Predictors of cerebral aneurysm persistence and occlusion after flow diversion: a single-institution series of 445 cases with angiographic follow-up

*Matthew T. Bender, MD,[1] Geoffrey P. Colby, MD, PhD,[2] Li-Mei Lin, MD,[3] Bowen Jiang, MD,[1] Erick M. Westbroek, MD,[1] Risheng Xu, MD,[1] Jessica K. Campos, MD,[1] Judy Huang, MD,[1] Rafael J. Tamargo, MD,[1] and Alexander L. Coon, MD[1]

[1]Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Department of Neurosurgery, University of California, Los Angeles; and [3]Department of Neurosurgery, University of California, Irvine, California

OBJECTIVE Flow diversion requires neointimal stent overgrowth to deliver aneurysm occlusion. The existing literature on aneurysm occlusion is limited by heterogeneous follow-up, variable antiplatelet regimens, noninvasive imaging modalities, and nonstandard occlusion assessment. Using a large, single-center cohort with low attrition and standardized antiplatelet tapering, the authors evaluated outcomes after flow diversion of anterior circulation aneurysms to identify predictors of occlusion and aneurysm persistence.

METHODS Data from a prospective, IRB-approved database was analyzed for all patients with anterior circulation aneurysms treated by flow diversion with the Pipeline embolization device (PED) at the authors' institution. Follow-up consisted of catheter cerebral angiography at 6 and 12 months postembolization. Clopidogrel was discontinued at 6 months and aspirin was reduced to 81 mg daily at 12 months. Occlusion was graded as complete, trace filling, entry remnant, or aneurysm filling. Multivariate logistic regression was performed to identify predictors of aneurysm persistence.

RESULTS Follow-up catheter angiography studies were available for 445 (91%) of 491 PED procedures performed for anterior circulation aneurysms between August 2011 and August 2016. Three hundred eighty-seven patients accounted for these 445 lesions with follow-up angiography. The population was 84% female; mean age was 56 years and mean aneurysm size was 6.6 mm. Aneurysms arose from the internal carotid artery (83%), anterior cerebral artery (13%), and middle cerebral artery (4%). Morphology was saccular in 90% of the lesions, and 18% of the aneurysms has been previously treated. Overall, complete occlusion was achieved in 82% of cases at a mean follow-up of 14 months. Complete occlusion was achieved in 72%, 78%, and 87% at 6, 12, and 24 months, respectively. At 12 months, adjunctive coiling predicted occlusion (OR 0.260, p = 0.036), while male sex (OR 2.923, p = 0.032), aneurysm size (OR 3.584, p = 0.011), and incorporation of a branch vessel (OR 2.206, p = 0.035) predicted persistence. Notable variables that did not predict aneurysm occlusion were prior treatments, vessel of origin, fusiform morphology, and number of devices used.

CONCLUSIONS This is the largest single-institution study showing high rates of anterior circulation aneurysm occlusion after Pipeline embolization. Predictors of persistence after flow diversion included increasing aneurysm size and incorporated branch vessel, whereas adjunctive coiling predicted occlusion.

https://thejns.org/doi/abs/10.3171/2017.11.JNS171738

KEYWORDS Pipeline embolization device; flow diversion; cerebral aneurysm; vascular disorders

Flow-diverting stents function as a neoendothelialization scaffold to reconstruct the parent artery and exclude cerebral aneurysms from the circulation. Aneurysm cure is apparent only on follow-up imaging, and yet the literature on occlusion outcomes is flawed. Attrition is high,[14,20,22,29,33] antiplatelet tapering regimens inconsistent,[15,19,22,23] follow-up incomplete,[9,19,31] follow-up imaging often noninvasive,[14,33,36,43,44] and occlusion grading nonstandard.[34,36,42] This leads to flawed conclusions about the predictors of aneurysm occlusion after flow diversion

ABBREVIATIONS ACA = anterior cerebral artery; ACoA = anterior communicating artery; DSA = digital subtraction angiography; ICA = internal carotid artery; MCA = middle cerebral artery; PCoA = posterior communicating artery; PED = Pipeline embolization device; PUFS = Pipeline for Uncoilable or Failed Aneurysms.

ACCOMPANYING EDITORIAL DOI: 10.3171/2018.2.JNS1836.
SUBMITTED July 16, 2017. **ACCEPTED** November 10, 2017.
INCLUDE WHEN CITING Published online March 30, 2018; DOI: 10.3171/2017.11.JNS171738.

* M.T.B. and G.P.C. share first authorship of this work.

and can misdirect treatment strategies. With low attrition, standardized antiplatelet tapering, and a large number of patients treated at a single institution, we evaluated occlusion outcomes after flow diversion of anterior circulation aneurysms with the Pipeline embolization device (PED) (Medtronic) to identify predictors of occlusion and aneurysm persistence.

Methods

We analyzed a retrospective cohort of patients obtained from an IRB-approved, prospectively collected database of patients with aneurysms treated at a tertiary medical center.

The decision to treat was based on demographics, aneurysm size, location, irregularity, and growth, among other factors. Surgical and alternative endovascular treatments were considered before the decision to undertake flow diversion. Consistent with the PED literature,[8,14] over time a growing majority of treatments were "off-label," including treatment of small aneurysms and distal anterior circulation aneurysms. Pipeline placement was performed as previously described.[6,18] Patients recovered in the neurocritical care unit and were typically discharged to home on postembolization day 1. Demographic information, clinical history, and outcomes were collected from medical records. Anatomical and technical details were collected from intraprocedural events, angiograms, and operative reports. Follow-up consisted of catheter cerebral angiography at 6, 12, and often at 24 months postembolization. Clopidogrel was discontinued at 6 months and aspirin was reduced to 81 mg daily at 12 months. Occlusion was graded according to a modified version of the O'Kelly-Marotta scale based on the degree of filling as complete, trace filling, entry remnant, or aneurysm filling,[34] but without the degree of stasis assessment.

Statistical Analysis

Data are presented as mean and range for continuous variables and as frequency for categorical variables. Univariate analysis was carried out using unpaired t-tests and ANOVA tests. Univariate logistic regression was used to test predictors of aneurysm occlusion. Factors predictive at a level of $p < 0.2$ were then evaluated by multivariate logistic regression. A threshold of $p < 0.05$ was used to determine significance. Kaplan-Meier methodology was followed for generating time-to-occlusion curves. Statistical analysis was performed using Stata (version 14.0).

Results

A total of 491 PED procedures were performed for anterior circulation aneurysms between August 2011 and August 2016, and angiographic follow-up studies were available for 445 (91%). The mean age of the 387 patients who underwent 445 PED procedures with available follow-up imaging was 56 years, and 84% were female. The mean aneurysm size was 6.6 mm in diameter, and there were 85 large (19%) and 4 giant (1%) aneurysms. More than one aneurysm was treated during a single procedure in 7% of cases, with aneurysms commonly adjacent to one another. A minority of the treated aneurysms were previously ruptured (7%) or previously treated (18%). Saccular morphology was most common (90%), with 7% being fusiform and 3% being dissecting aneurysms or pseudoaneurysms. In 191 cases (43%), a branch vessel was incorporated into the aneurysm fundus or neck. This included true ophthalmic and posterior communicating artery (PCoA) aneurysms along the internal carotid artery (ICA) as well as anterior communicating artery (ACoA) aneurysms and middle cerebral artery (MCA) bifurcation aneurysms (Table 1).

TABLE 1. Demographics and anatomy

Characteristic	Value (range or %)
Total cases	445
Mean age (yrs)	56.1 ± 12.6 (20–88)
Female sex	372 (84)
Mean aneurysm size in mm (range)	6.6 ± 4.7 (1–31)
Small, no.	356 (80)
Large, no.	85 (19)
Giant, no.	4 (1)
>1 aneurysm treated	33 (7)
Prior SAH	66 (15)
Previously treated	79 (18)
Clip	19 (4)
Coil	53 (12)
Flow diversion	7 (2)
Multiple treatments	0 (0)
Morphology	
Saccular	401 (90)
Fusiform	30 (7)
Dissecting/pseudoaneurysm	14 (3)
Branch vessel included	191 (43)

SAH = subarachnoid hemorrhage.
Mean values are presented ± SD. Other values represent the number (%) of lesions.

Most aneurysms originated along the ICA (82%), including paraophthalmic (29%), true ophthalmic (17%), and cavernous segment (12%) aneurysms. The anterior cerebral artery (ACA) was the second most common vessel of origin (13%), led by true ACoA (7%) and A_1/A_2 segment aneurysms (4%). MCA bifurcation aneurysms (2%) accounted for a majority of aneurysms arising along the MCA (4%) (Table 2).

The mean fluoroscopy time and radiation exposure for PED procedures were 38 minutes and 2206 mGy, respectively. A single PED was deployed in most cases (92%). Adjunctive coiling was performed in 24 cases (5%), and balloon angioplasty was used to improve device apposition in 49 cases (11%). Contrast stasis was assessed on final control angiogram after PED placement and was divided evenly between contrast persisting into the arterial phase (32%, "mild"), capillary phase (29%, "moderate"), and venous phase (31%, "pronounced") (Table 3).

Overall, complete occlusion was achieved in 82% of cases at a mean and median follow-up of 14.5 ± 10.1 and

TABLE 2. Aneurysm locations

Aneurysm Location	No. of Lesions (%)
ICA	367 (82)
Cervical	11 (2)
Petrous	4 (1)
Cavernous	52 (12)
Ophthalmic	77 (17)
Paraophthalmic	131 (29)
Superior hypophyseal	8 (2)
PCoA	42 (9)
Clinoidal	18 (4)
Supraclinoid	16 (4)
Termination	8 (2)
ACA	59 (13)
A_1	4 (1)
A_1/A_2	18 (4)
ACoA	30 (7)
A_2/A_3	6 (1)
A_4	1 (0)
MCA	19 (4)
M_1	6 (1)
Bifurcation	10 (2)
M_2	3 (1)

12.0 months, respectively (range 2–61 months). At 6, 12, and 24 months, complete occlusion was achieved in 72%, 78%, and 87% of cases for which follow-up data were available, respectively (Table 4). These results are also displayed in a Kaplan-Meier survival curve (Fig. 1).

Multivariate logistic regression was performed to identify predictors of persistence at 6 and 12 months postembolization. At 6 months, advancing age (OR 1.024, p = 0.035) and increasing aneurysm size (OR 2.384, p = 0.016) were predictors of aneurysm persistence, while a history of subarachnoid hemorrhage (OR 0.375, p = 0.030) and adjunctive coiling (OR 0.060, p = 0.020) were predictors of aneurysm occlusion (Table 5). At 12 months, male sex (OR 2.923, p = 0.032), increasing aneurysm size (OR 3.584, p = 0.011), and branch vessel inclusion within the treated aneurysm (OR 2.206, p = 0.035) were predictors of persistence, while adjunctive coiling (OR 0.033, p = 0.036) predicted occlusion (Table 6). Notable variables that were tested but were not predictive of either persistence or occlusion included prior treatments, vessel of origin, device number, device diameter, and contrast stasis on final control angiogram after the embolization procedure.

The overall rate of major complications[17] with placement of anterior circulation PEDs was 3.5%, including a 1.1% rate of major stroke, a 1.8% rate of intracranial hemorrhage, and a 0.7% rate of subarachnoid hemorrhage, leading to 1.1% rate of mortality. The overall rate of minor complications was 8.8%, including a 0.9% rate of minor stroke, a 2.3% rate of transient ischemic attacks, a 1.4% rate of cranial nerve palsy, a 0.5% rate of iatrogenic dissection without stroke, a 3.5% rate of groin hematoma, and a 0.7% rate of groin infection.

TABLE 3. Procedural outcomes

Operative Characteristic	Value (range or %)
Total mean fluoroscopy time in mins	38.3 ± 25.3 (10–203)
Mean radiation exposure in mGy	2206 ± 1144 (259–9031)
No. of devices	1.08 ± 0.28 (1–3)
1	410 (92)
2	34 (8)
3+	1 (0)
Adjunct coil deployment	24 (5)
Verapamil infusion	53 (12)
Balloon angioplasty	49 (11)
PED thrombosis	17 (4)
PED cork/removal	34 (8)
Stasis	
None	11 (2)
Mild	143 (32)
Moderate	128 (29)
Pronounced	140 (31)
Occluded	23 (5)

Mean values are presented ± SD (range). Other values represent the number (%) of lesions.

Discussion

In this single-institution series of 491 anterior circulation cerebral aneurysms, of which 445 (91%) were in patients who underwent follow-up digital subtraction angiography (DSA), flow diversion with the PED achieved complete aneurysm occlusion in 72%, 78%, and 87% at 6, 12, and 24 months postoperatively, respectively. Multivariate logistic regression identified increasing aneurysm size and branch vessel inclusion within the aneurysm fundus or neck as predictors of aneurysm persistence and adjunctive coiling as a predictor of complete occlusion.

The best studies of flow diversion outcomes report on actuarial occlusion at fixed intervals following treatment; results in this series are comparable with those in the literature that show progressive occlusion in 56%–82% at 6 months,[9] 73%–87% at 12 months,[36,40,41] and 84%–93% at 24 months.[3,15,44] The original Pipeline for Uncoilable or

TABLE 4. Occlusion outcome

Outcome	6 Mos		12 Mos		24 Mos		Last FU	
	No.	%	No.	%	No.	%	No.	%
Complete occlusion	286	72	215	78	83	87	367	82
Trace filling	57	14	35	13	8	8	41	9
Entry remnant	14	4	9	3	1	1	9	2
Aneurysm filling	39	10	17	6	3	3	28	6
No. of aneurysms w/ data available for analysis	396	81	276	56	95	19	445	91
No imaging	95	19	215	44	396	81	46	9

FU = follow-up.
Values represent the numbers and percentages of lesions.

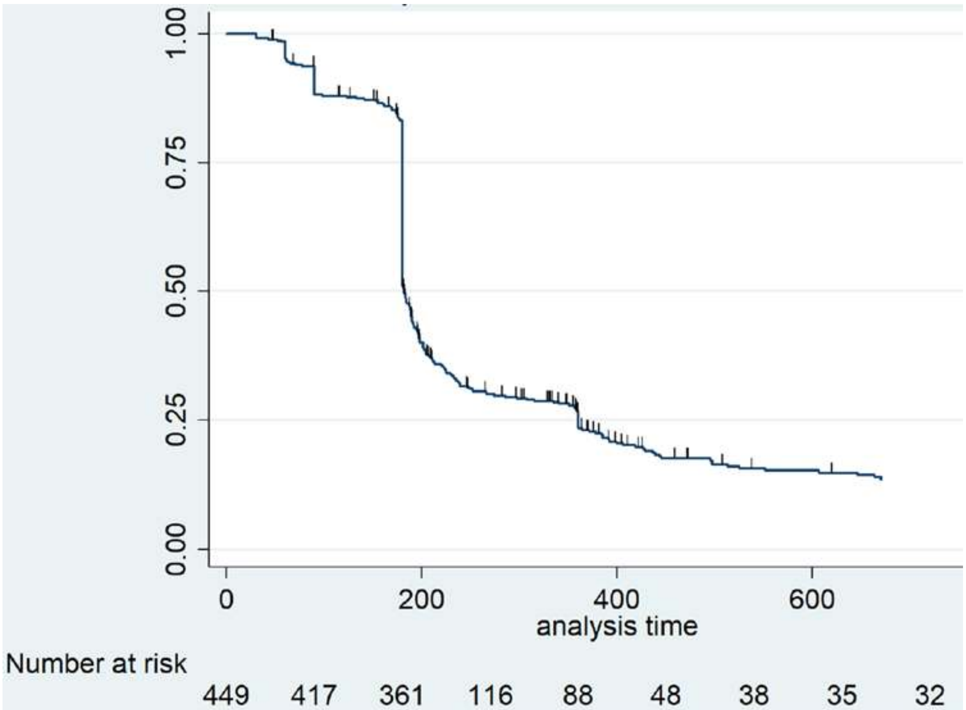

FIG. 1. Kaplan-Meier plot demonstrating the rates of aneurysm occlusion over time. Values on the x-axis represent days. *Hash marks* indicate censored patients. Figure is available in color online only.

Failed Aneurysms (PUFS) cohort of 109 aneurysms has been followed now for 5 years with complete occlusion increasing from 74% at 6 months to 95% at 5 years. PUFS is commendable for its low attrition rates, with angiographic results for 70% of patients at 3 years and 55% at 5 years; however, comparisons to PUFS are limited by its large aneurysm size (mean 18 mm), high number of devices (3 on average), and absence of bifurcation aneurysms.[3,4] Chiu et al. achieved similarly low attrition in a population of 98 patients with 119 aneurysms, in whom angiographic follow-up was available for 84%, 66%, and 89% at 6, 12, and 24 months, respectively. Perhaps more comparable to contemporary flow diversion series, more than half of aneurysms in that series were < 10 mm in size and 19% incorporated a major branch vessel. Occlusion rates were 82%, 84%, and 93% at 6, 12, and 24 months.[15] Yu et al. reported actuarial outcomes in a larger cohort of 143 patients with 178 aneurysms in whom complete occlusion was seen in 56%, 81%, and 84% at 6, 12, and 24 months. Attrition rates were higher in that study and vessel imaging was available in 42% and 33% at 12 and 24 months, respectively, and more than half of these results were from MR or CT angiography.[44] Even at 3 T, contrast-enhanced and time-of-flight MR angiograms are inferior modalities that overestimate total occlusion by more than 15% and 20%, respectively, compared to DS angiograms.[1]

The rates of high attrition[14,20,22,29,33] and follow-up with noninvasive vascular imaging[14,33,36,43] are just two limitations in the literature on outcomes after flow diversion. Another limitation is the reporting of occlusion outcomes at last follow-up, a heterogeneous end point that indirectly approximates the goals of treatment.[13,22,27,31,35,38,43] For example, Chalouhi et al. compared 178 patients treated with a single device or multiple devices and reported "latest occlusion" complete in 68% of patients at a mean follow-up of 7.0 months in the single-device group and 70% at 8.9 months in the multiple-device group. The latest occlusion represents a composite of 3-month, 6-month, 12-month, and longer DS angiography results at disparate stages of dual antiplatelet tapering, which prevents the drawing of conclusions about long-term occlusion and its predictors.[13] Others have reported occlusion outcomes prematurely at 3 or 6 months when patients have yet to complete antiplatelet tapering.[9,19,31] Our experience has shown that even for small aneurysms a significantly higher percentage of aneurysms will show complete occlusion at 6 months compared to 3 months, and this number will continue to increase after clopidogrel is stopped.[25] Another common problem is the reporting of occlusion outcomes from centers that follow different antiplatelet tapering protocols.[15,19,22,23] The present study avoids these limitations and represents a large, single-institution cohort with standardized antiplatelet tapering and high rates of DS angiographic follow-up, reporting actuarial occlusion outcomes. Kaplan-Meier time-to-occlusion plots are a visually compelling alternative for displaying occlusion outcomes (Fig. 1), although they have limitations in that they treat occlusion as a binary outcome and assume occlusion occurred at the time of fixed-interval follow-up angiography.

In the literature pertaining to flow diversion, the most consistent predictor of persistence after treatment has been branch vessel inclusion within the aneurysm fundus, although the relevant anatomical parameters have been variably defined.[7,15,24,32,36,43] On the more restrictive end of the spectrum, Kan et al. studied 701 PED placements across 6 institutions and found 15 aneurysms that incorporated

TABLE 5. Predictors of aneurysm occlusion and persistence at 6 months

	Univariate				Multivariate			
		CI		p		CI		p
Predictor Variable	OR	Low	High	Value	OR	Low	High	Value
Age	1.036	1.014	1.057	0.001	1.024	1.002	1.048	**0.035**
Male sex	1.761	1.001	3.098	0.049	1.978	0.982	3.986	0.056
Race								
White	2.882	1.075	7.728	0.035	1.912	0.704	5.194	0.203
Black	1.387	0.481	3.996	0.545	1.167	0.398	3.417	0.778
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
History of SAH	0.336	0.154	0.733	0.006	0.375	0.155	0.907	**0.030**
Previous treatment	0.917	0.671	1.253	0.587	—	—	—	—
Aneurysm size (cm)	1.950	1.229	3.093	0.005	2.384	1.176	4.832	**0.016**
Size (small vs large/giant)	1.773	0.490	6.419	0.383	—	—	—	—
Vessel of origin								
ICA	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
ACA	0.586	0.282	1.218	0.152	0.726	0.185	2.845	0.646
MCA	1.231	0.449	3.381	0.686	2.071	0.347	12.358	0.424
Morphology (saccular vs other)	2.064	0.995	4.282	0.051	1.450	0.555	3.785	0.448
Branch vessel w/in aneurysm	1.000	0.644	1.558	0.993	1.769	0.986	3.175	0.056
Fluoroscopy time (mins/10)	1.030	0.942	1.126	0.508	—	—	—	—
Radiation exposure (mGy/1000)	0.848	0.680	1.058	0.145	0.916	0.700	1.200	0.528
Coiling	0.110	0.015	0.828	0.032	0.060	0.005	0.639	**0.020**
>1 device	0.894	0.387	2.067	0.795	—	—	—	—
Cervical ICA tortuosity	1.034	0.653	1.638	0.886	—	—	—	—
Type 3/4 cavernous ICA	1.025	0.645	1.628	0.917	—	—	—	—
Verapamil infusion	0.282	0.112	0.762	0.012	0.426	0.159	1.142	0.090
Balloon angioplasty	0.496	0.224	1.098	0.084	0.506	0.201	1.272	0.148
Pipeline removal/cork	1.122	0.497	2.533	0.782	—	—	—	—
In situ thrombosis	0.373	0.057	2.456	0.305	—	—	—	—
PED diameter (mm)								
2.5–3	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
3.25–4.25	1.178	0.595	2.332	0.638	1.140	0.264	4.921	0.861
4.5–5	2.295	1.104	4.772	0.026	1.716	0.341	8.623	0.512
Stasis								
None/mild	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Moderate	1.394	0.809	2.399	0.231	1.417	0.703	2.858	0.330
Pronounced/occluded	0.989	0.580	1.686	0.969	0.973	0.502	1.884	0.936

Ref = reference value; – = variable not included in multivariate analysis because it did not meet the significance threshold for inclusion.
Boldface type indicates statistical significance.

an end vessel without distal collaterals. These included 7 fetal PCoA aneurysms and five ophthalmic artery aneurysms without an external carotid artery collateral supply. None of the aneurysms were occluded during a minimum of 12-month angiographic follow-up period.[24] In a study of PEDs used to treat 29 anterior circulation aneurysms, Tsang et al. observed total occlusion in 79% of the cases, with aneurysms arising from a fetal-type PCoA accounting for 4 of 6 refractory cases.[43] Chiu et al. provided fewer specifics about their definition of branch vessel incorporation but followed patients longer and found this may delay but does not preclude aneurysm obliteration. In their study of PED for 119 unruptured aneurysms, 23 that incorporated a branch vessel showed lower occlusion rates at 6 and 12 months (57% vs 84% overall) but not 24+ months (86% vs 93% total).[15] We used a permissive definition, including all PCoA aneurysms, ACoA aneurysms, MCA bifurcation aneurysms, and true ophthalmic aneurysms, accounting for 43% of the series. Even with our more inclusive definition, a branch vessel incorporated into the aneurysm was a predictor of persistence at 12 months. The increased representation of bifurcation aneurysms in our series may explain why occlusion outcomes are lower than in some other large series.[15,40]

TABLE 6. Predictors of aneurysm occlusion and persistence at 12 months

	Univariate				Multivariate			
		CI		p		CI		p
Predictor Variable	OR	Low	High	Value	OR	Low	High	Value
Age	1.038	1.009	1.069	0.010	1.030	0.999	1.060	0.053
Male sex	2.058	1.020	4.152	0.044	2.923	1.097	7.791	**0.032**
Race								
White	1.468	0.475	4.533	0.504	—	—	—	—
Black	1.817	0.548	6.022	0.329	—	—	—	—
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
History of SAH	0.639	0.253	1.613	0.344	—	—	—	—
Previous treatment	0.926	0.619	1.385	0.709	—	—	—	—
Aneurysm size (cm)	2.878	1.527	5.425	0.001	3.584	1.335	9.617	**0.011**
Size (small vs large/giant)	1.166	0.228	5.947	0.853	—	—	—	—
Vessel of origin								
ICA	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
ACA	0.593	0.218	1.613	0.306	0.511	0.063	4.117	0.528
MCA	2.151	0.673	6.872	0.196	2.676	0.210	34.150	0.449
Morphology (saccular vs other)	1.785	0.791	4.031	0.163	1.004	0.352	2.860	0.993
Branch vessel w/in aneurysm	1.473	0.833	2.603	0.182	2.206	1.056	4.613	**0.035**
Fluoroscopy time (mins/10)	1.089	0.966	1.229	0.161	1.061	0.872	1.291	0.556
Radiation exposure (mGy/1000)	1.021	0.803	1.299	0.861	—	—	—	—
Coiling	0.260	0.033	2.000	0.194	0.033	0.001	0.795	**0.036**
>1 device	1.265	0.436	3.669	0.664	—	—	—	—
Cervical ICA tortuosity	1.303	0.732	2.322	0.368	—	—	—	—
Type 3/4 cavernous ICA	1.511	0.849	2.690	0.161	1.143	0.568	2.301	0.708
Verapamil infusion	0.388	0.113	1.335	0.133	0.472	0.145	1.538	0.213
Balloon angioplasty	0.994	0.382	2.589	0.992	—	—	—	—
Pipeline removal/cork	0.498	0.143	1.739	0.275	0.318	0.077	1.314	0.114
In situ thrombosis	0.778	0.176	3.441	0.741	—	—	—	—
PED diameter								
2.5–3	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
3.25–4.25	1.102	0.468	2.595	0.824	1.936	0.220	16.997	0.551
4.5–5	1.902	0.749	4.831	0.176	2.455	0.255	23.588	0.436
Stasis								
None/mild	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Moderate	0.930	0.475	1.821	0.832	—	—	—	—
Pronounced/occluded	0.699	0.344	1.420	0.322	—	—	—	—

Boldface type indicates statistical significance.

Prior flow diversion studies have shown decreasing occlusion rates with increasing aneurysm size, although in most series this has not reached statistical significance as it did in the present study. In a single-institution study of 251 aneurysms of which 182 had angiographic follow-up, Saatci et al. observed complete occlusion at 6 months in 94% of small aneurysms, 88% of large aneurysms, and 90% of giant aneurysms, but they did not report statistical significance.[40] Smaller single-institution studies with fewer than 100 patients who had undergone angiographic follow-up have also reported higher occlusion rates for small aneurysms,[15,32] but the studies were underpowered to detect a statistical difference.[20,41] In a meta-analysis of 29 studies and 1654 aneurysms, Brinjikji et al. observed a similar effect with complete occlusion at 6 months in 80% of small, 74% of large, and 76% of giant aneurysms. This did not achieve statistical significance on univariate analysis, with multiple-device constructs and adjunctive coiling presumably bolstering occlusion rates for larger aneurysms, and multivariate analysis could not be performed due to data heterogeneity.[9] In a study of 171 patients, Park et al. assessed aneurysm size as a dichotomous variable and found size was predictive of persistence at a threshold of > 15 mm but not > 10 mm.[36] When dichotomized at a similarly arbitrary cutoff of 10 mm in the present study, aneurysm size was not a significant predictor of occlusion; however, when assessed as a continuous variable, increasing aneurysm size was a predictor of persistence on multivariate analysis at both 6- and 12-month DSA follow-up examinations.

While branch vessel inclusion and increasing fundus size predicted aneurysm persistence, adjunctive coiling, which may be performed for a variety of reasons, was in this study a predictor of aneurysm occlusion. Reasons to use coils along with a flow-diverting stent include altering hemodynamics to prevent delayed rupture of large or giant aneurysms, speeding thrombosis in the presence of significant irregularity, and mechanically reinforcing the PED to prevent foreshortening in fusiform aneurysms. Although not typically the goal of adding coils to a Pipeline construct, improved occlusion outcomes are an increasingly recognized benefit. Nossek et al. reported 100% complete occlusion in 28 aneurysms treated with the PED and adjunctive coiling, although follow-up DSA studies were available for just 53%, and no comparison group was provided.[33] Lin et al. likewise observed complete occlusion in 93% of 29 patients treated with the PED and coiling as compared with complete occlusion in 75% of 75 patients treated with PED alone ($p = 0.03$), although the treatment groups differed in terms of aneurysm size and morphology, and a multivariate analysis was not performed.[26] Park et al. reported on 171 aneurysms treated with the PED at two institutions, among which 36% received adjunctive coiling. Complete occlusion rates were 82% for lesions treated with the PED and coils versus 68% for those treated with the PED alone, and PED without coils predicted residual aneurysm at follow-up on multivariate analysis.[36] Adjunctive coiling adds technical complexity to the Pipeline procedure—jailed catheter techniques impact device apposition, and rates of balloon remodeling were higher in these cases (43%) than in cases without adjunctive coiling (10%). Variations in treatment selection across institutions are evident in the comparatively small percentage (5%) of aneurysms in this series for which coils were used adjunctively with PEDs, but the results were confirmatory as adjunctive coiling predicted aneurysm occlusion on multivariate analysis.

There were a number of variables that notably did not predict aneurysm occlusion or persistence in this study. First, without specifying their number or nature, prior treatments were the strongest predictor of aneurysm persistence on multivariate analysis in the initial Canadian experience with 97 PED procedures.[35] Shapiro et al. suggested that the presence of a prior laser-cut stent was uniquely predictive of treatment failure,[41] while McAuliffe et al. observed a more pervasive effect in the initial Australian experience with the PED, which showed a 93% occlusion rate at 6-month DSA follow-up in 40 patients without prior treatments and a 69% occlusion rate among 16 aneurysms with prior treatments.[30] Others have observed no significant effect of prior procedures on occlusion outcomes,[15,20] as we did in a large population of 79 patients who had undergone prior treatments, predominantly coiling. Second, multiple-device PED constructs may be used to increase metal surface area coverage or to extend coverage in vessels with longer diseased segments. In this study, there were 413 single-PED procedures and 36 multiple-PED procedures. Occlusion rates at 6 and 12 months were 72% and 74% for single-PED compared to 72% and 77% for multiple-PED procedures, respectively. Kabbasch et al. observed 100% occlusion in multiple-PED constructs at median 7-month angiographic follow-up compared with 70% in single-PED cases,[21] although multiple other studies have found no relationship between device number and occlusion outcomes,[13,20,41] as we did in the present study. Third, fusiform aneurysms have in some studies been more persistent after treatment due to variations in metal coverage with changing vessel caliber and curvature.[20,31,41] Fusiform morphology was not a predictor of persistence in other studies with low attrition and long follow-up,[15] as it was in the present study, suggesting this may delay but not preclude occlusion. Other variables that were evaluated and found not to be predictors of aneurysm occlusion include device generation and aneurysm stasis on end-embolization angiography.

Because of the latent nature of cure in cases of flow diversion and because of the propensity for recurrence in cases of coiling and, to a lesser extent, microsurgery, it is difficult to directly compare occlusion outcomes achieved with the different modalities. Microsurgical clipping has been called a "definitive" treatment, but there are definite percentages of patients who 1) cannot undergo clipping and instead undergo wrapping, 2) have incomplete clipping with residual aneurysm, and 3) experience regrowth of their aneurysm after clipping. The rate of wrapping in recent surgical series ranges from 2.6% to 5.2%;[5,11,37] the rate of residual aneurysm after clipping ranges from 4.6% to 7.8%;[10,12] and the rate of regrowth ranges from 1.5% to 2.9%.[10,12] This implies a ceiling for durable, complete occlusion rates of 84%–91% in patients taken to the operating room for a craniotomy and surgical treatment. Recanalization after endovascular coiling is more accepted. Representative studies have estimated recanalization rates between 20% and 30% at 1–2 years for coiling,[16,39] slightly better for stent-assisted coiling with approximately 15% recanalization at 1 year.[28,45] Occlusion outcomes with flow diversion improve over time, as demonstrated by complete occlusion rates of 72%, 78%, and 87% at 6, 12, and 24 months, respectively, in the present study. Occlusion outcomes will continue to improve in this population, as they did in the PUFS cohort, which recently reported a 95% complete occlusion rate 5 years posttreatment.[2] Recurrence after documented occlusion has not been reported with flow diversion in the PUFS cohort or elsewhere.

This study is limited by its retrospective nature. It is a large but heterogeneous patient cohort and may be underpowered to detect differences in occlusion outcomes with certain aneurysm characteristics (e.g., large size, distal anterior circulation location, fusiform morphology) or treatment characteristics (e.g., multiple devices). Multivariate logistic regression for predictors of aneurysm occlusion was performed to account for treatment selection biases, both acknowledged and silent. Angiographic follow-up was incomplete, as expected for a tertiary referral center, but with DSA studies available in 91% of patients, it compared favorably to other published studies in the literature pertaining to flow diversion. There are multiple grading scales for occlusion after flow diversion,[36,42] and we used a modified version of the oldest.[34] While this may obscure external comparisons, it does not affect the internal validity and conclusions about predictors of aneurysm occlusion and persistence after flow diversion.

Conclusions

Aneurysm cure is a latent effect of endovascular treatment with flow diversion. Rigorous follow-up continues to characterize the types of aneurysms that respond best. Rates of occlusion after Pipeline embolization for anterior circulation aneurysms in this large single-institution study were high. Durable predictors of aneurysm persistence after flow diversion included increasing aneurysm size and aneurysms with an incorporated branch vessel, while adjunctive coiling predicted occlusion.

References

1. Attali J, Benaissa A, Soize S, Kadziolka K, Portefaix C, Pierot L: Follow-up of intracranial aneurysms treated by flow diverter: comparison of three-dimensional time-of-flight MR angiography (3D-TOF-MRA) and contrast-enhanced MR angiography (CE-MRA) sequences with digital subtraction angiography as the gold standard. **J Neurointerv Surg 8:**81–86, 2016
2. Becske T, Brinjikji W, Potts MB, Kallmes DF, Shapiro M, Moran CJ, et al: Long-term clinical and angiographic outcomes following Pipeline Embolization Device treatment of complex internal carotid artery aneurysms: five-year results of the Pipeline for Uncoilable or Failed Aneurysms trial. **Neurosurgery 80:**40–48, 2017
3. Becske T, Kallmes DF, Saatci I, McDougall CG, Szikora I, Lanzino G, et al: Pipeline for Uncoilable or Failed Aneurysms: results from a multicenter clinical trial. **Radiology 267:**858–868, 2013
4. Becske T, Potts MB, Shapiro M, Kallmes DF, Brinjikji W, Saatci I, et al: Pipeline for uncoilable or failed aneurysms: 3-year follow-up results. **J Neurosurg 127:**81–88, 2017
5. Beitzke M, Leber KA, Deutschmann H, Gattringer T, Poltrum B, Fazekas F: Cerebrovascular complications and granuloma formation after wrapping or coating of intracranial aneurysms with cotton gauze and human fibrin adhesives: results from a single-center patient series over a 5-year period. **J Neurosurg 119:**1009–1014, 2013
6. Bender MT, Lin LM, Colby GP, Lubelski D, Huang J, Tamargo RJ, et al: P2Y12 hyporesponse (PRU>200) is not associated with increased thromboembolic complications in anterior circulation Pipeline. **J Neurointerv Surg 9:**978–981, 2017
7. Briganti F, Napoli M, Leone G, Marseglia M, Mariniello G, Caranci F, et al: Treatment of intracranial aneurysms by flow diverter devices: long-term results from a single center. **Eur J Radiol 83:**1683–1690, 2014
8. Brinjikji W, Lanzino G, Cloft HJ, Siddiqui AH, Boccardi E, Cekirge S, et al: Risk factors for ischemic complications following Pipeline Embolization Device treatment of intracranial aneurysms: results from the IntrePED Study. **AJNR Am J Neuroradiol 37:**1673–1678, 2016
9. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF: Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. **Stroke 44:**442–447, 2013
10. Brown MA, Parish J, Guandique CF, Payner TD, Horner T, Leipzig T, et al: A long-term study of durability and risk factors for aneurysm recurrence after microsurgical clip ligation. **J Neurosurg 126:**819–824, 2017
11. Bruneau M, Amin-Hanjani S, Koroknay-Pal P, Bijlenga P, Jahromi BR, Lehto H, et al: Surgical clipping of very small unruptured intracranial aneurysms: a multicenter international study. **Neurosurgery 78:**47–52, 2016
12. Burkhardt JK, Chua MHJ, Weiss M, Do ASS, Winkler EA, Lawton MT: Risk of aneurysm residual regrowth, recurrence, and de novo aneurysm formation after microsurgical clip occlusion based on follow-up with catheter angiography. **World Neurosurg 106:**74–84, 2017
13. Chalouhi N, Tjoumakaris S, Phillips JLH, Starke RM, Hasan D, Wu C, et al: A single Pipeline Embolization Device is sufficient for treatment of intracranial aneurysms. **AJNR Am J Neuroradiol 35:**1562–1566, 2014
14. Chalouhi N, Zanaty M, Whiting A, Yang S, Tjoumakaris S, Hasan D, et al: Safety and efficacy of the Pipeline Embolization Device in 100 small intracranial aneurysms. **J Neurosurg 122:**1498–1502, 2015
15. Chiu AHY, Cheung AK, Wenderoth JD, De Villiers L, Rice H, Phatouros CC, et al: Long-term follow-up results following elective treatment of unruptured intracranial aneurysms with the Pipeline Embolization Device. **AJNR Am J Neuroradiol 36:**1728–1734, 2015
16. Choi DS, Kim MC, Lee SK, Willinsky RA, Terbrugge KG: Clinical and angiographic long-term follow-up of completely coiled intracranial aneurysms using endovascular technique. **J Neurosurg 112:**575–581, 2010
17. Colby GP, Bender MT, Lin LM, Beaty N, Caplan JM, Jiang B, et al: Declining complication rates with flow diversion of anterior circulation aneurysms after introduction of the Pipeline Flex: analysis of a single-institution series of 568 cases. **J Neurosurg** [epub ahead of print January 12, 2018. DOI: 10.3171/2017.7.JNS171289]
18. Colby GP, Lin LM, Gomez JF, Paul AR, Huang J, Tamargo RJ, et al: Immediate procedural outcomes in 35 consecutive pipeline embolization cases: a single-center, single-user experience. **J Neurointerv Surg 5:**237–246, 2013
19. Fischer S, Vajda Z, Aguilar Perez M, Schmid E, Hopf N, Bäzner H, et al: Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections. **Neuroradiology 54:**369–382, 2012
20. Jabbour P, Chalouhi N, Tjoumakaris S, Gonzalez LF, Dumont AS, Randazzo C, et al: The Pipeline Embolization Device: learning curve and predictors of complications and aneurysm obliteration. **Neurosurgery 73:**113–120, 2013
21. Kabbasch C, Mpotsaris A, Behme D, Dorn F, Stavrinou P, Liebig T: Pipeline embolization device for treatment of intracranial aneurysms—the more, the better? A single-center retrospective observational study. **J Vasc Interv Neurol 9:**14–20, 2016
22. Kallmes DF, Brinjikji W, Boccardi E, Ciceri E, Diaz O, Tawk R, et al: Aneurysm Study of Pipeline in an Observational Registry (ASPIRe). **Intervent Neurol 5:**89–99, 2016
23. Kallmes DF, Brinjikji W, Cekirge S, Fiorella D, Hanel RA, Jabbour P, et al: Safety and efficacy of the Pipeline embolization device for treatment of intracranial aneurysms: a pooled analysis of 3 large studies. **J Neurosurg 127:**775–780, 2017
24. Kan P, Srinivasan VM, Mbabuike N, Tawk RG, Ban VS, Welch BG, et al: Aneurysms with persistent patency after treatment with the Pipeline Embolization Device. **J Neurosurg 126:**1894–1898, 2017
25. Lin LM, Colby GP, Kim JE, Huang J, Tamargo RJ, Coon AL: Immediate and follow-up results for 44 consecutive cases of small (<10 mm) internal carotid artery aneurysms treated with the pipeline embolization device. **Surg Neurol Int 4:**114, 2013
26. Lin N, Brouillard AM, Krishna C, Mokin M, Natarajan SK, Sonig A, et al: Use of coils in conjunction with the Pipeline embolization device for treatment of intracranial aneurysms. **Neurosurgery 76:**142–149, 2015
27. Lin N, Lanzino G, Lopes DK, Arthur AS, Ogilvy CS, Ecker RD, et al: Treatment of distal anterior circulation aneurysms with the pipeline embolization device: a US multicenter experience. **Neurosurgery 79:**14–22, 2016

28. Linzey JR, Griauzde J, Guan Z, Bentley N, Gemmete JJ, Chaudhary N, et al: Stent-assisted coiling of cerebrovascular aneurysms: experience at a large tertiary care center with a focus on predictors of recurrence. **J Neurointerv Surg 9:**1081–1085, 2017
29. Lylyk P, Miranda C, Ceratto R, Ferrario A, Scrivano E, Luna HR, et al: Curative endovascular reconstruction of cerebral aneurysms with the Pipeline embolization device: the Buenos Aires experience. **Neurosurgery 64:**632–643, N6, 2009
30. McAuliffe W, Wycoco V, Rice H, Phatouros C, Singh TJ, Wenderoth J: Immediate and midterm results following treatment of unruptured intracranial aneurysms with the Pipeline Embolization Device. **AJNR Am J Neuroradiol 33:**164–170, 2012
31. Monteith SJ, Tsimpas A, Dumont AS, Tjoumakaris S, Gonzalez LF, Rosenwasser RH, et al: Endovascular treatment of fusiform cerebral aneurysms with the Pipeline Embolization Device. **J Neurosurg 120:**945–954, 2014
32. Moshayedi H, Omofoye OA, Yap E, Oyekunle TO, Sasaki-Adams DM, Solander SY: Factors affecting the obliteration rate of intracranial aneurysms treated with a single Pipeline embolization device. **World Neurosurg 104:**205–212, 2017
33. Nossek E, Chalif DJ, Chakraborty S, Lombardo K, Black KS, Setton A: Concurrent use of the Pipeline Embolization Device and coils for intracranial aneurysms: technique, safety, and efficacy. **J Neurosurg 122:**904–911, 2015
34. O'Kelly CJ, Krings T, Fiorella D, Marotta TR: A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents. **Interv Neuroradiol 16:**133–137, 2010
35. O'Kelly CJ, Spears J, Chow M, Wong J, Boulton M, Weill A, et al: Canadian experience with the Pipeline embolization device for repair of unruptured intracranial aneurysms. **AJNR Am J Neuroradiol 34:**381–387, 2013
36. Park MS, Mazur MD, Moon K, Nanaszko MJ, Kestle JRW, Shah LM, et al: An outcomes-based grading scale for the evaluation of cerebral aneurysms treated with flow diversion. **J Neurointerv Surg 9:**1060–1063, 2017
37. Perrini P, Montemurro N, Caniglia M, Lazzarotti G, Benedetto N: Wrapping of intracranial aneurysms: single-center series and systematic review of the literature. **Br J Neurosurg 29:**785–791, 2015
38. Puffer RC, Piano M, Lanzino G, Valvassori L, Kallmes DF, Quilici L, et al: Treatment of cavernous sinus aneurysms with flow diversion: results in 44 patients. **AJNR Am J Neuroradiol 35:**948–951, 2014
39. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, et al: Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. **Stroke 34:**1398–1403, 2003
40. Saatci I, Yavuz K, Ozer C, Geyik S, Cekirge HS: Treatment of intracranial aneurysms using the Pipeline flow-diverter embolization device: a single-center experience with long-term follow-up results. **AJNR Am J Neuroradiol 33:**1436–1446, 2012
41. Shapiro M, Becske T, Nelson PK: Learning from failure: persistence of aneurysms following pipeline embolization. **J Neurosurg 126:**578–585, 2017
42. Suh SH, Cloft HJ, Lanzino G, Woodward K, Kallmes DF: Interobserver agreement after Pipeline embolization device implantation. **AJNR Am J Neuroradiol 34:**1215–1218, 2013
43. Tsang ACO, Fung AMY, Tsang FCP, Leung GKK, Lee R, Lui WM: Failure of flow diverter treatment of intracranial aneurysms related to the fetal-type posterior communicating artery. **Neurointervention 10:**60–66, 2015
44. Yu SC, Kwok CK, Cheng PW, Chan KY, Lau SS, Lui WM, et al: Intracranial aneurysms: midterm outcome of pipeline embolization device—a prospective study in 143 patients with 178 aneurysms. **Radiology 265:**893–901, 2012
45. Zheng Y, Song Y, Liu Y, Xu Q, Tian Y, Leng B: Stent-assisted coiling of 501 wide-necked intracranial aneurysms: a single-center 8-year experience. **World Neurosurg 94:**285–295, 2016

Disclosures

A.L.C. is a consultant and proctor for Medtronic, Stryker, Microvention, and Sequent and is a consultant for InNeruroCo. G.P.C. receives research support from Medtronic and Stryker and is a consultant for Microvention. L.M.L. receives research support from Microvention and Stryker and is a consultant for Medtronic. J.H. owns stock in LONGEVITI.

Author Contributions

Conception and design: Bender, Colby. Acquisition of data: Coon, Bender, Colby, Jiang, Westbroek, Xu, Campos. Analysis and interpretation of data: Bender, Colby, Jiang. Drafting the article: Coon, Bender, Jiang. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bender. Statistical analysis: Bender.

Supplemental Information

Previous Presentations

Portions of the work were presented in abstract form at the Congress of Neurological Surgeons Annual Meeting, Boston, MA, October 7–11, 2017.

Correspondence

Alexander Coon: Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore, MD. acoon2@jhmi.edu.