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ABSTRACT

BACKGROUND AND PURPOSE: Flow diversion has gradually become a standard treatment for intracranial aneurysms of the anterior circulation. Recently, the off-label use of the flow diverters to treat posterior circulation aneurysms has also increased despite initial concerns of rupture and the suboptimal results. This study aimed to explore the change in complication rates and treatment outcomes across time for posterior circulation aneurysms treated using flow diversion and to further evaluate the mechanisms and variables that could potentially explain the change and outcomes.

MATERIALS AND METHODS: A retrospective review using a standardized data set at multiple international academic institutions was performed to identify patients with ruptured and unruptured posterior circulation aneurysms treated with flow diversion during a decade spanning January 2011 to January 2020. This period was then categorized into 4 intervals.

RESULTS: A total of 378 procedures were performed during the study period. Across time, there was an increasing tendency to treat more vertebral artery and fewer large vertebrobasilar aneurysms ($P = .05$). Moreover, interventionalists have been increasingly using fewer overlapping flow diverters per aneurysm ($P = .07$). There was a trend toward a decrease in the rate of thromboembolic complications from 15.8% in 2011–13 to 8.9% in 2018–19 ($P = .34$).

CONCLUSIONS: This multicenter experience revealed a trend toward treating fewer basilar aneurysms, smaller aneurysms, and increased usage of a single flow diverter, leading to a decrease in the rate of thromboembolic and hemorrhagic complications.

Flow diversion has become an established treatment for intracranial aneurysms. The initial FDA approval for the Pipeline Embolization Device (PED; Covidien) was to treat large and giant

wide-neck intracranial aneurysms in the ICA, from the petrous to the superior hypophyseal segments.¹ This indication was expanded to include wide-neck ICA aneurysms up to the carotid

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terminus of all sizes in February 2019.² In December 2019, the Flow Redirection Endoluminal Device (FRED; MicroVention) was approved by the FDA with indications similar to those of the PED.

Despite the remarkable advancements in technology, flow diverters were being used reluctantly to treat posterior circulation aneurysms. However, due to the challenging nature of posterior circulation aneurysms, including their high risk of rupture and the suboptimal results associated with the use of standard techniques, the off-label use of flow diverters in the treatment of these aneurysms has gradually increased, with several studies attempting to evaluate the risks and benefits.³⁻¹⁴ In a propensity-matched comparison between the PED and FRED for the treatment of posterior circulation aneurysms, Griessenauer et al¹⁵ reported no significant differences in aneurysm occlusion or neurologic complications between the devices.

A recent multicenter study investigated the change in complication rates across time for anterior circulation aneurysms treated by the PED.¹⁶ A significant decline in complications was noted, which was attributed to the continuous improvement in clinical practice and experience with the PED, including the increased use of platelet function testing before the procedures.¹⁷ In this study, we aimed to examine changes in complication rates and outcomes with time for posterior circulation aneurysms treated by the PED and FRED, given that both devices had no significant difference in treatment outcomes.¹⁵ We further sought to evaluate the mechanisms and covariates that could explain these changes.

MATERIALS AND METHODS

Patient Population

A retrospective review of prospectively maintained databases at multiple academic institutions in the United States, Canada, Europe, and Asia was performed to identify patients with posterior circulation aneurysms treated with flow diversion using the PED or FRED during a decade spanning January 2011 to January 2020. Inclusion criteria consisted of adult patients (18 years of age or older) with the pathology and treatment mentioned above. Both ruptured and unruptured aneurysms with all morphologies (ie, saccular and fusiform) were included. All consecutive patients who fit the inclusion criteria at the participating center were included. Then, these patients were categorized on the basis of the treatment year to four 2-year intervals, except for the first 3 years due to low case numbers: 2011–2013, 2014–2015, 2016–2017, and 2018–2019. We collected the following information retrospectively: patient demographics, aneurysm characteristics, antiplatelet regimen,

procedural details, complications, and angiographic and functional outcomes. Institutional review board approval was obtained at all centers. Patient consent was not required for this study, given that it was a retrospective analysis of de-identified data.

Complications and Outcomes

Thromboembolic complications occurring from the date of the procedure to the last follow-up were included. Intraprocedural thromboembolic complications were identified on DSA as either thrombus formation, slow filling of a previously normal-filling vessel, or complete vessel occlusion. Intraprocedural thromboembolism was treated at the discretion of the interventionalist performing the procedure. Postprocedural thromboembolic complications were identified using a combination of clinical and radiographic findings. Postprocedural imaging was performed at the discretion of the individual institutions. Routine screening for clinically silent ischemic stroke was not performed in all centers. Postprocedural imaging performed to detect an ischemic stroke could include any combination of a noncontrast CT, CTA, or MR imaging. Only ischemic strokes in the territory of the treated vessel were included. An ischemic complication was considered symptomatic if the patient reported symptoms attributable to thromboembolism or demonstrated signs attributable to thromboembolism, including both transient and permanent signs and symptoms. Hemorrhagic complications were identified intraoperatively as contrast extravasation on DSA or on postprocedural imaging. Hemorrhagic complications occurring from the time of the procedure until the last follow-up were included. Hemorrhages were counted as symptomatic if the patient reported symptoms or demonstrated signs attributable to hemorrhage. In contrast to ischemic complications, all vascular territories were included. Minor complications were defined as intraprocedural technical complications and vascular-access complications, which did not result in permanent deficits.

The angiographic outcome was assessed using DSA, MRA, or CTA. Aneurysm occlusion was categorized as complete occlusion (100%), near-complete occlusion (90%–100%), and partial occlusion (< 90%). Functional outcome was assessed using the mRS at the last follow-up. An mRS of 0–2 was considered a favorable outcome.

Statistical Analysis

Statistical analysis was conducted using R statistical and computing software (Version 4.0.2; <http://www.r-project.org/>). Numeric variables were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test, depending on the number of groups, while categorical variables were compared using the χ^2 test. Univariable and multivariable logistic regression analyses were performed to identify predictors of good outcome (mRS 0–2) and thromboembolic and hemorrhagic complications. The examined covariates included age, sex, smoking, pretreatment mRS, multiple aneurysms, aneurysm location, aneurysm shape, aneurysm size, previous SAH, prior treatment, number of devices, antiplatelet regimen changed, and adjunctive coiling. Covariates that had a *P* value ≤ 0.1 in the univariable analysis were included in the multivariable analysis. A *P* value $< .05$ was considered statistically significant.

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Table 1: Change in treatment outcome with time^a

	2011–2013 (n = 76)	2014–2015 (n = 118)	2016–2017 (n = 94)	2018–2019 (n = 90)	P Value	Total (n = 378)
Last follow-up imaging lapsed time (months) ^b	14.0 [28.8]	24.0 [24.0]	14.0 [16.5]	6.80 [5.00]	<.001	13.0 [20.6]
Last follow-up clinical time from treatment (months) ^c	22.5 [40.5]	29.0 [29.0]	17.0 [17.3]	6.50 [6.00]	<.001	13.0 [24.0]
Follow-up occlusion rate ^d						
Complete occlusion (100%)	47 (66.2%)	75 (68.9%)	69 (77.5%)	46 (67.7%)	.273	237 (70.3%)
Incomplete occlusion (<90%)	15 (21.1%)	14 (12.8%)	7 (7.9%)	12 (17.6%)		48 (14.2%)
Near-complete occlusion (90%–99%)	9 (12.7%)	20 (18.3%)	13 (14.6%)	10 (14.7%)		52 (15.4%)
Retreatment ^e	9 (12.2%)	13 (11.2%)	5 (5.4%)	3 (3.5%)	.092	30 (8.2%)
mRS on last follow-up ^f						
0–2	66 (88.0%)	96 (84.2%)	82 (87.2%)	78 (88.6%)	.793	322 (86.8%)
3–6	9 (12.0%)	18 (15.8%)	12 (12.8%)	10 (11.4%)		49 (13.2%)
Follow-up mRS ^f						
Improved	23 (30.7%)	28 (24.6%)	21 (22.3%)	10 (11.4%)	.034	82 (22.1%)
No change	40 (53.3%)	65 (57.0%)	58 (61.7%)	68 (77.2%)		231 (62.3%)
Worsened	12 (16.0%)	21 (18.4%)	15 (16.0%)	10 (11.4%)		58 (15.6%)
Neurologic complications						
Thromboembolic	12 (15.8%)	19 (16.1%)	10 (10.6%)	8 (8.9%)	.342	49 (13.0%)
Thromboembolic (symptomatic)	9 (11.8%)	14 (11.9%)	3 (3.2%)	7 (7.8%)	.107	33 (8.7%)
Hemorrhagic	5 (6.6%)	5 (4.2%)	4 (4.3%)	3 (3.3%)	.781	17 (4.5%)
Hemorrhagic (symptomatic)	3 (3.9%)	4 (3.4%)	3 (3.2%)	3 (3.3%)	.994	13 (3.4%)
Other procedural related complications	7 (9.2%)	9 (7.6%)	4 (4.3%)	5 (5.6%)	.57	25 (6.6%)
Mortality ^f	6 (8.0%)	9 (7.9%)	5 (5.3%)	6 (6.8%)	.881	26 (7.0%)

^a Continuous variables are presented as median [IQR]. Otherwise, data are No. (%).

^b Data missing for 46 patients.

^c Data missing for 56 patients.

^d Data missing for 41 patients.

^e Data missing for 10 patients.

^f Data missing for 7 patients.

RESULTS

Patient and Aneurysm Characteristics

A total of 378 procedures using either the PED or FRED were performed to treat posterior circulation aneurysms during the study period. The median age of the patients was 57 years, with an observed female/male ratio of 1:1. There was no significant difference in patient characteristics among the different periods as seen in the Online Supplemental Data.

Across time, there was an increasing tendency to treat vertebral artery, posterior cerebral artery, and PICA aneurysms, with a lower rate of treating large vertebrobasilar fusiform aneurysms and superior cerebellar artery aneurysms ($P = .05$). Also, there was a tendency to treat smaller aneurysms across time, but this tendency was not found to be statistically significant ($P = .27$) (Online Supplemental Data).

Treatment Outcome

There was an increasing rate of using a single device for aneurysm treatment across time, from 72.4% in 2011–13 to 87.8% in 2018–19 ($P = .07$). At a mean follow-up of 13 months, complete or near-complete occlusion (>90%) was achieved in 84.5% of aneurysms. There was no significant change in the occlusion rate during 9 years of flow-diversion experience. However, the rate of retreatment decreased with time from 12.2% in 2011–13 to 3.5% in 2018–19 ($P = .09$). Similarly, the percentage of patients with reported worsening of their clinical outcome had declined across the years, from 16% in 2011–13 to 11.4% in 2018–19 ($P = .03$).

Thromboembolic complications occurred in 13% of procedures, of which 8.7% were symptomatic. There was a trend toward a decrease in the rate of thromboembolic complications

from 15.8% in 2011–13 to 8.9% in 2018–19 ($P = .3$). There was also a nonsignificant decline in the rate of hemorrhagic complications ($P = .78$) and mortality ($P = .88$) (Table 1 and Figure).

Factors Associated with Complication Rates

Univariable analyses for determinants of thromboembolic complications are shown in Table 2. In a multivariable analysis, having a pretreatment mRS of 3–5 (adjusted OR, 3.00; 95% CI, 1.30–6.68; $P = .008$) and multiple aneurysms (adjusted OR, 2.55; 95% CI, 1.16–5.42; $P = .017$) was significantly associated with a higher risk of thromboembolic complications. On the other hand, vertebral artery aneurysms (as opposed to the basilar artery) (OR, 0.41; 95% CI, 0.18–0.90; $P = .025$) and saccular shape (as opposed to fusiform aneurysms) (OR, 0.43; 95% CI, 0.18–0.95; $P = .045$) were significantly associated with a lower risk of thromboembolic complications.

Univariable and multivariable logistic regression analyses for predictors of hemorrhagic complications are shown in the Online Supplemental Data. In a multivariable analysis, only a pretreatment mRS of 3–5 (OR, 10.15; 95% CI, 3.51–30.71; $P < .001$) was found to be associated with a higher risk of hemorrhagic complications (Online Supplemental Data).

DISCUSSION

This study reports a multicenter experience with flow diversion of posterior circulation aneurysms and the learning curve built on that experience. During the study period, there was a significant increase in the tendency to treat vertebral artery, posterior cerebral artery, and PICA aneurysms. Conversely, there was a lower tendency to treat large vertebrobasilar aneurysms. Moreover, interventionalists

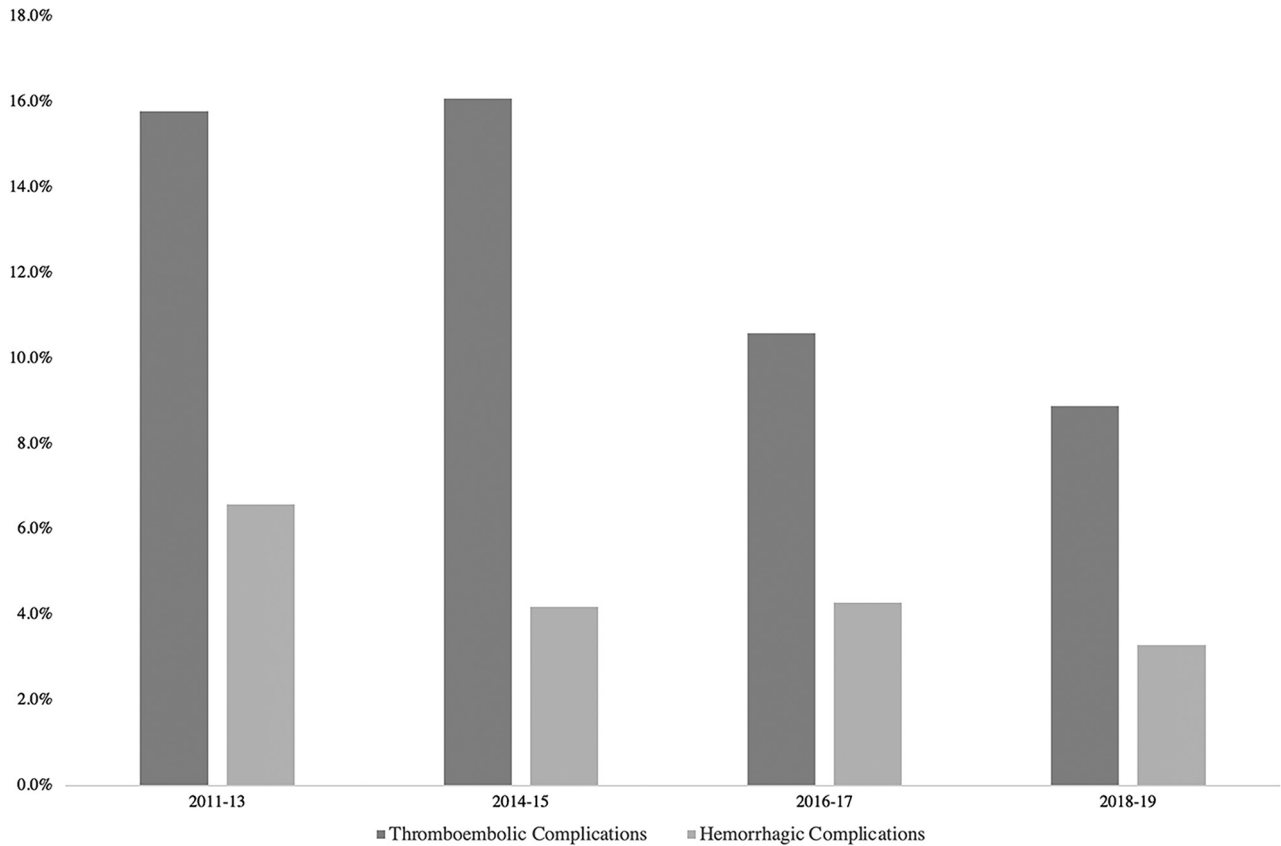


FIGURE. The rates of thromboembolic and hemorrhagic complications during the study years.

have increasingly used fewer overlapping flow diverters per aneurysm, which could also be related to treating smaller aneurysms. There was also a decline in the rate of symptomatic thromboembolic complications and retreatment rates across time. This was significantly correlated with treating saccular aneurysms and smaller aneurysms and the increased use of a single flow diverter.

To evaluate the performance of flow diversion for the treatment of posterior circulation aneurysms, Griessenauer et al¹⁸ reported the largest cohort of posterior circulation aneurysms treated with the PED. A total of 129 consecutive patients (median age, 58 years; male/female ratio of 1:1.7) underwent 129 procedures to treat 131 aneurysms. Complete or near-complete occlusion (>90%) was achieved in 79% of cases. Major (≥ 2 points of mRS change) and minor complications (<2 of mRS change), including thromboembolic and hemorrhagic strokes, occurred in 8.5% and 16.3% of patients, respectively.¹⁸ The same group also performed a propensity-matched comparison between the PED and FRED for the treatment of posterior circulation aneurysms and reported no significant differences in aneurysm occlusion or neurologic complications.¹⁵

As for the concern about the fate of posterior circulation branches following flow diversion, Adeeb et al¹⁹ found that major branching arteries in the posterior circulation including the PICA, anterior inferior cerebellar artery, and superior cerebellar artery had a low incidence of branch occlusion after coverage with flow diverters. However, occlusion of these terminal branches may carry a risk of ischemic complications, particularly when the anterior

inferior cerebellar artery is affected. On the other hand, the vertebral and the posterior cerebral arteries had relatively higher incidences of occlusions, 35% and 24%, respectively, which were attributed to the rich collateral supply. Neither branch occlusion nor ischemic complications were associated with aneurysm morphology. There was also no significant effect of the number of flow-diverting devices on branch occlusion.¹⁹

Changes in Practice to Reduce Complications

Flow diverters are designed to divert the blood flow away from the aneurysm, therefore allowing intra-aneurysmal thrombus formation followed by neointimal growth across the neck of the aneurysm. This mechanism theoretically presents an ideal treatment for large, partially thrombosed fusiform vertebrobasilar aneurysms.²⁰ In the multicenter study by Griessenauer et al,¹⁷ the rate of major complications (≥ 2 points in mRS score change) in fusiform aneurysms was 11.5%. However, a study by Natarajan et al¹⁰ showed decreased morbidity (14%–8.3%) and mortality rates (57%–0%) following treatment of those subtypes of aneurysms in their practice across time. One of the proposed reasons behind this decline in complication rates is related to moving away from the treatment of holobasilar aneurysms that are partially thrombosed because these aneurysms have a higher risk of occluding critical perforators that may only be supplied through tenuous channels crossing the thrombus. Other proposed reasons included careful attention to antiplatelet therapy, limiting the number of PEDs, and use of adjunctive coiling.¹⁰

Table 2: Predictors of thromboembolic complications^a

	Thromboembolic Complications	
	Univariable	Multivariable
Age (yr)	1.00 (0.98–1.03, <i>P</i> = .811)	
Sex		
Female	Ref	
Male	0.97 (0.53–1.76, <i>P</i> = .910)	
Smoking	1.39 (0.64–2.87, <i>P</i> = .381)	
Pretreatment mRS		
0–2	Ref	Ref
3–5	3.13 (1.48–6.38, <i>P</i> = .002)	3.00 (1.30–6.68, <i>P</i> = .008)
Multiple aneurysms	2.52 (1.23–4.98, <i>P</i> = .009)	2.55 (1.16–5.42, <i>P</i> = .017)
Aneurysm location		
Basilar artery	Ref	Ref
Posterior cerebral artery	1.00 (0.33–2.66, <i>P</i> = .997)	1.20 (0.38–3.42, <i>P</i> = .747)
Posterior inferior cerebellar artery	0.40 (0.06–1.54, <i>P</i> = .244)	0.52 (0.08–2.17, <i>P</i> = .421)
Superior cerebellar artery	0.69 (0.04–4.24, <i>P</i> = .735)	0.75 (0.04–5.50, <i>P</i> = .806)
Vertebral artery	0.45 (0.21–0.94, <i>P</i> = .032)	0.41 (0.18–0.90, <i>P</i> = .025)
Vertebrobasilar junction	2.25 (0.76–6.25, <i>P</i> = .126)	1.56 (0.46–5.03, <i>P</i> = .461)
Aneurysm shape		
Fusiform/dolichoectatic/dissecting	Ref	Ref
Saccular	0.40 (0.18–0.81, <i>P</i> = .017)	0.43 (0.18–0.95, <i>P</i> = .045)
Size of aneurysm (mm)	1.04 (1.00–1.07, <i>P</i> = .021)	1.01 (0.97–1.05, <i>P</i> = .612)
Previous SAH		
None	Ref	
<2 weeks	1.50 (0.61–3.33, <i>P</i> = .348)	
>2 weeks	0.69 (0.11–2.51, <i>P</i> = .633)	
Prior treatment		
None	Ref	
Endovascular	0.71 (0.16–2.11, <i>P</i> = .585)	
Operation	6.62 (0.26–169.46, <i>P</i> = .184)	
Both	NA	
Number of devices		
1	Ref	Ref
≥2	3.51 (1.84–6.64, <i>P</i> < .001)	1.79 (0.82–3.82, <i>P</i> = .136)
Antiplatelet regimen changed	0.72 (0.04–4.00, <i>P</i> = .759)	
Adjunctive coiling	0.76 (0.30–1.68, <i>P</i> = .531)	

Note:—NA indicates not applicable; Ref, reference variable for comparison.

^a Covariates that have *P* < .1 in the univariable analysis were included in the multivariable analysis. Data are OR (95% CI, *P* Value).

In a meta-analysis of posterior nonsaccular aneurysms treated with flow diversion, Kiyofuji et al¹¹ added that treatment of aneurysms of <10 mm was associated with fewer complications compared with those larger than 10 mm (18% versus 29%). They also found that aneurysms located within the vertebral artery (83%) had a better outcome compared with the vertebrobasilar junction and proximal basilar artery (33%), mid-/distal basilar artery, and holobasilar artery (18%).¹¹ This finding is potentially related to the abundance of perforators along the basilar artery compared with the vertebral artery. Additionally, the holobasilar fusiform dolichoectatic aneurysm is the product of the unique and poorly understood pathophysiology distinct from other aneurysms. In our study, we have noticed significant changes across the years that align with these recommendations. Additionally, basilar artery aneurysms and fusiform shape were independent predictors of thromboembolic complications compared with their vertebral artery aneurysms and saccular counterparts. Thus, interventionalists transitioned to treating more vertebral artery aneurysms and fewer large vertebrobasilar aneurysms across the years, particularly asymptomatic ones. Also, the median size of aneurysms treated declined from 9 mm in 2011–13 to 7.7 mm in 2018–19. Despite the significant change in the size and location of aneurysms treated,

there was no significant change in the rate of fusiform aneurysms treated, per se, across time.

One of the other factors suggested by Natarajan et al¹⁰ to reduce complications was limiting the number of overlapping flow diverters, because more devices were associated with an increased risk of perforator occlusion due to greater metal coverage. In our study, there was a significant shift to using only 1 device across time, from 72.4% of procedures in 2011–13 to 87.8% in 2018–19.

Moreover, as implied in the previous study on anterior circulation aneurysms, careful monitoring of platelet testing before procedures and switching to appropriate antiplatelet regimens in cases of clopidogrel nonresponders may have played a role in the drop of thromboembolic complications.^{16,17} The rate of platelet function testing in this study (72.9%) was lower than the ones reported by previous PED studies (96.1% and 88.5%).^{16,21}

Poor clinical status (mRS 3–5) at presentation was an independent predictor of treatment complications. These patients were more likely to present with a ruptured aneurysm (70.2%) compared with patients with an mRS of 0–2 (19.3%, *P* < .001). Patients with poor clinical status and ruptured aneurysms were more prone to complications related to brain injury and delayed cerebral ischemia.²² Those patients were also more likely to

present with fusiform aneurysms (76.6%) than patients with an mRS of 0–2 (64.5%, $P = .07$). Moreover, 17% of these patients had large or giant aneurysms (>20 mm) compared with 11.7% of patients with an mRS of 0–2 ($P = .2$). All these factors might have contributed to the increased rate of complications in this subgroup of patients.

Limitations

The primary limitations of the current study include its retrospective design and variability in the management of patients across centers. Retrospective studies are subject to incomplete data sets, selection bias, and unidentified confounders. The inclusion of multiple institutions improves the generalizability of the findings but introduces variability in patient management. This also introduces variation in aneurysm measurement and the device compaction rate. However, the use of a standardized datasheet among all centers and the large number of cases included should improve the generalization of the results. Although the study addresses improvement in patient and aneurysm selection, it does not account for improvement in the catheters and implants across the years. Screening of silent ischemic complications postoperatively was not routinely performed, which might underestimate the true thromboembolic rate. Moreover, the variability in the follow-up imaging protocol, especially with the use of noninvasive modalities (ie, CTA and MRA), introduces another bias, given that those modalities are less reliable in assessing endoleaks in fusiform aneurysms.

CONCLUSIONS

This is the largest study that evaluates the real-world practice trends in the treatment of posterior circulation aneurysms using flow diversion. Across the years, fewer basilar and vertebrobasilar junction aneurysms were treated, but more aneurysms of the vertebral artery. The average diameter of treated aneurysms has also decreased. These practice changes align with prior studies that showed a dire outcome from treatment of large and partially thrombosed fusiform basilar aneurysms. This led to a gradual decline in the rate of thromboembolic and hemorrhagic complications.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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