



Pipeline Embolization Devices for the Treatment of Intracranial Aneurysms, Single-Center Registry: Long-Term Angiographic and Clinical Outcomes from 1000 Aneurysms

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BACKGROUND: Prospective studies have established the safety and efficacy of the Pipeline™ Embolization Device (PED; Medtronic) for treatment of intracranial aneurysms (IA).

OBJECTIVE: To investigate long-term outcomes from the Pipeline Embolization Devices for the Treatment of Intracranial Aneurysms (PEDESTRIAN) Registry.

METHODS: The PEDESTRIAN Registry data were retrospectively reviewed, which included patients (March 2006 to July 2019) with complex IAs treated with PED. Patients with unfavorable anatomy and/or recurrence following previous treatment were included and excluded those with acute subarachnoid hemorrhage. The primary angiographic endpoint was complete occlusion and long-term stability. Clinical and radiological follow-up was performed at 3 to 6 mo, 12 mo, and yearly thereafter.

RESULTS: A total of 835 patients (mean age 55.9 ± 14.7 yr; 80.0% female) with 1000 aneurysms were included. Aneurysms varied in size: 64.6% were small (≤ 10 mm), 25.6% were large (11–24 mm), and 9.8% were giant (≥ 25 mm). A total of 1214 PEDs were deployed. Follow-up angiography was available for 85.1% of patients with 776 aneurysms at 24.6 ± 25.0 mo (mean). Complete occlusion was demonstrated in 75.8% of aneurysms at 12 mo, 92.9% at 2 to 4 yr, and 96.4% at >5 yr. During the postprocedural period, modified Rankin Scale scores remained stable or improved in 96.2% of patients, with stability or improvement in 99.1% of patients >5 yr. The overall major morbidity and neurological mortality rate was 5.8%.

CONCLUSION: This study demonstrated high rates of long-term complete aneurysm occlusion, stable or improved functional outcomes, and low rates of complications and mortality. Clinical and angiographic outcomes improved over long-term follow-up, demonstrating that endovascular treatment of IA with PED is safe and effective.

KEY WORDS: Flow diverter, Follow-up studies, Intracranial aneurysm, Stroke, Subarachnoid hemorrhage, Pipeline Embolization Device

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The introduction of flow diverters (FD) to treat intracranial aneurysms (IA) represented a pivotal moment in the field of interventional neuroradiology, allowing occlusion of the aneurysm and parent vessel reconstruction via neointimalization across

ABBREVIATIONS: ASPIRe, Aneurysm Study of Pipeline in an Observational Registry; FD, flow diverter; HR, Hazard-Ratio; IA, intracranial aneurysm; ICA, internal carotid artery; IntrePED, International Retrospective Study of Pipeline Embolization Device; PED, Pipeline Embolization Device; PEDESTRIAN, Pipeline Embolization Devices for the Treatment of Intracranial Aneurysms; PREMIER, Prospective Study on Embolization of Intracranial Aneurysms with the Pipeline Device; PRU, P2Y12 reaction unit; PUFFS, Pipeline for Uncoilable or Failed Aneurysms; RRC, Raymond Roy Classification

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the stent strut.¹ The Pipeline™ Embolization Device (PED) (Medtronic, Dublin, Ireland) is the most extensively investigated FD available on the market.² Initially, treatment with the PED was aimed principally at wide-necked and uncoilable aneurysms located in the anterior circulation below the internal carotid artery (ICA) bifurcation.³⁻⁶ As experience with PED grew and the technology matured, its use has expanded to include less complex and posterior circulation aneurysms, along with a greater understanding of associated complications⁷⁻¹²; however, long-term follow-up data on these new indications are limited. Here, we report the results of the Pipeline Embolization Devices for the Treatment of Intracranial Aneurysms (PEDESTRIAN) registry. We report the clinical and radiographic results from 1000 aneurysms of various size and morphology treated with the PED, including those patients with long-term follow-up (≥ 5 yr).

METHODS

Study Design and Patient Population

PEDESTRIAN is a single-center prospective registry conducted to evaluate the safety and efficacy of the PED for patients with IAs treated in routine clinical practice at a tertiary level neurosurgical center. Data were collected between March 2006 and July 2019. The decision to use PED, PED Flex, or PED Flex with Shield Technology (PED Shield) was determined by a multidisciplinary team that considered alternative treatment strategies and the availability of different device generations during 13 yr of commercialization in Argentina. Written informed consent was obtained from all patients. The institutional ethics committee approved the protocol, which complied with the declaration of Helsinki.

Anatomic inclusion criteria comprised (1) a wide-neck (≥ 4 mm) or unfavorable aspect ratio (≤ 1.5); (2) previous unsuccessful aneurysm treatment with another endovascular technique; (3) complex morphology for which additional coil placement was deemed challenging or prone to high risk of recurrence; (4) fusiform, partially thrombosed aneurysms or a history of multiple recurrences; and (5) in patients with posterior circulation aneurysms, the potential benefits of the PED were discussed.

Exclusion criteria comprised (1) acute aneurysm rupture or any intracranial hemorrhage; (2) very complex posterior circulation aneurysms or fusiform vertebro-basilar aneurysms; (3) history of bleeding disorder; and/or (4) low platelet count ($< 150 \times 10^9/L$).

Antiplatelet Procedure

Patients treated before 2011 were pretreated with clopidogrel (75 mg) and aspirin (100 mg) for at least 5 to 7 d before PED treatment. Platelet function tests were performed on all patients from 2011 onwards. With the use of aspirin and P2Y12 inhibitors, thrombocyte inhibition levels were assessed using the VerifyNow assay (Accumetrics, San Diego, California) and the standard thrombocyte aggregation test. After the introduction of VerifyNow testing, hyporesponders to clopidogrel were switched to an alternative antiplatelet agent. After 2015, all patients were switched to prasugrel 10 mg daily. The procedure was performed only if platelet inhibition was $> 30\%$ from baseline. A P2Y12 reaction unit inhibition of 30% to 40% was generally used

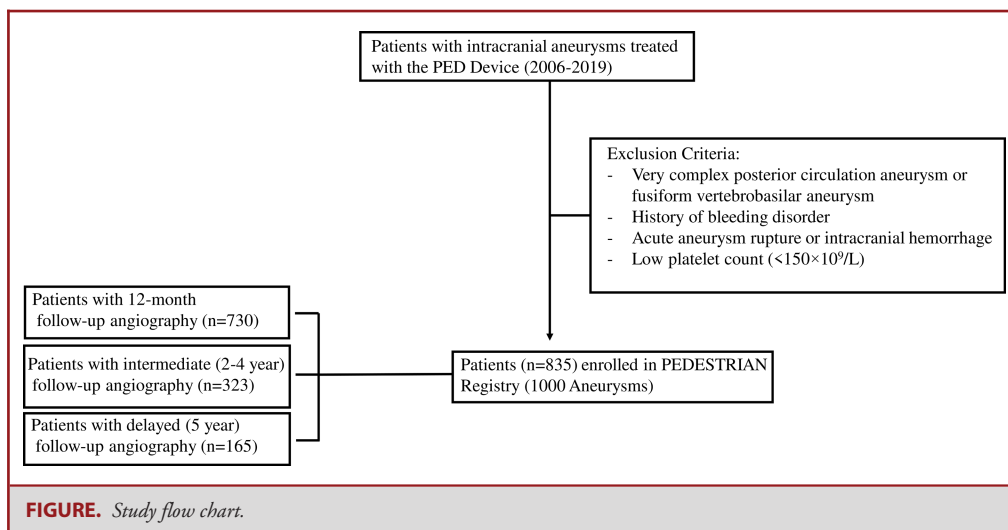
TABLE 1. Patient and Aneurysm Characteristics

| Characteristic | Frequency |
|--------------------------------------|----------------------|
| Age, yr | 55.9 \pm 14.7 |
| Female | 80.4% (671/835) |
| Male | 19.6% (164/835) |
| Comorbidities | |
| Hypertension | 45.0% (376/835) |
| Smoker | 18.2% (152/835) |
| Family history of aneurysm | 6.7% (56/835) |
| Baseline mRS 0-2 | 93.6% (782/835) |
| Clinical presentation | |
| Incidental | 35.8% (299/835) |
| Neurological mass effect | 19.6% (164/835) |
| Ischemic stroke | 3.7% (31/835) |
| Headache | 24.9% (208/835) |
| Other SAH | 15.9% (133/835) |
| Multiple aneurysms | 29.0% (242/835) |
| Previously treated with PED | 17% (144/835) |
| Aneurysm morphology | |
| Saccular | 84.2% (842/1000) |
| Dissection | 11.0% (110/1000) |
| Fusiform | 3.8% (38/1000) |
| Bliстер | 6.0% (6/1000) |
| Aneurysm size | |
| Small (≤ 10 mm) | 64.6% (646/1000) |
| Large (11-24 mm) | 25.6% (256/1000) |
| Giant (≥ 25 mm) | 9.8% (98/1000) |
| Dome height (saccular aneurysms), mm | 8.1 \pm 6.9 (1-50) |
| Dome width (saccular aneurysms), mm | 6.4 \pm 5.3 (1-45) |
| Neck width (saccular aneurysms), mm | 4.5 \pm 2.7 (1-28) |
| Aspect ratio | 1.7 |
| Aneurysm location, % (n/N) | |
| Anterior circulation | 91.0% (910/1000) |
| Posterior circulation | 9.0% (90/1000) |
| ICA | 86.7% (867/1000) |
| PCoA | 20% (199/1000) |
| MCA | 4.1% (41/1000) |
| PCA | 1% (10/1000) |
| BA | 3.7% (37/1000) |
| ACoA/ACA | 1.4% (14/1000) |
| ACoA | 64.2% (9/14) |
| ACA | 35.8% (5/14) |
| VA | 2.9% (29/1000) |
| PICA | 1% (10/1000) |

ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; PCA = posterior cerebral artery; PCoA = posterior communicating artery; PED = Pipeline Embolization Device; PICA = posterior inferior cerebellar artery; SAH = subarachnoid hemorrhage; SD = standard deviation; VA = vertebral artery. Data are % (n/N) or mean \pm SD.

as a minimum degree of preprocedure P2Y12 receptor inhibition. Patients with inhibition $< 30\%$ were reloaded and the assay rechecked. Patients found to be allergic to clopidogrel or prasugrel were switched to ticagrelor.

In patients without antiplatelet therapy, intravenous aspirin (500 mg) and tirofiban (Aggrastat™) or intra-arterial abciximab (ReoPro™) was



used pretreatment and during the procedure as an antithrombotic agent. Dual antiplatelet medication was continued for 6 mo postprocedure for anterior circulation aneurysms and 12 mo for posterior circulation aneurysms. Aspirin was to be continued for life.

Procedural Technique

All patients were treated under general anesthesia via a transfemoral arterial approach, using either a biplane (Philips Allura X-per FD20/10 Biplane) or monoplane (Allura X-per FD 20 Monoplane Cardiovascular X-Ray System) angiography suite. Following arterial access, intravenous heparin was administered in all patients to maintain an activated clotting time between 250 and 300 s. After standard angiographic projection, an intra-arterial 3D rotational angiogram was performed in all patients to determine the optimal working position with 3D reconstructions and stent simulation program.

PEDs were deployed following a standard procedure. A triaxial system was used in all cases to maximize support during forward loading of the system and to optimize stent opening and apposition. At first, catheters and microcatheters such as Envoy MP 6 (Cordis Neurovascular) and Guider 6 Fr (Boston Scientific) were used over an 8 Fr multipurpose guiding catheter. Subsequently, a Renegade Hi-Flo (Boston Scientific) and Masstransit (Cordis Neurovascular) microcatheter were used with a 6-Fr-long sheath, typically a Shuttle (Cook Medical, Bloomington, Indiana), placed in the proximal common carotid artery or internal carotid artery (ICA) through which a distal access catheter tracked into the distal cervical ICA. A 0.027-inch microcatheter was used to deliver the PED in all cases, typically the Marksman (Medtronic) or Excelsior XT27 (Stryker Neurovascular, Fremont, California).

The decision to implant more than one PED device was based on anatomic circumstances or angiographic findings after implantation of the first, such as (1) unchanged contrast flow within the aneurysm; (2) a deceleration of contrast circulation within the IA without contrast stagnation into the venous phase; (3) fusiform IA with incomplete reconstruction of the parent artery; or (4) acute complete occlusion of the IA. Indications for coiling were (1) large or giant aneurysms and (2) partially thrombosed aneurysms. When coiling was

performed in conjunction with PED treatment, a “jailing” technique was used.

Study Endpoints

Procedural success was defined as: (1) PED deployment with complete coverage of the aneurysm neck and correct wall apposition; (2) preserved patency of the parent artery; and (3) absence of intraoperative complications. PED apposition and visualization of small vessel perforators (50-100 microns) was assessed using flat-panel intra-arterial rotational angiography (VasoCT, Philips Healthcare, Best, the Netherlands).

Angiographic and clinical follow-up was performed at 3, 6, and 12 mo and annually thereafter. The primary angiographic endpoint was complete aneurysm occlusion using the Raymond Roy Classification (RRC I, II, and III)¹³ during follow-up and long-term stability. Two independent senior interventional neuroradiologists blinded to the procedure reviewed all angiograms. Clinical outcome was assessed using the modified Rankin Scale (mRS). Major adverse cerebrovascular events included death, stroke, target vessel reintervention, and nonfatal myocardial infarction. A health questionnaire was sent to living patients with questions regarding eventual re-admissions and cerebrovascular events. Long-term survival data were obtained from municipal civil registries.

Statistical Analysis

Discrete variables are displayed as counts and percentages, and continuous variables as mean \pm standard deviation if normally distributed or as median (interquartile range) in case of non-Gaussian distribution. Comparisons between groups were performed using independent samples Student *t* test for continuous variables and Fisher exact tests for categorical variables. Cox proportional hazard models were used to assess risk reduction of adverse events. Patients lost to follow-up were considered at risk until the date of last contact and censored thereafter. Logistic regression analyses were performed to identify independent predictors of events, including within the model clinical, angiographic, and procedural variables that were significant at univariate analysis. All analyses were performed using SPSS software, version 25 (Chicago, Illinois). A 2-sided *P* value $< .05$ indicated statistical significance.

RESULTS

Baseline Patient and Aneurysm Characteristics

A total of 835 patients (mean age 55.9 ± 14.7 yr; 80.4% [671/835] female) with 1000 aneurysms were included (Table 1). A patient inclusion flowchart is presented in the Figure. In total, 376 (45.0%) patients were diagnosed with hypertension, 152 (18.2%) were smokers and 56 (6.7%) had a known family history of aneurysms. The majority of patients had a baseline mRS ≤ 2 (93.6% [782/835]). The majority of patients had a single aneurysm (71.0% [593/835]), and 144 (17.2%) patients had undergone previous treatment with the PED.

The majority (64.6% [646/1000]) of aneurysms were small (≤ 10 mm), 25.6% (256/1000) were large (11-24 mm), and 9.8% (98/1000) were giant (≥ 25 mm). Most aneurysms (84.2% [842/1000]) were saccular. The mean saccular aneurysm dome height was 8.1 ± 6.9 mm, dome width was 6.4 ± 5.3 mm, and neck width was 4.5 ± 2.7 mm, and mean aspect ratio was 1.7. The majority (91.0% [910/1000]) were located in the anterior circulation, with most arising from the ICA (86.7% [867/1000]). Aneurysms located in the posterior circulation (9.0% [90/1000]) were primarily located on the vertebral artery (2.9% [29/1000]).

Operative Results

In total, 1214 PEDs were deployed, with a single device in 84.2% (842/1000) and ≤ 2 devices in 95.8% (958/1000) of cases (Table 2). Adjunctive coiling was performed in 9.3% (93/1000). Intraoperative technical complications occurred in 4.8% (48/1000) of treated aneurysms, with incomplete wall apposition of the device requiring balloon angioplasty representing the majority of technical complications (3.3% [33/1000]).

Radiographic Results

Follow-up catheter angiography was available for 87.4% (730/835) of patients with 861 aneurysms at mean 24.6 ± 25.0 mo. Twelve-month angiography revealed RRC I (complete) occlusion of 75.8% (588/776) of aneurysms, whereas 4.4% (34/776) had a residual neck (RRC II) and 19.8% (154/776) showed residual filling (RRC III). Intermediate angiographic follow-up (2-4 yr) was available for 38.7% (323/835) of patients, at which time RRC I occlusion was observed in 92.9% (300/323), RRC II in 3.1% (10/323), and RRC III in 4.0% (13/323). Delayed angiography beyond 5 yr was available for 19.8% (165/835) patients, at which time RRC I occlusion was observed in 96.4% (159/165), RRC II 1.8% (3/165), and RRC III in 1.8% (3/165). No cases of aneurysm recanalization occurred.

On logistic regression, factors that influenced 12-mo complete aneurysm occlusion were age (Hazard-Ratio (HR) 0.98 [95% CI 0.96-0.99]; $P < .0001$), male sex (HR 0.60 [95% CI 0.39-0.92]; $P = .02$), and hypertension (HR 0.69 [95% CI 0.47- 0.99]; $P = .047$).

TABLE 2. Procedural Characteristics and Outcomes

| Characteristic | Frequency |
|---|---------------------------|
| Devices deployed | 1214 |
| Devices/aneurysm | |
| 1 | 84.2% (842/1000) |
| ≤ 2 | 95.8% (958/1000) |
| Adjunctive coiling | 9.3% (93/1000) |
| Intraoperative complications | 4.8% (48/1000) |
| Incomplete wall apposition requiring balloon angioplasty | 3.3% (33/1000) |
| Wire perforation | 0.1% (1/1000) |
| Distal thrombosis/embolism | 0.2% (2/1000) |
| In stent thrombosis | 0.2% (2/1000) |
| Mean angiographic follow-up, mo | 24.6 ± 25.0 (N = 861) |
| Aneurysm occlusion | |
| 12-mo follow-up | 77.6% (776/1000) |
| RRC I | 75.8% (588/776) |
| RRC II | 4.4% (34/776) |
| RRC III | 19.8% (154/776) |
| Intermediate follow-up (2-4 yr) | 32.3% (323/1000) |
| RRC I | 92.9% (300/323) |
| RRC II | 3.1% (10/323) |
| RRC III | 4.0% (13/323) |
| Delayed follow-up (>5 yr) | 16.5% (165/1000) |
| RRC I | 96.4% (159/165) |
| RRC II | 1.8% (3/165) |
| RRC III | 1.8% (3/165) |
| Aneurysm recanalization | 0% (0/1000) |
| mRS (≤ 30 d postprocedure) | |
| Stable | 92.9% (776/835) |
| Improved from >2 preoperative to ≤ 2 postoperative | 3.2% (27/835) |
| Worsened from ≤ 2 preoperative to >2 postoperative | 2.0% (17/835) |
| Worsened from >2 preoperative to mRS 6 | 0.1% (1/835) |
| mRS 6 | 2.2% (18/835) |
| mRS (30 d postprocedure to last follow-up) | |
| Stable | 97.4% (813/835) |
| Improved from >2 preoperative to ≤ 2 postoperative | 1.0% (8/835) |
| Worsened from ≤ 2 preoperative to >2 postoperative | 1.7% (14/835) |
| Retreatment | 4.0% (40/1000) |
| Complications | |
| Stroke | 3.6% (30/835) |
| In stent thrombosis | 2.5% (21/835) |
| Hemorrhage | 1.8% (15/835) |
| Aneurysm rupture | 1.4% (12/835) |
| Intraparenchymal hemorrhage | 0.4% (3/835) |
| All-cause mortality | 4.6% (38/835) |
| Neurological mortality | 3.1% (26/835) |

mRS = modified Rankin Scale; RRC = Raymond Roy Classification; SAH = subarachnoid hemorrhage; SD = standard deviation.
Data are % (n/N) or mean \pm SD.

TABLE 3. Patient and Aneurysm Characteristics in PUF5, IntrePED, ASPIRe, and PEDESTRIAN

| Characteristic | PUF5 ² | IntrePED ²¹ | ASPIRe ²² | PEDESTRIAN |
|-----------------------------------|-------------------|------------------------|----------------------|----------------------|
| Patients (N) | 108 | 793 | 191 | 835 |
| Age, yr | | | | |
| Mean ± SD (N) | 57.0 ± 11.3 (108) | 56.9 ± 14.2 (789) | 59.9 ± 12.5 (191) | 55.9 ± 14.7 |
| Median | 59.0 | 58.0 | 60.0 | 58.0 |
| Range | 30.2-75.0 | 3.0-86.0 | 25.0-89.0 | 7.0-88.0 |
| Sex | | | | |
| Male | 11.1% (12/108) | 20.3% (161/793) | 16.2% (31/191) | 19.64% (164/835) |
| Female | 88.9% (96/108) | 79.7% (632/793) | 83.8% (160/191) | 80.35% (671/835) |
| Aneurysms (N) | 108 | 906 | 207 | 1000 |
| Aneurysm size, mm | | | | |
| Mean ± SD (N) | 18.2 ± 6.5 (108) | 10.7 ± 7.7 (896) | 14.5 ± 6.9 (207) | 8.1 ± 6.9 (saccular) |
| Median | 17.5 | 9.0 | 12.0 | 7.2 |
| Range | 6.2-36.1 | 1.0-55.0 | 0.9-41.0 | 1.0-50.0 (saccular) |
| Aneurysm neck, mm | | | | |
| Mean ± SD (N) | 8.8 ± 4.3 (108) | 6.2 ± 4.9 (812) | 7.1 ± 4.2 (202) | 4.5 ± 2.7 mm |
| Median | 8.1 | 5 | 6 | 7 |
| Range | 4.1-36.1 | 0.8-53.0 | 0.0-32.0 | 1.0-28.0 mm |
| Aneurysm location, % (n/N) | | | | |
| ICA | 100% (108/108) | 91.8% (685/746) | 98.4% (185/188) | 86.7% (867/1000) |
| PCoA | 0% | 8.2% (61/746) | 1.6% (3/188) | 20% (199/1000) |
| MCA | 0% | 4.9% (44/906) | 1.4% (3/207) | 4.1% (41/1000) |
| PCA | 0% | 1.7% (15/906) | 0.5% (1/207) | 1% (10/1000) |
| BA | 0% | 4.9% (44/906) | 2.9% (6/207) | 3.7% (37/1000) |
| ACoA/ACA | 0% | 2.3% (21/906) | 2.9% (6/207) | 1.4% (14/1000) |
| ACoA | 0% | 57.1% (12/21) | 83.3% (5/6) | 64.2% (9/14) |
| ACA | 0% | 42.9% (9/21) | 16.7% (1/6) | 35.8% (5/14) |
| VA | 0% | 3.6% (33/906) | 1.4% (3/207) | 2.9% (29/1000) |
| PICA | 0% | 0.3% (3/906) | 0% | 1% (10/1000) |
| Multiple PEDs, % (n/N) | 98.1% (105/107) | 34.1% (308/904) | 18.8% (39/207) | 15.8% (158/1000) |
| Devices/aneurysm | 3 | N/A | 1.20 | 1.21 |
| Devices | N/A | N/A | 191 | 1214 |

ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PCoA = posterior communicating artery; PED = Pipeline Embolization Device; PICA = posterior inferior cerebellar artery; SD = standard deviation; VA = vertebral artery. Table republished from Kallmes et al,¹⁶ with modification, by permission from JNSPG.

Clinical Results

Retreatment was required in 4.0% (40/1000) of aneurysms, of which 92.5% (37/40) involved implanting another FD device. In one aneurysm, additional coils were placed using a “jail” technique, lateral to the implanted PED despite it being in position across the aneurysm neck.

In the periprocedural period (≤ 30 d), 92.9% (776/835) of patients remained stable with improvement in mRS from >2 preoperatively to ≤ 2 postoperatively in 3.2% (27/835). Worsening of mRS from ≤ 2 preoperatively to >2 postoperatively was observed in 4.2% (35/835) of patients, of which 51% (18/35) were mRS 6 in the periprocedural period. Between 30 d and last recorded clinical follow-up (mean 29 ± 31.1 mo), 97.4% (813/835) of patients had a stable mRS. mRS remained stable or improved in 96.2% (803/835) of patients in the periprocedural period, increasing to 99.1% (828/835) in the longer term (≤ 5 yr).

Multivariate analysis identified age (HR 1.04; 95% CI, 1.01-1.07, $P = .002$) and nonsaccular aneurysm morphology (HR 2.91; 95% CI, 1.06-7.97, $P = .038$) as independent predictors of mRS worsening. No significant differences in worsening were identified between anterior (3.7%) and posterior (5.7%) aneurysm location ($P = .36$), likely due to the large difference in the group sizes (anterior, $n = 749$; posterior, $n = 87$).

Complications

Stroke-related complications occurred in 3.6% (30/835) of patients, the majority of which were caused by in-stent thrombosis (2.5% [21/835]). Nine deaths occurred due to stroke. We found a trend towards lower rates of thromboembolic complications since the implementation of prasugrel, with 26 (4.4%) patients on clopidogrel developing stroke compared with 4 (1.6%) patients on prasugrel (odds ratio 2.74; 95% CI

TABLE 4. Follow-up and Outcomes in PUFs, IntrePED, ASPIRe, and PEDESTRIAN

| | PUFS ² | IntrePED ²¹ | ASPIRe ²² | PEDESTRIAN |
|--|-------------------|------------------------|----------------------|--------------------------|
| Angiographic follow-up, mo | N/A | – | 54% | 87.5% (731/835) |
| Mean ± SD (N) | 50.0 ± 16.9 (101) | N/A | 9.2 ± 4.3 (115) | 24.6 ± 25.0 |
| Median | 60.1 | N/A | 7.6 | 13 |
| Range | 6.6-67.5 | N/A | 3.6-27.2 | 1.0-144 |
| Complete occlusion | | | | |
| 180 d (–20/+42 d) | 73.6% (78/106) | N/A | 78.6% (33/42) | 68.2% (202/296) |
| 1 yr | 86.8% (79/91) | N/A | 78.9% (15/19) | 75.8% (588/776) |
| 3 yr | 93.4% (71/76) | N/A | N/A | 92.9% (300/323) (2-4 yr) |
| 5 yr | 95.2% (59/62) | N/A | N/A | 96.4% (159/165) (>5 yr) |
| Complications | | | | |
| Major morbidity | 4.7% (5/107) | 6.1% (48/793) | 4.7% (9/191) | 2.7% (23/835) |
| Neurological mortality | 2.8% (3/107) | 3.8% (30/793) | 1.6% (3/191) | 3.1% (26/835) |
| Major morbidity and neurological mortality | 5.6% (6/107) | 7.7% (61/793) | 5.8% (11/191) | 5.8% (44/835) |
| All-cause mortality | 3.7% (4/107) | 4.2% (33/793) | 3.7% (7/191) | 4.6% (38/835) |

N/A = not applicable; SD = standard deviation.

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0.95-7.95, $P = .06$). Hemorrhagic complications occurred in 1.8% (15/835) of patients, resulting in 11 deaths. The overall morbidity rate, including from subarachnoid hemorrhage, was 2.7% (23/835). The all-cause mortality rate was 4.6% (38/835), with a neurological mortality rate of 3.1% (26/835). Using Cox logistic regression, only aneurysm size was found to be a significant predictor of neurological death (HR 6.37 [95% CI 2.41-16.81], $P = .0002$).

DISCUSSION

This retrospective study of 1000 aneurysms from the PEDESTRIAN Registry demonstrated high rates of long-term complete aneurysm occlusion, stable or improved functional outcomes, and low rates of complications and mortality. Clinical and angiographic outcomes progressively improved over long-term follow-up, demonstrating IA treatment with PED is safe and effective in a large cohort of aneurysms.

The Pipeline for Uncoilable or Failed Aneurysms trial (PUFS) was a multicenter, prospective, interventional single-arm trial assessing patients with aneurysms arising from the ICA measuring at least 10 mm and neck width at least 4 mm.³ Complete occlusion without major parent artery stenosis or adjunctive use of an embolic agent was observed in 73.6% aneurysms at 180 d, which increased to 86.8% at 1 yr. At 180 d, 87.9% patients had mRS ≤ 1 , and 5.6% experienced a major ipsilateral stroke. Recently, 5-yr follow-up results of PUFs showed progressive occlusion reaching 95.2%.¹⁴ Collectively, these results demonstrate progressive occlusion of aneurysms over time and low risk of delayed rupture. PEDESTRIAN had a larger patient cohort and smaller mean aneurysm size, and aneurysms were implanted with approximately one-third fewer devices per aneurysm (Table 3). Despite these differences, comparable rates of long-term complete

occlusion and complications were observed, with a slightly higher rate of mortality in PEDESTRIAN (Table 4), likely explained by the inclusion of posterior circulation aneurysms, which are known to be challenging.¹⁵

The International Retrospective Study of Pipeline Embolization Device (IntrePED) study was a retrospective analysis from 17 centers around the world.¹⁵ The overall neurological mortality rate was 3.8%. Morbidity and mortality rates were highest in posterior circulation aneurysms (16.4%). Morbidity was higher for giant aneurysms compared to large and small aneurysms (25.8% vs 8.8% vs 5.4%, $P < .01$). After excluding ruptured, dissecting, and fusiform aneurysms, the overall morbidity and mortality rate in IntrePED dropped to 5.7%. Spontaneous aneurysmal rupture occurred in only 5 patients (0.6%), the majority of which occurred within 30 d. The ischemic stroke rate was 4.7%, the majority of which occurred within 30 d, with higher stroke rates amongst patients with posterior circulation aneurysms (7.3%) and giant aneurysms (14.5%). PEDESTRIAN had a larger patient cohort and a smaller mean aneurysm size (Table 3) and a similar percentage of posterior circulation aneurysms.¹⁶ In IntrePED, multiple devices were used in approximately twice as many aneurysms, and there was a higher rate of major morbidity and neurological mortality, whereas mortality rates were comparable (Table 4).¹⁶

The Aneurysm Study of Pipeline in an Observational Registry (ASPIRe) was a prospective, international, multicenter postmarket registry study that evaluated occlusion rates and neurological adverse events.¹⁷ Complete occlusion rates were nearly 75% for patients with angiographic follow-up (median 7.8 mo). Major neurological morbidity at 6 mo occurred in 6.8% of patients, of whom 3 suffered neurological mortality. Compared to ASPIRe, PEDESTRIAN had a larger patient cohort, a smaller mean aneurysm size, neck size, and larger proportion of posterior

circulation aneurysms (Table 3).¹⁶ PEDESTRIAN had slightly lower rates of complete occlusion at 6 mo and 1 yr, although both studies had similar rates of major morbidity and neurological mortality (Table 4).¹⁶

The Prospective Study on Embolization of Intracranial Aneurysms with the Pipeline Device (PREMIER)⁴ was a prospective, multicenter, single-arm trial evaluating the PED in the treatment of wide-necked IAs. At 1 yr, the rate of complete aneurysm occlusion without major parent artery stenosis was 76.8%. Three patients experienced a major stroke, with 1 resulting in neurological death, yielding a morbidity rate of 1.4% and mortality rate of 0.7%. This was the first prospective multicenter study to evaluate the use of the PED in small/medium, unruptured, aneurysms of the ICA or vertebral artery, and demonstrated efficacy levels in line with the previous reports and PEDESTRIAN, as well as low morbidity and mortality rates.

Limitations

Our study has several limitations inherent to the retrospective, single-center design of data analysis, which may limit generalizability of the data, as well as the lack of core lab adjudication.

CONCLUSION

PEDESTRIAN, the largest study to date on the PED, demonstrates high rates of long-term complete occlusion, stable or improved functional outcomes, and low rates of complications and mortality. Clinical and angiographic outcomes progressively improved over long-term follow-up, demonstrating that endovascular treatment of IA with PED is safe and effective.

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