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Flow Diverter Therapy With the Pipeline Embolization Device Is Associated With an Elevated Rate of Delayed Fluid-Attenuated Inversion Recovery Lesions

Mina G. Safain, MD; Marie Roguski, MD, MPH; Robert S. Heller, MD; Adel M. Malek, MD, PhD

Background and Purpose—Flow diversion using the Pipeline Embolization Device is reported as a safe treatment of aneurysms. Complete aneurysm occlusion, however, occurs in a delayed fashion with initial persistent filling of the aneurysm dome. We hypothesized that this transflow across metallic struts may be associated with thromboembolic events.

Methods—Forty-one consecutive patients undergoing aneurysm treatment with the Pipeline Embolization Device and a comparison group of 78 Neuroform stent-mediated embolizations were studied. Patients' charts, procedure notes, platelet function, and anticoagulation state were analyzed. Serial magnetic resonance images were assessed for the presence of newly occurring diffusion-weighted imaging and fluid-attenuated inversion recovery (FLAIR) lesions at multiple postprocedure time ranges (average days post procedure [Pipeline Embolization Device/Neuroform]: T1=1, T2=73/107, T3=174, T4=277/335, and T5=409). In addition, diffusion-weighted imaging or FLAIR burden was estimated by lesional diameter summation.

Results—Pipeline patients were more likely to have new ipsilateral FLAIR lesions at all time points studied (30.6% versus 7.2% of patients at T=2 and 34.5% versus 6.2% at T=4). The mean FLAIR burden was significantly increased for Pipeline patients (10.1 versus 0.7 mm at T=2 and 8.8 versus 1.9 mm at T=4). Overall 34% (14/41) of Pipeline patients experienced a new FLAIR lesion at anytime when compared with 10% (8/78) of Neuroform stent-coil patients. Postprocedural diffusion-weighted imaging did not predict future FLAIR lesions suggesting a nonprocedural cause.

Conclusions—The Pipeline Embolization Device is associated with increased rate of de novo FLAIR lesions occurring in a delayed fashion and distinct from perioperative diffusion-weighted imaging lesions. The cause and clinical effect of these lesions are unknown and suggest the need for prudent follow-up and evaluation. **(*Stroke*. 2016;47:789-797. DOI: 10.1161/STROKEAHA.115.010522.)**

Key Words: diffusion magnetic resonance imaging ■ embolization, therapeutic ■ ischemia ■ magnetic resonance imaging ■ stents ■ stroke

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Flow diversion is a recent and rapidly developing advance in the endovascular management of intracranial aneurysms.[1] Initially, the Pipeline for the Treatment of Uncoilable and Failed Aneurysms (PUFS)[2] trial demonstrated safety and efficacy of the Pipeline Embolization Device (PED) leading to Food and Drug Administration approval. In addition, multiple recent reports have touted the utility of the PED for its ability to easily treat previously challenging aneurysms with high occlusion rates and low complication rates.[2–11] Furthermore, cost-effectiveness studies have seemed to demonstrate that flow diversion may provide cost savings when compared with standard stent–assisted coil techniques and that a greater benefit is found in large or giant aneurysms.[12–14] Therefore, many centers have trended toward the liberal utilization of this technology in both on- and off-label applications of the device.

We have been interested in studying the PED since its initial use at our institution in October 2011. We have recently reported on the higher rate of ipsilateral periprocedural diffusion-weighted imaging (DWI) lesions after PED deployment than conventional stent-coil methods.[7] This high periprocedural rate has been replicated by an outside group with an almost identical rate of 50.9% when compared with 52% of patients in our initial study.[15] In this light, we have elected to follow PED patients closely and assess them for delayed ischemic events. To study this, we analyzed all post-treatment and follow-up magnetic resonance images (MRI) for indications of delayed fluid-attenuated inversion recovery (FLAIR) lesions in a prospectively maintained database of both PED and Neuroform-stent-mediated coil embolization of intracranial aneurysms. We hypothesized that PED-treated patients would demonstrate

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From the Cerebrovascular and Endovascular Division, Department of Neurosurgery, Tufts Medical Center and Tufts University School of Medicine, Boston, MA.

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Correspondence to Adel M. Malek, MD, PhD, Department of Neurosurgery, Tufts Medical Center, 800 Washington St, 178, Proger 7, Boston, MA 02111. E-mail amalek@tuftsmedicalcenter.org

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an increased delayed FLAIR burden when compared with standard stent–assisted coiling methods with another commonly used intracranial stent, the Neuroform open-cell design stent.

Methods

Patient Selection

All patients who have undergone aneurysm embolization at our institution using the PED (starting in October 2011), and other stent devices have been documented in a prospectively maintained database. All PED patients were included up to February 2014. In addition, all consecutive patients who underwent Neuroform (Stryker, Freemont, CA) stent-mediated embolization of an intracranial aneurysm at our institution between May 2006 and April 2013 were included for radiographic comparison. Medical charts, radiographic studies, and endovascular procedures were reviewed for data collection. Variables recorded included patient age, sex, clinical presentation, length of follow-up, aneurysm location, aneurysm size, degree of obliteration at last follow-up, multiple radiographic parameters of the stent, and comorbidities including hypertension, hypercholesterolemia, diabetes mellitus type 2, and smoking status. This study was approved by the Institutional Review Board of Tufts Medical Center.

Pipeline Embolization Device

The PED is a braided mesh cylinder that is composed of 48 strands of 25% platinum and 75% cobalt-nickel alloy.[16] The PED has pore sizes ranging from 0.02 to 0.05 mm^2 and a metal area coverage between 30% and 35%.[16–19] This metal area coverage provides the flow diversion properties of the device.

Procedure

All patients underwent catheter-based cerebral angiograms including biplane digital subtraction angiography, 3-dimensional-rotational angiography, and conebeam computed tomographic angiography (CBCT-A) imaging performed on the Siemens Axiom-Artis VB22N system (Siemens Medical, Malvern, PA). Aneurysm measurements were determined from pretreatment digital subtraction angiography and 3D-rotational angiography studies and were defined as the greatest diameter of the aneurysm in any plane. The aneurysm neck was defined as the greatest diameter in any plane at the junction with the parent artery. All stents were deployed under general endotracheal anesthesia with the administration of an antiplatelet regimen consisting of clopidogrel bisulfate 75 mg/d and acetylsalicylic acid 325 mg/d beginning at least 7 days before the procedure as well as intraoperative intravenous anticoagulation with heparin to an activated clotting time of 230 to 250 s. Platelet aggregometry was obtained in all Pipeline patients 1 to 24 hours before stent deployment and in all recent (after 2011) Neuroform stent deployment. Point-of-care platelet function tests (Aspirin Reactivity Unit and P2Y12 Reactivity Unit) were used in addition to platelet aggregometry on availability at our institution. These tests were obtained in 11 of the PED patients. Appropriate platelet inhibition was a prerequisite for stent deployment. Our platelet aggregation study protocol and cutoff values for appropriate platelet inhibition have been documented previously.[7] Stents were evaluated for appropriate wall apposition using digital subtraction angiography and the more detailed conebeam computed tomographic angiography. All patients were continued on a heparin drip overnight after the procedure for 12 to 18 hours with a goal partial thromboplastin time of 50 to 70 s until MRI was obtained on postoperative day 1 confirming no complications requiring further intravenous anticoagulation. Daily clopidogrel was continued for a minimum of 3 months post procedure, whereas daily aspirin was continued indefinitely.

Clinical and Radiographic Follow-Up

Because the PED is a relatively recent technology, clinical and radiographic follow-up was performed at more frequent intervals than traditional endovascular embolization patients. Patients had an MRI and magnetic resonance angiography within 24 hours of placement of a PED. Patients were scheduled for follow-up at a clinic appointment at 1 week, 3 months, 6 months, 1 year, and annually thereafter barring the appearance of any significant clinical or radiographic findings. MRI/MR angiography were obtained at 3 to 6 months and again at ≈1 year. Clinically stable patients had catheter-based cerebral angiography performed at 2 to 3 months and 6 or 12 months post implantation to evaluate angiographic obliteration, rule out in-stent stenosis, and to guide weaning of dual-antiplatelet therapy.

MRI Review and Measurements

The postembolization MRI and each subsequent follow-up MRI for every patient were scored by 2 independent reviewers (M.G.S. and R.S.H) for the presence of restricted DWI and FLAIR lesions both ipisilateral and contralateral to the stent (Figures 1 and 2; Figure I in the online-only Data Supplement). An absolute value of the number of DWI and FLAIR lesions on each MRI was recorded for each patient and termed the DWI or FLAIR count. Importantly, on each follow-up MRI, only new independent DWI and FLAIR lesions not present on any previous MRI were scored. In this manner, we could assess independent and newly occurring lesions at each MRI obtained rather than carry persistent DWI or FLAIR lesions. As a second measure, a DWI and FLAIR burden was calculated for each MRI by totaling the maximal diameter of each lesion into 1 value. In this way, a lesion burden could be compared between different MRIs and stent types. Radiographic outcomes were assessed at 5 time points for patients who underwent Pipeline-mediated embolization and at 3 time points for patients who underwent Neuroform-mediated embolization. Inter-reader reliability was calculated between the 2 scoring researchers.

Statistical Analysis

Statistical analysis was completed using SAS version 9.3 (SAS Institute, Cary, NC). Baseline demographics, clinical information, and radiographic outcomes were recorded. Continuous variables were analyzed using Student *t* tests and Wilcoxon rank-sum tests, as appropriate, and categorical variables were studied using Fisher exact test. Generalized Estimating Equations models were used to evaluate changes in DWI and FLAIR on repeated poststenting MRI scans and to adjust for correlation between each individual subject's measurements.[20] A Poisson distribution and log link function were used for discrete count data, such as DWI and FLAIR count, and a Binomial distribution and logit link function were used for binary variables. The models included fixed effects for stent type, time, and an interaction between stent type and time. Adjustments were made for age and sex, and the effects of other clinical variables, such as medical comorbidities, were assessed. All statistical tests were 2 tailed, and statistical significance was set at 0.05. No adjustments were made for multiple comparisons. *P* values are reported to 2 significant digits, and mean values are reported as ±SD.

Results

Patient and Aneurysm Demographics

The cohort comprised 41 patients who underwent Pipeline flow-diverter therapy and 78 patients who underwent Neuroform stent-mediated coiling of their aneurysms. The patients were matched with regards to age, sex, and presence of medical comorbidities (Table 1). Patients undergoing Pipeline treatment had a lower prevalence of current smoking, but this difference did not reach statistical significance (P=0.07). The mean aneurysm neck, height, and width measurements were comparable in both groups. Aneurysms in the Pipeline group were all located in the anterior circulation from the cavernous to ophthalmic segments of the internal carotid artery. Twenty-five patients in the Neuroform group had aneurysms in the

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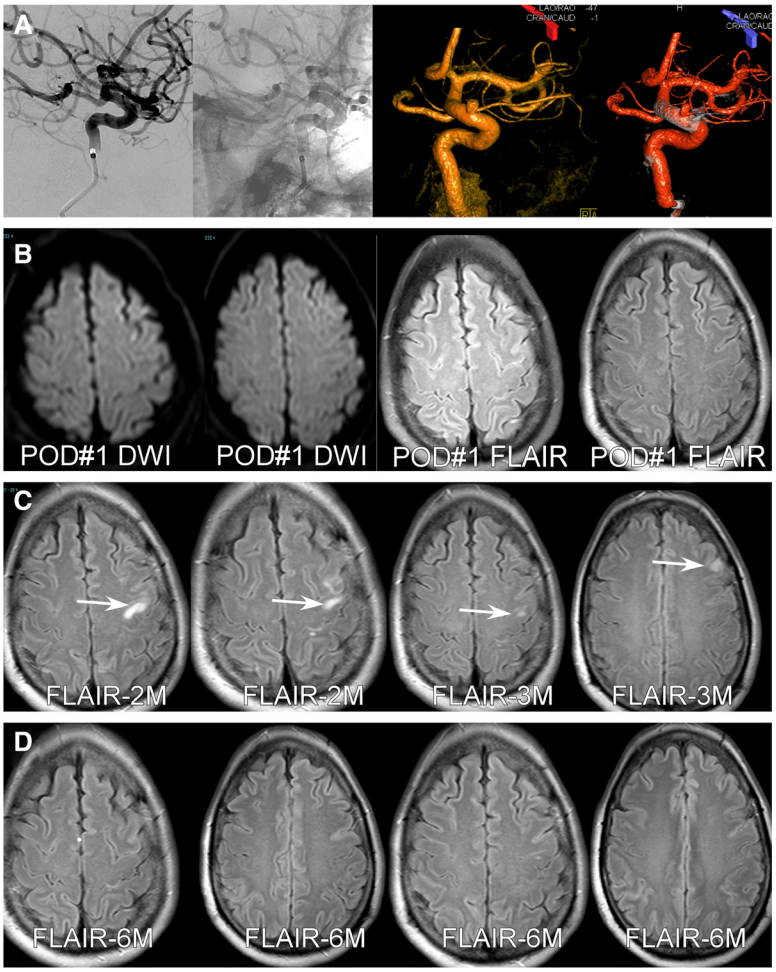


Figure 1. A 48-year-old women with headaches who was incidentally found to have a left 3 mm carotid-ophthalmic artery aneurysm and was treated with a Pipeline stent. **A**, Intraprocedural lateral angiograms and 3-dimensional reconstructions demonstrating the left 3 m carotid-opthalmic artery aneurysm, pre and post stent deployment, respectively. **B**, Magnetic resonance image (MRI) obtained on postoperative day (POD) 1 demonstrating no diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR) lesions. **C**, MRIs obtained at 2 months demonstrating new FLAIR lesions (white arrows). MRI at 3 months demonstrating one FLAIR lesion resolving and a new lesion not previously present at 2 mo, respectively (white arrows). **D**, MRI obtained at 6 mo demonstrating resolution or resolving previously seen FLAIR lesions.

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posterior circulation (1 posterior cerebral artery aneurysm and 23 basilar aneurysms) and 53 patients had aneurysms in the anterior circulation (41 patients with aneurysms from the cavernous to ophthalmic segments of the internal carotid artery). Patients received similar doses of heparin (Table 1) and had similar preprocedural and intraprocedural laboratory values (Table 2).

Initial MRI Findings

Patients who underwent Pipeline-mediated embolization of their aneurysms were more likely than Neuroform stent-coiled patients to have diffusion restriction present on the postprocedure day 1 MRI (54% versus 14%; $P<0.0001$; Figure 3; Table 3). Twenty-four of these 41 PED patients have previously been reported to have a postprocedure day 1 MRI DWI lesion in 52% which is similar to the 54% rate reported here.[7] In addition, the mean count of diffusion restriction foci was higher in the PED group than in the Neuroform group (3.0±4.4 versus 0.27±0.76; $P<0.0001$). Accordingly, the mean diffusion restriction burden was also significantly higher in the PED group (16.7±25.5 versus 1.2±3.4 mm; $P<0.0001$). In the PED group, all new diffusion lesions and burden were found ipsilateral to the stent. One patient in the Neuroform group had a contralateral DWI lesion as previously reported.[21]

Increased Delayed FLAIR Lesions in PED Patients on Follow-Up MRIs

The mean duration of last radiographic follow-up for patients who underwent Pipeline-mediated embolization was 317.6 days (median, 351; interquartile range, 151.3–455 days). Similarly, the mean duration of last radiographic follow-up for patients who underwent Neuroform-mediated embolization was 291 days (median, 277; interquartile range, 189–350 days). The majority of patients in both groups had follow-up duration of >100 days (82.5% and 87.2% in Pipeline and Neuroform groups, respectively). Patients undergoing Pipeline embolization were more likely than Neuroform stent-coil patients to have FLAIR changes on MRI at all measurement occasions (Table 3). The mean FLAIR burden and mean FLAIR count were also greater in the Pipeline group at all measured time points (Table 3). In both groups, all new FLAIR lesions were found ipsilateral to stent deployment. Most importantly, the rate of new foci of FLAIR abnormality remained significantly higher in patients who underwent Pipeline-mediated embolization even at later measurement occasions (34.5% versus 6.2%; measurement occasion, 4; $P=0.001$; Figure 3). A similar trend was seen with respect to mean FLAIR counts, but no appreciable difference was found with DWI counts at later time periods (FLAIR, 1.2±2.4 versus 0.3±1.3; measurement occasion, 4; $P=0.0008$; Figure 3 and DWI, 0.10±0.56 versus 0.06±0.5; measurement occasion,

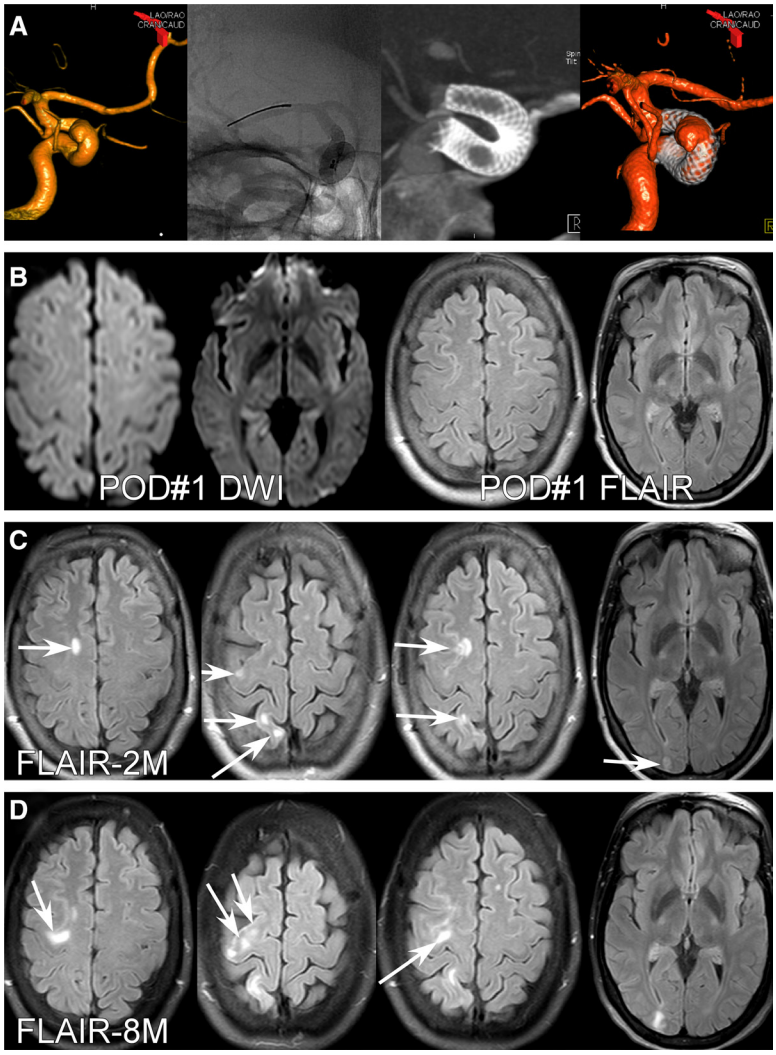


Figure 2. A 51-year-old women with headaches who was incidentally found to have a wide 6-mm necked 4x3 mm carotid-ophthalmic artery aneurysm and was treated with a Pipeline stent. **A**, Intraprocedural lateral angiograms and 3-dimensional reconstructions demonstrating the right 2×3 mm carotid artery aneurysm pre and post stenting. **B**, Magnetic resonance images (MRIs) obtained on postoperative day (POD) 1 demonstrating no diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR) lesions. **C**, MRI obtained at 2 mo demonstrating multiple new FLAIR lesions ipsilateral to the stent (white arrows). **D**, MRI obtained at 8 mo demonstrating resolving FLAIR lesions from the 2-mo time point but new (white arrows) additional FLAIR lesions.

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4; *P*=0.57). Overall, 34% (14/41) of Pipeline patients experienced a new FLAIR lesion at anytime during the study period compared with 10% (8/78) of Neuroform stent-coil patients. Of the 14 Pipeline patients who experienced a new FLAIR lesion, 5 (12.2%) had new FLAIR lesions at all 4 measurement occurrences, 3 (7.3%) had new FLAIR lesions at 3 measurement occurrences, 1 (2.4%) had new FLAIR lesions at 2 measurement occurrences, and 5 (12.2%) had a new FLAIR lesion at only 1 measurement occurrence. For these 14 patients, the earliest mean detection time that any FLAIR occurred was 51 days. Twenty-seven patients (65.9%) had no new FLAIR lesions at any time during the study. No delayed ipsilateral hemorrhages occurred in this series.

Regression Modeling: Comparison of Neuroform and Pipeline Cohorts

Using regression modeling, patients who underwent Pipeline flow diverter embolization were more likely to have new FLAIR abnormalities noted at the first follow-up MRI scan at ≈100 days post procedure (odds ratio, 6.1; 95% confidence interval [CI], 1.8–21.0; measurement occasion, 2; *P*=0.004) than those who underwent Neuroform stent-coiling. However, unlike the trend toward lower proportions of patients with new diffusion restriction over time, there was no evidence for change over time in the proportion of patients presenting with FLAIR abnormalities in either group (*P*=0.52). Thus, the proportion of patients with new FLAIR lesions on follow-up imaging remained higher even at the last comparative time point (34.5% versus 6.2%; measurement occasion, 4; *P*=0.001). This trend persisted after adjustment for age and sex.

Confirming previously reported results, patients who underwent Pipeline flow diverter embolization were more likely to demonstrate diffusion restriction on postoperative day 1 than patients who underwent Neuroform stent-coil embolization (odds ratio, 5.0; 95% CI, 1.7–14.4; *P*<0.0001). There, however, was no difference by a mean follow time of 300 days (measurement occurrence, 4; *P*=0.56). This trend persisted after adjustment for age and sex.

Identical trends were observed when count data, including the number of new DWI foci and the number of new FLAIR lesions, were used as the outcome measure.

Regression Modeling: Predictors of DWI and New FLAIR Lesions Within the Pipeline Cohort

The role of demographic factors, medical comorbidities, and clinical factors was assessed within the cohort of patients

Table 1. Demographic Data, Clinical Characteristics, and Radiographic Features of Patients

	Pipeline	Neuroform	*P* Value
n	41	78	
Mean age, y, ±SD	55.9±11.4	55.7±13.1	0.94
Range	18–77.1	30–86.3	
Sex (men)	5/41 (12.2%)	11/78 (14.1%)	0.99
HTN	21/41 (51.2%)	46/78 (59.0%)	0.44
DM	4/41 (9.8%)	10/78 (12.8%)	0.77
Hyperlipidemia	18/41 (43.9%)	29/78 (37.2%)	0.56
Statin use	10/20 (50%)	13/40 (32.5%)	0.26
History of ever smoking	25/41 (61%)	50/78 (64.1%)	0.84
Currently smoking	9/41 (22.0%)	31/78 (39.7%)	0.07
Aneurysm features, cm, ±SD			
Neck	0.45±0.22	0.53±0.77	0.47
Height	0.71±0.56	0.64±0.53	0.47
Width	0.69±0.46	0.63±0.69	0.63
Procedural medications			
Heparin dose	3989±1991 (25)	4423±1835 (73)	0.32
Heparin/BMI	157.9±55.6 (25)	148.5±55.9 (44)	0.50

Number in parentheses for procedural medications indicates number of patients with data available for parameter. BMI indicates body mass index; DM, diabetes mellitus; and HTN, hypertension.

undergoing Pipeline-mediated embolization of their aneurysms to identify possible predictors of new diffusion restriction or FLAIR abnormality.

Our most important finding during regression modeling was that the presence of diffusion restriction on the initial postprocedural MRI did not predict the occurrence of later development of FLAIR lesions (odds ratio, 1.9; 95% CI, 0.45–7.8; measurement occurrence, 2, 3, 4, 5; *P*=0.39). This suggests that these FLAIR lesions are likely to be independent of intra- and periprocedural factors associated with stent deployment.

Age and diabetes mellitus were found to be statistically associated with development of new areas of diffusion restriction (*P*=0.05 for both). Sex, smoking status, hypertension, diabetes mellitus, hyperlipidemia, platelet function tests, or heparin dose to body mass index ratio were not significant predictors of new DWI abnormalities in time-adjusted logistic regression models.

Sex was found to be a statistically associated with development of new FLAIR lesions over time with men demonstrating greater odds than women (odds ratio, 6.9; 95% CI, 1.1–43.8; *P*=0.04); age, smoking status, hypertension, diabetes mellitus, hyperlipidemia, platelet function tests, or heparin dose:body mass index ratio were not significantly associated with new FLAIR abnormalities in time-adjusted logistic regression models.

Inter-reader reliability was excellent for whether new foci of diffusion were present (κ=0.92; 95% CI, 0.84–0.99). The Pearson correlation coefficient for the 2 raters' counts of foci of diffusion restriction was 0.92. Inter-reader reliability was good for whether new areas of FLAIR abnormality were present (κ=0.68; 95% CI, 0.53–0.84). The Pearson correlation coefficient for the 2 raters' burden scores of new FLAIR abnormality was 0.7.

Clinical Outcome

During the study and follow-up period, 5.1% (4/78) of the Neuroform and 0% (0/41) of the PED group had temporary neurological complaints that resolved without intervention (*P*=0.29). These temporary complaints were unrelated to the aneurysm or neurological territory treated (ie, lightheadness or dizziness after treatment, temporary numbness not attributable to aneurysm location). These events were not associated with new DWI and FLAIR lesions. No patient in either group developed a new permanent neurological deficit.

Discussion

Flow-diverter technology is a recent and unique method for the endovascular treatment of aneurysms. Traditional methods

Table 2. Pre- and Intraprocedural Platelet Function and Activated Clotting Time

	Pipeline	Neuroform	*P* Value
ADP maximum platelet aggregation (%)	42.6±12.8 (40)	44.7±13.3 (16)	0.59
Lowest ADP maximum platelet aggregation (%)	34.8±17.2 (35)	31.8±14.8 (14)	0.57
Arachadonic acid maximum platelet aggregation (%)	12.9±5.4 (40)	13.7±5.9 (16)	0.62
Baseline ACT, s	144.8±15.3 (25)	147.0±12.1 (74)	0.47
Mean ACT, s	235±17.0 (25)	231.6±19.7 (75)	0.36
Mean and baseline ACT difference, s	64.2±19.1 (25)	58.4±16.4 (74)	0.14
Lowest ACT, s	202.2±25.7 (25)	197.2±19.2 (75)	0.30
Difference of lowest ACT from baseline ACT, s	57.4±24.6 (25)	50.2±21.1 (74)	0.16
Highest ACT, s	268.9±32.8 (25)	265.2±32.4 (75)	0.62
Difference of highest ACT from baseline ACT, s	124.1±33.2 (25)	118.4±32.9 (74)	0.46
ASA reactivity (ARU)	446.3±47.8 (11)	…	…
P2Y12 reactivity (PRU)	173.4±86.5 (11)	…	…

Number in parentheses indicates number of patients with data available for parameter. ACT indicates activated clotting time; ARU, aspirin reaction units; ASA, aspirin; and PRU, P2Y12 reaction units.

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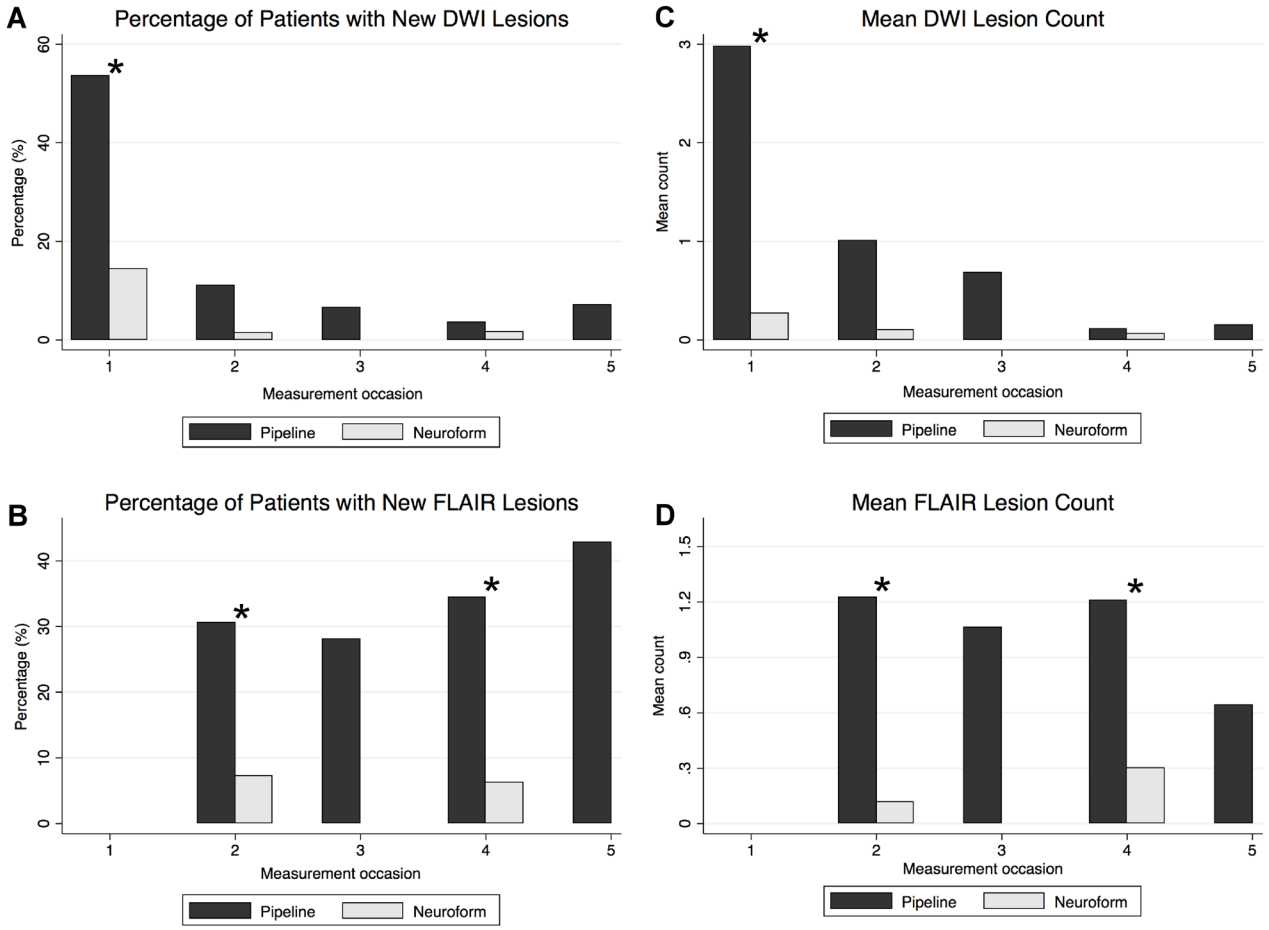


Figure 3. A and **B**, Percentage of patients over time who incur new diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) lesions, respectively. Pipeline-stented patients have a high initial rate of DWI lesions that decrease over time. However, they have a higher rate of FLAIR lesions that persists than Neuroform-stented patients. **C** and **D**, Mean DWI and FLAIR lesion counts over time demonstrating an increased number of independent DWI and FLAIR lesions in Pipeline patients when compared with Neuroform patients. *P<0.05.

of coil embolization with or without stent or balloon-assisted techniques are predicated on aneurysm exclusion from the circulation with the goal of having minimal to no flow within the aneurysm at the end of treatment procedure. Flow-diversion, however, relies on redirecting blood flow, and thereby causing stasis within the aneurysm. This stasis causes thrombosis and an inflammatory response with eventual sealing of the aneurysm neck by endothelialization and neointimal growth with the stent as a scaffold.[22] Importantly, until the aneurysm is completely occluded by thrombus and aneurysmal neck neointimal formation along the stent, there is still flow in and out of the aneurysm. It is unclear what the rate of thrombus egress or escape is during the process of transition from implantation until complete healing.

In the current study, we demonstrate that the PED is associated with continued new and independent ipsilateral FLAIR signal abnormalities that occur ≤1 year post Pipeline flow diverter deployment. At every measurement occurrence approximately one third of patients had a new FLAIR lesion (Table 3). These lesions were independent from any previous DWI or FLAIR lesion, suggesting a persistent delayed and de novo source generation process. This was in stark contrast with Neuroform-stent–assisted coil embolization, which had a near-negligible mean rate of new FLAIR burden (0.7 versus 10.1 mm; measurement occasion, 2 and 1.9 versus 8.8 mm; measurement occasion, 4; Table 3).

As is well-known, the differential for FLAIR lesions is broad and includes demyelination, gliosis, inflammatory processes including hypersensitivity reactions, neoplasm, infection, hemorrhage, vasogenic edema, and delayed ischemia.[23] In this study, however, FLAIR lesions were all found to be ipsilateral and distal to the distribution of the stented artery. No new contralateral FLAIR lesions were found in any PED patient. In addition, no patient had a diagnosis of a demyelinating or intracranial neoplastic disorder or was known a priori to have sensitivity to cobalt or nickel, main components of the PED, to explain the FLAIR findings. Furthermore, the lesions were either cortically based in the gray matter or involved the deep white mater distal to the stent, a pattern commonly found in ischemic lesions as opposed to other causes leading to FLAIR signal.[24] Although this study design cannot prove the cause of these FLAIR lesions, we hypothesize that these lesions are probably delayed ischemic events and most likely embolic from the stent/aneurysm complex. Review of our data supports this hypothesis because these delayed FLAIR events tended to decrease between 9 months

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Table 3. Radiographic Outcomes by Stent Type and Measurement Occurrence

	Postprocedure Day 1 T=1	T=2	T=3	T=4	T=5
Pipeline (no. of pts)	41	36	32	29	14
Neuroform (no. of pts)	78	69	…	64	…
Mean time (d±SD)					
Pipeline	1±0	73.4±64.4	174.3±121.7	276.8±146.7	409±141.3
Neuroform	1±0	107.1±78.4	…	335.0±173.7	…
New DWI present (Y/N)?					
Pipeline (%Y)	22/41 (54%)	4/36 (11%)	2/31 (6%)	1/29 (3.5%)	1/14 (7%)
Neuroform (%Y)	7/49 (14%)	1/69 (1.4%)	…	1/64 (1.6%)	…
New FLAIR present (Y/N)?					
Pipeline (%Y)	…	11/36 (30.6%)	9/32 (28.1%)	10/29 (34.5%)	6/14 (42.9%)
Neuroform (%Y)	…	5/69 (7.2%)	…	4/64 (6.2%)	…
Mean DWI count					
Pipeline	3.0±4.4	1.0±4.9	0.68±3.6	0.10±0.56	0.14±0.53
Neuroform	0.27±0.76	0.10±0.84	…	0.06±0.5	…
Mean FLAIR count					
Pipeline	…	1.2±2.8	1.1±2.3	1.2±2.4	0.6±0.9
Neuroform	…	0.1±0.5	…	0.3±1.3	…
Mean DWI burden, mm					
Pipeline	16.7±25.5	5.1±24.0	2.9±14.9	0.6±3.2	0.7±2.6
Neuroform	1.2±3.4	0.50±4.1	…	0.3±2.5	…
Mean FLAIR burden, mm					
Pipeline	…	10.1±31.0	10.1±26.9	8.8±18.7	4.4±6.3
Neuroform	…	0.7±3.4	…	1.9±9.6	…

Radiographic outcomes were assessed at 5 measurement occasions for patients who underwent Pipeline-mediated embolization (postprocedure day 1 [T1], T2, T3, T4, and T5) and at 3 measurement for patients who underwent Neuroform-mediated embolization (postprocedure day 1 [T1], T2, and T4). DWI indicates diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; N, no; pts, patients; T, time point; and Y, yes.

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and 1 year after stent deployment (Table 3; mean FLAIR burden measurement occurrence, 2, 3, 4 versus 5), possibly as the flow-diverter device was endothelialized and sealed. This coincides with the time period reported for complete aneurysm obliteration and therefore complete absence of flow within and out of the aneurysm after PED deployment. Leung et al[25] in a systematic review of 10 studies (414 patients with 448 aneurysms) of the PED reported an aneurysm obliteration rate of 82.9% at a 6-month time period. Likewise, other authors have reported obliteration rates of 85% to 95% from 6 months to 1 year post Pipeline deployment.[10,26,27] An important similarity of all these studies is that in some patients, there is a delayed period of 6 months to 1 year where there is ongoing aneurysm flow stasis, thrombus formation, and neointimal growth along the aneurysmal neck utilizing the stent as scaffolding. We have noted in this study a decrease in the number of FLAIR lesions that coincides with the predicted time of complete aneurysm occlusion giving additional credibility to our embolic hypothesis.

Although in this series, these FLAIR lesions do not seem to yield any apparent clinical deficit, they are concerning. Multiple previous carotid artery stenting studies have demonstrated that small DWI and FLAIR lesions after stenting are associated with neurocognitive decline.[28–31] Like our current study, most patients do not display overt clinical neurological deficits, but when tested with detailed neurocognitive tests are found to have decline when compared with their pretreatment states.[31] Although neurocognitive studies are fraught with bias, the finding of increased ipsilateral clinically silent possibly embolic lesions after PED deployment should cause some unease about the risk to patients within the first year of deployment.

We have also redemonstrated in this study that deployment of the PED is associated with a greater amount of periprocedural DWI lesions when compared with Neuroform stent use. We have previously reported a 52% (13/25) rate of acute DWI lesions in another cohort of PED patients when compared with a 9% (7/78) rate in Neuroform stent-coil patients.[7,21] The current study demonstrates similar consistent results with 54% (22/41) in PED patients and 14% (7/49) in the Neuroform cohort.

The current study has many limitations. First, it is a single-center retrospective review of a prospectively maintained database with the inherent drawbacks of a nonrandomized study. We consider the result as hypothesis generating to lead to a broader multicenter analysis. We have tried to eliminate observer bias by having 2 independent reviewers' evaluate each MRI independently blinded to the others' findings. Interreader reliability was good to excellent for all measurements made. Second, a limitation of this study is the small sample

size studied (n=41 PED and n=78 Neuroform). We plan to continue to accrue patients to the current prospective database as well as follow this current patient cohort for future imaging analysis. This, however, is a fairly large sample from a single-center and has the advantage of a single operator and uniform technique of pre- and postoperative care to limit the bias imparted by different surgeons as a possible cause of these delayed FLAIR lesions. Although our data suggest that these FLAIR lesions are not associated with periprocedural DWI, having uniform postoperative management is a strength of this data. Larger multicenter prospective studies with larger sample size and additional reviewers may aid in defining this phenomenon in more detail. Finally, patients in this study group were screened with MRI at a higher than normal frequency given our previous reports of a significantly higher rate of ipsilateral perioperative DWI lesions after PED deployment than conventional stent-coil methods.[7] This high periprocedural rate has been replicated by an outside group with an almost identical rate of 50.9% when compared with 52% of patients in our initial study.[15] At this time, it is unclear whether this increased rate of imaging in a purely clinical setting may be feasible or practical unless it is shown to alter patient management strategies. It will be important, however, to further study these findings in a research setting to determine both the cause and the clinical impact, if any, that may be caused by the readily identifiable increased rate of FLAIR lesions with the PED.

Conclusions

The PED is associated with increased rate of de novo FLAIR lesions occurring in a delayed fashion and distinct from perioperative DWI lesions. The cause and clinical effect of these lesions are unknown and suggest the need for prudent follow-up and evaluation.

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Disclosures

None.

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