Safety and efficacy of the Pipeline embolization device for treatment of intracranial aneurysms: a pooled analysis of 3 large studies

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OBJECTIVE The authors performed a pooled analysis of 3 studies—IntrePED (International Retrospective Study of the Pipeline Embolization Device), PUFS (Pipeline for Uncoilable or Failed Aneurysms Study), and ASPIRe (Aneurysm Study of Pipeline in an Observational Registry)—in order to assess angiographic outcomes and clinical safety of the Pipeline embolization device (PED).

METHODS IntrePED was a retrospective study, while PUFS and ASPIRe were prospective studies. For each patient included in these studies, the authors collected baseline demographic data, aneurysm characteristics, and procedural details. The primary outcomes for this combined analysis were clinical outcomes, including neurological morbidity and mortality and major ipsilateral intracranial hemorrhage and ischemic stroke. The secondary outcomes were angiographic occlusion rates, which were available for ASPIRe and PUFS only.

RESULTS A total of 1092 patients with 1221 aneurysms were included across the 3 studies. The mean aneurysm size was 12.0 ± 7.8 mm and the mean neck size was 6.6 ± 4.8 mm. The major ipsilateral ischemic stroke rate was 3.7% (40/1091). The major ipsilateral intracranial hemorrhage rate was 2.0% (22/1091). The major neurological morbidity rate was 5.7% (62/1091). The neurological mortality rate was 3.3% (36/1091). The combined major morbidity and neurological mortality rate was 7.1% (78/1091). The complete occlusion rates were 75.0% at 180 days (111/148) and 85.5% at 1 year (94/110). The overall aneurysm retreatment rate was 3.0% (33/1091) at a mean follow-up time of 10.2 ± 10.8 months.

CONCLUSIONS Endovascular treatment of intracranial aneurysms with the PED is safe and effective. Angiographic occlusion rates progressed with follow-up. Rates of stroke, hemorrhage, morbidity and mortality, and retreatment were low, especially given the fact that the aneurysms treated were generally large and wide necked.

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KEY WORDS aneurysm; endovascular; stroke; vascular disorders; interventional neurosurgery

TREATMENT with the Pipeline embolization device (PED, Covidien/Medtronic) is widely accepted as an excellent option for patients with intracranial aneurysms.^{1,4,5,19} Flow diverter devices such as the PED were initially developed for treatment of wide-necked and large

and giant aneurysms, aneurysms that are typically difficult to treat with endosaccular coiling, with or without stent assistance. High rates of complete aneurysm occlusion have been reported in a number of studies, even in large and giant aneurysms.^{1,4,5,7,8,17,19}

ABBREVIATIONS ASPIRe = Aneurysm Study of Pipeline in an Observational Registry; ICA = internal carotid artery; IntrePED = International Retrospective Study of the Pipeline Embolization Device; IQR = interquartile range; PED = Pipeline embolization device; PUFS = Pipeline for Uncoilable or Failed Aneurysms Study.

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TABLE 1. Patient characteristics

Characteristic	PUFS	IntrePED	ASPIRe	Total
Age, yrs				
Mean $\pm$ SD (N)	57.0 $\pm$ 11.3 (108)	56.9 $\pm$ 14.2 (789)	59.9 $\pm$ 12.5 (191)	57.4 $\pm$ 13.7 (1088)
Median	59.0	58.0	60.0	58.0
Range	30.2–75.0	3.0–86.0	25.0–89.0	3.0–89.0
Sex				
Male	11.1% (12/108)	20.3% (161/793)	16.2% (31/191)	18.7% (204/1092)
Female	88.9% (96/108)	79.7% (632/793)	83.8% (160/191)	81.3% (888/1092)
Procedure time, mins				
Mean $\pm$ SD (N)	121.8 $\pm$ 62.6 (108)	101.6 $\pm$ 50.5 (754)	112.9 $\pm$ 54.9 (190)	105.7 $\pm$ 53.1 (1052)
Median	109.5	90.0	107.0	92.0
Range	39.0–427.0	10.0–376.0	0.0–369.0	0.0–427.0
Clinical follow-up, days				
Mean $\pm$ SD (N)	1540.8 $\pm$ 639.0 (108)	667.4 $\pm$ 268.1 (793)	200.4 $\pm$ 169.7 (191)	672.1 $\pm$ 459.3 (1092)
Median	1841	637.0	188.0	604.5
Range	0–2051	2–1839	0–826	0–2051
Angiographic follow-up, mos				
Mean $\pm$ SD (N)	50.0 $\pm$ 16.9 (101)	—	9.2 $\pm$ 4.3 (115)	28.3 $\pm$ 23.7 (216)
Median	60.1	—	7.6	14.1
Range	6.6–67.5	—	3.6–27.2	3.6–67.5

To date, a majority of previously published studies are small single-institution case series, and their results may not be generalizable to the overall patient population. IntrePED (International Retrospective Study of the Pipeline Embolization Device), PUFS (Pipeline for Uncoilable or Failed Aneurysms Study), and ASPIRe (Aneurysm Study of Pipeline in an Observational Registry) represent large, multicenter studies that followed predefined protocols to fully characterize the safety and efficacy of the PED. These studies include a broad range of aneurysm types, locations, and sizes and represent the experience of a wide number of practitioners. In this study, we present a pooled analysis of patients included in these studies to better evaluate both clinical safety and angiographic outcomes of PED treatment.

Methods

Patient Population

All centers included in these 3 studies acquired institutional review board or ethics committee approval for the studies. All patients included in PUFS (NCT00777088),² IntrePED,¹⁰ and ASPIRe (NCT01557036) were included in this combined analysis. PUFS was a prospective single-arm clinical trial involving 108 patients with 108 aneurysms; it included only patients with wide-necked (≥ 4 mm) aneurysms or aneurysms with no discernable neck and large (10–24.9 mm) or giant (≥ 25 mm) aneurysms of the internal carotid artery (ICA) from the petrous to the superior hypophyseal segments with a follow-up time of 5 years. IntrePED was a retrospective postmarket registry of 793 patients with 906 aneurysms, including both ruptured and unruptured aneurysms (no size or location criteria) with a follow-up time of up to 3 years. The IntrePED study

did not include angiographic outcomes as it was designed to assess safety-related outcomes only. ASPIRe was a prospective postmarket registry involving 191 patients with 207 aneurysms with a follow-up time of up to 2 years; size and location inclusion criteria for ASPIRe followed the country-specific PED instructions for use.

We pooled data from these 3 studies including patients with unruptured and ruptured aneurysms. Data on the following baseline characteristics were collected and analyzed: age, sex, aneurysm size, aneurysm neck size, aneurysm type (saccular, fusiform, dissecting, other), aneurysm location, and aneurysm rupture status (Tables 1 and 2).

Outcomes

The primary outcomes of this study were complication rates. Complications studied included major ipsilateral ischemic stroke, major ipsilateral intracranial hemorrhage, major neurological morbidity, neurological mortality, combined major neurological morbidity and mortality and all-cause mortality. In PUFS, a major stroke or other neurological event was defined as a stroke with symptoms present after 7 days of the initial event with an increase in the NIH stroke scale by at least 4 points. In IntrePED and ASPIRe, a major neurological event (stroke, hemorrhage, or morbidity) was defined as an ongoing clinical deficit at 7 days following the event. For angiographic outcomes, data were available from ASPIRe and PUFS only. In the IntrePED registry, images were not collected and imaging was not a prespecified outcome. All adverse events were adjudicated by an independent adverse events committee that was completely independent of the funding source.

The secondary outcomes were angiographic results

TABLE 2. Aneurysm characteristics

Characteristic	PUFS	IntrePED	ASPIRe	Total
No. of aneurysms	108	906	207	1221
No. of patients	108	793	191	1092
Aneurysm size, mm				
Mean $\pm$ SD (N)	18.2 $\pm$ 6.5 (108)	10.7 $\pm$ 7.7 (896)	14.5 $\pm$ 6.9 (207)	12.0 $\pm$ 7.8 (1211)
Median	17.5	9.0	12.0	10.2
Range	6.2–36.1	1.0–55.0	0.9–41.0	0.9–55.0
Aneurysm neck, mm				
Mean $\pm$ SD (N)	8.8 $\pm$ 4.3 (108)	6.2 $\pm$ 4.9 (812)	7.1 $\pm$ 4.2 (202)	6.6 $\pm$ 4.8 (1122)
Median	8.1	5.0	6.0	5.4
Range	4.1–36.1	0.8–53.0	0.0–32.0	0.0–53.0
Aneurysm location, % (n/N)				
ICA/PCoA	100.0% (108/108)	82.3% (746/906)	90.8% (188/207)	85.3% (1042/1221)
ICA	100.0% (108/108)	91.8% (685/746)	98.4% (185/188)	93.9% (978/1042)
PCoA	0.0% (0/108)	8.2% (61/746)	1.6% (3/188)	6.1% (64/1042)
MCA	0.0% (0/108)	4.9% (44/906)	1.4% (3/207)	3.8% (47/1221)
PCA	0.0% (0/108)	1.7% (15/906)	0.5% (1/207)	1.3% (16/1221)
BA	0.0% (0/108)	4.9% (44/906)	2.9% (6/207)	4.1% (50/1221)
ACoA/ACA	0.0% (0/108)	2.3% (21/906)	2.9% (6/207)	2.2% (27/1221)
ACoA	0.0% (0/108)	57.1% (12/21)	83.3% (5/6)	63.0% (17/27)
ACA	0.0% (0/108)	42.9% (9/21)	16.7% (1/6)	37.0% (10/27)
VA	0.0% (0/108)	3.6% (33/906)	1.4% (3/207)	2.9% (36/1221)
PICA	0.0% (0/108)	0.3% (3/906)	0.0% (0/207)	0.2% (3/1221)
Ruptured aneurysms, % (n/N)	0.0% (0/108)	8.4% (76/906)	0.0% (0/207)	6.2% (76/1221)
Multiple PEDs used, % (n/N)	98.1% (105/107)	34.1% (308/904)	18.8% (39/207)	37.1% (452/1218)

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; PICA = posterior inferior cerebellar artery; VA = vertebral artery.

following PED treatment. For angiographic outcomes, data were available from ASPIRe and PUFS only. Angiographic follow-up was available at 180 days and 1 year for ASPIRe and PUFS and at 3 and 5 years for PUFS only. All angiographic outcomes were adjudicated by a core laboratory using the Raymond-Roy occlusion scale. The core laboratory was completely independent of the funding source. In addition to clinical and angiographic outcomes, mean procedure time was reported.

Statistical Analysis

Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc.). Summary statistics are presented for all data available using means and standard deviations for continuous variables and frequency tabulations for categorical variables. Most statistical analyses were performed on a per-patient basis. Some patients had more than 1 aneurysm treated with a PED. In these patients, the largest aneurysm was used to classify patients into the 3 aneurysm size categories. Some analyses, including aneurysm characteristics and multiple PED use, were performed across all aneurysms rather than across patients.

Role of the Funding Source

For all 3 studies, an academic principal investigator and an academic steering committee supervised trial design

and operations. The principal investigators and steering committees were independent of the funding source. The steering committees interpreted the results. The 2 lead authors of this paper (D.F.K. and W.B.) drafted the initial manuscript and the remaining authors critically revised it. The study sponsor did not play a role in manuscript preparation. The study sponsor was responsible for site management, data management, statistical analysis, and safety reporting. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Baseline Characteristics

A total of 1092 patients with 1221 aneurysms were included in this study (Tables 1 and 2). There were 108 patients with 108 aneurysms enrolled in PUFS, 793 patients with 906 aneurysms were enrolled in IntrePED, and 191 patients with 207 aneurysms were enrolled in ASPIRe. In the combined patient population, 81.3% of patients (888/1092) were female and 18.7% of patients (204/1092) were male. The patients' mean age was 57.4 $\pm$ 13.7 years. Overall, the mean aneurysm size was 12.0 $\pm$ 7.8 mm and the mean aneurysm neck size was 6.6 $\pm$ 4.8 mm. For PUFS, the mean aneurysm size was 18.2 $\pm$

TABLE 3. Clinical outcomes: major complications

Complication	PUFS (n/N)	IntrePED (n/N)	ASPIRe (n/N)	Total (n/N)
Major ipsilateral ischemic stroke	2.8% (3/107)	4.3% (34/793)	1.6% (3/191)	3.7% (40/1091)
Major ipsilateral intracranial hemorrhage	1.9% (2/107)	1.8% (14/793)	3.1% (6/191)	2.0% (22/1091)
Major morbidity	4.7% (5/107)	6.1% (48/793)	4.7% (9/191)	5.7% (62/1091)
Neurological mortality	2.8% (3/107)	3.8% (30/793)	1.6% (3/191)	3.3% (36/1091)
Major morbidity & neurological mortality	5.6% (6/107)	7.7% (61/793)	5.8% (11/191)	7.1% (78/1091)
All-cause mortality	3.7% (4/107)	4.2% (33/793)	3.7% (7/191)	4.0% (44/1091)

6.5 mm and the median size was 17.5 mm (interquartile range [IQR] 11.8–23.3 mm). For IntrePED, the mean aneurysm size was 10.7 ± 7.7 mm and median size was 9.0 mm (IQR 5.0–15.0 mm). For ASPIRe, the mean aneurysm size was 14.5 ± 6.9 mm and the median size was 12.0 mm (IQR 10.0–18.9 mm). At baseline, 6.2% of aneurysms (76/1221) were ruptured. Multiple PEDs were used in 37.1% of cases (452/1218). The mean procedure time was 105.7 ± 53.1 minutes. A majority of aneurysms (93.9%, 1042/1221) were located in the ICA. There were 64 aneurysms (6.1%, 64/1042) in the posterior communicating artery, 47 aneurysms (3.8%, 47/1221) in the middle cerebral artery, 50 aneurysms (4.1%, 50/1221) in the basilar artery, 27 aneurysms in the anterior communicating artery or anterior cerebral artery (2.2%, 27/1221), 36 aneurysms in the vertebral artery (2.9%, 36/1221), and 3 aneurysms in the posterior inferior cerebellar artery (0.2%, 3/1221).

Complications

Complication data were available for 1091 patients (Table 3). The overall rate of major ipsilateral ischemic stroke was 3.7% (40/1091). Major ipsilateral intracranial hemorrhage occurred in 2.0% of cases (22/1091). Major neurological morbidity occurred in 5.7% of cases (62/1091). Neurological mortality occurred in 3.3% of cases (36/1091). Combined major neurological morbidity and mortality occurred in 7.1% of cases (78/1091). The all-cause mortality rate was 4.0% (44/1091).

Angiographic Outcomes

Angiographic outcomes were available at 180 days and 12 months for both ASPIRe and PUFS and at 3 and 5 years for PUFS only (Table 4). The sizes of the aneurysms at each time point are summarized in Table 5. The mean length of angiographic follow-up was 28.3 ± 23.7 months. Complete occlusion rates were 75.0% (111/148), 85.5% (94/110), 93.4% (71/76), and 95.2% (59/62) at 180 days and 1, 3, and 5 years, respectively. Overall aneurysm retreatment rates were low at 3.0% (33/1091) at a

mean follow-up time of 10.2 ± 10.8 months. IntrePED had the lowest reported retreatment rate—1.9% (15/793) at a mean follow-up time of 6.6 ± 6.1 months. Retreatment rates for PUFS and ASPIRe were similar—6.5% (7/107) at a mean follow-up time of 24.5 ± 12.2 months and 5.8% (11/191) at a mean follow-up time of 6.1 ± 7.3 months, respectively.

Discussion

Our study of 1092 patients with 1221 aneurysms demonstrates that flow diversion treatment of intracranial aneurysms is safe and effective. Complete occlusion rates were over 85% at 1 year and over 95% at 5 years. In addition, the rates of stroke, hemorrhage, morbidity, and mortality were low, especially given the fact that treated aneurysms were generally large and wide necked and included both ruptured and unruptured lesions. While a number of studies and meta-analyses have been published regarding the outcomes of flow diverter treatment of intracranial aneurysms, the current study is the largest study with individual patient data to date. In addition, all clinical outcomes were adjudicated by an independent clinical events committee, and all angiographic outcomes were validated by an independent core laboratory.

Our findings corroborate the findings of many recently published meta-analyses on the safety and efficacy of flow diverter treatment of intracranial aneurysms. Two recently published large meta-analyses of flow diverter treatment demonstrated morbidity and mortality rates of 5%–7% and 3%–4%, respectively.^{1,3} Meanwhile, our combined analysis with adjudicated clinical outcomes found major morbidity and neurological mortality rates of 5.7% and 3.3%, respectively.

Prior studies have demonstrated high angiographic cure rates when treating large aneurysms with flow diverters such as the PED. In general, complete occlusion rates at 6–12 months range between 70% and 85%.^{2,11,12,14,15,18} Such studies corroborate our findings that the rates of complete

TABLE 4. Angiographic outcomes: complete aneurysm occlusion

Follow-Up	PUFS (n/N)	IntrePED (n/N)	ASPIRe (n/N)	Total (n/N)
180 days (–20/+42 days)	73.6% (78/106)	—	78.6% (33/42)	75.0% (111/148)
1 yr ($\pm$ 42 days)	86.8% (79/91)	—	78.9% (15/19)	85.5% (94/110)
3 yrs	93.4% (71/76)	—	—	93.4% (71/76)
5 yrs	95.2% (59/62)	—	—	95.2% (59/62)

TABLE 5. Summary of aneurysm sizes and each follow-up period for angiographic outcomes

Aneurysm Size	180-Day Angio FU for PUFS	1-Yr Angio FU for PUFS	3-Yr Angio FU for PUFS	5-Yr Angio FU for PUFS	Last Angio FU Visit for ASPIRe Patients
Mean, mm*	18.3 ± 6.4 (106)	18.4 ± 6.5 (91)	17.9 ± 6.2 (76)	18.4 ± 6.9 (62)	14.2 ± 6.2 (126)
Median, mm	17.8	18.0	17.2	18.3	12.0
IQR, mm	12.2–23.5	12.0–24.2	11.9–22.5	11.5–24.0	10.0–17.1

Angio = angiographic; FU = follow-up.

* Values in parentheses are numbers of aneurysms.

occlusion at 6 and 12 months were 75% and 85%, respectively. One meta-analysis of nearly 1500 patients with 1700 aneurysms treated with flow diverters demonstrated complete occlusion rates of 76% at last follow-up.³ Most studies in this meta-analysis had a maximum follow-up of 6–12 months. Series reporting angiographic outcomes at more than 1 year after treatment generally report complete occlusion rates of over 90%, similar to our study.^{3,16} It is important to note that 3- and 5-year angiographic outcome data were only collected in PUFS.

When comparing angiographic and clinical outcomes of PED treatment of wide-necked and large aneurysms to reported outcomes of stent-assisted coiling and coiling alone, it appears as though PED treatment results in higher rates of angiographic occlusion with similar rates of morbidity and mortality. This is especially important in the context of the challenges associated with repeated treatments over time with conventional endovascular techniques resulting in poorly defined cumulative morbidity.^{6,13} In a series of over 150 large and giant ICA aneurysms treated with coil embolization, Chalouhi et al. noted a 12% complication rate with recurrence and retreatment rates greater than 30%.⁶ In our study, PED treatment resulted in low overall retreatment rates, with a mean of 3.0% at a mean follow-up of 10.2 months.

In a meta-analysis of over 2000 cases of wide-necked aneurysms treated with coiling and stent-assisted coiling, Zhao et al. found long-term complete occlusion rates of 70%–80% with recanalization rates of about 10%.²⁰ The long-term rate of good neurological outcome was approximately 90% for both groups, and procedure-related complications resulting in morbidity or mortality occurred in approximately 3% of patients. Other large studies have demonstrated mortality rates ranging from 3% to 9% and permanent morbidity rates ranging from 4% to 6% following stent-assisted coiling of intracranial aneurysms.⁹

Limitations

Our study has limitations. Most of the patients included in this combined analysis were included in either a prospective study (PUFS), a prospective postmarket registry (ASPIRe), or a retrospective registry (IntrePED). Because of this, there was no overall standardization in the perioperative management, including the use of platelet testing. In most cases, sites followed their standard of practice for treating aneurysms with PED and there was a wide range of treatment regimens (i.e., platelet testing and antiplatelet therapy) between centers. However, all study adverse events collected were pre-specified and were evaluated

by an independent clinical events committee to maintain consistency. Another potential limitation of this study is the fact that the indications for treatment varied between centers, which can result in a degree of selection bias. Angiographic outcomes were not available for a vast majority of patients included in this study. Three- and 5-year angiographic outcomes were only available for PUFS. Nonetheless, our study represents the largest study with individual patient data reporting clinical outcomes of patients treated with the PED to date.

Conclusions

Our combined analysis of 3 large studies of the PED in the treatment of intracranial aneurysms with a broad range of sizes and locations and ruptured status confirms that treatment of intracranial aneurysms with the PED is both safe and effective, with progressively increasing occlusion rates over time, low rates of neurological morbidity and mortality, and low retreatment rates in long-term follow-up. These findings should be considered when determining the best therapeutic option for intracranial aneurysms.

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Disclosures

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Author Contributions

Conception and design: Brinjikji. Acquisition of data: Brinjikji. Analysis and interpretation of data: Brinjikji, Kallmes. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Brinjikji, Cekirge, Fiorella, Hanel, Jabbour, Lopes, Lylyk, McDougall, Siddiqui. Approved the final version of the manuscript on behalf of all authors: Brinjikji. Statistical analysis: Brinjikji.

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