Published in final edited form as:

J Clin Neurosci. 2019 July ; 65: 23–27. doi:10.1016/j.jocn.2019.04.024.

Impact of Age on Cerebral Aneurysm Occlusion after Flow Diversion

Anna Luisa Kühn, MD PhD¹, Peter Kan, MD², Nils Henninger, MD PhD³, Visish Srinivasan, MD², Katyucia de MacedoRodrigues, MD¹, Ajay K. Wakhloo, MD PhD⁴, Matthew J. Gounis, PhD¹, Ajit S. Puri, MD¹

¹Division of Neuroimaging and Intervention, Department of Radiology and New England, Center for Stroke Research, University of Massachusetts, Worcester, MA, USA

²Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA

³Department of Neurology, University of Massachusetts, Worcester, MA, USA

⁴Lahey Clinic and Medical Center, Department of Neurointerventional Radiology, Burlington, MA, USA

Abstract

The purpose of this study was to evaluate safety and efficacy of the pipeline embolization device (PED) in different patient age groups with unruptured intracranial aneurysms (UIA).

All patients with UIA treated with the PED between 2011 and 2017 were included. Based on their age, patients were trichotomized to: young (< 45 years), middle-aged (46-<65years) and older (> 65 years) groups. Patient's vascular risk factors, presenting symptoms and mRS on admission were collected. Follow-up imaging was evaluated for presence/absence of aneurysm occlusion. Clinical outcome at discharge, 3-9 months and 12-18 months was also documented when available.

A total of 260 patients harboring 307 aneurysms (young=57, middle-age=144 and older age group=64). Most aneurysms were located in the anterior circulation (94.8%). Overall morbidity and mortality was 2.3% each (6/260). At 3-9 months near complete to complete aneurysm occlusion was 82.5% (47/57) in the young age group, 82.6% (100/121) in the middle age, and 70.2% (40/57) in the older age group. At 12-18-month, near complete to complete occlusion was

Correspondence to: Ajit S. Puri, MD, Division of Neuroimaging and Intervention and New England Center for Stroke Research, Department of Radiology, University of Massachusetts, 55 Lake Avenue North, Worcester, MA 01655, USA, Phone: 508-334-8329, Fax: 774-441-6421, ajit.puri@umassmemorial.org.

Competing Interest Statement

PK is a consultant for Stryker Neurovascular, Covidien, and MicroVention.

NH serves on the advisory board of Omniox, Inc.

AKW is a consultant for Stryker Neurovascular; research grant: Philips Healthcare, Wyss Institute; speaker: Harvard Postgraduate Course, Miami Cardiovascular Institute, Stocks in InNeuroCo.

MJG: Has been a consultant on a fee-per-hour basis for Cerenovus, Imperative Care, InNeuroCo, Medtronic Neurovascular, Phenox, Route 92 Medical, Stryker Neurovascular; holds stock in InNeuroCo, Imperative Care and Neurogami; and has received research support from the Research support from the National Institutes of Health (NIH), Anaconda, Cerenovus, Cook Medical, Gentuity, Imperative Care, InNeuroCo, Magneto, Microvention, Medtronic Neurovascular, MIVI Neurosciences, Neuravi, Philips Healthcare, Rapid Medical, Route 92M, Stryker Neurovascular, and the Wyss Institute.

ASP is a consultant for Codman Neurovascular and Covidien; research grant from Stryker Neurovascular and Covidien, Stocks in InNeuroCo.

ALK, VS and KdMR have no competing interests.

100% in the young age group (32/32), 91.4% (64/70) in the middle age, and 78.4% (29/37) in the older age group. After adjustment for potential confounders, older age patients less frequently achieved near complete to complete occlusion by 3 years than younger subjects ($p=0.009$, HR 1.34 95%, CI 1.08-1.66).

Our results indicate feasibility and safety of PED across different age groups. Further study is required to determine age-related factors relating to aneurysm occlusion after PED to improve outcome and patient counseling.

Keywords

flow diverter; pipeline embolization device; unruptured; intracranial aneurysm; age; stent; occlusion

Introduction

Endovascular coil embolization of intracranial aneurysms has proven to be superior to neurosurgical clipping for both ruptured and unruptured aneurysms [1-3]. Unfortunately, recanalization and subtotal aneurysm occlusion still remains a problem [1,4,5]. Also, several types of aneurysms still pose a treatment challenge, for example large, wide-neck aneurysms or fusiform and blister aneurysms. With the introduction of flow diversion technology, more aneurysms have become amenable to endovascular treatment. Intracranial aneurysm treatment with flow diverters excludes the aneurysm from the blood circulation and allows for neointimal formation over the device, ultimately leading to vascular remodeling of the parent artery.

Despite the vast amount of literature reporting successful use of flow diversion technology for intracranial aneurysm treatment, it is not well established if patient age could have an impact on aneurysm occlusion rates and mortality. While advanced age has been found to be a risk factor for peri-procedural morbidity and mortality after endovascular coiling and neurosurgical clipping [6-8], limited information is available for patients treated with flow diversion.

Therefore, the aim of our study was to evaluate the safety and efficacy of the pipeline embolization device in patients of different age groups with UIA and focus on aneurysm occlusion and post-procedural mortality rates.

Methods

This retrospective study was approved by each hospital's institutional review board and the need for individual patient consent was waived.

Patient Selection

We included all patients with UIA that were treated with the PED at the University of Massachusetts Medical Center or at the Baylor College of Medicine between August 2010 and August 2017.

Based on their age, patients were trichotomized to: young (< 45 years), middle-aged (46- <65years) and older (≥ 65 years) groups (Figure 1).

Data Collection

Information on patient vascular risk factors, presenting symptoms, and pre-admission mRS was collected. Follow-up imaging was evaluated for aneurysm occlusion categorized as complete (100%), near complete (aneurysm occlusion ≥ 90%) or partial (aneurysm occlusion <90%) and the presence of intimal hyperplasia (modified Raymond-Roy classification).

Patient clinical outcome at discharge, 3-9 and 12-18-month follow-up was documented. When available, 20-36 months follow up was also included.

Statistical Analysis

Univariate comparisons were performed with χ^2 , Fisher exact, Mann-Whitney U, and ANOVA on Ranks, as appropriate. Kaplan-Meier survival analysis was used to determine the 3-year event-free survival (complete and near-complete aneurysm occlusion denoted the event of interest). The log-rank test was used for univariate comparisons of event-free survival between age groups. To determine whether increasing age was associated with the 3-year event-free survival independent of pertinent baseline characteristics we constructed Cox proportional hazards models. The proportional hazards assumption was assessed and satisfied in all models. Models were adjusted for hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, and tobacco use (absent vs. present). Variables were sequentially removed (likelihood ratio) from the models at a significance level of 0.1 to achieve a parsimonious model. We then repeated the analysis forcing all covariates into the model (optional). A two-sided $p < 0.05$ was considered significant for all analyses. All statistical analyses were performed using IBM SPSS Statistics Version 22 (IBM, Armonk, NY).

Results

Patient Population

We included a total of 260 patients harboring 307 aneurysms with 52 patients in the young age group, 144 in the middle age and 64 in the older age group. Male-to-female ratio was approximately 1:6.

Hypertension (53.4%), dyslipidemia (30.2%) and smoking (28.7%) were the most frequently encountered vascular risk factors in all age groups. Smoking was the most common risk factor in the young age group, followed by hypertension and dyslipidemia. In the middle age group, hypertension was more frequently seen, followed by smoking and dyslipidemia. Hypertension and dyslipidemia were the leading vascular risk factors in the older age group, followed by smoking.

Preprocedure mRS ranged from 0 to 4 with 250 patients having an mRS of 0, 3 patients an mRS of 1, 1 patient an mRS of 2, 4 patients an mRS of 3 and 2 patients an mRS of 4.

Aneurysm Characteristics

All aneurysms were found incidentally. The majority of the aneurysms were located in the anterior circulation (n=291, 94.8%; Figure 2). Of the 16 aneurysms located in the posterior circulation 9 (56.3%) involved the intracranial vertebral artery. Figure 2 summarizes the aneurysm location as well as prevalence of a positive family history for intracranial aneurysms stratified by the three defined age groups.

Aneurysm neck sizes measured between 2 to 12 mm and aneurysm sizes ranged between $2 \times 2 \times 2$ mm and $17 \times 15 \times 21$ mm (AP $\times$ TRV $\times$ SI) with mean maximum aneurysm diameter of 3.9 mm in the young age group, 5.5 mm in the middle-age group and 6.9 mm in the older age group. The majority of aneurysms were treated with a single PED. Fifty aneurysms were treated with multiple flow diverters.

Antiplatelet Therapy

Patients were given aspirin (81 mg) and clopidogrel (75 mg) daily for at least 5 days prior to the elective procedure. Therapeutic antiplatelet effect was ensured prior to the intervention; defined in our practice by VerifyNow P2Y₁₂ assay showing at least 50% platelet inhibition or PRU of less than 200 with platelet aggregation assay.

Postoperatively, dual antiplatelet therapy was continued for 6 months in order to prevent thromboembolism and stent occlusion. Beyond the 6-month follow-up time point patients were maintained on lifelong aspirin treatment.

Discharge functional outcome

Median mRS at discharge was 0 for all age groups. The majority of patients had no change in mRS from baseline to discharge (95.8%). Overall morbidity was 2.3% (6/260). Two cases of delayed intra-parenchymal hemorrhage (IPH) between 1 day and 2 weeks post procedure occurred in the middle age group resulting in worsening mRS (from 0 to 4 and 1 to 3). One case of delayed IPH was seen in the old age group with worsening mRS from 0 to 3. Three patients in the middle age group suffered a stroke post treatment (mRS from 0 to 1 and 0 to 3 in two cases). Overall mortality was 2.3% (6/260) with 1 death in the young age group (1/52, 1.9%), 2 deaths in the middle age group (2/144, 1.4%) and 3 deaths in the older age group (3/64, 4.7%). Cause of death was in-stent thrombosis with subsequent extensive posterior circulation infarction during aneurysm re-treatment in one young patient, and related to IPH in all other patients.

Mid-term functional outcome

The median mRS was zero at 3-9 and 12-18-month follow-up, respectively. All patients in the middle-age group who suffered an intracranial bleed post-procedure showed improvement in their mRS on follow-up evaluation. The patient with an mRS of 3 returned to baseline mRS of 0 which was stable on further follow-up evaluations. The other middle-aged patient with an intracranial bleed improved from an mRS of 4 to an mRS of 3. The patient in the older age group who suffered an intracranial bleed remained at an mRS of 3 throughout the follow-up. The postprocedural mRS of 1 in a middle-age patient who suffered a stroke post-procedure remained unchanged over the course of the follow-up. No

follow-ups were available for the remaining 2 patients in the middle-age group who suffered a stroke post-procedure.

Procedure-related Outcomes

All aneurysm follow-ups were performed with digital subtraction angiography.

Near complete to complete aneurysm occlusion at 3-9 and 12-18 months was overall seen in 79.2% (187/236) and 89.9% (125/139), respectively. Near complete to complete aneurysm occlusion was seen in 82.5% (47/57) in the young age group, in 82.6% (100/121) in the middle age and in 70.2% (40/57) in the older age group at 3-9 months. On 12-18-month follow-up, near complete to complete occlusion was seen in 100% of the young age group (32/32), in 91.4% (64/70) of the middle age and in 78.4% (29/37) in the older age group. Twenty-seven aneurysms (young=5, middle-age=14, old=8), which demonstrated near complete occlusion at 3-9 months, progressed to complete occlusion at 12-18 months in 5 cases. Eight aneurysms showed stable near complete occlusion. For 3 of those 8 aneurysms a 20-36-month follow-up was available showing complete occlusion. Another 2 aneurysms without 12-18-month follow-up showed stable near complete occlusion at 20-36 months. Previous partial aneurysm occlusion at 3-9 months (young=10, middle-age=16, old=9) progressed to complete or near complete occlusion at 12-18 months in 17 cases. Eight aneurysms showed stable partial occlusion at 12-18 months. Four patients required placement of a second PED due to migration of the device resulting in suboptimal aneurysm neck coverage by the initially placed device on follow-up evaluation.

There were 27 cases of mild intimal hyperplasia (IH, <50%) at 3-9 months (14.2%, young=4, middle-age=16, old=7). Resolution of mild IH at 12-18 months was seen in 7 cases. There were 5 cases of moderate IH (50-75%) at 6 months (young=2, middle-age=2, old=1). One case resolved, one case improved to only mild IH and another case remained stable at 12-18 months. Two cases did not have follow-up. There were 3 patients with severe IH (>75%) at 6-month follow-up who, showed stable or improved (moderate IH) in one case each at 12-18 and 20-36-month follow-up. The third patient did not have any follow-up.

There were some cases which did not follow the early and mid term follow up time points. All patients in the young group had early (3-9 month) follow up. In the middle age group, 8 patients had their first follow up angiogram 12-18 months after the intervention, 7/8 (87.5%) showed complete occlusion and 1 showed partial occlusion. In the old age group 4 patients had their first follow up angiogram at 12-18 months after intervention, 2/4 (50%) showed complete occlusion and 2 showed partial occlusion.

Table 1 summarizes the procedure-related outcomes.

Figure 3 shows the cumulative probability of complete or near complete aneurysm occlusion during the 3-year follow-up period stratified by age groups. Overall, there was a significant difference between groups ($p=0.006$, log-rank test). After adjustment, Cox-regression analyses confirmed that patient age (trichotomized) was independently associated with the 3-year aneurysm occlusion ($p=0.009$ HR 1.34 95%-CI 1.08-1.66) whereby older patients achieved aneurysm occlusion later.

Discussion

Since its introduction to the neurointerventional field, flow diversion technology has revolutionized endovascular treatment of intracranial aneurysms. The PED is FDA approved for treatment of large or giant wide-necked aneurysms along the petrous to superior hypophyseal segment of the internal carotid artery (ICA) [9]. However, over the past years, studies and case series have shown that the PED can successfully treat aneurysms of smaller diameter and beyond the ICA [10-15].

As the current literature does not provide much information on performance of the FD in regards to age-related mortality and aneurysm occlusion status, our aim was to examine the databases of two large centers performing aneurysm treatment with flow diversion and evaluate for patient mortality and aneurysm occlusion status in patients of different age groups.

Our study found that patient's in the older age group less frequently achieved near complete to complete occlusion by 3 years when compared to the other subject groups ($p=0.009$, HR 1.34 95%, CI 1.08-1.66). This observation is in line with a recent publication by Adeeb et al [16]. The PED represents an endoluminal device which redirects blood flow away from the aneurysm sac and promotes aneurysm occlusion and parent vessel remodeling over time. Complete aneurysm occlusion and vessel wall remodeling are achieved by neointimal formation across the device construct and aneurysm orifice. Atherosclerotic changes in the elderly population may decrease the flow diverting properties of the device and mostly rely on aneurysm occlusion though neointimal formation along the device construct. Unfortunately, reendothelialization capacity declines with age [17,18] resulting in delayed or incomplete aneurysm occlusion in elderly patients. Further studies on factors influencing neointimal formation are, however, needed to support current theories.

Initially, flow diversion was used to treat complex, giant and fusiform aneurysms. However, with more data available which supports efficacy and safety of flow diverters for treatment of smaller (<7 mm) aneurysms [19-21], the device is now being used more often in patients with small and less complex aneurysms. Our older patient group showed the largest mean aneurysm diameter of 6.9 mm. While aneurysm size certainly plays a role in aneurysm occlusion, we feel that 1-2 mm difference in mean aneurysm diameter between the middle age (5.5 mm) and older age group is not solely able to explain the detected difference in time-to-aneurysm occlusion.

In our cohort, near complete to complete occlusion was seen in 82.5% (47/57) in the young age group, 82.6% (100/121) in the middle age, and 70.2% (40/57) in the older age group at 3-9 months. At 12-18 months, near complete to complete occlusion was seen in 100% in the young age group (32/32), 91.4% (64/70) in the middle age, and 78.4% (29/37) in the older age group.

A recent retrospective, multicenter analysis for age-related complications with the PED using data from the International Retrospective Study of the Pipeline Embolization Device (IntrePED) [22] included 197 patients with 224 unruptured cerebral aneurysms. This analysis reports an all-cause mortality ranging from 0.5-8.3% in the different patient age

groups. We had an overall mortality and morbidity rate of 2.3% each. Our morbidity and mortality rate in the middle age group was 3.7% and 1.4%, respectively. Mortality rate in the young and older age group was 1.9% and 4.7%, respectively. No change in mRS from baseline to discharge was seen in 95.8% of patients overall.

Study Limitations

Limitations of our study include its retrospective nature and limited follow-up for some of our patients, especially because the definitive treatment results of flow diversion technology rely on progressive reduction of aneurysm filling over time. The aneurysms treated in our study are distributed throughout the intracranial circulation, and are at locations at which aneurysms are known to take longer to achieve complete occlusion or which overall have a decreased occlusion rate, for example MCA bifurcation aneurysms [23,24] or fetal PCom artery aneurysms [25-30].

Conclusion

Our results indicate feasibility and safety of the PED across different age groups. Further study is required to determine age-related factors relating to aneurysm occlusion after PED to improve outcome and patient counseling.

Acknowledgments

Funding Statement: Nils Henninger is supported by NS091499 from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The remaining authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002;360:1267–74. 10.1016/S0140-6736(02)11314-6. [PubMed: 12414200]
2. McDougall CG, Spetzles RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, Albuquerque FC. The Barrow Ruptured Aneurysm Trial. *J Neurosurg* 2012;116:135–44. 10.3171/2011.8.JNS101767. [PubMed: 22054213]
3. Hwang JS, Hyun MK, Lee HJ, Choi JE, Kim JH, Lee NR, Kwon JW, Lee E. Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. *BMC Neurol* 2012;12:99 10.1186/1471-2377-12-99. [PubMed: 22998483]
4. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005;366:809–17. 10.1016/S0140-6736(05)67214-5. [PubMed: 16139655]
5. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, Lamoureux J, Chagnon M, Roy D. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke* 2003;34:1398–403. 10.1161/01.STR.0000073841.88563.E9. [PubMed: 12775880]

6. Becske T, Kallmes DF, Saatci I, McDougall CG, Szikora I, Lanzino G, Moran CJ, Woo HH, Lopes DK, Berez AL, Cher DJ, Siddiqui AH, Levy EI, Albuquerque FC, Fiorella DJ, Berentei Z, Marosfoi M, Cekirge SH, Nelson PK. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. *Radiology* 2013;267:858–68. 10.1148/radiol.13120099. [PubMed: 23418004]
7. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flowdiverters: a meta-analysis. *Stroke* 2013;44:442–7. 10.1161/STROKEAHA.112.678151. [PubMed: 23321438]
8. Arrese I, Sarabia R, Pintado R, Delgado-Rodriguez M. Flow-diverter devices for intracranial aneurysms: systematic review and meta-analysis. *Neurosurgery* 2013;73:193–200. 10.1227/01.neu.0000430297.17961.f1 [PubMed: 23624409]
9. Food US and Administration Drug. Pipeline embolization device PMA P100018. Summary of safety and effectiveness data. 2011
10. Martin AR, Cruz JP, O’Kelly C, Kelly M, Spears J, Marotta TR. Small pipes: preliminary experience with 3-mm or smaller pipeline flow-diverting stents for aneurysm repair prior to regulatory approval. *AJNR Am J Neuroradiol* 2015;36:557–61. 10.3174/ajnr.A4170. [PubMed: 25395659]
11. Kühn AL, Hou SY, Perras M, Brooks C, Gounis MJ, Wakhloo AK, Puri AS. Flow diverter stents for unruptured saccular anterior circulation perforating artery aneurysms: safety, efficacy, and short-term follow-up. *J Neurointerv Surg* 2015;7:634–40. 10.1136/neurintsurg-2014-011237. [PubMed: 25051964]
12. Dabus G, Grossberg JA, Cawley CM, Dion JE, Puri AS, Wakhloo AK, Gonsales D, Aguilar-Salinas P, Sauvageau E, Linfante I, Hanel RA. Treatment of complex anterior cerebral artery aneurysms with Pipeline flow diversion: mid-term results. *J Neurointerv Surg* 2017;9:147–51. 10.1136/neurintsurg-2016-012519. [PubMed: 27382125]
13. Puri AS, Massari F, Asai T, Marosfoi M, Kan P, Hou SY, Howk M, Perras M, Brooks C, Clarencon F, Gounis MJ, Wakhloo AK. Safety, efficacy, and short-term follow-up of the use of Pipeline Embolization Device in small (<2.5 mm) cerebral vessels for aneurysm treatment: single institution experience. *Neuroradiology* 2016;58:267–75. 10.1007/s00234-015-1630-5. [PubMed: 26700827]
14. Yavuz K, Geyik S, Saatci I, Cekirge HS. Endovascular treatment of middle cerebral artery aneurysms with flow modification with the use of the Pipeline embolization device. *AJNR Am J Neuroradiol* 2014;35:529–35. 10.3174/ajnr.A3692. [PubMed: 24072620]
15. Pistocchi S, Blanc R, Bartolini B, Piotin M. Flow diverters at and beyond the level of the circle of Willis for the treatment of intracranial aneurysms. *Stroke* 2012;43:1032–8. 10.1161/STROKEAHA.111.636019. [PubMed: 22282890]
16. Adeeb N, Moore JM, Wirtz M, Griessenauer CJ, Foreman PM, Shallwani H, Gupta R, Dmytriw AA, Motiei-Langroudi R, Alturki A, Harrigan MR, Siddiqui AH, Levy EI, Thomas AJ, Ogilvy CS. Predictors of Incomplete Occlusion following Pipeline Embolization of Intracranial Aneurysms: Is It Less Effective in Older Patients? *AJNR Am J Neuroradiol* 2017;38:2295–300. 10.3174/ajnr.A5375 [PubMed: 28912285]
17. Gennaro G, Ménard C, Michaud SE, Rivard A. Age-dependent impairment of reendothelialization after arterial injury: role of vascular endothelial growth factor. *Circulation* 2003;107:230–3. [PubMed: 12538420]
18. Xia WH, Yang Z, Xu SY, Chen L, Zhang XY, Li J, Liu X, Qiu YX, Shuai XT, Tao J. Age-related decline in reendothelialization capacity of human endothelial progenitor cells is restored by shear stress. *Hypertension* 2012;59:1225–31. 10.1161/HYPERTENSIONAHA.111.179820. [PubMed: 22547440]
19. Chalouhi N, Zanaty M, Whiting A, Yang S, Tjoumakaris S, Hasan D, Starke RM, Hann S, Hammer C, Kung D, Rosenwasser R, Jabbour P. Safety and efficacy of the Pipeline Embolization Device in 100 small intracranial aneurysms. *J Neurosurg* 2015;122:1498–502. 10.3171/2014.12.JNS14411. [PubMed: 25635478]
20. Griessenauer CJ, Ogilvy CS, Foreman PM, Chua MH, Harrigan MR, He L, Fusco MR, Mocco JD, Stapleton CJ, Patel AB, Sonig A, Siddiqui AH, Thomas AJ. Pipeline Embolization Device for Small Intracranial Aneurysms: Evaluation of Safety and Efficacy in a Multicenter Cohort. *Neurosurgery* 2017;80:579–87. 10.1227/NEU.0000000000001377. [PubMed: 27489165]

21. Awad AW, Moon K, Yoon N, Mazur MD, Kalani MYS, Taussky P, McDougall CG, Albuquerque FC, Park MS. Flow diversion of tandem cerebral aneurysms: a multi-institutional retrospective study. *Neurosurg Focus* 2017;42:E10. 10.3171/2017.2.FOCUS1731
22. Brinjikji W, Kallmes DF, Cloft HJ, Lanzino G. Age-related outcomes following intracranial aneurysm treatment with the Pipeline Embolization Device: a subgroup analysis of the IntrePED registry. *J Neurosurg* 2016;124:1726–30. 10.3171/2015.5.JNS15327. [PubMed: 26544776]
23. Caroff J, Neki H, Mihalea C, D'Argento F, Abdel Khalek H, Ikka L, Moret J, Spelle L. Flow-Diverter Stents for the Treatment of Saccular Middle Cerebral Artery Bifurcation Aneurysms. *AJNR Am J Neuroradiol* 2016;37:279–84. 10.3174/ajnr.A4540. [PubMed: 26405085]
24. Topcuoglu OM, Akgul E, Daglioglu E, Topcuoglu ED, Peker A, Akmangit I, Belen D, Arat A. Flow Diversion in Middle Cerebral Artery Aneurysms: Is It Really an All-Purpose Treatment? *World Neurosurg* 2016;87:317–27. 10.1016/j.wneu.2015.11.073. [PubMed: 26723288]
25. Zanaty M, Chalouhi N, Starke RM, Jabbour P, Ryken KO, Bulsara KR, Hasan D. Failure of the Pipeline Embolization Device in Posterior Communicating Artery Aneurysms Associated with a Fetal Posterior Cerebral Artery. *Case Rep Vasc Med* 2017;2017:9895414. 10.1155/2017/9895414. [PubMed: 28638672]
26. Golshani K, Ferrell A, Zomorodi A, Smith TP, Britz GW. A review of the management of posterior communicating artery aneurysms in the modern era. *Surg Neurol Int* 2010;1:88. 10.4103/2152-7806.74147. [PubMed: 21206898]
27. Wallace AN, Kayan Y, Austin MJ, Delgado Almandoz JE, Kamran M, Cross DT 3rd, Moran CJ, Osbun JW, Kansagra AP. Pipeline embolization of posterior communicating artery aneurysms associated with a fetal origin posterior cerebral artery. *Clin Neurol Neurosurg* 2017;160:83–7. 10.1016/j.clineuro.2017.06.014. [PubMed: 28692909]
28. Kan P, Duckworth E, Puri A, Velat G, Wakhloo A. Treatment failure of fetal posterior communicating artery aneurysms with the pipeline embolization device. *J Neurointerv Surg* 2016;8:945–8. 10.1136/neurintsurg-2015-011959. [PubMed: 26363511]
29. Roy AK, Howard BM, Haussen DC, Osbun JW, Halani SH, Skukalek SL, Tong F, Nogueira RG, Dion JE, Cawley CM, Grossberg JA. Reduced Efficacy of the Pipeline Embolization Device in the Treatment of Posterior Communicating Region Aneurysms with Fetal Posterior Cerebral Artery Configuration. *Neurosurgery* 2018;82:695–700. 10.1093/neuros/nyx293. [PubMed: 28541503]
30. Daou B, Valle-Giler EP, Chalouhi N, Starke RM, Tjoumakaris S, Hasan D, Rosenwasser RH, Hebert R, Jabbour P. Patency of the posterior communicating artery following treatment with the Pipeline Embolization Device. *J Neurosurg* 2017;126:564–9. 10.3171/2016.2.JNS152544. [PubMed: 27153163]

Figure 1: Age distribution.

Age of the studied patient population follows a normal distribution (dashed line). Based on this we defined patients between the 25th and 75th percentile as middle-age (46 to 64 years), those below the 25th percentile as young (< 45 years), and those above the 75th percentile as old (> 65 years).

Figure 2: Aneurysm characteristics and family history.

Overview of the aneurysm location in the anterior versus posterior circulation in the studied cohort as well as prevalence of a positive family history for intracranial aneurysms within the different age groups. Overall, the majority of aneurysms were found in the anterior circulation with n=61 (21%) in the young age group, n=152 (52.2%) in the middle-age group and n=78 (26.8%) in the older age group. The middle-age group had the highest proportion of subjects with family members with intracranial aneurysms (n=25, 11.6%). ICA indicates internal carotid artery; PComA = posterior communicating artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; ACom = anterior communicating artery; VA = vertebral artery; PCA = posterior cerebral artery; SCA = superior cerebellar artery; AICA = anterior inferior cerebellar artery; PICA = posterior inferior cerebellar artery.

Figure 3: Probability of complete or near-complete aneurysm occlusion stratified by age groups. Shown are the Kaplan-Meier curves for the 3-year cumulative probability of aneurysm occlusion stratified by age (green = young age group; blue = middle age group; red=old age group). There was a significant between-group difference indicating later aneurysm occlusion in the old age group ($p=0.006$).

Table 1:

Summary of procedure-related outcomes.

	Young age group	Middle-age group	Older age group
Near complete and complete aneurysm occlusion at 3-9 months (%)	82.5%	82.6%	70.2%
Near complete and complete aneurysm occlusion rate at 12-18 months (%)	100%	91.4%	78.4%
Mild intimal hyperplasia (n)	4	16	7
Moderate intimal hyperplasia (n)	2	2	1
Severe intimal hyperplasia (n)	0	2	1
Intraparenchymal hemorrhage (n)	0	2	1
Mortality (n)	1	2	3

Procedure-related outcomes. n=number of patients