

International Retrospective Study of the Pipeline Embolization Device: A Multicenter Aneurysm Treatment Study

D.F. Kallmes, R. Hanel, D. Lopes, E. Boccardi, A. Bonafé, S. Cekirge, D. Fiorella, P. Jabbour, E. Levy, C. McDougall, A. Siddiqui, I. Szikora, H. Woo, F. Albuquerque, H. Bozorgchami, S.R. Dashti, J.E. Delgado Almandoz, M.E. Kelly, R. Turner IV, B.K. Woodward, W. Brinjikji, G. Lanzino, and P. Lylyk



ABSTRACT

BACKGROUND AND PURPOSE: Flow diverters are increasingly used in the endovascular treatment of intracranial aneurysms. Our aim was to determine neurologic complication rates following Pipeline Embolization Device placement for intracranial aneurysm treatment in a real-world setting.

MATERIALS AND METHODS: We retrospectively evaluated all patients with intracranial aneurysms treated with the Pipeline Embolization Device between July 2008 and February 2013 in 17 centers worldwide. We defined 4 subgroups: internal carotid artery aneurysms of ≥ 10 mm, ICA aneurysms of < 10 mm, other anterior circulation aneurysms, and posterior circulation aneurysms. Neurologic complications included spontaneous rupture, intracranial hemorrhage, ischemic stroke, permanent cranial neuropathy, and mortality. Comparisons were made with *t* tests or ANOVAs for continuous variables and the Pearson χ^2 or Fisher exact test for categorical variables.

RESULTS: In total, 793 patients with 906 aneurysms were included. The neurologic morbidity and mortality rate was 8.4% (67/793), highest in the posterior circulation group (16.4%, 9/55) and lowest in the ICA < 10 -mm group (4.8%, 14/294) ($P = .01$). The spontaneous rupture rate was 0.6% (5/793). The intracranial hemorrhage rate was 2.4% (19/793). Ischemic stroke rates were 4.7% (37/793), highest in patients with posterior circulation aneurysms (7.3%, 4/55) and lowest in the ICA < 10 -mm group (2.7%, 8/294) ($P = .16$). Neurologic mortality was 3.8% (30/793), highest in the posterior circulation group (10.9%, 6/55) and lowest in the anterior circulation ICA < 10 -mm group (1.4%, 4/294) ($P < .01$).

CONCLUSIONS: Aneurysm treatment with the Pipeline Embolization Device is associated with the lowest complication rates when used to treat small ICA aneurysms. Procedure-related morbidity and mortality are higher in the treatment of posterior circulation and giant aneurysms.

ABBREVIATIONS: IntrePED = International Retrospective Study of Pipeline Embolization Device; IPH = intraparenchymal hemorrhage; PED = Pipeline Embolization Device

Endoluminal flow-diverter therapy has gained widespread acceptance for the treatment of intracranial aneurysms.¹⁻⁴ High rates of complete aneurysm occlusion have been reported, even in

large and giant aneurysms, with the use of endoluminal flow diverters.¹⁻⁷ The Pipeline Embolization Device (PED; Covidien, Irvine, California) received CE mark approval in 2008 for the embolization of cerebral aneurysms and received US FDA approval in 2011 (PMA P100018) for the treatment of large and giant wide-neck aneurysms in the internal carotid artery, from the petrous to the superior hypophyseal segments. While numerous previous studies have reported overall rates of adverse events similar to

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From the Department of Radiology (D.F.K., W.B., G.L.), Mayo Clinic, Rochester, Minnesota; Department of Neurosurgery (R.H.), Mayo Clinic, Jacksonville, Florida; Department of Neurological Surgery (D.L.), Rush University Medical Center, Chicago, Illinois; Department of Neuroradiology (E.B.), Niguarda CA' Granda Hospital, Milan, Italy; Department of Neuroradiology (A.B.), Hôpital Gui de Chauliac, Montpellier, France; Department of Radiology (S.C.), Hacettepe University Hospitals, Ankara, Turkey; Department of Neurological Surgery (D.F., H.W.), Stony Brook University Medical Center, Stony Brook, New York; Department of Neurosurgery (P.J.), Thomas Jefferson University, Philadelphia, Pennsylvania; Department of Neurosurgery (E.L., A.S.), University at Buffalo, State University of New York, Buffalo, New York; Department of Neurosurgery (C.M., F.A.), Barrow Neurological Associates, Phoenix, Arizona; National Institute of Neurosciences (I.S.), Budapest, Hungary; Department of Neurology (H.B.), Oregon Health and Science University, Portland, Oregon; Norton Neuroscience Institute (S.R.D.), Louisville, Kentucky; Department of Radiology (J.E.D.A.), Neuroscience Institute, Abbott Northwestern Hospital, Minneapolis, Minnesota; Division of Neurosurgery, Department of Surgery (M.E.K.), University of Saskatchewan, Saskatoon, Saskatchewan, Canada;

Department of Neurosciences (R.T.), Medical University of South Carolina, Charleston, South Carolina; Vista Radiology PC (B.K.W.), Knoxville, Tennessee; and Department of Neuroscience (P.L.), Equipo de Neurocirugía Endovascular Radiología Intervencionista, Buenos Aires, Argentina.

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Please address correspondence to David Kallmes, MD, Mayo Clinic, 200 First St SW, OLI-112 SMH, Rochester, MN 55905; e-mail: Kallmes.david@mayo.edu

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those in other endovascular procedures, case reports and small case series documenting severe and “unexpected” complications have raised questions about the safety of these devices.^{1,3,8,9} Severe and unexpected adverse events include spontaneous rupture of treated aneurysms and intraparenchymal intracranial hemorrhage unrelated to aneurysm rupture.^{8,10-12} These reports led to policies in some regions mandating concomitant coil embolization with flow-diverter therapy to mitigate the risk of spontaneous aneurysm rupture.¹³

Most previous literature on flow-diversion therapy comprised single-center case series, either retrospective or prospective, and has substantial selection bias, which may affect the rates of severe and unexpected adverse events. These biases may be diminished through pooling of consecutive patients treated at multiple centers in a “real-world” setting, with homogeneous end points and methods of data analysis. The International Retrospective Study of Pipeline Embolization Device (IntrePED) registry was designed for this purpose and to determine rates of important neurologic safety events following PED placement for intracranial aneurysm treatment.

MATERIALS AND METHODS

Study Design and Participants

We retrospectively evaluated all patients with intracranial aneurysms treated with the Pipeline Embolization Device between July 2008 and February 2013 in 6 countries in 17 centers experienced in PED use. Local institutional review boards or ethics committees approved the study and use of patients’ retrospective data. An institutional review board/ethics committee waiver of informed consent (and Health Insurance Portability and Accountability Act Waiver of Authorization for US sites) or a sponsor institutional review board/ethics committee–approved informed consent form was obtained from each participating site. Written informed consent was obtained from each patient, if required. This observational registry was funded and supported by Covidien, with scientific oversight of the study steering committee members. Physicians who contributed data for this study were endovascular-trained neurointerventionalists. Each site that participated was required to have at least 1 physician who had treated a minimum of 10 PED cases before the time of institutional review board/ethics committee approval for the study. Unless an investigator had been a participant in a clinical study before commercialization of the PED, this study captures the investigators’ experience as new users of the device. A majority of the 26 IntrePED physicians were new users, and their early cases were included in the registry.

Data were collected from the time of the first commercial use of PED at a site until the time of institutional review board/ethics committee approval of the study protocol for that site. Investigational centers were required to provide data on all consecutive patients to eliminate selection bias, provided that the patients fulfilled the following conditions: 1) received PED treatment for an intracranial aneurysm after the date of regulatory approval in that region or country, and 2) had a clinical evaluation following treatment during the window of time before institutional review board/ethics committee approval. Because this was a retrospective study, there were no patients lost to follow-up.

Seven hundred ninety-three patients treated for 906 aneurysms were enrolled. Many patients (38%) had been previously reported in the literature.¹⁴⁻²⁹ We defined 4 primary anatomic/size subgroups: internal carotid artery aneurysms ≥ 10 mm (“large ICA”), ICA aneurysms of < 10 mm (“small ICA”), other anterior circulation aneurysms (“other anterior”), and posterior circulation aneurysms.

Procedures

Because this was a retrospective study, procedural details and perioperative patient management varied across centers. All centers used a common study protocol that specified the data to be collected, study end points, events of interest, and statistical analyses. The Steering Committee defined neurologic “clinical safety events of interest” a priori, including spontaneous rupture of the target aneurysm causing subarachnoid hemorrhage or cavernous carotid fistula, intraparenchymal hemorrhage (IPH) (both ipsilateral and contralateral), ischemic stroke, parent artery stenosis, and permanent cranial neuropathy. Site investigators identified events of interest according to the study protocol through retrospective review of the patient’s record. All events of interest were reviewed in detail by an Adverse Events Review Committee, comprising of 3 members of the Steering Committee, including the overall study principal investigator. The committee determined the category of event and whether the event was major or minor. A “major” adverse event was defined as an ongoing clinical deficit at 7 days following the event. “Minor” adverse events were defined as events that resolved within 7 days with no clinical sequelae. All major adverse events are included in the neurologic morbidity and mortality rates. Long-term neurologic morbidity and mortality rates included morbidity and mortality due to adverse events occurring any time in the postoperative period (< 30 days and ≥ 30 days). Information collected during the study was standardized across centers and included baseline characteristics of patients and aneurysms, procedural information, prespecified clinical safety events of interest, and follow-up clinic visits or telephone calls. A list of data collected for each patient/aneurysm is provided in the On-line Appendix. Because this was a retrospective study, the timing of the patient follow-up evaluations was conducted per institution standard of care.

Statistical Analysis

Statistical analyses were performed by using SAS, Version 9.1 or higher (SAS Institute, Cary, North Carolina). Summary statistics are presented for all data available by using means and SDs for continuous variables and frequency tabulations for categorical variables. Comparisons between groups for continuous variables were evaluated by using *t* tests or ANOVAs and the Fisher exact test or Pearson χ^2 for binary categorical variables. Most statistical analyses were performed across patient groups—that is, on a per-patient basis. Because some patients had > 1 aneurysm treated with a PED, however, each patient’s first aneurysm was used to classify patients into the 4 anatomic/size subgroups, and the largest aneurysm was used to classify patients into the 3 aneurysm size categories. Some analyses, including aneurysm characteristics and spontaneous ruptures across aneurysm-size groups, were performed across all aneurysms rather than across patients.

Table 1: Aneurysm characteristics

| Aneurysm Characteristics | Anterior ICA ≥10 mm (n = 311) | Anterior <10 mm (n = 349) | Posterior (n = 59) | Other Anterior ≥10 mm (n = 178) | Total (n = 896) ^a | P Value |
|----------------------------------|----------------------------------|------------------------------|-----------------------|------------------------------------|------------------------------|------------|
| Aneurysm size (mm) | | | | | | |
| Mean ± SD | 16.8 ± 6.2 | 5.2 ± 2.2 | 14.5 ± 9.0 | 9.8 ± 7.9 | 10.7 ± 7.7 | <.001 |
| Median, range | 15.0, 10.0–42.0 | 5.0, 1.0–9.9 | 11.8, 1.7–45.0 | 7.2, 1.0–55.0 | 9.0, 1.0–55.0 | |
| Aneurysm type | | | | | | |
| Small | 0 | 349/349 (100%) | 19/58 (32.8%) | 105/178 (59.0%) | 473/897 (52.8%) | |
| Large | 268/311 (86.2%) | 0 | 29/58 (50.0%) | 60/178 (33.7%) | 357/897 (39.8%) | |
| Giant | 43/311 (13.8%) | 0 | 10/58 (17.2%) | 13/178 (7.3%) | 66/897 (7.3%) | |
| Aneurysm neck (mm) | | | | | | |
| Mean ± SD | 8.5 ± 5.1 | 4.1 ± 2.2 | 9.3 ± 8.4 | 5.3 ± 5.1 | 6.2 ± 4.9 | <.001 |
| Median, range | 7.6, 0.9–50.0 | 4.0, 0.8–22.0 | 8.0, 1.7–53.0 | 4.0, 1.0–50.0 | 5.0, 0.8–53.0 | |
| Aneurysm shape | | | | | | |
| Fusiform | 49/311 (15.8%) | 17/349 (4.9%) | 17/59 (28.8%) | 29/178 (16.3%) | 112/897 (12.5%) | <.001 |
| Saccular | 239/311 (76.9%) | 305/349 (87.4%) | 25/59 (42.4%) | 118/178 (66.3%) | 686/897 (76.5%) | |
| Dissecting | 10/311 (3.2%) | 8/349 (2.3%) | 13/59 (22.0%) | 22/178 (12.4%) | 53/897 (5.9%) | |
| Other | 13/311 (4.2%) | 19/349 (5.4%) | 4/59 (6.8%) | 9/178 (5.1%) | 46/897 (5.1%) | |
| Aneurysm location | | | | | | |
| Internal carotid artery | 311/311 (100%) | 349/349 (100%) | 0 | 0 | 660/897 (73.6%) | <.001 |
| Middle cerebral artery | 0 | 0 | 0 | 43/178 (24.2%) | 43/897 (4.8%) | |
| Posterior cerebral artery | 0 | 0 | 15/59 (25.4%) | 0 | 15/897 (1.7%) | |
| Basilar artery | 0 | 0 | 44/59 (74.6%) | 0 | 44/897 (4.9%) | |
| Other | 0 | 0 | 0 | 135/178 (75.8%) | 135/897 (15.1%) | |
| Presented with ruptured aneurysm | 12/311 (3.9%) | 24/345 (7.0%) | 4/59 (6.8%) | 34/176 (19.3%) | 74/891 (8.2%) | <.001 |
| Multiple PEDs used | 143/311 (46.0%) | 97/347 (28.0%) | 19/59 (32.2%) | 47/178 (26.4%) | 306/895 (34.2%) | <.001 |

Note:—n indicates the number of aneurysms.

^a Aneurysm size was not reported for 10 aneurysms.

Role of the Funding Source

An academic principal investigator and an academic steering committee supervised the trial design and operations. The steering committee interpreted the results, and the principal investigator wrote the report. The study sponsor was responsible for site management, data management, statistical analysis, and safety reporting. The corresponding author was the academic principal investigator for the study and had full access to all study data and the final responsibility for the decision to submit for publication.

RESULTS

Seven hundred ninety-three patients with 906 aneurysms (76 [8.4%] ruptured, 824 [91%] unruptured, and 6 [0.7%] unknown) were included. Three hundred eleven aneurysms (34.3%) were ICA ≥10 mm, 349 aneurysms (38.5%) were ICA <10 mm, 59 aneurysms (6.5%) were in the posterior circulation, and 178 aneurysms (19.6%) were ≥10 mm and located in anterior circulation locations other than the ICA. Combined location/size information was not available for 9 aneurysms. Posterior circulation aneurysms were generally large, with an average size of 14.5 ± 9.0 mm. Patients with non-ICA anterior circulation aneurysms presented with aneurysm rupture in 19.3% of cases (34/176), a significantly higher rate than that in the other groups (*P* < .001). Four hundred seventy-three aneurysms (52.8%) were small, 357 aneurysms (39.8%) were large, and 66 aneurysms (7.3%) were giant. Median follow-up was 19.3 months with 706 (89%) patients having follow-up of >12 months. Size information was not available for 10 aneurysms.

Multiple PEDs were used in 308 cases (34.2%). Patients with ICA aneurysms ≥10 mm had the highest rate of multiple PED use (46.0%, 143/311) and were significantly more likely to receive treatment with multiple PEDs compared with the other groups (*P* < .001). Mean procedure time was 101 minutes 30 seconds ±

50 minutes 30 seconds and was highest in the ICA aneurysms ≥10-mm group (111 minutes 24 seconds ± 56 minutes 36 seconds) (*P* < .01). Aneurysm data are summarized in Table 1.

The 30-day morbidity and mortality rate was 6.3% (50/793) with a 30-day neurologic morbidity rate of 5.7% (44/793) and a 30-day neurologic mortality rate of 2.6% (21/793). The long-term neurologic morbidity and mortality rate was 8.4% (67/793) with a neurologic morbidity rate of 7.4% (59/793) and a neurologic mortality rate of 3.8% (30/793). Individual morbidity and mortality rates did not add up to the total combined morbidity and mortality rate because some patients had >1 neurologic morbidity. The morbidity and mortality rates were highest in the posterior circulation group (16.4%, 9/55) and lowest in the ICA <10 mm group (4.8%, 14/294). The morbidity and mortality rates were higher in patients with giant aneurysms compared with those with large and small aneurysms (25.8% versus 8.8% versus 5.4%, *P* < .01). When patients with ruptured, dissecting, or fusiform aneurysms were excluded, the overall morbidity and mortality rate was 5.7%.

The spontaneous rupture rate was 0.6% (5/793), with 2 of the 5 events being cavernous carotid fistulas with clinical sequelae. Four of the 5 cases occurred within 30 days. There was no difference in the spontaneous rupture rate among the 4 groups (*P* = .17). Spontaneous rupture was higher in giant aneurysms (4.5%, 3/66) compared with large (0.6%, 2/357) and small aneurysms (0.0%, 0/473) (*P* < .001). Overall the intraparenchymal hemorrhage rate was 2.4% (19/793). There was no difference in the hemorrhage rate among the primary patient subgroups (*P* = .73) or among aneurysm sizes (*P* = .24). Fifteen (79%) of the 19 hemorrhages occurred within 30 days of the procedure.

The ischemic stroke rate was 4.7% (37/793). A majority of strokes occurred within 30 days of treatment (26/793, 3.3%). The

Table 2: Complications by aneurysm location and size subgroups

| Complications | Anterior ICA ≥10 mm (n = 275) | Anterior ICA <10 mm (n = 294) | Posterior (n = 55) | Other Anterior (n = 165) | Total (n = 793) ^a | 95% CI; P Value |
|---|----------------------------------|----------------------------------|-----------------------|-----------------------------|---------------------------------|--------------------|
| Mean aneurysm size (mm) | 16.8 ± 6.2 | 5.2 ± 2.2 | 14.5 ± 9.0 | 9.8 ± 7.9 | 10.7 ± 7.7 | (10.2–11.2); <.001 |
| Spontaneous rupture | 4 (0.7%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 5 (0.6%) | (0.2%–1.5%); .17 |
| Intraparenchymal hemorrhage | 6 (2.2%) | 6 (2.0%) | 1 (1.8%) | 6 (3.6%) | 19 (2.4%) | (1.3%–3.4%); .73 |
| Ischemic stroke | 15 (5.5%) | 8 (2.7%) | 4 (7.3%) | 10 (6.1%) | 37 (4.7%) | (3.2%–6.2%); .16 |
| Parent artery stenosis | 1 (0.4%) | 1 (0.4%) | 0 (0.0%) | 0 (0.0%) | 2 (0.3%) | (0%–0.7%); 1.0 |
| Cranial neuropathy | 2 (0.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (0.3%) | (0%–0.7%); .30 |
| Neurologic morbidity | 24 (8.7%) | 14 (4.5%) | 5 (9.1%) | 16 (9.7%) | 59 (7.4%) | (5.6%–9.2%); .16 |
| Neurologic mortality | 11 (4.0%) | 4 (1.4%) | 6 (10.9%) | 9 (5.5%) | 30 (3.8%) | (2.5%–5.1%); <.01 |
| Neurologic morbidity and mortality (all patients) | 26 (9.5%) | 14 (4.8%) | 9 (16.4%) | 18 (10.9%) | 67 (8.4%) | (6.5%–10.3%); .01 |
| Neurologic morbidity and mortality (patients with unruptured aneurysms) | 24/263 (9.2%) | 11/270 (4.1%) | 7/51 (13.7%) | 11/131 (8.4%) | 53/717 (7.4%) | (5.5%–9.3%); .03 |
| Neurologic morbidity and mortality (patients with ruptured aneurysms) | 2/12 (16.7%) | 3/24 (12.5%) | 2/4 (50.0%) | 7/34 (20.6%) | 14/76 (18.4%) | (10.0%–27.1%); .35 |
| Neurologic morbidity and mortality (excluding ruptured, dissecting, or fusiform aneurysms) | 15 (7.0%) | 9 (3.6%) | 3 (12.0%) | 6 (6.8%) | 33 (5.7%) | (4.1%–7.3%); .19 |

Note:—n indicates the number of patients.

^a Numbers do not sum across categories and subcategories because some patients experienced >1 event.

Table 3: Occurrence of complications by time

| Complications | <72 Hours | | 72 Hours–30 Days | | >30 Days | | Total (n = 793) ^a | P Value |
|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|---------------------------------|---------|
| | Anterior (n = 738) | Posterior (n = 55) | Anterior (n = 738) | Posterior (n = 55) | Anterior (n = 738) | Posterior (n = 55) | | |
| Spontaneous rupture | 1 (0.1%) | 0 (0%) | 3 (0.4%) | 0 (0%) | 1 (0.1%) | 0 (0%) | 5 (0.6%) | .51 |
| Intraparenchymal hemorrhage | 3 (0.4%) | 1 (1.8%) | 11 (1.5%) | 0 (0%) | 4 (0.5%) | 0 (0%) | 19 (2.4%) | .83 |
| Ischemic stroke | 17 (2.3%) | 2 (3.6%) | 7 (0.9%) | 0 (0%) | 9 (1.2%) | 2 (3.6%) | 37 (4.7%) | .58 |
| Parent artery stenosis | 0 (0%) | 0 (0%) | 1 (0.1%) | 0 (0%) | 1 (0.1%) | 0 (0%) | 2 (0.3%) | .63 |
| Cranial neuropathy | 0 (0%) | 0 (0%) | 2 (0.3%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.3%) | .58 |
| Neurologic morbidity | 20 (2.7%) | 3 (5.5%) | 21 (2.8%) | 0 (0%) | 13 (1.8%) | 2 (3.6%) | 59 (7.4%) | .56 |
| Neurologic mortality | 4 (0.5%) | 1 (1.8%) | 13 (1.8%) | 2 (3.6%) | 7 (0.9%) | 3 (5.5%) | 30 (3.8%) | <.01 |
| Neurologic morbidity and mortality (all patients) | 23 (3.1%) | 3 (5.5%) | 22 (3.0%) | 2 (3.6%) | 13 (1.8%) | 4 (7.3%) | 67 (8.4%) | <.01 |
| Neurologic morbidity and mortality (patients with unruptured aneurysms) | 19/664 (2.9%) | 3/51 (5.9%) | 16/664 (2.4%) | 1/51 (2.0%) | 11/664 (1.7%) | 3/51 (5.9%) | 53/717 (7.4%) | .08 |
| Neurologic morbidity and mortality (patients with ruptured aneurysms) | 4/70 (5.7%) | 0/4 (0%) | 6/70 (8.6%) | 1/4 (25.0%) | 2/70 (2.9%) | 1/4 (25.0%) | 14/76 (18.4%) | .17 |
| Neurologic morbidity and mortality (excluding ruptured, dissecting, or fusiform aneurysms) | 13/549 (2.4%) | 1/25 (4.0%) | 12/549 (2.2%) | 0/25 (0%) | 5/549 (0.9%) | 2/25 (8.0%) | 33/575 (5.7%) | .41 |

Note:—n indicates the number of patients.

^a Numbers do not sum across categories and subcategories because some patients experienced >1 event.

highest stroke rates were seen in patients with posterior circulation aneurysms (7.3%, 4/55) and the “other anterior circulation” group (6.1%, 10/165). The anterior circulation ICA <10-mm group had the lowest stroke rates (2.7%, 8/294) ($P = .16$). When studying differences based on aneurysm size, patients with giant aneurysms had the highest stroke rates (14.5%, 9/62) compared with patients with large (5.0%, 17/339) and small aneurysms (2.8%, 11/386) ($P < .01$).

In-stent stenosis occurred in 0.3% (2/793) with no significant differences among groups ($P = 1.0$). Permanent cranial neuropathy occurred in 0.3% (2/793) of patients with no significant differences among groups ($P = .30$). These data are summarized in Tables 2–4.

Neurologic mortality was 3.8% (30/793) and was significantly different among the 4 primary patient subgroups ($P < .01$). The 30-day mortality rate was 2.5% (20/793), which represented nearly two-thirds of all mortality observed in the average 19.3 months of follow-up. Patients with posterior circulation aneurysms had the highest rate of neurologic mortality (10.9%, 6/55), and patients with anterior ICA <10-mm aneurysms had the low-

est neurologic mortality (1.4%, 4/294). The mortality rate was significantly higher in patients with giant aneurysms compared with those with large and small aneurysms, respectively (9.6% versus 5.0% versus 1.8%, $P < .01$). The overall mortality rate in patients who presented with ruptured aneurysms was 10.5% (8/76), with no significant differences among groups ($P = .11$). These data are summarized in Tables 2–4.

In addition to the above-listed major events, 5 cases of intracranial hemorrhage, 15 cases of ischemic strokes, and 5 cases of parent artery stenosis were also observed as minor events in which the patient’s symptoms resolved within 7 days of the event occurrence with no clinical sequelae. Three additional deaths were reported due to non-neurologic reasons.

DISCUSSION

This large multicenter study of flow-diversion therapy demonstrated a neurologic morbidity and mortality rate of 8.4%. Most adverse events were ischemic strokes from thromboembolic complications and were substantially more common in large, anterior circulation aneurysms and posterior circulation aneurysms com-

Table 4: Complications by aneurysm size

| Complications | Small (n = 386) (N = 473) | | Large (n = 339) (N = 357) | | Giant (n = 62) (N = 66) | | Total (n = 793) ^{a,b} (N = 906) | P Value |
|---|---------------------------|--------------------|---------------------------|--------------------|-------------------------|--------------------|---|---------|
| | Anterior (n = 372) | Posterior (n = 14) | Anterior (n = 309) | Posterior (n = 30) | Anterior (n = 52) | Posterior (n = 10) | | |
| Mean aneurysm size (mm) | 5.1 ± 2.2 | 6.0 ± 2.6 | 14.8 ± 4.0 | 15.0 ± 4.3 | 28.8 ± 5.3 | 29.1 ± 7.2 | 10.7 ± 7.7 | <.001 |
| Spontaneous rupture | 0 (0%) | 0 (0%) | 2 (0.5%) | 0 (0%) | 3 (5.8%) | 0 (0%) | 5 (0.6%) | <.01 |
| Intraparenchymal hemorrhage | 7 (1.9%) | 0 (0%) | 8 (2.6%) | 0 (0%) | 3 (5.8%) | 1 (10.0%) | 19 (2.4%) | .24 |
| Ischemic stroke | 10 (2.7%) | 1 (7.1%) | 16 (5.2%) | 1 (3.3%) | 7 (13.5%) | 2 (20.0%) | 37 (4.7%) | <.01 |
| Parent artery stenosis | 1 (0.3%) | 0 (0%) | 1 (0.3%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.3%) | 1.0 |
| Cranial neuropathy | 0 (0%) | 0 (0%) | 2 (0.6%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.3%) | .41 |
| Neurologic morbidity | 18 (4.8%) | 1 (7.1%) | 24 (7.8%) | 1 (3.3%) | 12 (23.1%) | 3 (30.0%) | 59 (7.4%) | <.01 |
| Neurologic mortality | 6 (1.6%) | 1 (7.1%) | 15 (4.9%) | 2 (6.7%) | 3 (5.8%) | 3 (30.0%) | 30 (3.8%) | <.01 |
| Neurologic morbidity and mortality ^a (all patients) | 19 (5.1%) | 2 (14.3%) | 27 (8.7%) | 3 (10.0%) | 12 (23.1%) | 4 (40.0%) | 67 (8.4%) | <.01 |
| Neurologic morbidity and mortality (patients with unruptured aneurysms) | 11/321 (3.4%) | 1/12 (8.3%) | 23/291 (7.9%) | 3/29 (10.3%) | 12/51 (23.5%) | 3/9 (33.3%) | 53/717 (7.4%) | <.01 |
| Neurologic morbidity and mortality (patients with ruptured aneurysms) | 8/51 (15.7%) | 1/2 (50.0%) | 4/18 (22.2%) | 0/1 (0%) | 0/1 (0%) | 1/1 (100%) | 14/76 (18.4%) | .23 |
| Neurologic morbidity and mortality (excluding ruptured, dissecting, or fusiform aneurysms) | 11/294 (3.7%) | 0/7 (0%) | 12/217 (5.5%) | 2/13 (15.4%) | 7/37 (18.9%) | 1/5 (20.0%) | 33/574 (5.7%) | <.01 |

Note:—n indicates the number of patients; N, number of aneurysms.

^a Six patients did not have aneurysm size reported.

^b Numbers do not sum across categories because some patients experienced >1 event.

pared with small, anterior circulation aneurysms. Spontaneous aneurysm rupture was rare, occurring in 0.6% of patients, with 3/5 events occurring within giant aneurysms. Intraparenchymal hemorrhage, unrelated to rupture of the target aneurysm but resulting in major neurologic deficit, was noted in 2.4% of patients. These results are important because they provide clarity regarding the previously noted severe and unexpected adverse events associated with flow-diversion therapy in a real-world setting. Our data suggest strongly that spontaneous aneurysm rupture is not of clinical concern in non-giant aneurysms. Parenchymal hemorrhage remains of concern, especially because its etiology is unclear.

Our findings corroborate those of numerous previously published smaller studies and meta-analyses. Previously published studies have demonstrated morbidity and mortality rates ranging from 0%–12% and 0%–7%, respectively.^{30–32} Two large meta-analyses of flow-diverter treatment demonstrated morbidity rates of 5.0%–7.3% and mortality rates of 2.8%–4.0%.^{1,3} Our study, which is the largest clinical study of PED to date to our knowledge, demonstrated a 30-day morbidity rate of 5.5% (44/793) and a 30-day mortality rate of 2.5% (20/793).

Posttreatment aneurysm rupture is a serious concern of flow-diverter therapy. Concerns for postoperative aneurysm rupture with flow diverters are so serious that Balt Extrusion issued a medical device alert instructing practitioners not to use the Silk flow diverter (Balt Extrusion, Montmorency, France) without coils due to the “potential for patient death.”¹³ In their meta-analysis of flow-diverter treatment, which included the PED and Silk flow-diverter devices, Brinjikji et al³ found an overall postoperative rupture rate of 4%, with an early rupture rate of 3% with a significantly higher rupture rate in large and giant aneurysms. Our study demonstrated a posttreatment rupture rate of <1%, 3/5 occurring among patients with giant aneurysms. While postoperative rupture rates are minimal in patients with small and large aneurysms, postoperative rupture remains a real and significant complication of Pipeline treatment in patients with giant aneurysms.

Spontaneous IPH is a poorly understood complication of

flow-diverter treatment. Hemorrhagic transformation of ischemic stroke, hemodynamic alteration from flow-diverter placement, dual antiplatelet therapy, potential association with intraprocedural foreign body emboli, and the significant role of P2Y12 receptor overinhibition are proposed mechanisms.^{8,14,15,33} Prior studies have reported rates ranging from 0% to 10% for this complication.^{8,30,34,35} In their meta-analysis, Brinjikji et al³ found an IPH rate of 3.0%. Arrese et al¹ found a postoperative hemorrhage rate of 1.8%, not stratifying by SAH and IPH. Our study found an IPH rate of 2.4%. Similar to prior studies, our study found no difference in IPH rates by aneurysm size or location.³

Ischemic strokes due to thromboembolism and perforator infarctions are well-described complications of flow-diverter treatment. Ischemic stroke may result from stent wall thrombus formation and occlusion, parent artery occlusion, or distal thromboembolic events. Our study found an ischemic stroke rate of 4.7%, with higher rates in posterior circulation aneurysms compared with the ICA aneurysm <10-mm group (7.3% versus 2.7%).^{1,3,9,36} Similar to Brinjikji et al,³ we also found that the stroke rate increased with aneurysm size as patients with large and giant aneurysms had higher stroke rates than those with small aneurysms. Intraoperatively, acute thrombus formation can be mitigated by prompt injection of glycoprotein IIb/IIIa platelet inhibitors; however, it is difficult to reduce the long-term risk of thromboembolic events associated with flow-diverter treatment.³⁷

Endosaccular coiling (with or without stent assistance) is an alternative to flow-diverter therapy. A systematic review of stent-assisted coiling by McLaughlin et al³⁸ found an intraprocedural complication rate of 4.0%, a postprocedural thromboembolic event rate of 4.3%, and a delayed in-stent stenosis rate of 5.3%. These complication rates are similar to the findings of our study on the PED. In a study of stent-assisted coiling in patients with subarachnoid hemorrhage, Bodily et al³⁹ found a clinically significant thromboembolic event rate of 6%. A meta-analysis by Shapiro et al⁴⁰ found that the overall procedural complication rate associated with stent coiling was 19%, the thromboembolic complication rate was 10%, and the periprocedural mortality was

2.1%. In the Neuroform stent (Stryker Neurovascular, Kalamazoo, Michigan) experience in 284 patients, Fiorella et al⁴¹ reported a cumulative ischemic stroke rate of 8.8% and a 2.8% neurovascular death rate. They also reported that 15.1% of the cases had major recanalization requiring retreatment. Pötin et al⁴² reported results on the treatment of aneurysms with coils, with and without stents, in 1137 patients. The rate of permanent neurologic procedure-related complications was 7.4% of the procedures with stents versus 3.8% in the procedures without stents ($P = .64$). Procedure-induced mortality occurred in 4.6% of the procedures with stents versus 1.2% in the procedures without stents ($P = .006$). The rate of thrombotic complications in the stent group was 14.8%, accounting for 11.1% of mortalities.⁴² Retrospective studies comparing flow diversion with the PED with coiling (with and without stent assistance) have demonstrated that the PED provides higher aneurysm occlusion rates with similar morbidity and mortality rates.^{23,43} In our study, anterior circulation aneurysms measuring <10 mm had the lowest neurologic morbidity and mortality rates (4.8%). These findings corroborate those of a previous study comparing the PED with stent-assisted coiling of patients with small, unruptured anterior circulation aneurysms, which demonstrated a complication rate of 5% in the PED group and 3% in the stent-assisted coiling group.⁴³ Given the wide range of treatment options available for the endovascular treatment of intracranial aneurysms, careful study and stratification of outcomes by aneurysm location and size are recommended to determine the best treatment for each patient. Ultimately, further comparative studies, especially in the case of small ICA aneurysms, are needed to determine which subsets of intracranial aneurysms would benefit most from PED placement compared with endosaccular coiling.

Limitations

Our study has limitations. It was a retrospective study in which sites followed their standard of practice for treating aneurysms with PED, and there was a wide range of treatment regimens (eg, antiplatelet therapy) among centers. However, all study adverse events collected were prespecified in the study protocol and were adjudicated by the Adverse Events Review Committee to maintain consistency in the study results. Patients who underwent failed embolization or who did not have follow-up were excluded per the study design. There was no systematic imaging of patients required in this study because sites were required to follow their standard procedures. There was no protocol regarding the minimum duration of follow-up, and follow-up timing was per standard of care for the treating physician and institution. Another limitation of the study is that the reporting of major and minor complications was based on the duration of symptoms, not their severity or degree of disability. Information regarding management of the major and minor complications was not collected. A broad range of aneurysm types and sizes was included in this registry (ie, saccular/blister/ruptured/fusiform/dissecting), and subgroup analyses were not performed for the subset of blister/fusiform/dissecting aneurysms in this study. Last, 38% of these patients had been included in prior publications.

CONCLUSIONS

Our study suggests that the treatment of intracranial aneurysms with PED is associated with the lowest complication rates when used to treat small aneurysms of the ICA. The rates of procedural-related morbidity and mortality are not negligible. Patients with posterior circulation aneurysms and giant aneurysms are at higher risk of ischemic stroke. Patients with large or giant aneurysms are at higher risk of ischemic stroke and SAH compared with small aneurysms. The neurologic morbidity and mortality rate drops when patients with difficult-to-treat aneurysms (ruptured, dissecting, or fusiform) are excluded. The complication rates with PED are comparable with those of other endovascular treatment options such as stent-assisted coiling. These findings should be considered when selecting the best therapeutic option for intracranial aneurysms.

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