Pipeline for uncoilable or failed aneurysms: 3-year follow-up results

Tibor Becske, MD,1,2 Matthew B. Potts, MD,1,3 Maksim Shapiro, MD,1,2 David F. Kallmes, MD,4 Waleed Brinjikji, MD,4 Isil Saatci, MD,5 Cameron G. McDougall, MD,6 István Szikora, MD, PhD,7 Giuseppe Lanzino, MD,4 Christopher J. Moran, MD,8 Henry H. Woo, MD,9 Demetrius K. Lopes, MD,10 Aaron L. Berez, MD,11 Daniel J. Cher, MD,12 Adnan H. Siddiqui, MD, PhD,13 Elad I. Levy, MD,13 Felipe C. Albuquerque, MD,6 David J. Fiorella, MD, PhD,9 Zsolt Berentei, MD,7 Miklós Marosfői, MD,7 Saruhan H. Cekirge, MD,5 and Peter K. Nelson, MD1,3

Departments of 1Radiology, 2Neurology, and 3Neurological Surgery, Neurointerventional Service, NYU School of Medicine, NYU Langone Medical Center, New York, New York; 4Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota; 5Department of Radiology, Bayindir Hospital, Ankara, Turkey; 6Department of Neurological Surgery, Barrow Neurological Institute, Phoenix, Arizona; 7National Institute of Neurosciences, Budapest, Hungary; 8Division of Interventional Neuroradiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri; 9Department of Neurosurgery, Stony Brook Hospital, Stony Brook, New York; 10Department of Neurological Surgery, Rush University Medical Center, Chicago, Illinois; 11Alembic, LLC, Mountain View; 12Wild Iris Consulting, Palo Alto, California; and 13Departments of Neurological Surgery and Radiology, University of Buffalo, Buffalo, New York

OBJECTIVE The long-term effectiveness of endovascular treatment of large and giant wide-neck aneurysms using traditional endovascular techniques has been disappointing, with high recanalization and re-treatment rates. Flow diversion with the Pipeline Embolization Device (PED) has been recently used as a stand-alone therapy for complex aneurysms, showing significant improvement in effectiveness while demonstrating a similar safety profile to stent-supported coil treatment. However, relatively little is known about its long-term safety and effectiveness. Here the authors report on the 3-year safety and effectiveness of flow diversion with the PED in a prospective cohort of patients with large and giant internal carotid artery aneurysms enrolled in the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial.

METHODS The PUFS trial is a prospective study of 107 patients with 109 aneurysms treated with the PED. Primary effectiveness and safety end points were demonstrated based on independently monitored 180-day clinical and angiographic data. Patients were enrolled in a long-term follow-up protocol including 1-, 3-, and 5-year clinical and imaging follow-up. In this paper, the authors report the midstudy (3-year) effectiveness and safety data.

RESULTS At 3 years posttreatment, 74 subjects with 76 aneurysms underwent catheter angiography as required per protocol. Overall, complete angiographic aneurysm occlusion was observed in 71 of these 76 aneurysms (93.4% cure rate). Five aneurysms were re-treated, using either coils or additional PEDs, for failure to occlude, and 3 of these 5 were cured by the 3-year follow-up. Angiographic cure with one or two treatments of Pipeline embolization alone was therefore achieved in 92.1%. No recanalization of a previously completely occluded aneurysm was noted on the 3-year angiograms. There were 3 (2.6%) delayed device- or aneurysm-related serious adverse events, none of which led to permanent neurological sequelae. No major or minor late-onset hemorrhagic or ischemic cerebrovascular events or neurological deaths were observed in the 6-month through 3-year posttreatment period. Among 103 surviving patients, 85 underwent functional outcome assessment in which modified Rankin Scale scores of 0–1 were demonstrated in 80 subjects.

CONCLUSIONS Pipeline embolization is safe and effective in the treatment of complex large and giant aneurysms of the intracranial internal carotid artery. Unlike more traditional endovascular treatments, flow diversion results in progres-
The treatment of complex wide-neck aneurysms of the internal carotid artery (ICA) remains a challenge. If left untreated, large and giant aneurysms of the ICA have a 5-year cumulative rupture risk of up to 40% depending on location of the lesion. Surgical options, including clip occlusion or bypass and trapping, are associated with a high morbidity rate, while previous endovascular options were associated with high recurrence and re-treatment rates. The Pipeline Embolization Device (PED) was a novel endoluminal device for the treatment of intracranial aneurysms introduced for human use in 2006. Its safety and efficacy were demonstrated in two prospective trials—the Pipeline Embolization Device for the Intracranial Treatment of Aneurysms (PITA) trial and the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial. The latter was a multicenter, prospective study of the PED for the treatment of large and giant aneurysms of the petrous through superior hypophyseal segments of the ICA. In the PUFS trial, the primary effectiveness end point of complete aneurysm occlusion at 6 months without significant (>50%) stenosis or use of adjunctive embolization devices was achieved in 73.6% of aneurysms, while 5.6% of patients met the primary safety end point of major ipsilateral stroke or neurological death at 6 month. By 1 year, complete aneurysm occlusion was observed in 86.8% of aneurysms. These results led to Federal Drug Administration approval for the PED in the treatment of large and giant aneurysms of the petrous through superior hypophyseal segments of the ICA. The long-term effectiveness, durability, and safety of the PED, however, are not known. Here we report the 3-year angiographic and clinical follow-up results from the PUFS cohort.

Methods

Industry Support and Registration

The PUFS trial was supported by funding from ev3/Covidien. It is registered at clinicaltrials.gov (NCT00777088).

Study Enrollment and Patient Selection

One-hundred eight patients from 10 centers were enrolled in this study between November 2008 and July 2009 under a US Food and Drug Administration investigational device exemption. Complete enrollment criteria have been previously described. Briefly, patients were included if they had an aneurysm of the petrous through superior hypophyseal segment of the ICA measuring larger than 10 mm in diameter with a neck of at least 4 mm. Exclusion criteria included subarachnoid hemorrhage within the past 60 days, any intracranial hemorrhage or major surgery within the last 42 days, a history of abnormal bleeding or low platelet count, a previously placed stent at the target aneurysm, a contraindication to CT or MRI, a known allergy to platinum or cobalt and chromium alloys, evidence of active infection, intolerance to antiplatelet medications, or significant stenosis of the ipsilateral carotid artery. Patients who had undergone prior treatments (i.e., coiling) of the target aneurysm were not excluded unless a stent had been previously placed across the neck of the aneurysm.

Baseline Assessments

Prior to placement of the PED, patients underwent a baseline neurological examination and a detailed ophthalmological assessment to document the presence of oculomotor cranial neuropathy or deficits in visual acuity and visual fields.

Dual Antiplatelet Therapy

Patients were asked to take aspirin (325 mg per day orally for 2 days) and clopidogrel (75 mg per day for 7 days or loading dose of 600 mg) prior to PED placement. After the procedure, patients were asked to take 325 mg of aspirin daily for at least 6 months and 75 mg of clopidogrel daily for at least 3 months (most were maintained on combination antiplatelet therapy for 6 months). Platelet inhibition studies were optional.

Description of the Study Device and Placement Procedure

Placement of the PED was performed as previously described. In brief, all procedures were performed after induction of general anesthesia using standard transfemoral approaches. PEDs were deployed through a standard 0.027-in-inner-diameter catheter (Hi-Flo Renegade, Boston Scientific; or Marksman Catheter, ev3/Covidien). The size and number of stents placed were selected at the discretion of each treating operator.

Follow-Up Assessments

Patients underwent repeat neurological examinations at 30 days, 180 days, 1 year, and 3 years, and angiography at 180 days, 1 year, and 3 years after PED placement. Follow-up imaging was interpreted by an independent core radiology laboratory (CRL) consisting of 3 neuroradiologists. Each CRL member independently adjudicated aneurysms for degree of occlusion (complete occlusion, residual neck, or residual aneurysm), the presence and degree of in-stent stenosis, and the occurrence of implant migration.

Safety Reporting

Any negative change in a patient’s health was considered an adverse event and recorded. Investigators were asked to judge the relationship of each adverse event to the PED, the PED placement procedure, and any preex-
existing conditions. An independent clinical events committee (CEC) reviewed and adjudicated each serious adverse event.

**Study End Points**

The primary effectiveness end point of the PUFS study was complete occlusion of the target aneurysm without major (> 50%) stenosis of the parent artery or adjunctive use of a complementary embolic agent as seen on a 180-day angiogram and judged by the independent CRL. A case was considered successful if at least 2 of the 3 core laboratory members agreed that it met these criteria. In addition, the primary safety end point of the PUFS study was the incidence of major ipsilateral stroke (defined as an increase of ≥ 4 points on the National Institutes of Health Stroke Scale and present after 7 days as adjudicated by the CEC) or neurological death within 180 days of PED placement.

We now report the following prespecified secondary end points observed at the 3-year time point: 1) complete aneurysm occlusion, 2) incidence of significant in-stent stenosis, 3) occurrence of delayed device-related adverse events, and 4) functional outcomes based on the modified Rankin Scale (mRS) score.

**Statistical Analysis**

Summary statistics (counts and percentages) were tabulated. Exact binomial confidence intervals for major study end points were calculated. All statistical calculations were performed using R.

**Results**

Baseline characteristics were reported in the initial PUFS report. Overall patient disposition at the 3-year time point is shown in Fig. 1. Of the 107 patients with 109 treated aneurysms, there were 4 recorded deaths (3 occurring within the first 180 days, and 1 additional non-neurological death occurring at 2 years posttreatment in a patient with a recurrent malignancy). In addition, 9 patients were discontinued from the trial before their 3-year examination (6 subjects were lost to follow-up and consent was withdrawn in 3 cases). An additional 6 subjects did not undergo 3-year imaging evaluation. Overall, 85 patients with 87 aneurysms had 3-year follow-up imaging, and 85 patients underwent a 3-year neurological examination. Follow-up imaging modalities included conventional angiography in 74 subjects (76 aneurysms), MRI or MR angiography (MRA) in 7 subjects (7 aneurysms), and CT angiography (CTA) in 4 subjects (4 aneurysms). Five patients with incomplete occlusions received additional endovascular treatment prior to 3-year follow-up examination—one with a postembolization carotid-cavernous fistula was treated underwent aneurysm coiling while the remaining 4 received additional PEDs.

**Secondary Effectiveness End Points**

Table 1 details the angiographic occlusion rates for the 76 aneurysms in the 74 patients who had a 3-year conventional angiogram. Overall, 71 aneurysms were completely occluded (93.4%, 95% CI 85.3%–97.8%, p = 5.249e−16). The CRL could not determine completeness of angiographic occlusion in 1 case (1.3%). Two aneurysm remnants (2.6%) and 2 neck remnants (2.6%) were observed. In comparison, at 180 days after treatment, there were 6 aneurysm remnants, 8 neck remnants, and 1 carotid-cavernous fistula. Table 2 details the angiographic fate of those 15 aneurysms at 180-day, 1-year, and 3-year follow-ups. Of the 5 patients who received additional endovascular treatment, 3 had complete occlusion by 3 years. Of the 10 remnants that were not re-treated, 7 were occluded at 3 years (Fig. 2), 2 remained open (1 was subsequently re-treated), and 1 patient had no angiographic follow-up. Excluding cases that were re-treated prior to the 3-year angiogram, complete occlusion in a single session of Pipeline embolization was achieved in 68 patients (89.5%). Ex-
including the case that was re-treated with coils, complete occlusion was achieved with one or two sessions of PED alone in 70 patients (92.1%). Of the 11 aneurysms with imaging other than digital subtraction angiography (DSA) at 3 years, 9 had had prior angiograms showing complete aneurysm occlusion, and none had imaging findings suggesting recanalization.

Table 3 shows the degree of parent artery stenosis in aneurysms of patients with 3-year angiographic follow-up. Overall 74 (97.4%) of 76 treated vessels were free of significant (> 50%) stenosis 3 years after PED placement.

Secondary Safety End Points

Six occurrences of the primary PUFS safety end point of major ipsilateral stroke or neurological death were reported in the PUFS report.2 Between the 180-day and 3-year follow-ups, there were no additional occurrences of either end point. There were 3 serious adverse events deemed by the CEC as “probably” or “definitely” related to the device after the 180-day time point. These included 2 cases of amaurosis fugax and 1 case of a neurologically silent parent vessel occlusion. None of these resulted in permanent neurological sequelae.

Functional Outcome

Table 4 summarizes functional outcomes in the safety arm of the trial. Eighty-five of these patients underwent 3-year clinical follow-up examinations, and an mRS score of 0 or 1 was recorded in 80 (95.2%).

Discussion

Based on the results of the multicenter PITA26 and PUFS2 trials, as well as several other multicenter4,17,20,28,47 and institutional1,3,10,12,15,16,19,31,32,34,39 experiences, treatment of large and giant ICA aneurysms with the PED is becoming more widespread. Given that the PED only received CE Mark in Europe in 2009 and FDA approval in the United States in 2011, long-term experience with it is limited. The PUFs trial is the second-largest prospective trial of PED for large and giant ICA aneurysms published to date47 and the first to report 3-year angiographic and clinical outcomes. Complete occlusion rates were demonstrated in 93.4% of the aneurysms with 3-year catheter angiography studies (up from 73.6% observed at 180 days) and without any additional cases of major stroke or neurological death.

Other endovascular therapies for large and giant aneurysms, including coiling alone or balloon- and stent-assisted coiling, are associated with high recurrence rates.6,24,37 In contrast, the majority of treated aneurysms in the PUFS cohort that were incompletely occluded at 6 months continued to progressively occlude over time (Fig. 3). Five aneurysms in the effectiveness arm of the study required additional intervention with a PED (4 aneurysms) or coils (1 aneurysm) between 6 months and 3 years after initial treatment, leading to complete occlusion in 3 by the 3-year follow-up. In total, 10 of 15 remnants were completely occluded at 3 years. Importantly, no recanalization involving a previously completely occluded aneurysm was observed at 3 years. In addition, there was no evidence of recanalization in the 11 patients who underwent non-catheter angiography (CTA or MRA) at 3 years postembolization.

In the initial PUFS report, 5 intracranial hemorrhagic events were observed before 6 months—2 that met the primary safety end point and an additional 3 that were minimally symptomatic.2 All occurred within 1 month of treatment and none were due to rupture of the target aneurysm. Delayed hemorrhagic events after Pipeline embolization, either rupture of the target aneurysm or hemorrhage distal to the site of embolization, have been reported in the literature.9,11,13,29,40,48 In the PUFS cohort, no additional cases of intracranial hemorrhage were observed between 1 month and 3 years, suggesting that the risk of delayed hemorrhage dramatically decreases after the early postembolization period. Overall, there have been no instances of target aneurysm rupture in the PUFS cohort at any time postembolization.

To date, this is the largest cohort of patients treated with the PED to have 3-year clinical and angiographic follow-
up. It is also one of the largest cohorts of large and giant aneurysms managed with any treatment modality to have 3-year clinical and angiographic follow-up. Of the original 107 treated patients, an mRS score was known at 3 years in 89. This included 4 deaths, 3 of which were considered neurological in etiology. Of the 85 patients examined at 3 years, 94% had an mRS of 0 or 1. Such long-term results further confirm the safety of Pipeline embolization for large and giant ICA aneurysms.

It is important to emphasize that the PUFS results cannot necessarily be generalized to small aneurysms or aneurysm in other locations for which the PED has been used, including the ICA terminus, middle cerebral artery, anterior cerebral artery, and posterior circulation. The incidence of large and giant aneurysms in these locations is relatively rare compared with that in those included in PUFS and the experience using the PED to treat such aneurysms is therefore more limited. Future prospective studies of Pipeline embolization for these indications will be required.

Conclusions

In summary, flow diversion with the PED is a safe and effective treatment of large and giant ICA aneurysms with-

TABLE 3. Stenosis of the parent artery on 3-year angiogram

<table>
<thead>
<tr>
<th>Stenosis Grade</th>
<th>No. of Lesions (n = 76*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%–25%</td>
<td>66 (86.8%)</td>
</tr>
<tr>
<td>&gt;25%–50%</td>
<td>8 (10.5%)</td>
</tr>
<tr>
<td>&gt;50%–75%</td>
<td>0</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>2 (2.6%)</td>
</tr>
</tbody>
</table>

* 76 aneurysms in 74 patients.

TABLE 4. Overall 3-year functional outcomes

<table>
<thead>
<tr>
<th>mRS Score</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
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<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Unknown*</td>
<td>18</td>
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</table>

* No 3-year mRS recorded.
out delayed (> 6 months) permanent neurological complications. Unlike more traditional endovascular treatments, flow diversion results in progressive vascular remodeling that leads to complete aneurysm obliteration over longer-term follow-up without delayed aneurysm recanalization and/or growth.

References


FIG. 3. Closure of large ophthalmic segment aneurysm with additional Pipeline embolization. This 72-year-old woman presented with worsening headaches and was found to have a large left ophthalmic segment aneurysm (A, lateral DSA image). 3D rotational angiography demonstrated a maximal dome diameter of 1.26 cm and a neck of 8.48 mm (B). Of note, the left ophthalmic artery arose just proximal to the aneurysm. This aneurysm was treated with 4 overlapping PEDs (C, unsubtracted lateral angiogram obtained post-PED placement) without complication, and stagnation was noted in the aneurysm dome (D, lateral angiogram). Six-month angiographic follow-up revealed residual aneurysm encircling a portion of the reconstructed ICA ophthalmic segment (E, lateral angiogram). This residual appeared to be running off into the ophthalmic artery. One-year angiographic follow-up showed persistent filling of this aneurysm (F, lateral angiogram), so it was again treated with 2 additional overlapping PEDs. Angiographic follow-up at 18 months (6 months after re-treatment) showed continued filling of this residual aneurysm (G, lateral angiogram) but complete occlusion was achieved without additional treatment by 3 years (2 years after re-treatment; H, lateral angiogram). Of note, the left ophthalmic artery also no longer filled from the left ICA at this time but the patient’s vision remained intact. s/p = status post.
Three-year PUFS results


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Disclosures
Dr. Saatci reports being a consultant for Covidien, from which he has also received clinical or research support for the study described (includes equipment or material). Dr. McDougall reports being a consultant for MicroVention and eV3. Dr. Szikora reports being a consultant for Covidien, Stryker Neurovascular, Sequent Medical, Codman Neurovascular. Dr. Lanzino reports being a consultant for Covidien. Dr. Moran reports being a consultant for Medtronic Neurovascular. Dr. Woo reports having ownership in Vascular Simulations LLC; being a consultant for MicroVention Inc.; and receiving royalties for intellectual properties from Codman and Shurtleff. Dr. Cher reports being a consultant for Covidien. Dr. Siddiqui reports financial interests in StimSox, Valor Medical, Neuro Technology Investors, Cardinal, Medina Medical Systems, Buffalo Technology Partners, Inc., and International Medical Distribution Partners. He is a consultant to (paid per project or per hour) Codman, Medtronic, GuidePoint Global Consulting, Penumbra, Stryker, MicroVention, W.L. Gore & Associates, Three Rivers Medical, Inc., Corindus, Inc., Amnis Therapeutics, Ltd., CereVasc, LLC, Pulsar Vascular, The Stroke Project, Inc., Cerebrotech Medical Systems, Inc., Rapid Medical, Lazarus (acquired by Medtronic), Medina Medical (acquired by Medtronic), Reverse Medical (acquired by Medtronic), Covidien (acquired by Medtronic), Neuravi, Silk Road Medical, and Rebound Medical. He is the primary investigator or on national steering committees for Penumbra, 3D Separator Trial; Covidien (Now Medtronic), SWIFT PRIME and SWIFT DIRECT Trials; MicroVention, FRED Trial; MicroVention, CONFIDENCE Study; LARGE Trial; POSITIVE Trial; Penumbra, COMPASS Trial; and Penumbra, INVEST Trial. He is a board member of the Intersocietal Accreditation Committee. Dr. Albuquerque is a consultant for eV3/Covidien. Dr. Marosfoi reports being a consultant for Covidien, MicroVention, and Sequent. Dr. Berez reports holding stock in Medtronic. Dr. Nelson reports being a consultant for Covidien.

Author Contributions
Conception and design: Cher, Berez, Nelson. Acquisition of data: Becske, Shapiro, Kallmes, Brinjikji, Saatci, McDougall, Szikora, Lanzino, Moran, Woo, Lopes, Siddiqui, Levy, Albuquerque, Fiorella, Berentei, Marosfoi, Cekirge, Nelson. Analysis and interpretation of data: Becske, Potts, Shapiro, Kallmes, Brinjikji, Saatci, McDougall, Szikora, Lanzino, Moran, Woo, Lopes, Cher, Siddiqui, Levy, Albuquerque, Fiorella, Berentei, Marosfoi, Cekirge, Nelson. Drafting the article: Becske, Potts, Shapiro, Kallmes, Brinjikji, Saatci, McDougall, Szikora, Lanzino, Moran, Woo, Lopes, Cher, Siddiqui, Levy, Albuquerque, Fiorella, Berentei, Marosfoi, Cekirge, Nelson. Reviewing the submitted version of manuscript: Becske, Potts, Shapiro, Kallmes, Brinjikji, Saatci, McDougall, Szikora, Lanzino, Moran, Woo, Lopes, Cher, Siddiqui, Levy, Albuquerque, Fiorella, Berentei, Marosfoi, Cekirge, Nelson. Approved the final version of the manuscript on behalf of all authors: Becske. Statistical analysis: Cher.

Correspondence
Tibor Becske, NYU School of Medicine, NYU Langone Medical Center, 660 First Ave., 7th Fl., New York, NY 10016. email: tibor.becske@nyumc.org