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Pipeline embolization of posterior circulation aneurysms: a multicenter study of 131 aneurysms

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OBJECTIVE Flow diversion for posterior circulation aneurysms performed using the Pipeline embolization device (PED) constitutes an increasingly common off-label use for otherwise untreatable aneurysms. The safety and efficacy of this treatment modality has not been assessed in a multicenter study.

METHODS A retrospective review of prospectively maintained databases at 8 academic institutions was performed for the years 2009 to 2016 to identify patients with posterior circulation aneurysms treated with PED placement.

RESULTS A total of 129 consecutive patients underwent 129 procedures to treat 131 aneurysms; 29 dissecting, 53 fusiform, and 49 saccular lesions were included. At a median follow-up of 11 months, complete and near-complete occlusion was recorded in 78.1%. Dissecting aneurysms had the highest occlusion rate and fusiform the lowest. Major complications were most frequent in fusiform aneurysms, whereas minor complications occurred most commonly in saccular aneurysms. In patients with saccular aneurysms, clopidogrel responders had a lower complication rate than did clopidogrel nonresponders. The majority of dissecting aneurysms were treated in the immediate or acute phase following subarachnoid hemorrhage, a circumstance that contributed to the highest mortality rate in those aneurysms.

CONCLUSIONS In the largest series to date, fusiform aneurysms were found to have the lowest occlusion rate and the highest frequency of major complications. Dissecting aneurysms, frequently treated in the setting of subarachnoid hemorrhage, occluded most often and had a low complication rate. Saccular aneurysms were associated with predominantly minor complications, particularly in clopidogrel nonresponders.

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KEYWORDS aneurysm; basilar artery; vertebral artery; endovascular; flow diversion; posterior circulation; Pipeline; vascular disorders

Management of posterior circulation aneurysms is particularly challenging. The rupture risk of posterior circulation aneurysms is higher when compared with aneurysms of the anterior circulation. In the International Study of Unruptured Intracranial Aneurysms (ISUIA), the annual risk of rupture of a posterior circulation aneurysm, including those in the posterior communicating artery (PCoA) location, ranged from 0.5% for aneurysms < 7 mm to 10% for those ≥ 25 mm in maximum diameter.[24] Excluding the PCoA location, the

ABBREVIATIONS BA = basilar artery; DSA = digital subtraction angiography; ISUIA = International Study of Unruptured Intracranial Aneurysms; mRS = modified Rankin Scale; PCA = posterior cerebral artery; PCoA = posterior communicating artery; PED = Pipeline embolization device; PICA = posterior inferior cerebellar artery; SAH = subarachnoid hemorrhage; VA = vertebral artery.

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annual rupture risk for a posterior circulation aneurysm of any size is 1.8%; this is significantly higher than for an anterior circulation aneurysm (0.49%).[6] In the ISUIA, aneurysm location in the posterior circulation was a predictor of poor outcome with both surgical and endovascular techniques in electively treated patients.[24] Fusiform aneurysms, however, were excluded from the ISUIA. In the International Subarachnoid Aneurysm Trial (ISAT), ruptured posterior circulation aneurysms were underrepresented because most participating centers did not assume clinical equipoise and favored endovascular therapy.[16] Even though endovascular therapy is preferred over surgical clipping for most posterior circulation aneurysms, conventional methods such as primary coil embolization or stent- or balloon-assisted coiling are suboptimal for a number of these aneurysms. Flow diversion performed using the Pipeline embolization device (PED; Ev3/Covidien) has emerged as a treatment option for challenging aneurysms in the anterior circulation.[2] To this point, most reports on the off-label use of the PED for posterior circulation aneurysms are from single centers.[1,3,5,9,15,18,19,22] We collected data on posterior circulation aneurysms treated with PED placement from academic centers in North America and Europe, and we report safety and efficacy stratified by aneurysm morphology.

Methods

A retrospective review of prospectively maintained databases at 8 academic institutions in North America and Europe was performed for the years 2009 to 2016 to identify patients with posterior circulation aneurysms treated with the PED. Both ruptured and unruptured aneurysms were included; centers categorized aneurysms by morphology (i.e., dissecting, fusiform [including dolichoectatic and transition[11]], and saccular). To assure consistency across centers, an illustration of each aneurysm type was drawn (Fig. 1), and distributed along with corresponding sample digital subtraction angiograms. Dissecting aneurysms were defined as aneurysms that most likely resulted from an injury to the arterial layers resulting in an irregular expansion of the vessel in longitudinal fashion. Fusiform aneurysms incorporated the entire vessel circumferentially. Saccular aneurysms were defined by their domelike shape, with an appreciable neck. The following information was collected: patient demographic data, aneurysm characteristics, platelet function test results, antiplatelet regimen, procedural details, angiographic and functional outcomes, and complications. Aneurysm measurements were obtained using digital subtraction angiograms, except in a few cases of partially thrombosed aneurysms in which axial images were analyzed. Institutional review board approval was obtained at all centers.

Procedure Details

Patients received 325 mg aspirin daily and 75 mg clopidogrel daily for 3–14 days prior to the intervention. Platelet function testing was performed at the discretion of the individual interventionalists. Patients undergoing treatment of a ruptured aneurysm received a dose of 650 mg aspirin and 600 mg clopidogrel prior to the intervention. Patients underwent local anesthesia with sedation or general anesthesia at the discretion of individual interventionalists, and all patients received anticoagulation with heparin throughout the procedure. Activated clotting time was used in most cases to guide heparin administration intraprocedurally, with a target of 250–300; typical dosing consisted of a 3000- to 5000-U bolus at the beginning of the procedure, with hourly dosing of 1000 U. The type of guide catheter and microcatheter used for PED insertion was at the discretion of the individual interventionalists. The placement and apposition of the PED to the vessel wall was documented using fluoroscopy. Dual-antiplatelet therapy was continued for at least 3 months after the procedure, and aspirin indefinitely thereafter.

Complications and Outcomes

Thromboembolic complications occurring from the date of the procedure up to the last follow-up were included. Intraprocedural thromboembolic complications were identified on digital subtraction angiography (DSA) as either thrombus formation, slow filling of a previously normally filling vessel, or vessel dropout. Intraprocedural thromboembolism was treated at the discretion of the interventionalist performing the procedure, and could include additional antiplatelet medication, anticoagulation, thrombolytics, mechanical thrombectomy, or observation. Postprocedural thromboembolic complications were identified using a combination of clinical and radiographic findings. Postprocedural imaging was performed at the discretion of the individual institutions and was only obtained if there was a clinical concern. Routine screening for clinically silent ischemic strokes was not performed. Postprocedural imaging obtained to detect an ischemic stroke could include any combination of a noncontrast CT, CTA, or MRI. An ischemic complication was considered symptomatic if the patient reported symptoms attributable to thromboembolism or demonstrated signs attributable to thromboembolism; this includes transient or resolving signs and symptoms.

Hemorrhagic complications were identified intraoperatively as contrast extravasation on DSA, on low-contrast imaging DSA, or on postprocedure imaging obtained due to clinical concern. Hemorrhagic complications occurring from the time of the procedure up until the last follow-up were included. Hemorrhages were counted as symptomatic if the patient reported symptoms or demonstrated signs attributable to a hemorrhage. In contrast to ischemic complications, all vascular territories and arterial puncture sites were included.

Angiographic outcome was assessed using DSA, MRA, or CTA. Aneurysm occlusion after PED treatment was categorized as complete (100%), near-complete (90%–99%), or partial (< 90%) occlusion. Functional outcome was assessed using the modified Rankin Scale (mRS) at last follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (IBM Corp.). In univariable analysis, variables were compared between groups by Mann-Whitney test for numeri-

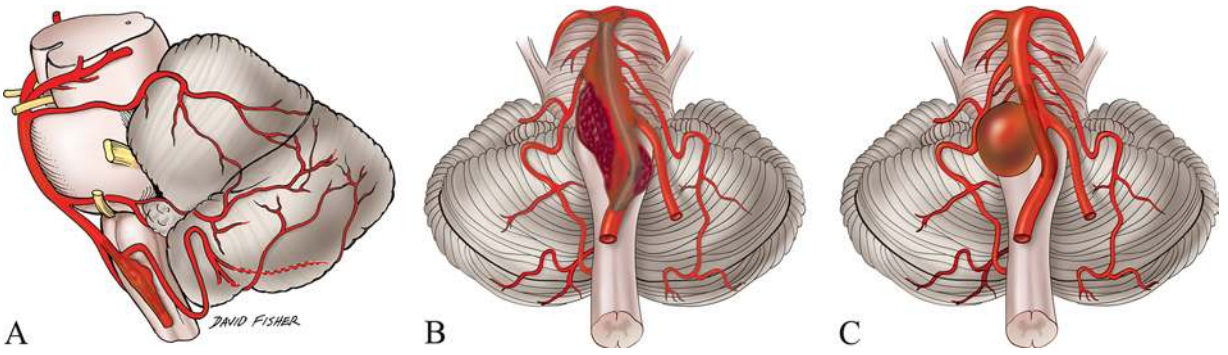

FIG. 1. Artist's renderings of posterior circulation aneurysm morphology: dissecting (**A**), fusiform (**B**), and saccular (**C**). Copyright Christoph Griessenauer. Published with permission. Figure is available in color online only.

cal variables and by chi-square test for categorical variables. Statistical significance was defined as $p < 0.05$. Multivariable logistic regression was performed on candidate predictor variables to identify the ones that were independently associated with occlusion and complications after controlling for potential confounders. Efforts were undertaken to account for interactions and collinearity between variables.

Results

Patient and Aneurysm Characteristics

A total of 129 consecutive patients (median age 58 years, male/female ratio of 1:1.7) underwent 129 procedures to treat 131 posterior circulation aneurysms with the PED. Twenty-nine (22.1%) dissecting, 53 (40.5%) fusiform, and 49 (37.4%) saccular lesions were included. Treatment of 39 aneurysms (29.8%) was performed in the immediate, acute, or remote setting of subarachnoid hemorrhage (SAH). Fusiform aneurysms were largest in terms of maximum diameter, aneurysm height, and width. More than half of patients (55%) had a neurological deficit attributable to the aneurysm prior to their procedure. Sixty-six percent of PEDs placed immediately after aneurysmal SAH were placed for dissecting aneurysms. Platelet function testing was performed in 59.7% of patients, and the rate of clopidogrel nonresponders was 18.2% (Table 1).

Occlusion of Posterior Circulation Aneurysms After Flow Diversion Using the PED

At a median follow-up of 11 months, complete (100%) or near-complete (90%–99%) occlusion was recorded in 78.1% of aneurysms. Dissecting aneurysms had the highest occlusion rate (89.7%) and fusiform the lowest (71.2%). Retreatment with endovascular techniques was most frequent in dissecting and fusiform aneurysms (Table 2). Younger patients with dissecting aneurysms had higher occlusion rates. No other variable was associated with occlusion in dissecting aneurysms. Fusiform aneurysms had the highest number of PEDs (median 2) placed, and no predictors of occlusion were identified. Saccular aneurysms of the basilar artery (BA) were least likely to occlude when compared with saccular aneurysms in other locations (Tables 3–5).

Complications From Flow Diversion Using the PED

Major complications (≥ 2 points in mRS score change) were most common in fusiform aneurysms (11.5%). Minor complications (< 2 points in mRS change) occurred most often in saccular aneurysms (18.8%). Among dissecting aneurysms, larger aneurysms and ones with intraluminal thrombus had higher complication rates. In fusiform aneurysms, males more commonly experienced complications. In saccular aneurysms, clopidogrel responders had a lower complication rate than nonresponders (OR 0.04, 95% CI 0.002–0.6, $p = 0.02$) (Tables 6–8).

Procedures Performed in the Setting of SAH

Adjunctive coiling was performed in 40% of aneurysms treated in the immediate and acute setting of SAH. The breakdown by morphology showed that it was performed in 26.7% of dissecting, 0% of fusiform, and 75% of saccular aneurysms. In dissecting aneurysms, minor and major complications as well as mortality were encountered more frequently when treatment was performed in the setting of immediate or acute SAH, albeit this observation did not reach statistical significance. In fusiform and saccular aneurysms, treatment performed in the immediate or acute SAH phase was associated with a higher mortality rate (Table 9).

Mortality Rate

There were 14 (11.2%) deaths in the current series. Of these, 9 patients (64.3%) had a history of SAH, with 7 (77.8%) of those treated within 2 weeks of aneurysm rupture. The mortality rate was highest among patients with dissecting aneurysms (17.9%), followed by saccular (10.9%) and fusiform (7.8%) aneurysms. Ten patients died within 1 month of follow-up (71.4%). Three patients (21.4%) were treated in the setting of aneurysmal SAH and died from sequelae unrelated to the Pipeline embolization procedure. One patient had rebleeding from a ruptured aneurysm 1 day after Pipeline placement, and another patient presenting with brainstem stroke died of that. Another patient died of medical problems unrelated to the procedure. The remaining 8 (57.1%) deaths were related to Pipeline embolization, with varying degrees of likelihood. Five patients died of immediate complications of the procedure (hemorrhage [2], thromboembolic [2], and both

TABLE 1. Baseline characteristics in 129 patients with 131 posterior circulation aneurysms

Parameter	Total	Dissecting	Fusiform	Saccular	p Value
No. of aneurysms	131	29	53	49	NA
No. of procedures	129	29	52	48	NA
Sex					
Female	82 (63.6%)	23 (79.3%)	25 (48.1%)	34 (70.8%)	0.008
Male	47 (36.4%)	6 (20.7%)	27 (51.9%)	14 (29.2%)	
Median age in yrs (range)	58 (29–82)	57 (30–82)	56.5 (29–78)	58.5 (30–76)	0.68
Smoking*	40/120 (33.3%)	7/27 (25.9%)	16/50 (32%)	17/43 (39.5%)	0.48
Additional cerebral aneurysms	32 (24.8%)	6 (20.7%)	10 (19.2%)	16 (33.3%)	0.22
Presenting symptoms					
Asymptomatic	28 (21.7%)	3 (10.3%)	9 (17.3%)	16 (33.3%)	0.06
Headache/dizziness	30 (23.3%)	6 (20.7%)	11 (21.2%)	13 (27.1%)	
Neurological deficit	71 (55%)	20 (69%)	32 (61.5%)	19 (39.6%)	
SAH					
Immediate; <24 hrs	18 (13.7%)	12 (41.4%)	2 (3.8%)	4 (8.2%)	<0.01
Acute; <2 wks	7 (5.3%)	3 (10.3%)	0	4 (8.2%)	
Remote; >2 wks	14 (10.7%)	6 (20.7%)	2 (3.8%)	6 (12.2%)	
Pretreatment mRS score					
0–2	101 (78.3%)	19 (65.5%)	44 (84.6%)	38 (79.2%)	0.13
3–5	28 (21.7%)	10 (34.5%)	8 (15.4%)	10 (20.8%)	
Aneurysm location					
VA	46 (35.1%)	15 (51.7%)	20 (37.7%)	11 (22.4%)	0.001
PICA	9 (6.9%)	3 (10.3%)	0	6 (12.2%)	
Vertebrobasilar	18 (13.7%)	0	14 (26.4%)	4 (8.2%)	
BA	46 (35.1%)	9 (31%)	14 (26.4%)	23 (46.9%)	
SCA	4 (3.1%)	1 (3.4%)	0	3 (6.1%)	
PCA	8 (6.1%)	1 (3.4%)	5 (9.4%)	2 (4.1%)	
Median aneurysm measurements in mm (range)					
Maximal diameter	12 (2–73)	7 (1–24)	18 (2–73)	10.4 (3–45)	<0.01
Neck size	5.5 (2–15)	7.5 (2–10)	NA	5.35 (2–15)	0.13
Height	10.1 (1–73)	5.2 (1–24)	18.5 (1–73)	9 (2–45)	<0.01
Width	9.5 (1–35)	5 (1–23)	14 (2–35)	8.5 (2–35)	<0.01
Daughter sac	26 (19.8%)	5 (17.2%)	14 (26.4%)	7 (14.3%)	0.29
Intraaneurysmal thrombus	40 (30.5%)	8 (27.6%)	22 (41.5%)	10 (20.4%)	0.06
Prior treatment					
Endovascular	14 (10.7%)	2 (6.9%)	1 (1.9%)	11 (22.4%)	0.03
Surgery	2 (1.5%)	0	1 (1.9%)	1 (2%)	
Both	1 (0.8%)	0	0	1 (2%)	
Platelet function test	77 (59.7%)	12 (41.4%)	33 (63.5%)	32 (66.7%)	0.07
Clopidogrel nonresponders	14 (18.2%)	4 (33.3%)	6 (18.2%)	4 (12.5%)	0.28
Treatment of nonresponders					
Continue clopidogrel	8 (57.1%)	1 (25%)	5 (83.3%)	2 (50%)	0.24
Switch to ticagrelor	5 (35.8%)	2 (50%)	1 (16.7%)	2 (50%)	
Other	1 (7.1%)	1 (25%)	0	0	

NA = not applicable; SCA = superior cerebellar artery.

* Data were missing for 9 procedures.

TABLE 2. Outcome measures in 129 patients with 131 posterior circulation aneurysms

Parameter	Total	Dissecting	Fusiform	Saccular	p Value
Median no. of PEDs used (range)	1 (1–14)	1 (1–3)	2 (1–14)	1 (1–3)	0.0001
Adjunctive coiling	40 (31%)	6 (20.7%)	15 (28.8%)	19 (39.6%)	0.2
Median length of procedure in mins (range)*	107.5 (22–410)	107 (22–334)	102 (32–410)	110 (40–353)	0.27
Median time in mos to last angiographic follow-up (range)	11 (1–72)	15 (1–52)	9 (1–72)	12 (1–60)	0.11
Imaging modality at follow-up†					
DSA	64 (57.7%)	12 (48%)	23 (52.2%)	29 (69%)	0.5
CTA	20 (18%)	7 (28%)	9 (20.5%)	4 (9.5%)	
MRI/MRA	27 (24.3%)	6 (24%)	12 (27.3%)	9 (21.4%)	
Follow-up occlusion rate‡					
Complete; 100%	85 (66.4%)	24 (82.8%)	31 (59.7%)	30 (63.8%)	0.32
Near-complete; 90–99%	15 (11.7%)	2 (6.9%)	6 (11.5%)	7 (14.9%)	
Partial; <90%	28 (21.9%)	3 (10.3%)	15 (28.8%)	10 (21.3%)	
Retreatment					
Endovascular	11 (8.4%)	3 (10.3%)	5 (9.4%)	3 (6.1%)	0.76
Median time in mos to last clinical follow-up (range)§	8 (0.3–72)	14 (1–60)	6 (0.3–72)	13 (0.5–60)	0.13
Follow-up mRS score§					
0–2	99 (79.2%)	20 (71.4%)	40 (78.4%)	39 (84.8%)	0.37
3–5	12 (9.6%)	3 (10.7%)	7 (13.7%)	2 (4.3%)	
6—death	14 (11.2%)	5 (17.9%)	4 (7.8%)	5 (10.9%)	
Mortality w/in ≤30 days	8 (6.3%)	2 (7.1%)	3 (5.8%)	3 (6.5%)	0.54
Mortality after 30 days	6 (4.7%)	3 (10.7%)	1 (2%)	2 (4.4%)	
Change in mRS score§					
Improved	43 (34.4%)	15 (53.6%)	18 (35.3%)	10 (21.7%)	0.14
No change	54 (43.2%)	7 (25%)	21 (41.2%)	26 (56.4%)	
Worsened	28 (22.4%)	6 (21.4%)	12 (23.5%)	10 (21.7%)	
Complications¶					
Major complication; ≥2-point change in mRS score	13 (10.1%)	3 (10.3%)	6 (11.5%)	4 (8.3%)	0.68
Minor complications; <2-point change in mRS score	19 (14.7%)	2 (6.9%)	8 (15.4%)	9 (18.8%)	
Thromboembolic	29 (22.5%)	5 (17.2%)	13 (25%)	11 (22.9%)	0.72
Timing					
Intraprocedural	2 (1.6%)	0	0	2 (4.2%)	0.38
Postprocedural	27 (20.9%)	5 (17.2%)	13 (25%)	9 (18.7%)	
Location					
Brainstem	13 (10.1%)	1 (3.4%)	7 (13.5%)	5 (10.4%)	0.36
Cerebellum	13 (10.1%)	3 (10.3%)	5 (9.6%)	5 (10.4%)	1
PCA territory	10 (7.8%)	0	5 (9.6%)	5 (10.4%)	0.21
Hemorrhagic	10 (7.8%)	1 (3.4%)	4 (7.7%)	5 (10.4%)	0.54
Type					
Intraparenchymal	3 (2.3%)	0	1 (1.9%)	2 (4.2%)	0.78
Subarachnoid	7 (5.4%)	1 (3.4%)	3 (5.8%)	3 (6.2%)	
Timing					
Intraprocedural	1 (0.8%)	0	0	1 (2.1%)	0.65
Postprocedural	9 (7%)	1 (3.4%)	4 (7.7%)	4 (8.3%)	
Other complications					
Retained wire tip	3 (2.3%)	1 (3.4%)	1 (1.9%)	1 (2.1%)	0.13
Vasospasm	5 (3.9%)	4 (13.8%)	0	1 (2.1%)	
Perianeurysmal edema	2 (1.6%)	0	1 (1.9%)	1 (2.1%)	

* Data were missing for 9 procedures.
† Data were missing for 20 aneurysms.
‡ Data were missing for 3 aneurysms.
§ Data were missing for 4 procedures.
¶ Including deaths.

TABLE 3. Predictors of occlusion in 29 dissecting aneurysms treated with PEDs

Parameter	Univariable Analysis		
	Complete/ Near-Complete Occlusion, n = 26	Partial Occlusion, n = 3	p Value
Sex			
Female	20 (87%)	3 (13%)	0.35
Male	6 (100%)	0	
Median age in yrs (range)	55 (30–76)	69 (67–82)	0.02
Smoking*			
Yes	7 (100%)	0	0.47
No	17 (85%)	3 (15%)	
Presenting symptoms			
Asymptomatic	3 (100%)	0	
Headache/dizziness	5 (83.3%)	1 (16.7%)	0.74
Neurological deficit	18 (90%)	2 (10%)	
SAH			
No	7 (87.5%)	1 (12.5%)	
Immediate; <24 hrs	10 (83.3%)	2 (16.7%)	
Acute; <2 wks	3 (100%)	0	0.66
Remote; >2 wks	6 (100%)	0	
Pretreatment mRS score			
0–2	18 (94.7%)	1 (5.3%)	0.27
3–5	8 (80%)	2 (20%)	
Aneurysm maximal diameter			
<7 mm	12 (100%)	0	
7–12 mm	8 (80%)	2 (20%)	0.29
13–24 mm	6 (85.7%)	1 (14.3%)	
Aneurysm location			
VA	13 (86.7%)	2 (13.3%)	
PICA	3 (100%)	0	
BA	8 (88.9%)	1 (11.1%)	0.95
SCA	1 (100%)	0	
PCA	1 (100%)	0	
Intraaneurysmal thrombus			
Yes	7 (87.5%)	1 (12.5%)	1
No	19 (90.5%)	2 (9.5%)	
Prior treatment			
No	24 (88.9%)	3 (11.1%)	1
Endovascular	2 (100%)	0	
Adjunctive coiling			
Yes	6 (100%)	0	1
No	20 (87%)	3 (13%)	
Median no. of PEDs used (range)	1 (1–3)	1 (1–2)	0.96

* Data were missing for 2 aneurysms.

TABLE 4. Predictors of occlusion in 52 fusiform aneurysms treated with PEDs

Parameter	Univariable Analysis		
	Complete/ Near-Complete Occlusion, n = 37	Partial Occlusion, n = 15	p Value
Sex			
Female	20 (80%)	5 (20%)	0.23
Male	17 (63%)	10 (37%)	
Median age in yrs (range)	55 (29–78)	58 (36–77)	0.11
Smoking*			
Yes	13 (76.5%)	4 (23.5%)	0.7
No	23 (69.7%)	10 (30.3%)	
Presenting symptoms			
Asymptomatic	8 (88.9%)	1 (11.1%)	
Headache/dizziness	7 (63.6%)	4 (36.4%)	0.41
Neurological deficit	22 (68.8%)	10 (31.3%)	
SAH			
No	34 (70.8%)	14 (29.2%)	
Immediate; <24 hrs	1 (50%)	1 (50%)	0.54
Acute; <2 wks	0	0	
Remote; >2 wks	0	2 (100%)	
Pretreatment mRS score			
0–2	31 (70.5%)	13 (29.5%)	0.79
3–5	6 (75%)	2 (25%)	
Aneurysm maximal diameter			
<7 mm	1 (100%)	0	
7–12 mm	12 (75%)	4 (25%)	0.89
13–24 mm	13 (68.4%)	6 (31.6%)	
>24 mm	11 (68.8%)	5 (31.3%)	
Aneurysm location			
VA	14 (73.7%)	5 (26.3%)	
Vertebrobasilar	9 (64.3%)	5 (35.7%)	0.9
BA	10 (71.4%)	4 (28.6%)	
PCA	4 (80%)	1 (20%)	
Intraaneurysmal thrombus			
Yes	14 (66.7%)	7 (33.3%)	0.76
No	23 (74.2%)	8 (25.8%)	
Prior treatment			
No	35 (70%)	15 (30%)	
Endovascular	1 (100%)	0	0.66
Surgery	1 (100%)	0	
Adjunctive coiling			
Yes	11 (68.8%)	5 (31.3%)	0.8
No	26 (72.2%)	10 (27.8%)	
Median no. of PEDs used (range)	2 (1–14)	2 (1–9)	0.52

* Data were missing for 2 aneurysms.

TABLE 5. Predictors of occlusion in 47 saccular aneurysms treated with PEDs

Parameter	Univariable Analysis: Complete/ Near-Complete Occlusion, n = 37	Partial Occlusion, n = 10	p Value
Sex			
Female	27 (77.1%)	8 (22.9%)	0.65
Male	10 (83.3%)	2 (16.7%)	
Median age in yrs (range)	60.5 (30–76)	54 (42–73)	0.81
Smoking*			
Yes	16 (88.9%)	2 (11.1%)	0.37
No	17 (70.8%)	7 (29.2%)	
Presenting symptoms			
Asymptomatic	12 (70.6%)	5 (29.4%)	0.39
Headache/dizziness	9 (75%)	3 (25%)	
Neurological deficit	16 (88.9%)	2 (11.1%)	
SAH			
No	27 (79.4%)	7 (20.6%)	0.18
Immediate; <24 hrs	4 (100%)	0	
Acute; <2 wks	3 (100%)	0	
Remote; >2 wks	3 (50%)	3 (50%)	
Pretreatment mRS score			
0–2	27 (73%)	10 (27%)	0.06
3–5	10 (100%)	0	
Aneurysm maximal diameter			
<7 mm	7 (77.8%)	2 (22.2%)	0.15
7–12 mm	11 (68.8%)	5 (31.3%)	
13–24 mm	13 (100%)	0	
>24 mm	6 (66.7%)	3 (33.3%)	
Aneurysm location			
VA	11 (100%)	0	0.08
PICA	6 (100%)	0	
Vertebrobasilar	4 (100%)	0	
BA	15 (65.2%)	8 (34.8%)	
SCA	3 (100%)	0	
PCA	2 (100%)	0	
Intraaneurysmal thrombus			
Yes	7 (70%)	3 (30%)	0.45
No	30 (81.1%)	7 (18.9%)	
Prior treatment			
No	29 (82.9%)	6 (17.1%)	0.19
Endovascular	7 (70%)	3 (30%)	
Surgery	0	1 (100%)	
Both	1 (100%)	0	
Adjunctive coiling			
Yes	16 (80%)	4 (20%)	0.85
No	21 (77.8%)	6 (22.2%)	
Median no. of PEDs used (range)	1 (1–3)	1 (1–3)	0.97

* Data were missing for 5 aneurysms.

TABLE 6. Predictors of complications in 29 procedures in patients with dissecting aneurysms treated with PEDs

Parameter	Univariable Analysis: No Complications, n = 24	Complications, n = 5	p Value
Sex			
Female	18 (78.3%)	5 (21.7%)	0.21
Male	6 (100%)	0	
Median age in yrs (range)	56 (30–76)	69 (51–82)	0.14
Smoking*			
Yes	6 (85.7%)	1 (14.3%)	0.75
No	16 (80%)	4 (20%)	
Presenting symptoms			
Asymptomatic	3 (100%)	0	0.69
Headache/dizziness	5 (83.3%)	1 (16.7%)	
Neurological deficit	16 (80%)	4 (20%)	
SAH			
No	7 (87.5%)	1 (12.5%)	0.74
Immediate; <24 hrs	9 (75%)	3 (25%)	
Acute; <2 wks	3 (100%)	0	
Remote; >2 wks	5 (83.3%)	1 (16.7%)	
Pretreatment mRS score			
0–2	16 (84.2%)	3 (15.8%)	0.78
3–5	8 (80%)	2 (20%)	
Aneurysm maximal diameter			
<7 mm	12 (100%)	0	0.06
7–12 mm	8 (80%)	2 (20%)	
13–24 mm	4 (57.1%)	3 (42.9%)	
Aneurysm location			
VA	12 (80%)	3 (20%)	0.86
PICA	3 (100%)	0	
BA	7 (77.8%)	2 (22.2%)	
SCA	1 (100%)	0	
PCA	1 (100%)	0	
Intraaneurysmal thrombus			
Yes	5 (62.5%)	3 (37.5%)	0.08
No	19 (90.5%)	2 (9.5%)	
Prior treatment			
No	23 (85.2%)	4 (14.8%)	0.2
Endovascular	1 (50%)	1 (50%)	
Clopidogrel responders†			
Yes	8 (100%)	0	
No	3 (75%)	1 (25%)	0.14
Adjunctive coiling			
Yes	5 (83.3%)	1 (16.7%)	0.97
No	19 (82.6%)	4 (17.4%)	
Median no. of PEDs used (range)	1 (1–3)	2 (1–2)	0.27

* Data were missing for 2 procedures.
† Among patients in whom platelet function testing was performed.

TABLE 7. Predictors of complications in 52 procedures in patients with fusiform aneurysms treated with PEDs

Parameter	Univariable Analysis			Multivariable Analysis; OR (95% CI), p Value
	No Complications (n = 38)	Complications (n = 14)	p Value	
Sex				
Female	22 (88%)	3 (12%)	0.02	4.1 (0.9–18.8), p = 0.07
Male	16 (59.3%)	11 (40.7%)		
Median age in yrs (range)	58.5 (29–78)	53.6 (29–71)	0.43	
Smoking*				
Yes	14/16 (87.5%)	2/16 (12.5%)	0.13	
No	23/34 (67.6%)	11/34 (32.4%)		
Presenting symptoms				
Asymptomatic	7 (77.8%)	2 (22.2%)	0.05	1.5 (0.5–4), p = 0.47
Headache/dizziness	11 (100%)	0		
Neurological deficit	20 (62.5%)	12 (37.5%)		
SAH				
No	35 (72.9%)	13 (27.1%)	0.53	
Immediate; <24 hrs	1 (50%)	1 (50%)		
Acute; <2 wks	0	0		
Remote; >2 wks	2 (100%)	0		
Pretreatment mRS score				
0–2	34 (77.3%)	10 (22.7%)	0.11	
3–5	4 (50%)	4 (50%)		
Aneurysm maximal diameter				
<7 mm	0	1 (100%)	0.33	
7–12 mm	3 (50%)	3 (50%)		
13–24 mm	14 (73.7%)	5 (26.3%)		
>24 mm	21 (80.8%)	5 (19.2%)		
Aneurysm location				
VA	16 (84.2%)	3 (15.8%)	0.49	
Vertebrobasilar	9 (64.3%)	5 (35.7%)		
BA	9 (64.3%)	5 (35.7%)		
PCA	4 (80%)	1 (20%)		
Intraaneurysmal thrombus				
Yes	16 (76.2%)	5 (23.8%)	0.68	
No	22 (71%)	9 (29%)		
Prior treatment				
No	36 (72%)	14 (28%)	0.68	
Endovascular	1 (100%)	0		
Surgery	1 (100%)	0		
Clopidogrel responders†				
Yes	21 (77.8%)	6 (22.2%)	0.76	
No	5 (83.3%)	1 (16.7%)		
Adjunctive coiling				
Yes	13 (86.7%)	2 (13.3%)	0.16	
No	25 (67.6%)	12 (32.4%)		
Median no. of PEDs used (range)	2 (1–14)	2 (1–9)	0.13	

* Data were missing for 2 procedures.
† Among patients in whom platelet function testing was performed.

TABLE 8. Predictors of complications in 48 procedures in patients with saccular aneurysms treated with PEDs

Parameter	Univariable Analysis			Multivariable Analysis; OR (95% CI), p Value
	No Complications, n = 35	Complications, n = 13	p Value	
Sex				
Female	24 (70.6%)	10 (29.4%)	0.57	
Male	11 (78.6%)	3 (21.4%)		
Median age in yrs (range)	59 (32–76)	54 (30–76)	0.14	
Smoking*				
Yes	15 (88.2%)	2 (11.8%)	0.75	
No	16 (61.5%)	10 (38.5%)		
Presenting symptoms				
Asymptomatic	13 (81.3%)	3 (18.8%)	0.45	
Headache/dizziness	10 (76.9%)	3 (23.1%)		
Neurological deficit	12 (63.2%)	7 (36.8%)		
SAH				
No	26 (74.3%)	9 (25.7%)	0.11	
Immediate; <24 hrs	1 (25%)	3 (75%)		
Acute; <2 wks	3 (100%)	0		
Remote; >2 wks	5 (83.3%)	1 (16.7%)		
Pretreatment mRS score				
0–2	30 (78.9%)	8 (21.1%)	0.07	
3–5	5 (50%)	5 (50%)		
Aneurysm maximal diameter				
<7 mm	6 (66.7%)	3 (33.3%)	0.3	
7–12 mm	15 (88.2%)	2 (11.8%)		
13–24 mm	9 (69.2%)	4 (30.8%)		
>24 mm	5 (55.6%)	4 (44.4%)		
Aneurysm location				
VA	8 (72.7%)	3 (27.3%)	0.57	
PICA	5 (83.3%)	1 (16.7%)		
Vertebrobasilar	4 (100%)	0		
BA	15 (65.2%)	8 (34.8%)		
SCA	1 (50%)	1 (50%)		
PCA	2 (100%)	0		
Intraaneurysmal thrombus				
Yes	4 (40%)	6 (60%)	0.008	5.9 (0.5–68.4), p = 0.15
No	31 (81.6%)	7 (18.4%)		
Prior treatment				
No	23 (65.7%)	12 (34.3%)	0.33	
Endovascular	10 (90.9%)	1 (9.1%)		
Surgery	1 (100%)	0		
Both	1 (100%)	0		
Clopidogrel responders†				
Yes	24 (85.7%)	4 (14.3%)	0.006	0.04 (0.002–0.6), p = 0.02
No	1 (25%)	3 (75%)		
Adjunctive coiling				
Yes	14 (73.7%)	5 (26.3%)	0.92	
No	21 (72.4%)	8 (27.6%)		
Median no. of PEDs used (range)	1 (1–2)	1 (1–3)	0.049	3 (0.5–19.3), p = 0.25

* Data were missing for 5 procedures.

† Among patients in whom platelet function testing was performed.

TABLE 9. Results of PED placement in the setting of SAH

Aneurysm Morphology & Parameter	Univariable Analysis		p Value
	Immediate/Acute SAH	Other	
Dissecting	15	14	
Parameter			
Minor complications	2 (13.3%)	0%	0.29
Major complications	2 (13.3%)	1 (7.1%)	
Mortality	4 (26.7%)	1 (7.1%)	0.16
Fusiform	2	50	
Parameter			
Minor complications	1 (50%)	7 (14%)	0.37
Major complications	0%	6 (12%)	
Mortality	1 (50%)	3 (6%)	0.02
Saccular	8	40	
Parameter			
Minor complications	1 (12.5%)	8 (20%)	0.11
Major complications	2 (25%)	2 (5%)	
Mortality	2 (25%)	3 (7.5%)	0.09

[1]). Of the other 3 patients, 1 died of an unknown cause 1 month after retreatment with a second PED, another during salvage stent-assisted coiling for a foreshortened PED at 4 months of follow-up, and the third from a hypertensive hemorrhage probably exacerbated by antiplatelet agents at 26 months of follow-up (Table 10).

Discussion

The prognosis of patients with posterior circulation aneurysms varies based on aneurysm morphology, location, size, history of rupture, and presentation. Saccular posterior circulation aneurysms are characterized by a worse natural history and higher risk for treatment-associated complications compared with their anterior circulation counterparts.[24] Nonsaccular aneurysms of the vertebrobasilar system fare poorly, with a reported median survival of 7.8 years.[10] Ischemic stroke and neural compression are the leading neurological causes of death. The heterogeneity among these lesions complicates the decision whether to pursue conservative management or make an attempt to treat the aneurysm. Although endovascular therapy is generally preferred over microsurgery, certain posterior circulation aneurysms are not amenable to traditional endovascular techniques. Due to a need for alternative options, the off-label use of flow diversion in the posterior circulation has gained traction.[1,5,9,15,18,19,22] In an attempt to critically appraise this development, we analyzed data on posterior circulation aneurysms treated with PEDs at 8 high-volume academic institutions in North America and Europe; with 131 aneurysms, this represents the largest series to date and illustrates the rarity of otherwise untreatable posterior circulation aneurysms. Aneurysms were categorized according to their morphology into dissecting, fusiform, and saccular. Data provided for the overall cohort should be interpreted with caution and were provided for purpose of completion. Each aneurysm type was associated with unique characteristics that impact the safety and efficacy of flow diversion treatment, and should be evaluated individually.

Occlusion of Posterior Circulation Aneurysms After Flow Diversion

The complete and near-complete occlusion rate was 78.1%. The highest complete occlusion rate was found in dissecting aneurysms, followed by saccular and fusiform aneurysms, although this observation did not reach statistical significance. Previous reports of flow diversion for posterior circulation aneurysms have had case numbers too small to assess for a variety of predictors of occlusion.[1,3,5,9,15,18,19,22] Data from noncomparative studies suggest that posterior circulation aneurysms of smaller size[7] and of dissecting or saccular morphology show favorable complete to near-complete occlusion rates, ranging from 85.7% up to 100%.[1,5,7,15,19] Reported occlusion rates for fusiform and dolichoectatic aneurysms vary more widely, and range from 66%[5] to 90%,[17] and even up to 100%.[18] In the present study, age was the only factor associated with occlusion in dissecting aneurysms. Interestingly, aneurysm size did not correlate with occlusion rates for any of the 3 aneurysm morphologies. Saccular aneurysms of the BA were least likely to occlude compared with saccular aneurysms in other locations. Intraaneurysmal thrombus, the number of PEDs placed, and the use of adjunctive coils have all been associated with increased occlusion rates in previous reports;[14] however, they did not show any effect on aneurysm occlusion in the present study. Alternative treatment modalities for dissecting vertebral artery (VA) aneurysms include parent vessel sacrifice if the relationship of important branch vessels such as the posterior inferior cerebellar artery (PICA) with the aneurysm is favorable.[12] The neurovascular configuration of dissecting aneurysms included in this study, however, was deemed more suitable for flow diversion.

Complications From Flow Diversion Performed Using the PED

Major (≥ 2 points in mRS score change) and minor (< 2 in mRS score change) complications occurred in 10.1% and 14.7% of procedures, respectively. Thromboembolic complications occurred in 22.5% of procedures overall and equally affected the brainstem, cerebellum, and the posterior cerebral artery (PCA) territory. They were most common for fusiform aneurysms, but also occurred with other aneurysm types at lower frequencies. This invites the question whether the increased risk of thromboembolic complications in posterior circulation aneurysms is less a result of aneurysm morphology itself, but rather a consequence of covering a territory so rich in perforators without significant collateralization.[4] This location in the subset of fusiform aneurysms involves a relatively perforator-rich region as compared with dissecting aneurysms, which tended to involve only the VA. The vast majority of hemorrhagic complications (90%) occurred in the postprocedural period and included SAH (70%) and intraparenchymal hemorrhage (30%). The rate of hemorrhage (7.8%) was in line with previous reports.[4]

Of the 14 deaths, 64% were in patients who had a history of SAH, with 78% of those treated within 2 weeks of

TABLE 10. Deaths in 14 patients treated with PEDs

Age (yrs)	Sex	SAH	Aneurysm Location	Morphology	Maximal Diameter (mm)	Time from Procedure to Death (mos)	Cause of Death
60	F	Immediate	VA	Dissecting	14	<1	Sequelae of presenting aneurysmal SAH
76	F	Immediate	VA	Saccular	6.7	<1	SAH from intraop aneurysm rupture
56	F	Immediate	SCA	Saccular	12.6	<1	Acute in-stent thrombosis & occlusion of the distal 1/3 of the BA, basilar tip, & right P_1 segment of the PCA, resulting in multiple posterior circulation infarctions
52	F	None	BA	Saccular	25	<1	SAH after embolization w/ PED, followed by BA thrombosis
48	F	Immediate	BA	Fusiform	15	<1	Pontine infarct after embolization w/ PED
69	F	Immediate	VA	Dissecting	8	<1	SAH from aneurysmal rebleeding the day after embolization w/ PED
76	M	Acute	BA	Dissecting	7	<1	Sequelae of presenting aneurysmal SAH
71	M	None	BA	Fusiform	12	13	Underwent retreatment w/ 2nd PED at 12 mos, death 1 mo later of unknown cause
82	F	None	BA	Dissecting	24	6	Unrelated medical problems
55	F	None	Vertebro-basilar	Fusiform	60	<1	Progressive neurological decline secondary to presenting brainstem stroke
44	M	None	BA	Fusiform	29.6	<1	SAH
67	F	Immediate	VA	Dissecting	8	<1	Sequelae of presenting aneurysmal SAH
64	M	Remote	PICA	Saccular	8	4	On follow-up the PED was foreshortened & directed flow to the aneurysm; during salvage stent-assisted coiling, massive SAH occurred
51	F	Remote	VA	Saccular	8	26	Hypertensive cerebral hemorrhage (possibly exacerbated by antiplatelet agents)

aneurysm rupture. Given these findings, SAH represents the major comorbidity contributing to complications with Pipeline embolization of posterior circulation aneurysms, and warrants judicious use of the technology under this circumstance. The breakdown by aneurysm type showed that the mortality rate was highest in dissecting aneurysms because of their association with SAH. The complication rates compared favorably to the other aneurysm morphologies, indicating that this treatment modality and the use of dual-antiplatelet therapy are relatively safe in this situation. Major complications were most common in fusiform aneurysms. Acknowledging that miscellaneous complications such as groin hematoma, arterial dissections, or contrast nephropathy can also affect the mRS score, we believe that the number of patients assessed in this study limits the bias that these events might cause in a smaller sample.

Fusiform aneurysms remain one of the most challenging aneurysms to treat. Importantly, flow-diverter treatment of fusiform posterior circulation aneurysms is usually undertaken as a salvage maneuver for patients with worsening neurological status due to aneurysm mass effect, rather than to protect against hemorrhage. A number of previous reports support the notion that symptomatic posterior circulation aneurysms are more risky to treat with flow diversion.[1,17,18,22,23] Our study also found that patients presenting with neurological deficits tended to experience a higher rate of complications; however, this was not significant in multivariable analysis. Pipeline embolization of posterior circulation aneurysms with intraaneurysmal thrombus, which is most frequent in fusiform aneurysms, is particularly hazardous because critical perforators may only be supplied through tenuous channels crossing the thrombus.[18] Although not statistically significant in the present study, placement of multiple overlapping PEDs may be a risk factor for thromboembolic and hemorrhagic complications due to the increased resistance to perforator artery filling caused by the increased surface coverage area. In the absence of convincing evidence that more devices result in superior long-term occlusion rates, placement of the lowest number of PEDs possible may be preferred.

The utility of platelet function testing prior to flow diversion remains controversial.[8,13,20] In our study, platelet function was assessed in 59.7% of procedures, with the exception of procedures performed at Canadian centers and at one center in the US where platelet inhibition is not routinely assessed.[21] In saccular aneurysms, clopidogrel nonresponders were at higher risk for complications compared with responders. Interestingly, clopidogrel nonresponse is not significantly associated with nonsaccular aneurysms, and thus is probably only one of many contributing factors. In addition, it may be that the duration of dual-antiplatelet therapy also affects occlusion rates, and this merits further investigation. As evidenced by the Flow Diversion in the Treatment of Intracranial Aneurysms Trial (FIAT), in which a 46.2% rate of death or dependency following treatment of posterior circulation aneurysms was reported,[21] flow diversion in this setting can be dangerous and is often reserved for aneurysms without other treatment options. The present study demonstrates an evolution of the procedure driven by a growing experience with the PED that has led to reduced morbidity and mortality rates in the treatment of these challenging aneurysms.

Limitations of the Study

The primary limitations are the retrospective study design and lower case numbers in the individual aneurysm types, limiting the statistical analysis. Pipeline embolization for posterior circulation aneurysms was generally reserved as a last option for the particular aneurysm, and treatment decisions were ultimately at the discretion of the participating institution. The inclusion of multiple institutions, however, improves the generalizability of the findings, but introduces variability in patient management and follow-up imaging. Angiographic and functional outcome were assessed at the individual centers and not at a central location blinded to the management of the patient. We encourage participation in multicenter registries as an avenue to obtain additional insight into this treatment modality.

Conclusions

Aneurysm morphology is an important consideration in the treatment of posterior circulation aneurysms with the PED. Fusiform aneurysms are the most challenging to treat due to the fact that they had the lowest occlusion rate and highest frequency of major complications. Dissecting aneurysms, frequently treated in the setting of SAH, occluded most often and had a low procedural complication rate. The mortality rate, however, was the highest in dissecting aneurysms because of the natural history of SAH. Saccular aneurysms were associated with the highest rate of minor complications (particularly in clopidogrel nonresponders), and with acceptable occlusion rates.

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Disclosures

Dr. Cognard is a consultant for Medtronic, Stryker, and MicroVention. Dr. Levy has direct stock ownership in Intratech Medical, Ltd., NeXtGen Biologics, and Neuravi (sold the latter in April 2017). He is a consultant for Pulsar Vascular. He is receiving an honorarium for training and lectures for Covidien, and he serves on the advisory board for Abbott Vascular, Stryker, NeXtGen Biologics, MEDX, and Cognition Medical. Dr. Pereira is a consultant for Stryker, Medtronic, Balt, and Phenox. Dr. Siddiqui is a consultant for Covidien as well as for the following companies: Amnis Therapeutics, Ltd.; Cerebrotech Medical Systems, Inc.; CereVasc, LLC; Claret Medical, Inc.; Codman; Corindus, Inc.; GuidePoint Global Consulting; Medtronic; MicroVention; Neuravi; Penumbra; Pulsar Vascular; Rapid Medical; Rebound Therapeutics Corp.; Silk Road Medical; Stryker; The Stroke Project, Inc.; Three Rivers Medical, Inc.; and W.L. Gore & Associates. He has direct stock ownership in the following companies: Buffalo Technology Partners, Inc.; Cardinal Health; International Medical Distribution Partners; Medina Medical Systems; Neuro Technology Investors; StimMed; and Valor Medical. He is on the Advisory Board of the Intersocietal Accreditation Commission. He is Principal Investigator (PI)/National Steering Committee for 3D Separator Trial, COMPASS Trial, and INVEST Trial (Penumbra); PI/National Steering Committee for SWIFT PRIME and SWIFT DIRECT Trials (Medtronic); PI/National Steering Committee for FRED Trial and CONFIDENCE Study (MicroVention); and PI/National Steering Committee for LARGE Trial (Codman & Shurtleff). Dr. Thomas is on the Data Safety Monitoring Board of the SCENT flow diverter trial.

Author Contributions

Conception and design: Thomas, Griessenauer, Ogilvy, Adeeb. Acquisition of data: Griessenauer, Adeeb, Dmytriw, Foreman, Shallwani, Limbucci, Kumar, Matouk, Shakir. Analysis and interpretation of data: Thomas, Griessenauer, Ogilvy, Adeeb, Dmytriw, Foreman, Shallwani, Limbucci, Kumar, Matouk, Shakir, Renieri. Drafting the article: Griessenauer. Critically revising the article: all authors. Reviewed submitted version of manuscript: Thomas, Griessenauer, Ogilvy. Statistical analysis: Griessenauer, Adeeb. Administrative/technical/material support: Thomas, Griessenauer, Ogilvy, Mangiafico, Michelozzi, Siddiqui, Levy, Marotta, Cognard. Study supervision: Thomas, Griessenauer, Ogilvy, Mangiafico, Michelozzi, Krings, Pereira, Matouk, Harrigan, Siddiqui, Levy, Marotta, Cognard.

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