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

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OBJECTIVE The second-generation Pipeline embolization device (PED), Flex, has several design upgrades, including improved opening and the ability to be resheathed, in comparison with the original device (PED classic). The authors hypothesized that Flex is associated with a lower rate of major complications.

METHODS A prospective, IRB-approved, single-institution database was analyzed for all patients with anterior circulation aneurysms treated by flow diversion. The PED classic was used from August 2011 to January 2015, and the Pipeline Flex has been used since February 2015.

RESULTS A total of 568 PED procedures (252 classic and 316 Flex) were performed for anterior circulation aneurysms. The average aneurysm size was 6.8 mm. Patients undergoing treatment with the Flex device had smaller aneurysms (p = 0.006) and were more likely to have undergone previous treatments (p = 0.001). Most aneurysms originated along the internal carotid artery (89% classic and 75% Flex) but there were more anterior cerebral artery (18%) and middle cerebral artery (7%) deployments with Flex (p = 0.001). Procedural success was achieved in 96% of classic and 98% of Flex cases (p = 0.078). Major morbidity or death occurred in 3.5% of cases overall: 5.6% of classic cases, and 1.9% of Flex cases (p = 0.019). On multivariate logistic regression, predictors of major complications were in situ thrombosis (OR 4.3, p = 0.006), classic as opposed to Flex device (OR 3.7, p = 0.008), and device deployment in the anterior cerebral artery or middle cerebral artery as opposed to the internal carotid artery (OR 3.5, p = 0.034).

CONCLUSIONS Flow diversion of anterior circulation cerebral aneurysms is associated with an overall low rate of major complications. The complication rate is significantly lower since the introduction of the second-generation PED (Flex).

KEY WORDS cerebral aneurysm; Pipeline embolization; flow diversion; vascular disorders

Since its approval in Europe in 2009 and the United States in 2011, the Pipeline embolization device (PED; Medtronic) has been a breakthrough technology for the treatment of large, proximal carotid artery aneurysms as well as a broad range of small, distal anterior circulation and posterior circulation aneurysms. The second-generation device, the Pipeline Flex, received US FDA approval in 2015. This device has the same stent technology as the Pipeline classic, but the delivery system has been overhauled, allowing for resheathing, enhanced opening, and improved navigability. Reduced procedural time and radiation exposure have been demonstrated with the PED Flex. We hypothesized that the enhanced delivery system of PED Flex has also resulted in a signifi-
cant reduction in clinical adverse events. This is a retrospec-
tive series of all 568 anterior circulation aneurysms that were treated with Pipeline devices at Johns Hopkins
Medicine from 2011 to 2016 to assess procedural out-
comes, complications, and predictors thereof.

Methods

This was a retrospective cohort study from an institu-
tional review board–approved, prospectively collected da-
base of patients with aneurysms that were treated at a
tertiary medical center. All patients who underwent PED
placement for anterior circulation aneurysms between Au-
 gust 2011 and December 2016 were included in this study.
Patient consent was not required, as data are collected in
a de-identified manner on routine clinical practice at our
institution. Patients were started on a regimen of dual anti-
platelet therapy 7 days before their procedure. Assessment
of P2Y12 response (VerifyNow, Accumetrics) was per-
formed on a case-by-case basis, with increased frequency
after January 1, 2014, although still representing a minor-
ity of patients. Clinical signs of hyperresponse (e.g., sig-
nificant extremity bruising, bleeding gums, spontaneous
epistaxis) occasionally led to medication dose adjustment
and procedural rescheduling, with or without a confirmatory
low P2Y12 value. No action was taken for patients
with elevated P2Y12 reaction units (PRU; > 200). The
first-generation PED (PED classic) was used from August
2011 through January 2015, and the PED Flex was used in
all subsequent cases. PED placement was performed as previously described9 through an 8-Fr femoral sheath and
a triaxial system that consisted of a long guide sheath, dis-
tal access catheter, and 0.027-inch microcatheter. The
guide sheaths included the Flexor Shuttle guiding sheath
(0.087-inch inner diameter; Cook Medical), Neuron MAX
(0.088-inch inner diameter; Penumbra), and AXS Infinity
(0.088-inch inner diameter; Stryker Neurovascular). The
distal intracranial catheter included the Navien (0.058-
inch inner diameter; Medtronic), AXS Catalyst 5 (Cat5;
Stryker Neurovascular), and an intermediate catheter
(0.060-inch inner diameter; InNeuroCo). The microcath-
eters used included the Marksman (Medtronic) and Via27
(Sequent Medical/MicroVention Terumo Corp.). Patients
recovered in the neurocritical care unit and were typically
discharged home on postprocedure day 1. Demographic
information, clinical history, and outcomes were collected
from medical records. Anatomical and technical details
were collected from angiograms and operative reports
through March 2017. Major stroke was defined as a change
in the National Institutes of Health Stroke Scale score of
greater than 4 lasting more than 7 days; minor stroke was
a change in score of 4 or lower lasting fewer than 7 days
with corroborative imaging; and transient ischemic attack
(TIA) was a transient neurological deficit without corrobo-
rate imaging.

Statistical Analysis

Data are presented as means with SD and ranges for
continuous variables and as frequency for categorical vari-
ables. Univariate analysis was carried out using unpaired
t-tests and ANOVA tests. Bivariate logistic regression was
used to test covariates predictive of major complications
along with device type. Factors predictive at a level of p
< 0.2 were then evaluated by multivariate logistic regres-
sion. A threshold of p < 0.05 was used to determine sig-
nificance. Statistical analysis was performed using Stata
(version 14.0, StataCorp).

Results

A total of 568 procedures were performed in 494 pa-
tients (252 classic and 316 Flex cases). Overall, the aver-
age patient age was 56.3 years, and patients in 82% of the
cases were female. The average aneurysm size was 6.8
mm, and 79% of aneurysms were smaller than 10 mm. A
minority of patients had prior subarachnoid hemorrhage
(SAH; 15%), and a minority of aneurysms had been previ-
ously treated (18%). Patients treated with PED Flex were
younger (p = 0.004), had smaller aneurysms (p = 0.006),
and were more likely to have undergone previous treat-
ment, most commonly coiling (p = 0.001). Patients un-
dergoing PED classic were more likely to have cervical
internal carotid artery (ICA) tortuosity (p < 0.001), but the
2 groups had similar aortic and cavernous ICA anatomy
(Table 1).

With both PED classic and Flex, a majority of treated
aneurysms (89% and 75%, respectively) originated from
the ICA; however, there was an increasing percentage of
anterior cerebral artery (ACA; 18%) and middle cerebral
artery (MCA; 7%) aneurysms that were treated with PED
Flex (p = 0.001) (Table 2).

Procedural success was achieved in a greater percent-
age of PED Flex (98%) than PED classic (96%) cases,
although this was not statistically significant (p = 0.078).
PED Flex procedures required less fluoroscopy time (p <
0.001) and radiation exposure (p < 0.001), despite the fact
that more devices were used on average (p = 0.006). There
was a reduction in device removal with PED Flex (p <
0.001). Prophylactic intraarterial verapamil was used more
commonly with Pipeline Flex, as these devices were de-
ployed in a more distal circulation (p < 0.001). A trend to-
ward more adjunctive coiling with Flex (9%) as compared
with classic (6%) did not reach statistical significance (p
= 0.105). There were similar rates of balloon angioplasty
(13%) and stent thrombosis (4%), and 1 instance of wire
perforation (0.4%) with each device generation (Table 3).

The overall average length of stay was 2.3 days, and
94% of patients were discharged to home or to their pri-
or level of care (Table 4). The mean follow-up was 11.6
months with a median of 9.4 months. The overall rate of
major complications (encompassing major stroke, intra-
cranial hemorrhage [ICH], SAH, and mortality) was 3.5%
and was lower for PED Flex (1.9%) than for PED classi-
cic (5.6%) (p = 0.019). For PED classic, the rates of major
stroke, ICH, SAH, and mortality were 2.0%, 2.4%, 1.2%,
and 1.6%, respectively. For PED Flex, the rates were 0.3%,
1.3%, 0.3%, and 0.6%, respectively. There were no statisti-
cally significant differences by device generation for any
of these major complication subtypes when considered in-
dividually. Minor complications (encompassing TIA, mi-
nor stroke, exacerbation of cranial nerve palsy, iatrogenic
dissection without neurological deficit, groin hematoma,
and groin infection) were similar for the 2 generations of Pipeline device (p = 0.083).

Multivariate logistic regression was performed to identify predictors of major complications. Predictors of major complication were in situ thrombosis (OR 4.3, p = 0.006), PED classic as opposed to Flex device (OR 3.7, p = 0.008), and device deployment in the ACA or MCA as opposed to the ICA (OR 3.5, p = 0.034) (Table 5). Notable variables that were not predictive of major complication included aneurysm size, morphology, prior treatment, adjunctive coiling, balloon angioplasty, catheter technology, and anatomical features, including cervical tortuosity and high-grade cavernous anatomy.

**Discussion**

In this series of 494 patients who underwent 568 Pipeline procedures (252 PED classic and 316 PED Flex) for anterior circulation cerebral aneurysms over a 5-year period (2011–2016), there was a high rate of procedural success (97%) and low overall rate of major complications (3.5%), including major stroke, SAH, ICH, and mortality. Compared with the PED classic, Flex was associated with a higher rate of procedural success, less radiation, and a reduced rate of major complications (< 2%), which persisted on multivariate logistic regression after accounting for procedural and patient differences.

The types of aneurysms being treated with PEDs have changed since their introduction; initial success with large proximal carotid artery aneurysms gave way to treatment of small carotid artery aneurysms and finally to more distal anterior circulation aneurysms. This 5-year study incorporates all of these time points, and the outcomes compare favorably with those of published studies that include aneurysms of each type.

**Early prospective studies of PEDs** showed higher complication rates in a population of larger aneurysms. The major complication rate in the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial was 5.6%, with a mortality

**TABLE 1. Demographics and anatomy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>p</th>
<th>Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of cases</td>
<td>252</td>
<td></td>
<td>316</td>
<td></td>
</tr>
<tr>
<td>Age in yrs</td>
<td>54.6 ± 13.2</td>
<td>0.004</td>
<td>57.7 ± 12.3</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>20–88</td>
<td></td>
<td>21–86</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>210 (83.3)</td>
<td></td>
<td>258 (81.6)</td>
<td></td>
</tr>
<tr>
<td>Size in mm</td>
<td>7.4 ± 5.0</td>
<td>0.006</td>
<td>6.3 ± 5.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Range</td>
<td>1–25</td>
<td></td>
<td>1–37</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>185 (73.4)</td>
<td></td>
<td>265 (83.9)</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>66 (26.2)</td>
<td></td>
<td>46 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Giant</td>
<td>1 (0.4)</td>
<td>0.601</td>
<td>5 (1.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior SAH</td>
<td>28 (11.1)</td>
<td>0.002</td>
<td>55 (17.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Previous treatment</td>
<td>31 (12.3)</td>
<td>0.001</td>
<td>71 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Clip</td>
<td>11 (4.4)</td>
<td></td>
<td>13 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Coi</td>
<td>18 (7.1)</td>
<td>0.006</td>
<td>48 (15.2)</td>
<td>0.062</td>
</tr>
<tr>
<td>Flow diversion</td>
<td>2 (0.8)</td>
<td>12 (2.1)</td>
<td>10 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Significant cervical</td>
<td>113 (44.8)</td>
<td>0.000</td>
<td>85 (26.9)</td>
<td></td>
</tr>
<tr>
<td>ICA tortuosity</td>
<td></td>
<td></td>
<td>198 (34.9)</td>
<td></td>
</tr>
<tr>
<td>Cavernous ICA typea</td>
<td></td>
<td>0.062</td>
<td>Ia</td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>42 (16.7)</td>
<td></td>
<td>64 (20.3)</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>72 (28.6)</td>
<td></td>
<td>98 (31.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>44 (17.5)</td>
<td></td>
<td>62 (19.6)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>63 (25.0)</td>
<td></td>
<td>65 (20.6)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>29 (11.5)</td>
<td>0.851</td>
<td>27 (8.5)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>2 (0.8)</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Aortic arch type†</td>
<td>0.006</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45 (17.9)</td>
<td></td>
<td>27 (8.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>71 (28.2)</td>
<td></td>
<td>41 (13.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (6.7)</td>
<td></td>
<td>8 (2.5)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>119 (47.2)</td>
<td></td>
<td>240 (75.9)</td>
<td></td>
</tr>
<tr>
<td>NA = not available.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Values are presented as the number of aneurysms (%) unless stated otherwise. * Type I, mild tortuosity; types II and III, moderate tortuosity; and type IV, severe tortuosity. For more information, refer to Lin LM, Colby GP, Jiang B, et al: Classification of cavernous internal carotid artery tortuosity: a predictor of procedural complexity in Pipeline embolization. J Neurointerv Surg 7:628–633, 2015. † Type 1, great vessels originate at the same level as the upper convexity; type 2, great vessels originate between the upper and lower convexities; and type 3, great vessels originate below the lower convexity.

**TABLE 2. Aneurysm location**

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Classic</td>
</tr>
<tr>
<td>ICA</td>
<td>228 (89.1)</td>
</tr>
<tr>
<td>Cervical</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Petrous</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Cavernous</td>
<td>38 (14.8)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>50 (19.5)</td>
</tr>
<tr>
<td>Paraophthalmic</td>
<td>94 (36.7)</td>
</tr>
<tr>
<td>Superior hypophyseal</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Posterior communicating</td>
<td>13 (5.1)</td>
</tr>
<tr>
<td>Anterior choroidal</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Clinaloid</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td>Supraclinoid</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Termination</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>ACA</td>
<td>23 (9.0)</td>
</tr>
<tr>
<td>A1</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>A1/A2</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td>Anterior communicating</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td>A1/A2</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>A4</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>MCA</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>M1</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>M2</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Distal</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
rate of 1.9%, but the mean aneurysm size was 18 mm, and 20% of aneurysms were ≥ 25 mm. Similarly, the ASPIRe (Aneurysm Study of Pipeline in an Observational Registry) reported major morbidity of 6.8% and mortality of 1.6% among 191 on-label PED treatments for aneurysms with an average size of 14.5 mm. By comparison, the major complication rate in this study was 3.5% with a mortality rate of 1.1%. The paucity of giant aneurysms (1%) in the present study may limit direct comparisons to these early series, but within a population of small and large aneurysms, it is noteworthy that size was not a predictor of major complications. This corroborates the findings of the International Retrospective Study of the Pipeline Embolization Device (IntrePED), in which neurological morbidity and mortality was comparable for small (5%) and large (9%) anterior circulation aneurysms but was much higher for giant aneurysms (23%).

The rate of major complications in this series also compares favorably to that of other series reporting on PEDs for small, predominantly ICA aneurysms. Among 294 patients included in IntrePED with anterior circulation aneurysms smaller than 10 mm, the reported rates of ICH (2.0%), stroke (2.7%), major morbidity (4.5%), and neurological mortality (1.4%) were all higher than rates of similar complications observed in the current series. Likewise, in a prospective series of 145 patients from Hong Kong with an average aneurysm size of 7 mm and 97% anterior circulation aneurysms, the major complication rate was 4.9%, and the mortality rate was 1.4%. Complication rates similar to those in the present series have been reported in some studies of small aneurysms, albeit predominantly in the proximal ICA. Griesenauer and colleagues observed symptomatic complications in 6% and a modified Rankin Scale score greater than 2 in 4% of electively treated patients in a study of 117 patients who underwent PED for aneurysms ≤ 7 mm, of which 90% were located along the ICA. Chalouhi et al. reported 2% stroke and 1% ICH rates in 100 aneurysms smaller than 7 mm that were treated with PEDs, 92% of which were located along the ICA.

Major complication rates in this series remained low, despite treatment in locations that were more distal than the locations in other series of small aneurysms. In this series, 19% of PEDs were deployed in either the ACA or MCA where the risk of stroke is thought to be higher due to the necessity of covering perforating arteries or branches supplying a terminal circulation. Briganti et al. reported 2% stroke and 1% ICH rates in 100 aneurysms smaller than 7 mm that were treated with PEDs, 92% of which were located along the ICA.

TABLE 3. Procedural outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural success</td>
<td>242 (96.0)</td>
<td>311 (98.4)</td>
</tr>
<tr>
<td>Total fluoroscopy time in mins</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Radiation exposure in mGy</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No. of PEDs</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Adjunct coil deployment</td>
<td>14 (5.6)</td>
<td>29 (9.2)</td>
</tr>
<tr>
<td>Spasm (vera-plasty)</td>
<td>11 (4.4)</td>
<td>53 (16.8)</td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>25 (9.9)</td>
<td>47 (14.9)</td>
</tr>
<tr>
<td>PED thrombosis</td>
<td>6 (2.4)</td>
<td>17 (5.4)</td>
</tr>
<tr>
<td>Wire perforation</td>
<td>1 (0.4)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>PED cork/removal</td>
<td>38 (15.1)</td>
<td>8 (2.5)</td>
</tr>
</tbody>
</table>

Values are presented as the number of aneurysms (%) unless stated otherwise.

TABLE 4. Clinical outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS in days</td>
<td>2.60 ± 4.8</td>
<td>2.01 ± 3.3</td>
</tr>
<tr>
<td>Range</td>
<td>1–48</td>
<td>1–30</td>
</tr>
<tr>
<td>Discharge POD 1</td>
<td>158 (62.7)</td>
<td>235 (74.4)</td>
</tr>
<tr>
<td>Discharge home/prior level of care</td>
<td>236 (93.7)</td>
<td>300 (94.9)</td>
</tr>
<tr>
<td>Major complication</td>
<td>14 (5.6)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Minor complication</td>
<td>28 (11.1)</td>
<td>22 (7.0)</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (1.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>2 (0.8)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>5 (2.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>ICH</td>
<td>6 (2.4)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>SAH</td>
<td>3 (1.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Transient deficit</td>
<td>3 (1.2)</td>
<td>10 (3.2)</td>
</tr>
<tr>
<td>CN palsy</td>
<td>7 (2.8)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Intracranial dissection</td>
<td>0 (0.0)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>13 (5.2)</td>
<td>7 (2.2)</td>
</tr>
<tr>
<td>Groin infection</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

CN = cranial nerve; LOS = length of stay; POD = postoperative day.
Values are presented as the number of aneurysms (%) unless stated otherwise.
just 10 cases; however, we have had high occlusion rates and low complication rates using PED to treat uncoilable anterior communicating artery–region aneurysms. Given the anatomical challenges, it was not surprising that these more distal anterior circulation deployments were a predictor of major complications in this study, although the presence of more such treatments did not undermine the overall excellent results.

There was a significant reduction in the major complication rate from 5.6% to 1.9% with the transition from the Pipeline classic to the Flex in February 2015. While possible alternative explanations exist and will be addressed, we attribute this improvement primarily to the ease of using the newer generation device. As detailed elsewhere, the implant with PED Flex is the same as PED classic, but the delivery system was completely redesigned. The first modification is that the proximal end of the PED Flex was mounted on a pad that allows resheathing when up to 90% of the device is deployed. The authors of an early experience with Flex noted the use of resheathing for 18 of 39 devices (46%) to promote distal opening, to improve apposition, or to reposition the device with no associated dissection, perforation, or thromboembolic events. The second modification is that a stiffer stainless steel pusher wire was introduced to navigate tortuosity and facilitate retracking of the microcatheter. As noted in our initial report on 44 PED Flex cases, this facilitates bumping the device with the microcatheter or intermediate catheter to improve apposition and preserves access in situations in which additional devices or manipulation is needed. The third modification, at the distal end of the delivery system, was the abandonment of the capture coil in favor of Teflon sleeves and the addition of an angled-tip coil. This eliminates the need for torque to release the device and softens

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**TABLE 5. Logistic regression predictors of major complications**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Bivariate</th>
<th></th>
<th></th>
<th>p Value</th>
<th></th>
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<th>p Value</th>
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<td></td>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
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<tr>
<td></td>
<td>OR</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td>p Value</td>
<td>OR</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td>p Value</td>
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<td>Age</td>
<td>1.039</td>
<td>1.002</td>
<td>1.078</td>
<td>0.040</td>
<td>1.024</td>
<td>0.973</td>
<td>1.078</td>
<td>0.363</td>
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<td>Sex</td>
<td>0.524</td>
<td>0.119</td>
<td>2.291</td>
<td>0.391</td>
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<td></td>
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<tr>
<td>Race</td>
<td>White (ref)</td>
<td>1.922</td>
<td>0.686</td>
<td>5.385</td>
<td>0.214</td>
<td>1.922</td>
<td>0.686</td>
<td>5.385</td>
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<tr>
<td></td>
<td>Black</td>
<td>2.155</td>
<td>0.857</td>
<td>5.422</td>
<td>0.103</td>
<td>2.347</td>
<td>0.831</td>
<td>6.628</td>
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<td></td>
<td>Other</td>
<td>0.593</td>
<td>0.074</td>
<td>4.757</td>
<td>0.623</td>
<td>0.680</td>
<td>0.077</td>
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<td>History of SAH</td>
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<td>0.541</td>
<td>5.887</td>
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<td>1.317</td>
<td>0.462</td>
<td>3.748</td>
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<td>Previously treated</td>
<td>1.922</td>
<td>0.686</td>
<td>5.385</td>
<td>0.214</td>
<td>1.922</td>
<td>0.686</td>
<td>5.385</td>
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<tr>
<td></td>
<td>Aneurysm size (mm)</td>
<td>0.682</td>
<td>0.246</td>
<td>1.894</td>
<td>0.463</td>
<td>0.682</td>
<td>0.246</td>
<td>1.894</td>
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<tr>
<td></td>
<td>Size (small vs large/giant)</td>
<td>0.806</td>
<td>0.261</td>
<td>2.486</td>
<td>0.708</td>
<td>0.806</td>
<td>0.261</td>
<td>2.486</td>
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<td>ACA/MCA aneurysm</td>
<td>2.618</td>
<td>0.956</td>
<td>7.172</td>
<td>0.061</td>
<td>3.515</td>
<td>1.102</td>
<td>11.214</td>
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<td>Saccular aneurysm</td>
<td>0.675</td>
<td>0.154</td>
<td>2.962</td>
<td>0.602</td>
<td>0.675</td>
<td>0.154</td>
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<td>Classic device</td>
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<td>Fluoroscopy time (mins)</td>
<td>1.019</td>
<td>0.883</td>
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<td>0.799</td>
<td>1.019</td>
<td>0.883</td>
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<td>Radiation exposure (mGy)</td>
<td>1.062</td>
<td>0.684</td>
<td>1.650</td>
<td>0.788</td>
<td>1.062</td>
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<td>1.650</td>
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<td>Coiling</td>
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<td>0.094</td>
<td>5.670</td>
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<td>0.731</td>
<td>0.094</td>
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<td>0 (ref)*</td>
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<td>Infinity guide sheath</td>
<td>1.323</td>
<td>0.237</td>
<td>7.370</td>
<td>0.749</td>
<td>1.323</td>
<td>0.237</td>
<td>7.370</td>
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<td>CaTi distal intracranial catheter</td>
<td>1.138</td>
<td>0.226</td>
<td>5.734</td>
<td>0.876</td>
<td>1.138</td>
<td>0.226</td>
<td>5.734</td>
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<td>Via27 microcatheter</td>
<td>0.823</td>
<td>0.163</td>
<td>4.150</td>
<td>0.814</td>
<td>0.823</td>
<td>0.163</td>
<td>4.150</td>
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<td>Cervical ICA tortuosity</td>
<td>2.460</td>
<td>0.966</td>
<td>6.270</td>
<td>0.059</td>
<td>1.653</td>
<td>0.649</td>
<td>4.201</td>
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<td>Type III/IV cavernous ICA</td>
<td>1.034</td>
<td>0.401</td>
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<td>0.946</td>
<td>1.034</td>
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<td>Verapamil infusion</td>
<td>1.290</td>
<td>0.300</td>
<td>5.552</td>
<td>0.732</td>
<td>1.290</td>
<td>0.300</td>
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<td>Balloon angioplasty</td>
<td>2.689</td>
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<td>Pipeline removal/cork</td>
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<td>0.170</td>
<td>4.358</td>
<td>0.856</td>
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<td>In situ thrombosis</td>
<td>4.175</td>
<td>1.774</td>
<td>9.824</td>
<td>0.001</td>
<td>4.307</td>
<td>1.527</td>
<td>12.149</td>
</tr>
</tbody>
</table>

* Unavailable for review.
the tip of the delivery system to reduce the risk of dissec-
tion or perforation, although some have found it difficult
to recapture.22

These delivery system improvements have led to shorter
procedure times, but previous series were underpowered
to show improved safety. Le and colleagues compared
58 PED classic procedures with 38 Flex procedures and
saw statistically significant reductions in fluoroscopy time,
radiation exposure, and device deployment failure asso-
ciated with Flex, all of which were also observed in the
present study.16 In that series, the rate of permanent neu-
rological morbidity was 3.4% in the classic group and 0%
in the Flex group, but this difference was not significant.

The limited number of major complications described in
other reports of Flex appears to be related to the stent or
clinical scenario rather than the delivery system. Two
symptomatic anterior choroidal artery strokes in the first
30 Flex cases (6.6%) performed by Martínez-Galdámez
and colleagues both occurred in large aneurysms treated
with overlapping devices, which are known to be associ-
ated with higher risk.20 The one major complication in our
initial 44 cases (2.3%) was a stroke secondary to device
thrombosis in a patient who was noncompliant with pre-
scribed antiplatelet agents.8 The current study includes
568 total procedures (252 classic and 316 Flex), and on
multivariate logistic regression, Pipeline device generation
(in addition to intraprocedural stent thrombosis) was one
of the 2 most significant predictors of major complication.

There are possible alternative explanations for the dif-
fERENCE in complication rates that were observed in this
study—including an evolving patient population, impro-
ving catheter technology, and the user experience curve—all
doing of which, we believe, are secondary to the delivery system
improvements with Pipeline Flex. First, our practice has
evolved over time, and the patient population and type of
aneurysm treated have changed in subtle but significant ways. Patients treated with Flex were more likely to have recurrent aneurysms or aneurysms along the ACA or MCA, adding complexity to these cases. Patients treated with Flex were also younger, had smaller aneurysms, and had less
cervical tortuosity, all potentially reducing the complexity
of these cases. We performed a multivariate logistic regres-
sion accounting for these differences, and the device type
remained the strongest predictor of major complications.

A second alternative explanation is that just as the Pipe-
line device has been updated, catheter technology has
evolved and improved during the 5 years we have been us-
ing Pipeline. Our traditional triaxial setup, including the
Flexor Shuttle or Neuron MAX guide sheath, Navien dis-
tal intracranial catheter, and Marksman microcatheter, was
used for more than 95% of Pipeline classic cases. Alter-
natively, the Cat5 distal intracranial catheter was used for
48% of Flex procedures for its improved trackability and
stability.10 We have also come to favor the Via27 micro-
catheter for its resheathing ability and pushability and have
used it for 56% of Flex cases.17 These enhancements ap-
pear incremental, and no catheter was a significant predic-
tor of complications on bivariate or multivariate analysis.

A third alternative explanation for the observed differ-
cences in complication rates between Flex and classic de-
VICES is the existence of a learning curve, both in terms of
technical skill and case selection, that favored the newer
device. Jabbour and colleagues sought to demonstrate this
learning curve in their 109 patients treated with PEDs in
whom they observed a complication rate of 16.2% in the
first third and 5.6% in the final third.13 There were oth-
er differences between the groups, however, including a
reduction in the number of devices used for each proce-
dure, and “experience” was not a significant predictor of
complications on multivariate analysis. In a prospective,
consecutive series of 100 patients, Burrows and colleagues
failed to see a reduction in complications over time as they
surmounted the learning curve.5 They theorized that this
might be due to increased off-label treatments but provid-
ed limited information about the patients and aneurysms
treated. In that series, periprocedural technical events, such
as device migration or incomplete expansion, and transient
clinical events, such as stent thrombosis or worsening cra-
nial nerve palsy, were observed in a constant one-third of
patients over time.5 Attempting to account for the learning
curve, we repeated the multivariate analysis for predictors
of major complications while excluding the first 20 proce-
dures with each device type for each attending neurosur-
geon, and Pipeline classic remained a significant predictor
and the strongest predictor of major complications.

Increased awareness of variability in the response to
Plavix has led many interventionists to manipulate anti-
platelet medications to achieve a goal P2Y12 level, which
some have ventured explains lower complication rates in
recent PED series.11 Our approach to antiplatelet therapy,
however, did not change over the course of this study. Hy-
perresponse could lead to procedural rescheduling but has
always been primarily assessed clinically. We take no ac-
tion for a hyperresponse to Plavix (PRU > 200) and have
seen excellent outcomes in this population.2

The retrospective, nonrandomized nature of this study is
its main limitation and drives these differences in pa-
ient population, catheter technology, and operator experi-
ence. In addition, there is variability within the Pipeline
literature in how major complications are defined. For
instance, the primary end point of PUFs was major ipsilat-
ellateral stroke or neurological death, which excluded some
instances of hemorrhage, stroke, and fistula development
that were not associated with a decline in the modified
Rankin Scale score.1 IntrePED, on the other hand, distin-
guished between major and minor complications by the
persistence of symptoms beyond 7 days.15 We adhere more
closely to the latter definition. While this may muddy ex-
ternal comparisons, it does not affect internal validity or
alter the conclusion that Flex is associated with fewer com-
plications than Pipeline classic.

Conclusions

The type of anterior circulation aneurysms being treated
with flow diversion has evolved over time from primarily
large proximal carotid artery aneurysms to small carotid
artery aneurysms to more distal anterior circulation aneu-ysms. This study demonstrates that flow diversion can
be performed safely for a wide variety of anterior circulation
aneurysms with a low rate of major complications. The
introduction of Pipeline Flex was associated with a reduc-
tion in the risk of major complications, which persists on multivariate analysis.

References


Disclosures

Dr. Colby: consultant for MicroVention; and research support from and participant in clinical trials for Medtronic and Stryker. Dr. Lin: consultant for Medtronic Neurovascular; and receives research support from MicroVention and Stryker. Dr. Huang: ownership in Longeviti. Dr. Coon: consultant and proctor for Stryker Neurovascular, Medtronic, and MicroVention.

Author Contributions

Conception and design: Coon, Colby, Bender, Huang, Tamargo. Acquisition of data: Coon, Colby, Bender, Jiang, Westbrook, Varjavand, Campos. Analysis and interpretation of data: Coon, Colby, Bender, Lin, Beatty, Caplan, Jiang, Westbrook, Varjavand, Campos. Drafting the article: Coon, Colby, Bender, Lin, Beatty, Caplan, Jiang, Westbrook, Campos, Huang, Tamargo. Critically revising the article: Coon, Colby, Bender, Lin, Beatty, Caplan, Jiang, Westbrook, Campos, Huang, Tamargo. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Coon. Statistical analysis: Colby, Bender, Varjavand. Study supervision: Tamargo.

Supplemental Information

Previous Presentations

Portions of this study were presented as an oral presentation at the 2017 AANS Annual Scientific Meeting, Los Angeles, CA, April 22–26, 2017.

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