Treatment of Intracranial Aneurysms Using the Pipeline Flow-Diverter Embolization Device: A Single-Center Experience with Long-Term Follow-Up Results

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Treatment of Intracranial Aneurysms Using the Pipeline Flow-Diverter Embolization Device: A Single-Center Experience with Long-Term Follow-Up Results

BACKGROUND AND PURPOSE: Flow-diverting devices now offer a new treatment alternative for cerebral aneurysms. We present the results of a large single-center series of patients treated with the PED, including long-term follow-up.

MATERIALS AND METHODS: Between November 2008 and September 2011, sidewall aneurysms with a wide neck (>4 mm) or unfavorable dome-neck ratio (≤1.5); large/giant, fusiform, dissecting, blister-like, and recurrent sidewall aneurysms; aneurysms at difficult angles; and aneurysms in which a branch was originating directly from the sac were treated with the PED. Patients were premedicated with dual antiplatelet medications. Data, including demographics, aneurysm features, clinical presentation, complications, results, and follow-up information, for up to 2 years are presented.

RESULTS: Two hundred fifty-one aneurysms in 191 patients were treated. Of these, 96 (38.3%) were large or giant (>10 mm). In 34/251 (13.5%), PEDs were used for retreatment. Adjunctive coiling was performed in 11 aneurysms (2.1%). The mean number of devices per aneurysm was 1.3. One aneurysm ruptured in the fourth month posttreatment (0.5%), and symptomatic in-construct stenosis was detected in 1 patient (0.5%) treated with percutaneous transluminal angioplasty. Any event rate was 91.2% in 6 months, increasing to 94.6%.

CONCLUSIONS: Use of the PED is safe, efficacious, and durable in cerebral aneurysm treatment, with low morbidity-mortality and high occlusion rates as confirmed with mid- to long-term control angiography.

ABBREVIATIONS: ASA = acetyl salicylic acid; GCS = Glasgow Coma Scale; PAO = parent artery occlusion; PcomA = posterior communicating artery; PED = Pipeline Embolization Device

Although endovascular coiling has been proved effective in the treatment of cerebral aneurysms,1,2 there are still limitations in the treatment of wide-neck, large or giant, and nonsaccular fusiform aneurysms. Although self-expandable stents enabled the endovascular treatment of some previously so-called “uncoilable” aneurysms,3-5 parent artery occlusion with or without accompanying bypass surgery still seems to be the only treatment for many challenging aneurysms.6 Moreover, there is recurrence of some aneurysms necessitating ≥1 retreatment for the endovascular techniques, which are almost exclusively focused on embolization of the sac with or without adjunctive stent placement.7-10

The concept of flow change resulting in spontaneous aneurysm thrombosis was reported in aneurysms treated with the sole implantation of ≥1 stent.11-14 Now, in recent years, flow diversion performed with dedicated devices has emerged as a new concept, and several articles, including in vitro studies,15,16 case presentations,17-19 and, lately, several series,20-24 have offered promising results.

The PED (ev3 Neurovascular, Irvine, California) is a self-expanding, microcatheter-delivered, cylindrical mesh device composed of 48 braided individual cobalt chromium and platinum strands.18 The device has a 30%-35% metal surface area coverage when fully deployed.

Herein, we present the treatment and follow-up results of ≤2 years in a series of 251 aneurysms in 191 patients who were treated with the PED. This is not only the largest single-center series in which flow diverters were used, but it also provides long-term results.

Materials and Methods

This retrospective study included 251 aneurysms treated with PEDs in 191 consecutive patients (mean age, 49.2 years; age range, 26–71 years; except for 1 pediatric patient who was 13 years of age) between November 2008 and September 2011. One hundred twenty-nine patients were female and 62 were male. Following ethics committee approval, 17 of the patients were included in the Pipeline for Uncoilable or Failed Aneurysms Study. Written informed consent was obtained from each patient. Sidewall aneurysms with wide necks (≥4 mm) or unfavorable dome-neck ratios (≤1.5) (Fig 1), large or giant aneurysms that might have or already had mass effect (Fig 2), fusiform aneurysms (Fig 3), blisterlike aneurysms (Fig 4), recurrent sidewall aneurysms, dissecting aneurysms (Fig 2), aneurysms at difficult angles to the parent artery (so that catheterization of the aneurysm...
Fig 1. Preoperative 3D angiogram (A) shows a very wide-neck large ICA aneurysm. It could be reconstructed with several overlapping devices, creating a new vessel wall within the sac as seen on the perioperative DynaCT image (B). Postoperative CT obtained the same evening (C) reveals ipsilateral frontal intraparenchymal hemorrhage. 2D (D) and 3D (E) views of 6-month control angiography demonstrate the reconstruction of the parent artery and total occlusion of the aneurysm.

Fig 2. Lateral angiogram shows a giant dissecting ICA aneurysm (A). The intraoperative view demonstrates PEDs (sizes, 4 × 20 mm and 4.5 × 16 mm) opening to the normal size of the parent artery at the dissected segment (arrow in A) without necessitating balloon angioplasty. Note the contrast stagnation within the sac (B). Six-month control angiography (C) shows total occlusion of the aneurysm and reconstruction of the parent artery.
and coiling may have increased risk) (Fig 5), and aneurysms in which a branch was originating directly from the sac (therefore endosaccular obliteration or clipping was likely to compromise the branch or result in a neck remnant) were treated with the PED (Figs 6 and 7). We intended to treat 1 patient with a giant, very wide-neck, cavernous ICA aneurysm presenting with mass effect symptoms by using a PED; however, we failed to bypass the neck of the aneurysm, resulting in treatment of the aneurysm with parent artery occlusion following a balloon occlusion test, without complications. This patient was not included in the study because a PED was not used. This was the only technical failure during the course of the series.

The patients’ initial clinical presentations are shown in Table 1. Twenty-eight patients had vision disturbances due to mass effect of the relevant aneurysm. One patient had a previous history of subarachnoid hemorrhage and had mass effect symptoms after recurrence of the aneurysm after receiving the PED as a retreatment. This patient was not included in the study because a PED was not used. This was the only technical failure during the course of the series.

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Thirty-four aneurysms (34/251; 13.5%) in 32 patients (32/191; 16.8%) had PEDs as retreatment (Fig 6). Previous treatments are summarized in Table 2.

Thirty (12%) aneurysms were giant (>2.5 cm), 66 (26.3%) were large (25 mm ≥ aneurysm size >10 mm), and 155 (61.8%) were small (<10 mm). Two hundred twenty-three (88.8%) aneurysms were wide-neck (>4 mm and/or dome-neck ratio >1.5), 21(8.4%) were fusiform, and only 7 (2.8%) had a narrow neck.

Distribution of the aneurysm locations is shown in Table 3. A majority, 232/251 (92.4%), of the aneurysms were located in the anterior circulation, with only 19 aneurysms (7.6%) seen in the posterior circulation (Fig 3).

Treatment and Medication

All patients, including those treated during the acute period of SAH, were premedicated with a loading dose of 300 – 600 mg of clopidogrel (based on the duration of the premedication; the shorter the premedication period, the higher the loading dose), followed by 75 mg daily;
additionally, all patients received 300 mg of aspirin daily. Thrombo-
cyte inhibition levels were confirmed by using the VerifyNow P12Y12
assay (Accumetrics, San Diego, California) and a standard thrombo-
cyte aggregation test. The patient was treated only if the thrombocyte
inhibition level was above 30%. If the response was lower and without
resistance, additional loading doses or increased daily doses (eg, 150
mg daily) were administered. If clopidogrel resistance was detected,
clopidogrel was discontinued and ticlopidine was administered with a
dose of 600 mg twice daily as occurred in 24 patients. In all patients,
intravenous heparin was administered during the treatments to
maintain an activated clotting time of 250–300 seconds (2–2.5 times
the baseline value). Heparinization was not reversed at the conclusion
of the procedure unless the platelet inhibition level exceeded 70%. All
patients who had large or giant aneurysms received dexamethasone,
with an initial dose of 8 mg given during the procedure and continued
4 times; 4 mg daily afterward, at least for 1 week of full dose up to 2

Fig 5. Right carotid angiogram (A) demonstrates a small carotid cave aneurysm in a patient who had an anterior communicating artery aneurysm previously treated with coiling following
SAH. Six-month control angiography (B) shows occlusion of the aneurysm.

Fig 6. Preoperative 2D (A and B) angiograms show the ICA aneurysm in which the anterior choroidal artery is originating from the aneurysm at the neck. A single PED is placed covering
the neck, causing stagnation of the contrast within the sac (C). Six-month control angiography (D) demonstrates total occlusion of the aneurysm with the anterior choroidal artery preserved
(arrow).
weeks; then, the dose was tapered within a similar period. A clopidogrel regimen of 75 mg or ticlopidine, 600 mg twice daily, in addition to ASA, 300 mg per day (or ASA 100 mg, if side effects were noted, eg, ecchymosis and so forth), was maintained after the treatment until the first control angiography at 6 months; then, the dose was tapered within a similar period. A clopidogrel (or ticlopidine) was discontinued while ASA was continued as a life-long regimen.

All treatments were performed with the patient under general anesthesia by using biplane angiography units. 3D rotational angiography was performed in all patients, and working projections were determined. Parent artery measurements were obtained with the utmost precision by using 3D reconstructions and 2D working projections, not only with automatic calibration but also with reference to microcatheter/guiding catheter size.

In all patients, a 6F introducer sheath (Super Arrow-Flex Percutaneous Sheath Introducer set; Teleflex, Limerick, Pennsylvania or Pinnacle Destination; Terumo, Tokyo, Japan) was placed proximally in the parent artery (ie, the common carotid or subclavian artery), and then, a 6F guiding catheter (Envoy; Cordis Neurovascular, Miami Lakes, Florida or Fargo and Fargomax; Balt, Montmorency, France or Neuron; Penumbra, Alameda, California) was placed in the internal carotid or vertebral artery as distal as possible. The microcatheter of 0.027 inches in diameter (Rebar 27, Marksman; Coviden-ev3) was then navigated through different microguidewires as necessary. The microcatheter tip was placed distal enough so that while one manipulated the PED, the tip of the delivery wire would not be pushed beyond the tip of the microcatheter, but the microcatheter could be retrieved while stabilizing the wire. In a few exceptional cases where the neck of the large/giant aneurysm was very wide and could not be primarily bypassed with the designated microcatheter, the “HyperForm-loop technique,” as described previously, was used.

Table 1: Clinical presentations of the patients

<table>
<thead>
<tr>
<th>Presentation</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>83</td>
<td>43.5</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>31</td>
<td>16.2</td>
</tr>
<tr>
<td>Previous SAH from another aneurysm</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Visual findings due to mass effect</td>
<td>28</td>
<td>14.7</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>4.2</td>
</tr>
<tr>
<td>Total</td>
<td>191</td>
<td>100</td>
</tr>
</tbody>
</table>

* Incidental group includes asymptomatic patients and patients with symptoms (excluding SAH) unrelated to the aneurysms treated with a PED (ie, index aneurysms).
* SAH from the aneurysm treated with a PED.
* One of these patients had visual findings after the initial treatment and received a PED as a retreatment; this patient is cited in both groups.
* All symptoms (eg, ataxia, paresthesia, hemi-/quadriparesis, and so forth) other than those listed above, which may be due to mass effect and/or ischemia (such as perforator injury) and so forth.

Table 2: The previous treatments in the aneurysms that had Pipeline treatment for incomplete occlusion

<table>
<thead>
<tr>
<th>Previous Treatment</th>
<th>No. of Aneurysms/Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coiling with bare coils</td>
<td>18/17</td>
</tr>
<tr>
<td>Coiling with surface modified coils</td>
<td>2</td>
</tr>
<tr>
<td>Stent-assisted coiling</td>
<td>2</td>
</tr>
<tr>
<td>Bare stenting</td>
<td>2</td>
</tr>
<tr>
<td>Onyx</td>
<td>1</td>
</tr>
<tr>
<td>Silk flow diverter</td>
<td>2/1</td>
</tr>
<tr>
<td>Failed surgery</td>
<td>5</td>
</tr>
<tr>
<td>Surgical remnant/regrowth</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>34/32</td>
</tr>
</tbody>
</table>

Table 3: Localizations of the aneurysms treated with PED

<table>
<thead>
<tr>
<th>Localization</th>
<th>No. of Aneurysms</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrous ICA</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>Cavernous ICA</td>
<td>28</td>
<td>11.2</td>
</tr>
<tr>
<td>Supraclinoid aneurysms</td>
<td>134</td>
<td>53.4</td>
</tr>
<tr>
<td>PcomA aneurysms</td>
<td>21</td>
<td>8.4</td>
</tr>
<tr>
<td>AchoA aneurysms</td>
<td>28</td>
<td>11.2</td>
</tr>
<tr>
<td>ICA terminal bifurcation</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>M1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>MCA bifurcation</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>8</td>
<td>3.2</td>
</tr>
<tr>
<td>Distal aneurysms</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>251</td>
<td>100</td>
</tr>
</tbody>
</table>

Note:—AchoA indicates anterior choroidal artery.
* If the aneurysm involved both petrous and cavernous segments, it is included in this group, and this definition applies to 12/28 aneurysms in this group.
* The aneurysm is included in the supraclinoid group when it involves this segment, regardless of whether it extends to more than this segment proximally (eg, to the cavernous segment). The aneurysms at the posterior communicating and anterior choroidal artery origins and the terminal bifurcation are shown separately and are not included in this group.
* This group includes all aneurysms distal to the MCA bifurcation, all anterior cerebral artery aneurysms excluding the ones located at the ICA termination, and any aneurysm distal to basilar termination (ie, posterior cerebral artery aneurysms).
Table 4: Any clinical events during/immediately after or in the follow-up period

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>No. of Patients</th>
<th>Permanent Morbidity/Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Hematuria (requiring change in medical treatment)</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>GI bleeding (including the FU period)</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Associated with intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Retroperitoneal hematoma</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Associated with aneurysm treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to mass effect</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>SAH (aneurysm rupture)</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>In relation to PED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative thromboembolic event</td>
<td>4</td>
<td>1) Mortality (jailed PCA occlusion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Symptoms resolved totally</td>
</tr>
<tr>
<td>In-stent stenosis</td>
<td>8</td>
<td>3) Symptoms resolved totally</td>
</tr>
<tr>
<td>Mild</td>
<td>5</td>
<td>2) No intervention</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>3) PTAs performedg</td>
</tr>
<tr>
<td>Ischemic event in the FU period</td>
<td>1*</td>
<td>2 (14.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (14.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: FU indicates follow-up; GI, gastrointestinal; PTA, percutaneous transarterial angioplasty.

* Occurred in the patient who had resistance to clopidogrel and was on ticlopidine.

† Included in the group of complications that are attributed to intervention, but antithrombocytic medication may also have contributed.

‡ This patient had subarachnoid hemorrhage 4 months after the treatment; imaging still showed filling of the aneurysm despite significant decrease. Initially she had had hemiparesis, but this resolved totally.

§ One patient had an ischemic attack in the postoperative 4 months after he discontinued clopidogrel without consulting his doctor. The patient was medicated with IV heparin, and clopidogrel was loaded again. The symptom of monoparesis resolved totally. The same patient woke up from the general anesthesia with monoparesis but immediately became asymptomatic after volume loading and raising the blood pressure.

\* Mild refers to any intimal thickening causing stenosis <50%. Severe refers to stenosis ≥50%.

\* In 2 patients, stenosis was discovered in the control angiography but PTA was performed because the stenosis was considered significant (≥70%). The remaining patient had attacks of dysphasia which resolved after PTA, with no permanent morbidity.

The PED was deployed across the targeted landing zone through a process of repeating maneuvers, including microcatheter unsheathing, delivery-wire stabilization/advancement, and microcatheter loading. After the device was placed with full release, the microcatheter was advanced over the delivery wire until the capture coil marker was captured. The device apposition to the artery wall, both proximally and distally, was of extreme importance to avoid “unbalanced” flow into the sac (ie, the outflow being more restricted than the inflow), which may possibly increase the risk of aneurysm rupture. DynaCT angiography (Siemens, Erlangen, Germany) was performed when necessary to evaluate the device opening and apposition to the parent artery wall. In most cases, a single device was placed. Additional devices were deemed necessary when the device apposition distally and/or proximally was not favorable, if the aneurysm neck was not covered completely, if there was a 360° involvement of the parent artery wall, and if the flow into the aneurysm remained unchanged. Although the latter was not an absolute indication for multiple-device placement, it was taken into consideration, especially when the aneurysm was large or giant. When the aneurysm was small, a single device was considered sufficient. We tried to avoid covering a critical branch, such as the anterior choroidal artery, perforators, and so forth, with >1 device.

In 11 aneurysms, 6 of which were giant, 4 were large, and only 1 was small, coils were used adjunctively in the same session with the PED placement. In 1 giant fusiform vertebrobasilar junction aneurysm, coils were used primarily to occlude the contralateral vertebral artery flow. Two large aneurysms had nippers. Adjunctive coils were used in addition to PED placement when there was very high jet flow into the sac of a large/giant aneurysm with a relatively narrow neck (high aspect ratio) and the neck was located next to a sharp angle.

However, there were no objective criteria with proved value for adjunctive coiling indications, to our knowledge. In the only small aneurysm within this group, coils were used adjunctively because this particular aneurysm was treated in the acute stage of subarachnoid hemorrhage. Additionally, in the group of patients who had Pipeline placement as the retreatment (Table 2), 20 other aneurysms (in 19 patients) had coils from the previous treatments. Moreover, there were self-expandable stents at the aneurysm neck in 4 patients, 2 of whom had additional coils within the sac from the previous treatment. Overall, 34 aneurysms had additional endosaccular material (coils; Onyx, ev3) either placed adjunctively in the current PED treatment (11 aneurysms) or from the previous treatments (23 aneurysms). In 1 patient, there was a previously placed Silk flow diverter (Balt) covering 2 aneurysms.

Follow-Up

A 3-month clinical control and a CT or MR angiography control were obtained, if a patient had ongoing headache, large/giant aneurysms with mass effect symptoms, or a previous history of SAH and so forth. All patients were designated to have a clinical control and DSA at 6 months. If the 6-month control angiography revealed incomplete occlusion of the aneurysm or any intimal change within the device, an additional control DSA was performed during the 12th month. All patients were scheduled for an 18- or 24-month control DSA accordingly (ie, 1 year after the previous angiography). Clopidogrel and ticlopidine were discontinued after the 6-month control DSA, with ASA continuing life-long, unless there was any intimal hyperplasia. If so, then dual antiplatelet medication was maintained for a minimum of another 6 months until the next control DSA.
The patient recovered well with no neurologic deficit and was transferred to our center. Following premedication, she was taken for retreatment where the diagnostic angiography showed some contrast filling at the neck region. Two additional PEDs were placed with no adverse events. The 6-month control angiography (according to the initial therapy) showed complete occlusion of the aneurysm.

One patient had dysphasia 8 weeks postoperatively after the treatment of a left supraclinoid large ICA aneurysm with 3 PEDs. MR imaging showed an acute ischemic lesion in the Broca area, and the patient was emergently taken for angiography where significant stenosis of the left ICA at the edge of the PED and within the devices was noted. Balloon angioplasty was successful, and good antegrade flow was restored. This patient currently has undergone several control angiographies during 2 years and remains on clopidogrel with no symptoms.

Twenty-eight patients presented with a vision abnormality attributed to mass effect (Fig 2). Three patients worsened immediately following treatment. Two of these 3 regressed to their preoperative presentations during follow-up; therefore, 2 patients did not receive any benefit from treatment. The remaining patient had permanent additional morbidity. The aneurysms of these 3 patients were completely occluded in the control angiographies. Seventeen patients had total recovery of symptoms, and an additional 8 patients improved during follow-up, though the symptoms did not resolve completely.

At least 1 control angiography was performed in 182 of the patients (95.3%) with 239 (95.2%) aneurysms. Eight patients with 11 aneurysms had the first DSA control of 6 months pending; and among them, at least 6 months passed since the treatment in 4 patients with 6 aneurysms. One patient died after treatment and did not have a control angiography. According to the latest control, 118 aneurysms (47%) of 95 patients (49.7%) had undergone a 6-month angiography; 52 aneurysms (20.7%) of 38 patients (19.9%) had 1-year and 69 patients (49.7%) had undergone a 6-month angiography; 52 aneurysms (20.7%) of 38 patients (19.9%) had 1-year and 69 patients (49.7%) had undergone a 6-month angiography; 52 aneurysms (20.7%) of 38 patients (19.9%) had 1-year and 69 patients (49.7%) had undergone a 6-month angiography; 52 aneurysms (20.7%) of 38 patients (19.9%) had undergone an 18-month angiography; and among them, at least 6 months passed since the treatment in 4 patients with 6 aneurysms. One patient died after treatment and did not have a control angiography. According to the latest control, 118 aneurysms (47%) of 95 patients (49.7%) had undergone a 6-month angiography; 52 aneurysms (20.7%) of 38 patients (19.9%) had 1-year and 69 patients (27.5%) of 49 patients (25.7%) had 18-month or 2-year control angiographies.

This series included 46 aneurysms (Figs 6 and 7) in which a branch originated directly from the sac where endosaccular coiling or clipping at the neck would result in incomplete occlusion and/or compromise of the branch. Fusiform aneurysms, which involved perforating branches such as aneurysms of the basilar artery, distal vertebral artery, and the M1 segment of the middle cerebral artery, were not included in this group. This group is the subject of another study and will be analyzed there in detail. However, this group of aneurysms prompted us to find a new definition (ie, “remodeled artery”), which refers to an “infundibulum-like” appearance or a tortuous course of the branch resulting from the significant shrinkage of the aneurysm due to flow change (Fig 7). Sectional imaging confirmed the resolution of the sac in these

| Table 5: Six-month control angiography results in regard to aneurysm sizea |
|-----------------|-----|-----|-----|-----|-----|
| Degree of Occlusion | Small | Large | Giant | Total No. | % |
| Still filling | 136 (93.8%) | 56 (87.5%) | 27 (90%) | 219 | 91.8%–91.2% |
| Total | 145 | 64 | 30 | 239 | 100 |

a One patient with 1 aneurysm died after the treatment; 8 patients with 11 aneurysms (9 small and 2 large) have not yet undergone the 6-month control angiography. Therefore, a total of 12 aneurysms (4.8%) did not have control angiography.

b Including 1 patient who had subarachnoid hemorrhage in the fourth month and was retreated with additional PEDs for her remaining aneurysm filling.

c Represents the ratio of aneurysms that were occluded in the 6-month control without retreatment.

d Seven were retreated. Seven of the remaining showed further thrombosis with resultant aneurysm occlusion, and 6 are pending the next control after the discontinuation of the clopidogrel.
patients with such large/giant aneurysms. In this subgroup of aneurysms, 42 of 46 aneurysms had at least 1 control angiography at 6 months. Among these 42 aneurysms, 8 showed a so-called “remodelling” pattern (Fig 7).

The 6-month control angiography results, according to the aneurysm size, are given in Table 5. These include 1 patient who had a retreatment after bleeding in the fourth month; 219/239 aneurysms were occluded for a total occlusion rate of 91.6%. With the exception of 1, all other aneurysms that did not show complete obliteration at the 6-month control angiography (20/239) decreased in size in the first control angiography; in these cases, follow-up angiography was scheduled after an interval of 6 months following discontinuation of the clopidogrel/ticlopidine. Among these 20 aneurysms, 7 showed further thrombosis and became completely occluded. Six are still pending the second control after discontinuation of the clopidogrel. The remaining 7 were retreated with additional PED placement; only 1 has undergone control angiography after retreatment so far and that showed complete obliteration. In the entire series, a total of 8 aneurysms were retreated, 1 on bleeding (retreatment rate, 3.2% among the aneurysms and 4.2% in the patient group). In this subgroup, there were 1 giant, 3 large, and 4 small aneurysms. Two (1 was before and the other was after the 6-month control angiography) have had control angiographies so far, and both have shown total occlusion. When we analyzed the 6-month control results according to the aneurysm size, small aneurysms had a very high total obliteration rate of 136/145 (93.8%), whereas complete obliteration occurred in 56/64 (87.5%) of the large and 27/30 (90%) of the giant aneurysms. According to the last control angiography, 227/239 (95%) aneurysms were totally obliterated, including the 2 aneurysms with retreatment. Total occlusion without retreatment was 94.6% in this series.

### Discussion

Endosaccular coiling has become an accepted treatment for cerebral aneurysms. However, the higher aneurysm recurrence after coiling than after clipping, which may result in an increased risk of rebleeding in the former group, is still a concern and causes a higher retreatment rate. Therefore, not only the stable occlusion of the treated aneurysm but also more durable retreatment methods afterward are being investigated. Involvement of the parent artery with the aneurysm wall to a higher degree apparently results in aneurysm recurrence more frequently. Because of this, a treatment targeting the diseased parent artery wall rather than sole occlusion of the sac is likely to be more effective. Methods reinforcing the parent artery wall, such as by using the liquid embolic Onyx with or without endosaccular obliteration, have been used in the treatment of aneurysms that were more likely to recur. Excluding the treatment with covered stents, the first apparent evidence of long-term stability of parent artery reconstruction was noted in the treatment of large/giant aneurysms with the liquid embolic Onyx in conjunction with stents; however, this technique had its own limitations.

Alteration of flow quantity and direction has been a method for the treatment of some selected aneurysms. Previously it was limited to placement of a single or multiple stents or parent artery occlusion until the development of dedicated flow diverters (Pipeline and Silk). The results of previous PED studies are summarized in Table 6.

### Table 6: Summary of previous Pipeline series in comparison with this series

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Patients/AA</th>
<th>No of AA W Previous TX Failurea (%)</th>
<th>No of AA W Adjunctive Coilingb (%)</th>
<th>Morbidityc and Mortality (%)</th>
<th>Complete Occlusion at 6-Month DSA (%)</th>
<th>Control Angiography (%)</th>
<th>Retrx No of AA (%)</th>
<th>Peri-Post-Operative Intracranial Bleeding (%)</th>
<th>Perforator Infarct (%)</th>
<th>In-Stent Stenosis All %/Requiring TX % PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lylyk et al 200923</td>
<td>53/63</td>
<td>23/63</td>
<td>4/63 (6%)</td>
<td>0%</td>
<td>93%</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10%/0</td>
</tr>
<tr>
<td>Szikora et al 201024</td>
<td>18/19</td>
<td>1/19</td>
<td>10/19 (53%)</td>
<td>5.6%</td>
<td>94.4%</td>
<td>94.7%</td>
<td>0</td>
<td>1/19 (5.6%)</td>
<td>0</td>
<td>0/5.6</td>
</tr>
<tr>
<td>Nelson et al 201125</td>
<td>31/31</td>
<td>12/31</td>
<td>16/31 (52%)</td>
<td>5.6%</td>
<td>93.3%</td>
<td>96.8%</td>
<td>0</td>
<td>1/31 (3.2%)</td>
<td>0</td>
<td>0/3.2</td>
</tr>
<tr>
<td>Fischer et al 201126</td>
<td>100/101</td>
<td>30/101</td>
<td>3/101 (3%)</td>
<td>2%</td>
<td>52%</td>
<td>89%</td>
<td>8/101</td>
<td>4/88 (2.3%)</td>
<td>0</td>
<td>2.3%/0</td>
</tr>
<tr>
<td>McAuliffe et al 201227</td>
<td>54/57</td>
<td>16/57</td>
<td>12/68 (18%)</td>
<td>0%</td>
<td>85.7%</td>
<td>98.2%</td>
<td>2/57 (3.5%)</td>
<td>0</td>
<td>0</td>
<td>3.5%/0</td>
</tr>
<tr>
<td>Saatci et al 201228</td>
<td>191/251</td>
<td>34/251</td>
<td>11/251 (4%)</td>
<td>1%</td>
<td>91.2%</td>
<td>95.2%</td>
<td>8/251</td>
<td>3/191 (4.2%/1.6%)</td>
<td>1/191 (0.5%)</td>
<td>4.2%/1.6%</td>
</tr>
</tbody>
</table>

Note:—AA indicates aneurysms; TX, treatment; W, with DSA; Retrx, retreatment.

a Refers to the aneurysms that underwent previous endovascular or surgical treatment, including the failed treatment, incomplete treatment, and recurrences.
b Refers to the aneurysms in which coiling was performed as an adjunctive treatment in the same session with PED placement.
c Temporary deficits not included.
d Six (d) and 9 (e) aneurysms of these series were also included in the PITA trial.
e Refers to the rupture of a coexisting aneurysm.
f Refers to an iatrogenic ICA rupture.
g Includes 1 aneurysm rupture and 2 parenchymal hemorrhages.
h Includes 1 aneurysm rupture and 3 parenchymal hemorrhages.
i Additional treatment required due to PED displacement in 2 aneurysms.
j Includes 1 aneurysm rupture and 2 parenchymal hemorrhages.
dural, resulting in death in 9 patients and disabling morbidity in 1. In our series, we encountered 1 delayed aneurysm rupture (1/191; 0.5%) that occurred in the fourth month after the PED treatment, and the patient survived with no permanent neurologic deficit. Even if the large and giant aneurysms are taken into account, on the basis of the fact that almost all (if not exclusively) ruptured aneurysms reported in the literature are large or giant, in this subgroup, the rate of bleeding becomes 1/96 (1%) in our series.

Adjuvant aneurysm filling with coils may be considered to prevent aneurysm rupture; however, there have been ruptured cases despite additional coiling. Moreover, to our knowledge, there is no criterion to define the degree of coil packing sufficient to spare the aneurysm from rupture. In our series, adjuvant coiling has been performed in only 4.4% of the aneurysms. If the 9 large/giant aneurysms in which sac coiling was performed adjunctively were excluded from the cohort, the bleeding rate becomes 1.2%.

Differing from many other series, corticosteroid treatment is mandatory in our practice if the aneurysm is large or giant, to suppress the inflammatory reaction that may be caused by the thrombosis of the sac. Moreover, the platelet response to dual premedication is always investigated to provide an optimal level of at least 30% platelet inhibition. We question whether the medication protocol may play a role in the progression of thrombosis and accompanying inflammatory reaction when present. This assumption does not progress beyond the level of hypothesis due to a lack of evidence. Regarding the other case series of PEDs, Fischer et al24 reported 1 aneurysm rupture among 88 patients (1.1%). In the other PED series with follow-up,20,21,23,34 there was no index aneurysm rupture (Table 6). The premedication with double antiplatelets was variable and corticosteroid administration was not determinate in these series.

Parenchymal hemorrhage was another complication reported following the flow-diverter treatment, with possible causes including wire perforation, aneurysm rupture, antiplatelet medication, hemorrhage within ischemic tissue, and so forth. We encountered parenchymal hemorrhage in 2 patients in our series (2/191; 1.1%). In both patients, the platelet inhibition level was high (≥97%), and one of the patients (Fig 1) received subcutaneous low-molecular-weight heparin after the treatment, experiencing parenchymal hemorrhage in the same evening following the administration of the drug. In the second patient with parenchymal hemorrhage, the hematoma was remote from the catheterized artery and occurred many days after the treatment, making wire perforation a less likely cause. In our evaluation, we attributed the parenchymal hemorrhages to a high response to antiplatelet medication with or without accompanying anticoagulation. Fischer et al24 also re-
ported 3 parenchymal hemorrhages (3/88; 3.4%), suggesting microemboli and microinfarcts as the triggers.

Thromboembolic events may occur during the treatment, in the early follow-up, and also in the late phase. Possible causes include the following: 1) insufficient antiplatelet activity (low response or resistance, unauthorized drug dis-continuation, and so forth), 2) the device not opening properly (ie, incomplete opening or poor apposition to vessel wall), 3) compromise of covered branches, and 4) in-stent stenosis and so forth. In our series, 1 patient died from the consequences of P1 thrombosis after the posterior cerebral artery was jailed by 1 PED, despite additional thrombolytic and platelet glycoprotein IIb-IIIa inhibitor drug administration. Apart from this event, there was no perforator infarct in this series. Parent artery occlusion was reported more frequently in Silk series than in PED series. Among the PED experience, there was a basilar fusiform aneurysm treated with PED resulting in PAO after 2 years, despite dual antiplatelet therapy continued for 18 months, as reported by Fiorella et al. There is no consensus regarding the duration of antiplatelet medication. In our practice, 6 months is the minimum time of dual antiplatelet administration. However, there is no controlled study to clarify this issue, to our knowledge.

In-stent stenosis may occur occasionally with many, if not all, of the devices currently in use. It has also been reported with flow diveters up to 33%, in our series, inconstuct intimal hyperplasia was noted in 8/191 patients (4.2%). However, only 1 patient (0.5%) had clinical symptoms, which resolved totally following the percutaneous trans-arterial angioplasty, and the patient remained stable with clopidogrel not interrupted in the 30 months of follow-up. Last, this series consisted of long-term evaluation data so that nearly half of the patients (87/191: 45.6%) had at least 1 year and up to 34 months of clinical follow-up and up to 2 years of DSA control with no unfavorable clinical event or deteriorating angiographic findings. This outcome supports the device safety.

Conclusions

PED provides a solution for wide-neck, large/giant, fusiform aneurysms; too small aneurysms; and also small-but-difficult-to-coil aneurysms such as the ones from which a branch is originating. Our series confirmed the safety of this technique with low morbidity-mortality as well as its efficacy with high angiographic complete occlusion rates and long-term durability.

Disclosures: Isil Saatci—UNRELATED: Consultancy; consulting agreement with ev3; Payment for Lectures (including service on Speakers Bureau) (clarify); Payment for Development of Educational Presentations: honorarium for meetings and preparation of videos or demo materials for training of PED devices. Sarahan Cekirge—UNRELATED: Consultancy; consulting agreement with ev3; Payment for Lectures (including service on Speakers Bureau) honorarium for lectures in scientific meetings. Payment for Development of Educational Presentations: honorarium for meetings and preparation of videos or demo materials for training of PED devices. Other: consulting agreement with MicroVention.

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