CASE SERIES

Periprocedural outcomes and early safety with the use of the Pipeline Flex Embolization Device with Shield Technology for unruptured intracranial aneurysms: preliminary results from a prospective clinical study

Mario Martínez-Galdámez,1 Saleh M Lamin,2 Konstantinos G Lagios,3 Thomas Liebig,4 Elisa F Ciceri,5,6 Rene Chapot,7 Luc Stockx,8 Swarupsinh Chavda,2 Christoph Kabbasch,4 Giuseppe Farago,5 Hannes Nordmeyer,7 Thierry Boulanger,8 Mariangela Piano,9 Edoardo P Boccardi9

ABSTRACT

Background and purpose The Pipeline Embolization Device (PED) has become a routine first-line option for treatment of intracranial aneurysms (IAs). We assessed the early safety and technical success of a new version of PED, Pipeline Flex Embolization Device with Shield Technology (Pipeline Shield), which has the same design and configuration but has been modified to include a surface synthetic biocompatible polymer.

Materials and methods The Pipeline Flex Embolization Device with Shield Technology (PFLEX) study is a prospective, single-arm, multicenter study for the treatment of unruptured IAs using Pipeline Shield. The primary study endpoints included the occurrence of major stroke in the territory supplied by the treated artery or neurologic death at 1 year post-procedure. Secondary endpoints included the rate of Pipeline Shield-related or procedure-related serious or non-serious adverse events. Analyses were conducted to evaluate early safety findings in the 30-day post-procedure period as well as technical procedural success outcomes.

Results Fifty patients with 50 unruptured target IAs were enrolled. Mean aneurysm diameter was 8.82 ±6.15 mm. Thirty-eight aneurysms (76%) were small (<10 mm). Device deployment was technically successful with 98% of devices. Complete wall apposition was achieved immediately post-procedure in 48 cases (96%). No major strokes or neurologic deaths were reported in the 30-day post-procedure period.

Conclusions The results of this first experience with the new Pipeline Flex corroborate the early safety of the device. Mid-term and long-term follow-up examinations will provide data on safety outcomes at the 6-month and 1-year follow-up periods.

Clinical trial registration NCT02390037.

INTRODUCTION

Flow diverters have added a new dimension and represent a paradigm shift in the treatment of intracranial aneurysms (IAs).1 2 The Pipeline Embolization Device (PED; Medtronic Neurovascular, Irvine, California, USA) has become a routine first-line treatment option for an increasing patient population with IAs.1 3 The first-generation PED device, used for the embolization of cerebral aneurysms, received European CE mark approval in 2008 and US FDA approval in 2011.4 Its safety and efficacy have been demonstrated in numerous clinical studies, such as the Pipeline for Uncoilable and Failed Aneurysms (PUFS) trial,5 the International Retrospective Study of PED (IntrePED),6 the Aneurysm Study of Pipeline in an Observational Registry (ASPIRE) study,7 and several large clinical series.6 8 9 The IntrePED study reported a neurologic morbidity and mortality rate of 8.4%, where most of the adverse events were ischemic strokes from thromboembolic complications.6

A second-generation PED with a redesigned delivery system, the Pipeline Flex Embolization Device, received CE mark and FDA approvals in 2014 and 2015, respectively. The Pipeline Flex Embolization Device features the same implant as the first-generation PED and incorporates a resheathing mechanism to allow repositioning and redeployment of the implant.10 11 Recently, a ‘third generation of PED’ called Pipeline Flex Embolization Device with Shield Technology (Pipeline Shield) received CE mark approval in March 2015. The Pipeline Shield device features the same implant and delivery system as the Pipeline Flex device, with the addition of a new surface modification to potentially reduce its thrombogenicity.12 The Shield Technology is a surface modification where a synthetic phosphorylcholine (PC) polymer is covalently bonded to the strands that make up the Pipeline braid.12 PC has been used for years in biocompatible medical surfaces or stent coating in cardiology because it ‘resembles’ the polar head of the phospholipids of the cell membrane, and hence has the ability to reduce protein adsorption-thrombin generation.13-15 To date, two studies have been published assessing the thrombogenicity of the Pipeline Shield device compared with other flow diverters.16 17 One study was conducted in an in vitro setting and found Pipeline Shield to be less thrombogenic than Pipeline Flex, SILK, and FRED flow diverters.12 The other study was conducted in a preclinical model and found that the PC
modification of Pipeline Shield reduced the platelet-specific thrombogenicity of Pipeline Shield compared with the FRED flow diverter.16 The primary endpoint of the current Pipeline Flex Embolization Device with Shield Technology (PFLEX) study includes occurrence of major stroke in the territory supplied by the treated artery or neurologic death at 1 year post-procedure. The study is also assessing as a secondary endpoint the rate of Pipeline Shield-related or procedure-related serious or non-serious adverse events (SAEs). Follow-up assessments also include 6-month and 1-year post-procedure time points. We present early safety findings for the primary and secondary study endpoints in the 30-day post-procedure period as well as technical procedural success outcomes.

MATERIALS AND METHODS
Study design and participants
The PFLEX study was a prospective, interventional, single-arm trial of the Pipeline Shield for the treatment of IAs conducted at seven experienced neurovascular centers. Each participating site was required to have at least one physician trained and approved by the sponsor (Medtronic Neurovascular) in the use of the Pipeline with a history of completing at least 20 Pipeline device cases. The institutional review board or ethics committee of each institution approved the study protocol and informed consent form. Written informed consent was obtained from all patients.

Main patient inclusion criteria were as follows: (1) 18–80 years of age; (2) unruptured target IA with a parent artery vessel measuring 1.5–5.0 mm in diameter distal/proximal to target IA; and (3) IA located in the internal carotid artery (ICA) (up to the carotid terminus) or vertebral artery segment up to and including the posterior inferior cerebellar artery. Patients were excluded if they (1) had subarachnoid hemorrhage (SAH) or major surgery in the past 30 days; (2) had anatomy not appropriate for endovascular treatment due to severe intracranial vessel tortuosity, or stenosis determined from baseline or pre-procedure imaging, or a history of intracranial vasospasm not responsive to medical therapy; (3) had any known contraindication to Pipeline Shield as per instructions for use; or (4) were pregnant or breastfeeding women or women who wished to become pregnant during the duration of the study.

Baseline assessments
Patient demographic data, relevant comorbidities, and aneurysm characteristics such as type, size, and location were recorded at baseline. Patients underwent a baseline neurologic examination prior to placement of the Pipeline Shield device. An antiplatelet reactivity test was not mandatory and was done in 21 cases. For supplemental analyses, a P2Y12 receptor inhibition range of 60–240 P2Y12 Reaction Units (PRUs) was considered the reference and the Aspirin Reaction Unit (ARU) cut-off was 550.

Procedure
Antiplatelet therapy was mandatory prior to the procedure and was administered per local institutional protocol (see online supplementary table S1). Per site report, an initial 70–100 U/kg heparin bolus was administered intraoperatively to 18 of the patients and then discontinued (not reversed) at the end of the procedure. No postoperative heparin was administered to any patients.

Antiplatelet therapy was continued after discharge per standard of care. The following microcatheters were used during the procedures: Marksman (eV3, Irvine, California, USA), Headway (MicroVention, Tustin, California, USA), Reverse Micrcatheter (Reverse, Irvine, California USA), Echelon (eV3), or Excelsior (Stryker, Fremont, California, USA). Procedural characteristics such as procedure time, number of Pipeline Shield devices used, and device deployment success were collected. Angiographic images in standard and working views that corresponded to the treatment angiograms were interpreted by an independent core radiology laboratory. Aneurysm occlusion was classified using the Raymond–Roy Scale: class I, complete occlusion; class II, residual neck; and class III, residual aneurysm.

Follow-up assessments
Patients underwent repeat neurologic examinations prior to discharge and had a follow-up office visit or telephone call 30 days after the procedure.

Safety reporting
Investigators were required to report all SAEs in addition to adverse events with an underlying neurologic cause or those deemed to be related to the study device or procedure. For the purposes of this study protocol, stroke was defined as a focal neurologic deficit of presumed vascular origin persisting more than 24 hours from symptom onset for which a neuroimaging study or other quantitative study did not indicate a different etiology. The 24-hour criterion was excluded if the subject underwent cerebrovascular surgery or died during the first 24 hours of symptom onset. Stroke severity was graded by the investigator as major or minor. Major stroke was defined as a stroke that was present after 7 days and was associated with a worsening of the National Institutes of Health Stroke Scale (NIHSS) score by ≥4 points. Minor stroke was defined as a stroke that resolved completely within 7 days or worsening of NIHSS score by ≤3 points. An independent Clinical Events Committee (CEC) adjudicated all adverse events that occurred during the 30-day post-procedure period.

Statistical analysis
Data from the PFLEX study were analyzed based on the intent-to-treat population. Discrete variables were summarized using frequency and percentage. Continuous variables were summarized using the number of observations (N), mean, SD, median, and minimum and maximum values. All statistical analyses were performed using SAS V9.2 or higher (SAS Institute, Cary, North Carolina, USA).

RESULTS
Between March and October 2015, 50 patients with 50 unruptured target aneurysms were included in the PFLEX study. Although 50 aneurysms were considered as the target population for the study, there were two cases in which the device covered the arterial segments that each included an additional aneurysm. Baseline patient characteristics including demographics and medical history are shown in table 1. The mean age was 53.0±13.0 years and 41 (82%) patients were female. Twelve (24%) patients were hypertensive at baseline and 24 of the patients enrolled were current or former smokers. Previous SAH was reported in 11/50 (22%) cases.

Platelet reactivity testing results are shown in online supplementary table S2. Of the 21 patients who underwent platelet reactivity testing, three patients (14.3%) were considered to be clopidogrel hyperresponders, one patient (4.8%) was considered a hyper-responder, and five patients (23.8%) were considered aspirin borderline hyperresponders. The clopidogrel hyper-responder (PRU <60) was placed on clopidogrel every third day to reach the target PRU range (PRU >60). While two
of the three hyporesponders to clopidogrel (PRU >240) continued with the same dose with no medication adjustment, one patient received a double dose (150 mg/day). In four of the five hyporesponders to aspirin (ARU ≥550) there were no medication adjustments and one case received a double dose (200 mg/day). Decisions on antiaggregation management were made by the operator.

The baseline characteristics of the target aneurysms were evaluated by the core laboratory and are presented in table 2. Mean target aneurysm maximal diameter was 8.82±6.15 mm. Of the 50 target aneurysms, 38 (76.0%) were small (<10 mm), 11 (22.0%) were large (≥10 and <25 mm), and one (2.0%) was giant (≥25 mm) in size. Forty-seven (94.0%) aneurysms were saccular and three (6.0%) were fusiform. The majority (94%, n=47) of the aneurysms were located in the ICA (C4-cavernous segment: 14; C6-ophthalmic segment: 24; C7-communicating segment: 9; C6-ophthalmic segment: 24; C7-communicating segment: 9). Nine cases (18%) (site reported) and coils were used in seven cases (14%) (core laboratory reported). Stents were not used as an adjunct device in any of the patients.

Immediate post-procedure outcomes are presented in table 3. Of the 50 patients, five (10%) had complete stasis, 18 (36%) had significant stasis, and 27 (54%) did not have any disruption of inflow jet. Post-treatment complete occlusion was achieved in five cases (10%) and the rest had residual aneurysms. In all 50 cases the aneurysm neck was successfully covered by the Pipeline Shield device, with complete wall apposition in 48 patients (96.0%). In the remaining two patients, complete wall apposition could not be achieved. Poor apposition to the cephalad wall of the parent artery at the proximal margin was observed in one patient. There was incomplete apposition in the proximal segment in another patient; however, the device was well apposed around the anterior genu and across the neck of the aneurysm. The device was found to be extended to the posterior communicating artery origin. Side branches were covered in all 47 patients: ophthalmic artery in 40 (80%) cases, anterior choroidal artery in 14 (28.0%), posterior communicating artery in 16 (32.0%), and posterior inferior cerebellar artery in two (4.0%). No retreatments were reported during the 30-day post-procedure period.

CEC-adjudicated adverse event results are presented in table 4. No primary endpoint events of major stroke in the territory supplied by the treated artery or neurologic death occurred...
following the procedure, incomplete occlusion (class III on the Raymond–Roy Scale) was noted. Four days after the procedure the subject was readmitted to hospital with a severe right-sided headache with vomiting and vision disturbance. No neurologic deficits were noted, NIHSS was 0, and CT was unremarkable. The patient was treated with medications for this procedure-related event which resolved 4 days after onset.

**Case 2 (SAE diplopia)**

A patient in his/her 60s with a history of a previous SAH and baseline diplopia was treated with a 5.0 mm device with two successive attempts at resheathing for a previously ruptured recurrent aneurysm in the left ICA (C7 segment). The aneurysm measured $4.5 \times 4.3$ mm and had a neck size of 4.5 mm. Good wall apposition was achieved and the entire neck was covered. Following the procedure complete occlusion (class I on the Raymond–Roy Scale) was noted. No intraprocedural complications occurred. Two days after the procedure the subject’s baseline diplopia worsened. An MRI of the head with contrast and a time-of-flight intracranial MR angiogram showed that the left ICA Pipeline stent remained patent. There was persistent filling of the left posterior communicating artery aneurysm which was marginally reduced. Tiny multifocal cerebral infarctions (areas of restricted diffusion), which were likely embolic, were seen in the left caudate head, centrum semiovale, and the left cerebellum adjacent to the fourth ventricle. The diplopia was treated with an eye patch and resolved the next day. The event was deemed to be procedure-related and serious due to prolongation of the initial hospitalization.

**Case 3 (SAE retroperitoneal hematoma)**

A patient in his/her 20 s who was a former smoker was treated with a 4.0 mm device for an unruptured saccular IA located in the right ICA at the C6 (ophthalmic segment). The aneurysm measured $7 \times 6$ mm and had a neck size of 6 mm. The implant covered the entire neck and, following the procedure, a class III occlusion on the Raymond–Roy Scale was noted. No intraprocedural complications were seen. Following the procedure, on the same day, the subject developed hemodynamic instability due to prolonged bleeding from the access (femoral) puncture site. The subject appeared pale and clammy and complained of increased pain in the lower abdomen with an accompanying drop in blood pressure (systolic blood pressure 60 mm Hg). CT angiography of the diaphragm to thigh confirmed the presence of a high puncture of the common femoral artery at the level of the mid-inguinal ligament with active extravasation into the retroperitoneal space and a resultant large-volume retroperitoneal hematoma extending up to the level of the duodenum. The subject underwent an emergency surgical intervention for management of the hematoma. The hematoma was evacuated and no active bleeding was noted post-procedure. Aspirin therapy was continued while clopidogrel was temporarily discontinued. A follow-up CT of the abdomen demonstrated no signs of bleeding and this procedure-related SAE was considered resolved in 2 weeks.

**DISCUSSION**

The clinical experience of first- and second-generation PEDs has been well reported in previous studies. To our knowledge, this is the first multicenter clinical study describing the use of PED with Shield Technology. The findings from this analysis demonstrate a preliminary early safety profile with no incidence of major stroke or neurologic death. They also demonstrate a high rate of technical success, as 53 of the 54 Pipeline

### Table 3  Procedural outcomes as evaluated by the core laboratory

<table>
<thead>
<tr>
<th>Variable</th>
<th>Results, n (%) (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunctive devices used</td>
<td></td>
</tr>
<tr>
<td>Balloons</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Coils</td>
<td>7 (14.0%)</td>
</tr>
<tr>
<td>Post-deployment stasis</td>
<td></td>
</tr>
<tr>
<td>Complete stasis</td>
<td>5 (10.0%)</td>
</tr>
<tr>
<td>Significant stasis</td>
<td>18 (36.0%)</td>
</tr>
<tr>
<td>No disruption of inflow jet</td>
<td>27 (54.0%)</td>
</tr>
<tr>
<td>Aneurysm occlusion*</td>
<td></td>
</tr>
<tr>
<td>Complete occlusion</td>
<td>5 (10.0%)</td>
</tr>
<tr>
<td>Residual neck</td>
<td>0</td>
</tr>
<tr>
<td>Residual aneurysm</td>
<td>45 (90.0%)</td>
</tr>
<tr>
<td>Complete wall apposition</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48 (96.0%)</td>
</tr>
<tr>
<td>No</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td>Entire aneurysm neck covered by PFED</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (100.0%)</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Side branch covered by PFED</td>
<td></td>
</tr>
<tr>
<td>Ophthalmic artery</td>
<td>40 (80.0%)</td>
</tr>
<tr>
<td>Anterior choroidal artery</td>
<td>14 (28.0%)</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>16 (32.0%)</td>
</tr>
<tr>
<td>Posterior inferior cerebellar artery</td>
<td>2 (4.0%)</td>
</tr>
</tbody>
</table>

* Aneurysm occlusion assessed according to Raymond–Roy classification.

### Table 4  Adverse events during 30-day post-procedure period as adjudicated by the Clinical Events Committee (CEC)

<table>
<thead>
<tr>
<th>CEC-adjudicated events</th>
<th>Results, n (%) (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Retropertitoneal hemorrhage</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Non-serious</td>
<td></td>
</tr>
<tr>
<td>Access site hematoma</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Carotid artery dissection</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4.0%)</td>
</tr>
</tbody>
</table>

during the 30-day post-procedure period. There were five non-SAEs (all CEC-adjudicated), including access site hematoma (1), carotid artery dissection (1), cerebral infarction (1), and nausea (2). The cerebral infarction did not have any clinical consequences.

There were three SAEs (all CEC-adjudicated), including headache (1), diplopia (1), and retroperitoneal hemorrhage (1). All of the non-SAEs and SAEs were determined to be procedure-related. Descriptions of the three CEC-adjudicated SAEs are provided below.

**Case 1 (SAE headache)**

A patient in his/her 30 s with a target unruptured saccular giant IA measuring $28.6 \times 23.1$ mm and neck 9 mm wide located in the right ICA (C4 segment) was treated with a 4.00 mm device with no intraoperative complications. The entire neck of the aneurysm was covered and complete wall apposition achieved.
Shield devices (98%) were successfully implanted in the target sites. This finding corroborates the technical success rate found in a previous single-center study that used the second-generation device (Pipeline Flex).10

Safety outcomes from the current study correspond to findings from previous studies on earlier iterations of the PED.6 In the overall patient sample from the IntrePED study, the largest clinical study of PED to date, morbidity, mortality, and ischemic stroke rates at >30 days were 7.4%, 3.8%, and 4.5%, respectively. In the subgroup of patients with small aneurysms, the 30-day stroke rate was 2.7%.6 Considering that the vast majority of cases enrolled in the current PFLEX study were small aneurysms located in the ICA, our 30-day major stroke rate of 0% correlates with the results from the subgroup of IntrePED patients with similar characteristics. Additionally, a previous study that described the first preliminary experiences with the Pipeline Flex delivery system in 30 patients reported a 6.7% major clinical event rate but no minor events or deaths in the 30 days after treatment.4 Together, these findings demonstrate similar short-term safety outcomes between the second-generation and the current third-generation PED.

The complication rate using the first-generation PED has been strongly associated with the number of devices used and complex maneuvers, especially during the learning curve.4 The second-generation Pipeline with the modified delivery system (Pipeline Flex) allowed for a more precise deployment, lowering the average devices used per case.4 In the ‘third version’ of Pipeline (Pipeline Shield) the delivery system has not changed from the previous generation device, so no learning curve has been necessary. The average number of Pipeline Shield devices used in the current study (1.1±0.27 devices per case) is comparable to similar experiences with the second-generation device (Pipeline Flex).4 10 11 Also, as with previous descriptions using the current delivery system,4 10 11 no complications were related to reshethering maneuvers in our cohort.

In the current study there were no thromboembolic or any intracranial hemorrhagic events, despite the fact that some patients had prethrombotic conditions such as hyporesponsiveness to aspirin or clopidogrel, without medication adjustment. The IntrePED study, which used the first-generation PED device, reported an intracranial hemorrhage rate of 2.5%.6 A standard antiplatelet protocol is difficult to determine as there are no dedicated studies to establish dose, duration, and combination of medications. A continually increasing number of antiplatelet medications are available. Additionally, individual patient responses to certain antiplatelet medications have been found to vary significantly.21 22

The occurrence of hemorrhagic and thromboembolic complications can be predicted by monitoring the P2Y12 receptor inhibition prior to treatment.21 The preoperative PRU should be between 60 and 240 and ideally between 70 and 150.23 In the current study, 81% of the patients were well within the suggested range (PRU 60–240), which explains the absence of hemorrhagic and thromboembolic complications despite patients having prethrombotic conditions. A possible reason for this may be the effect of PC polymer-based Shield Technology.

Our early results in 50 aneurysms followed for 30 days post-procedure show comparable results with the published literature.4 10 18 The short follow-up period of this study is a limitation; however, we consider 30 days to be an acceptable early safety period considering that, in the IntrePED study, the majority of strokes occurred within 30 days of treatment. Long-term results are currently being evaluated and will be published when available. Another limitation is that our main subgroup of aneurysms comprised small size aneurysms located at the ICA, where the complication rate described in the literature is low. While the present study exhibited promising results, longer follow-up will provide the incidence of safety outcomes from 6-month and 1-year assessments of this new device. At present, standard antiplatelet regimens should be recommended based on this preliminary experience.

CONCLUSIONS

The results of this first experience with the new PED with Shield Technology demonstrated high technical success with no major complications. This surface modification does not increase the intraprocedural complication rate compared with previous generations of the device. The overall results of this study confirm the early safety of the device.

Author affiliations

1 Department of Interventional Neuroradiology/Endovascular Neurosurgery, Fundación Jiménez-Díaz, Madrid, Spain
2 Queen Elizabeth Hospital Birmingham, Edgbaston, UK
3 Department of Interventional Neuroradiology, Hellenic Air Force Hospital, Goudi, Greece
4 Department of Neuroradiology, Institut für Neuroradiologie, Charité, Berlin, Germany
5 Department of Interventional Neuroradiology, Foundation Neurological Institution ‘C Besta’, Milan, Italy
6 Department of Neuroradiology, Alfred Krupp Krankenhaus, Essen, Germany
7 Department of Neuroradiology, Ziekenhuizen Oost-Limburg, Genk, Belgium
8 Department of Neuroradiology, Ospedale Niguarda Ca’ Granda, Milan, Italy

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Contributors

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafted the work or revised it critically for important intellectual content; and provided final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

MM-G serves as a proctor and consultant for Medtronic. SML receives honoraria from Medtronic in relation to proctoring, speaking, and consulting. TL previously consulted and proctored for Covidien, Stryker, and MicroVention, and currently serves as a proctor and consultant for Scepter Medical. EPB receives honoraria from Medtronic and serves as a consultant for Medtronic.

Ethics approval

Institutional Review Board.

Provenance and peer review

Not commissioned; externally peer reviewed.

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