Recently, we have been using only a single device for most aneurysms. The expansion of the PED was documented under fluoroscopy or with additional DynaCT/Xpert CT angiography at the operator's discretion. Inadequate vessel wall apposition was remedied with Gateway balloon (Boston Scientific, Fremont, CA) angioplasty when needed. Placement of additional PEDs was considered at follow-up if the aneurysm remained unchanged or did not sufficiently decrease in size, despite treatment.

Our protocol and technique for stent-assisted coiling have been detailed previously.¹¹ Briefly, when the use of a stent was anticipated, patients were pretreated with daily 81 mg of aspirin and 75 mg of clopidogrel for 10 days before the procedure. Dual antiplatelet therapy was continued for 2 months after the intervention. Coiling was interrupted when the aneurysm was completely occluded or when no additional coils could be deployed. Stent-assisted coiling was typically performed using the microcatheter jailing technique in which the stent is deployed after the aneurysm is microcatheterized but before coil deployment.

The outcomes of 40 PED patients and 160 stent-coil patients matched for patient age, sex, aneurysm location, and aneurysm size were compared. Medical charts were reviewed retrospectively to determine patient demographics, aneurysm characteristics, procedural specifics, and procedural complications. Only procedural complications with clinical repercussions are reported. Angiographic follow-up (digital subtraction angiography or magnetic resonance angiography) was scheduled at 3 to 6 months, 1 year, 2 years, and 5 years after treatment. Aneurysm obliteration rates were determined as percentages and transformed into a dichotomic variable: complete obliteration (100%) and incomplete obliteration (<100%). Regardless of the need for further intervention, any filling at the neck or the dome of the aneurysm was considered <100% occlusion and classified as incomplete obliteration. Clinical outcomes at the last available follow-up were collected from follow-up notes of the attending physician and classified using the modified Rankin Scale (mRS).

Statistical Analysis

Data are presented as mean and range for continuous variables and as frequency for categorical variables. Matched analysis was performed as appropriate. Univariate conditional (matched) analysis was used to test covariates predictive of the following dependent variables: treatment complications, follow-up obliteration, and clinical outcome (mRS, 0–2 versus 3–6 and mRS, 0–1 versus 2–6). Interaction and confounding were assessed through stratification and relevant expansion covariates. Factors predictive in univariate analysis ($P < 0.20$)¹⁷ were entered into a multivariate conditional logistic regression analysis. P values of ≤ 0.05 were considered statistically significant. Statistical analysis was performed with Stata 10.0 (College Station, TX).

Results

Baseline Characteristics

Mean patient age was similar in the PED group (52.1±13.7 years) and the stent-coil group (52.6±11.4 years; $P=0.8$). The

proportion of female patients was 85% in both groups. Mean aneurysm size was 6.2±2.4 mm in the PED group and 6.0±1.6 mm in the stent-coil group ($P=0.3$). The proportion of aneurysms >6 mm was similar in PED (60%) and stent-coil patients (57%; $P=0.8$). Aneurysm locations (Table 1) were matched between the 2 groups.

Aneurysm Treatment

PED deployment was successful in all 40 patients. The number of PEDs used was 1.3±0.4 per aneurysm. A single PED was used in 26 (65%) aneurysms and 2 PEDs in 14 (35%) aneurysms. Balloon angioplasty was performed for optimal PED expansion in 1 (2.5%) patient.

In the stent-coil group (n=160), initial Raymond scores were I (complete occlusion) in 71 (44%) patients, II (residual neck) in 56 (35%) patients, and III (dome filling) in 33 (20.6%) patients.

Procedural Complications

Procedure-related complications occurred in 2 (5%) patients (1 ischemic event and 1 distal hemorrhage) in the PED group versus 5 (3%) patients (4 ischemic events and intraoperative rupture) in the stent-coil group ($P=0.7$). There was no procedure-related mortality in either group. No patient had a symptomatic side-branch occlusion after PED therapy. The following factors were tested for as predictors of complications: age, sex, aneurysm location, aneurysm size, aneurysm morphology, and type of treatment. In univariate analysis, older age (≥ 65 years; odds ratio [OR], 3.7; 95% confidence interval [CI], 0.8–17.7; $P=0.09$) predicted procedural complications. In multivariate analysis, there was a trend for older age (≥ 65 years) to predict complications (OR, 3.8; 95% CI, 0.7–17.7; $P=0.09$). The type of treatment was not a predictor of complications even after controlling for age.

Angiographic Outcome

Angiographic follow-up was available for 39 (97.5%) patients treated with PED and 147 (92%) patients treated with stent-assisted coiling. Median angiographic follow-up time was 7 months in the PED group and 15 months in the stent-coil group ($P < 0.001$). At the latest follow-up, a higher proportion of aneurysms treated with PED (80%; n=31) achieved complete obliteration (100%) compared with coiled aneurysms (70%; n=103) but the difference fell short of statistical significance ($P=0.2$; Table 2). In the stent-coil group (n=160), Raymond scores at the latest follow-up were I (complete occlusion) in 103 (70%) patients, II (residual neck) in 17 (11.5%) patients, and III (dome filling) in 28 (19%) patients.

Table 1. Aneurysm Locations

Aneurysm Location	PED (%)	Stent-Coil (%)
Carotid ophthalmic/paraclinoid	37 (92.5)	145 (90.7)
Carotid cavernous	1 (2.5)	5 (3.1)
Posterior communicating	1 (2.5)	5 (3.1)
Middle cerebral artery	1 (2.5)	5 (3.1)
Total	40	160

PED indicates pipeline embolization device.

The following factors were tested for as predictors of occlusion: age, sex, aneurysm location, aneurysm size, aneurysm morphology, type of treatment, complications, and follow-up time. In univariable analysis, factors predicting nonocclusion were increasing aneurysm size (OR, 1.23; 95% CI, 1.01–1.49; $P=0.04$) and carotid cavernous-posterior communicating artery-middle cerebral artery aneurysm location (ie, aneurysm locations with rates of complete occlusion <70%; $P=0.01$). In multivariable analysis, increasing aneurysm size (OR, 5; 95% CI, 1.4–14; $P=0.01$) and carotid cavernous-posterior communicating artery-middle cerebral artery aneurysm location (OR, 5; 95% CI, 1.4–14; $P=0.01$) remained statistically significant independent predictors of nonocclusion.

Retreatment was necessary in 4 (10%) patients in the PED group and 13 (9%; $P=0.8$) patients in the coil group. It should be noted that retreatment was undertaken for recurrences in all 13 patients in the stent-coil group, whereas none of the 4 patients in the PED group had a recurrence. In fact, aneurysm size decreased to some extent in 3 of the 4 PED patients but the decision was made to place additional devices to accelerate and increase the likelihood of further aneurysm thrombosis.

Clinical Outcome

Clinical follow-up was available for 39 (97.5%) patients in the PED group and 148 (93%) patients in the stent-coil group. Median follow-up time was 7 months in the PED group and 17 months in the stent-coil group ($P<0.001$). The proportion of patients with mRS 0 to 2 was 100% (39/39) in the PED group and 98% in the stent-coil group (99%; 146/148; $P=0.9$). The proportion of patients with mRS 0 to 1 was 95% (37/39) in the PED group and 96% in the stent-coil group (96%; 142/148; $P=0.9$). The following factors were tested for as predictors of outcome: age, sex, aneurysm location, aneurysm size, aneurysm morphology, type of treatment, and complications. In univariable analysis, increasing aneurysm size (OR, 5.9; 95% CI, 0.6–5.2; $P=0.1$) predicted a poor clinical outcome (mRS>1). In multivariable analysis, no factor was a significant predictor of poor clinical outcome.

Discussion

The only flow diverter currently approved by the FDA is the PED. Other flow diverters include Silk (Balt, Montmorency, France), Surpass (Stryker, Fremont, CA), and FRED (Microvention, Tustin, CA).¹⁸ The Silk stent has been extensively used outside the United States, and the Surpass has recently shown promising results in a small series from Europe.^{4,19,20}

Initially reserved for complex, giant, and fusiform aneurysms, flow diverters are currently increasingly used in the management of small and less complex aneurysms at some

institutions. Many interventionalists, however, remain wary of this approach and continue to prefer traditional endovascular strategies, especially for small aneurysms. A recent meta-analysis on flow diverters by Brinjikji et al,²¹ including 1451 patients with 1654 aneurysms, found procedure-related morbidity and mortality rates of 5% and 4%, respectively. The authors concluded that the risk of procedure-related morbidity and mortality with flow diverters is not negligible and should be taken into account when considering the best therapeutic option for intracranial aneurysms. Another meta-analysis of 15 studies that compiled 897 patients with 1018 aneurysms found an early mortality rate of 2.8%, a late mortality rate of 1.3%, and an overall neurological morbidity rate of 9.9%. The authors of the meta-analysis also found that available data supporting the use of flow diverters were heterogeneous and prone to publication biases, concluding that the use of flow diverters in patients eligible to more conventional treatments should be restricted to controlled clinical trials.

However, several studies have demonstrated convincingly that the PED carries a high safety and efficacy profile. In a large Turkish series of 191 patients treated with the PED, Saatci et al⁷ reported a 6-month occlusion rate of 91% with an impressive permanent morbidity rate of only 1%. A recent well-designed multicenter international trial reported a success rate of 99%, an occlusion rate of 74%, and a major ipsilateral stroke or neurological death rate of only 5.6%.⁷ Pistocchi et al² treated 30 aneurysms at and beyond the circle of Willis with flow diverters (Silk and Pipeline) reporting permanent neurological complication in only 3.7% and aneurysm occlusion in 82% of patients. Likewise, in a multicenter study of 143 patients with 178 aneurysms from Hong Kong, Yu et al⁸ reported a complete aneurysm occlusion rate of 84%, an overall neurological complication rate of 8.4%, and a periprocedural death or major stroke rate of 4.2% (median follow-up of 18 months). They concluded that PED should be considered a first choice for treating unruptured aneurysms. All these studies included a heterogeneous population of patients (no separate analysis was done for small aneurysms) and did not put the results of flow diversion in direct comparison with those of conventional endovascular techniques especially stent-assisted coiling, which has shown an excellent safety–efficacy profile in several large studies.^{11,12,22,23}

The present study is not the first to compare flow diverters with coiling. However, it is the first to specifically compare stent-assisted coiling with flow diversion, or even compare the 2 techniques in small aneurysms. In a small study, Lanzino et al²⁴ compared 22 paraclinoid aneurysms treated with the PED with historic controls. The authors reported a significantly higher rate of complete occlusion in PED patients (76%) than coiled patients (21%) with a similar rate of morbidity and concluded that long-term follow-up was important to validate flow diversion definitively as a superior therapeutic strategy for proximal internal carotid artery aneurysms. In a previous report, we have compared the periprocedural, angiographic, and clinical outcomes of flow diversion and coiling in unruptured, large, and giant (≥ 10 mm) aneurysms.¹⁰ We have found a similar complication rate in both groups (7.5%) along with a higher aneurysm occlusion rate (86% versus 41%) and a lower retreatment rate with flow diversion (2.8% versus 37%). In multivariable analysis, the odds of achieving occlusion of large aneurysms were

Table 2. Rates of Aneurysm Occlusion

Complete Aneurysm Occlusion			
	≤6 mo	7 to 12 mo	>12 mo
PED	21/27 (77%)	17/21 (81%)	6/8 (75%)
Stent-assisted coiling	21/30 (70%)	56/70 (80%)	40/53 (75%)

PED indicates pipeline embolization device.

>10× higher with flow diversion than with coiling. These results led us to conclude that flow diverters were a preferred option for large and giant aneurysms. In the present study, we sought to determine whether flow diversion is also a better strategy for small aneurysms (<10 mm), a subgroup in which stent-assisted coiling has traditionally generated favorable clinical and angiographic results. We found that flow diversion can be undertaken with no additional morbidity and similar clinical outcomes compared with stent-assisted coiling. There was also a trend toward higher occlusion rates with the PED (80% versus 70%), but the study was likely underpowered to detect small differences in angiographic outcomes between 2 highly efficient endovascular techniques. Although retreatment rates did not differ between the 2 groups, retreatment was always undertaken for a recurrence in stent-coiled patients, whereas in PED patients retreatment was undertaken because the aneurysm had not sufficiently decreased in size. We have also recently found that PED treatment requires significantly shorter fluoroscopy and procedure times compared with stent-assisted coiling.²⁵ Moreover, a recent study has demonstrated that PED embolization is more economical than stent-assisted coiling with a 27% reduction in the cost per millimeter of aneurysm treated,²⁶ although any cost benefit will also depend on aneurysm volume, coil type, and number of PEDs used.²⁷ Taken together, these data suggest that the indications of flow diversion can be safely extended to unruptured, small aneurysms (<10 mm). Some may argue, however, that stent-assisted coiling is a better option than flow diversion because of the higher immediate complete occlusion rate and the shorter period of dual antiplatelet therapy.

In the present study, the initial occlusion rate (Raymond score I, ie, 100% occlusion) with stent-assisted coiling was 48% increasing to 70% at follow-up. These rates are consistent with those reported in the literature. In a large study of 500 stent-coiled aneurysms by Geyik et al,²³ complete occlusion was achieved in 42.2% of the aneurysms initially, and the rate progressed to 90.8% at follow-up. Likewise, a systematic review of the literature on stent-assisted coiling by Shapiro et al²⁸ reported a 45% complete occlusion rate initially, increasing to 61% at follow-up. The morbidity rates with stent-assisted coiling in our study are largely in line with previously reported series. Lessne et al²⁹ reported a 5.4% rate of thromboembolic events, whereas Maldonado et al³⁰ reported a 2.9% combined morbidity–mortality rate after stent-assisted coiling of 76 aneurysms. Likewise, in the multicenter Enterprise registry, procedural data demonstrated a 6% temporary morbidity, 2.8% permanent morbidity, and 2% mortality.³¹

Although the complications of stent-assisted coiling are essentially limited to thromboembolic events and intraprocedural aneurysm ruptures,^{11,12} flow diversion carries the additional risk of distal parenchymal hemorrhage, delayed migration of the device, and delayed aneurysm rupture.^{9,32–36} Distal parenchymal hemorrhage may occur ipsilaterally or even contralaterally to the aneurysm and its mechanism may involve hemorrhagic conversion of ischemic lesions, embolized foreign material, loss of arterial autoregulation of the distal arteries, or dual antiplatelet therapy.^{5,37} Device migration is a recently recognized complication of flow diverters that is attributed to a mismatch in arterial diameter between inflow and outflow vessels. The migration may occur proximally or distally and

may lead to devastating complications, such as aneurysm rupture or thromboembolic events.³² Delayed aneurysm rupture is a dreaded complication of flow diversion that typically occurs in large and giant aneurysms. Its cause remains uncertain but may involve altered hemodynamics and enzymatic degradation of the aneurysm wall from thrombus formation. The complication rate in the present report was low with flow diversion and did not differ significantly from that of stent-assisted coiling. Finally, if PED therapy is not effective in achieving complete aneurysm obliteration, endovascular access to the aneurysm will have been permanently lost and the only options available for further treatment would be reduced to open surgery or additional placement of PEDs. Also, clip application for proximal control is possible only proximal to the PED because the device is irreversibly deformed by clip application.³⁸

Limitations

This study is retrospective in design and reflects the experience of a single center. We could not provide occlusion rates at standard time points. Instead, we have compared aneurysm occlusion rates at the latest follow-up. Although the 2 groups were well matched with regard to baseline characteristics, the clinical and angiographic follow-up time differed significantly. As such, the occlusion rate with PED would have been even higher if patients were followed up for longer periods, which further supports the efficacy of flow diverters.^{8,14} Improved endovascular technology and increasing operator experience with aneurysm embolization techniques could have favored the PED group. The retreatment rate with the PED is closely related to the number of devices deployed during the initial embolization procedure. Because we tend to use only a single device in most cases (with placement of further devices only if the aneurysm remains open at follow-up), the PED retreatment rate would have been even lower had we adopted a different strategy where multiple devices are deployed initially. Despite these limitations, this study is the first to provide a comparative analysis of clinical and angiographic outcomes in small aneurysms treated with PED and stent-assisted coiling. Randomized controlled trials comparing flow diversion and conventional endovascular techniques are currently underway. The Flow Diversion in Intracranial Aneurysm Treatment (FIAT) trial³⁹ is a randomized open label trial comparing flow diversion with best standard treatment in the management of difficult intracranial aneurysms. The trial is sponsored by the Center hospitalier de l'Université de Montréal and is currently recruiting participants. The LARGE aneurysm randomized trial⁴⁰ is an ongoing prospective, randomized, study comparing coil embolization versus flow diversion in large (>10 mm), anterior circulation intracranial aneurysms sponsored by the Medical University of South Carolina. Another trial is also taking place in France and compares the 2 techniques in unruptured saccular wide-neck intracranial aneurysms >7 mm.⁴¹

Conclusions

Both flow diversion and stent-assisted coiling are safe and highly effective techniques for treatment of unruptured, small saccular aneurysms of the anterior circulation. The PED was associated with similar aneurysm occlusion rates, periprocedural morbidity, and short-term clinical outcomes. These findings suggest that the indications of the PED can be safely extended to small

intracranial aneurysms that are amenable to conventional endovascular techniques. Larger studies and long-term follow-up are necessary to determine the optimal treatment that leads to the highest rate of obliteration and best clinical outcomes.

Disclosures

None.

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