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# Outcome of Flow Diverters with Surface Modifications in Treatment of Cerebral Aneurysms: Systematic Review and Meta-analysis

 Y.-L. Li,  A. Roalfe,  E.Y.-L. Chu,  R. Lee, and  A.C.O. Tsang



## ABSTRACT

**BACKGROUND:** Newer flow diverters are enhanced with antithrombogenic surface modifications like the Pipeline Embolization Device with Shield Technology and the Derivo Embolization Device and are purported to facilitate deployment and reduce ischemic events.

**PURPOSE:** Our aim was to review the safety and efficacy of surface-modified flow diverters in treating patients with cerebral aneurysms.

**DATA SOURCES:** We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses–compliant systematic review and meta-analysis covering 3 major data bases and gray literature between 2014 and 2019.

**STUDY SELECTION:** Two reviewers independently reviewed human studies of surface-modified flow diverters for eligibility based on predetermined criteria.

**DATA ANALYSIS:** The random effects model and Freeman-Tukey arcsine transformation were used to pool efficacy outcomes (technical success, aneurysm occlusion at 6 and 12 months) and safety outcomes (mortality, morbidity, all ischemia, and serious ischemia). Subgroup analysis was performed to compare outcomes between 2 different flow diverters.

**DATA SYNTHESIS:** Eight single-arm case series involving 911 patients and 1060 aneurysms were included. The median follow-up was 8.24 months. Pooled estimate for technical success was 99.6%, while the aneurysm occlusion at 6 and 12 months were 80.5%, and 85.6%, respectively. Pooled estimates for mortality, morbidity, total ischemia, and serious ischemia rates were 0.7%, 6.0%, 6.7%, and 1.8%, respectively. Most studies were of good quality, and no significant heterogeneity was observed.

**LIMITATIONS:** Limitations include a retrospective, observational design in some studies; heterogeneous and underreported antiplatelet therapy; and potential performance and ecologic bias.

**CONCLUSIONS:** Early-to-midterm safety and efficacy for surface-modified flow diverters appear comparable with older devices, especially for small, unruptured anterior circulation aneurysms. Long-term clinical data are required to further corroborate these results.

**ABBREVIATIONS:** DAPT = dual antiplatelet therapy; FD = flow diverter; HPC = hydrophilic polymer coating; SM = surface modification; SPED = Pipeline Flex Embolization Device with Shield Technology; DED = Derivo Embolization Device

Since their introduction in 2007, flow diverters (FDs) have revolutionized the endovascular treatment of cerebral aneurysms with expanding indications. Previously uncoilable aneurysms (wide-neck, giant, fusiform, tiny, blister, distally located) are increasingly treated with FDs.<sup>1</sup> The efficacy and long-term safety of first-generation FDs have been proved in several meta-analyses.<sup>2-6</sup>

A major limitation of flow diversion is ischemic stroke associated with stent thrombogenicity, necessitating dual-antiplatelet therapy and its associated risk. Since 2014, different manufacturers have incorporated surface modifications (SMs) to reduce FD thrombogenicity. Currently available devices include the Pipeline Flex Embolization Device with Shield Technology (SPED; Medtronic), the Derivo Embolization Device (DED; Acandis), and

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**Table 1: Overview of surface-modified flow diverters**

	Device		
	SPED	DED	p64/p48 MW HPC
Manufacturer	Medtronic	Acandis	phenox
Year of release	2014	2016	2017
Stent structure	Permanent mesh cylinder braided from platinum, tungsten, and cobalt-chromium-nickel alloy wires	24 Nitinol wires with radiopaque platinum core looped at the end, with a 48-wire braid	Drawn filled tubing wires with platinum core and nitinol coating
Diameter	2.5–5 mm	3.5–6 mm	p64: 2.5× 5 mm p48 MW: 1.75–2 mm
Length	10–35 mm	15–50 mm	p64: 9–30 mm p48 MW: 9–18 mm
Previous versions	1) PED; original device available since 2008 2) FPED: resheathable and available since 2014	A non-BlueXide (Acandis)-coated version was available briefly	p64/P48 MW non-HPC versions
Surface modifier Description	PC polymer (Shield technology) <3-nm PC polymer covalently bonded to stent braids	BlueXide 50-nm titanium oxide and titanium oxynitride surface finishing	pHPC Covalent bonding of the proprietary pHPC to the stent braids
Proposed mechanism	PC is a constituent of the red cell membranes, thus reduces platelet adhesion and activation	Reduces friction during delivery and expansion, thus reducing thrombogenicity	Mimics glycocalyx on the vessel wall to inhibit platelet plug formation

**Note:**—PC indicates phosphorylcholine; pHPC, phenox Hydrophilic Polymer Coating; FPED, Pipeline Flex without Shield coating.

p64 and p48 MW hydrophilic polymer coating (HPC) Flow Modulation Device (phenox) (Table 1). Although laboratory studies have demonstrated lower thrombogenicity compared with older FDs, their clinical efficacy and safety have not been extensively tested.<sup>7</sup>

This study synthesizes the current evidence regarding the clinical and radiologic outcomes of patients with cerebral aneurysms treated by these SM-FDs.

## MATERIALS AND METHODS

This is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses–compliant systematic review and meta-analysis.<sup>8</sup> The protocol was prospectively enrolled in the International Prospective Register of Systematic Reviews register.

### Search Strategy

A search was conducted in major online data bases (MEDLINE, EMBASE, Cochrane) for studies published between January 2014 (when the first SM-FD was introduced) and September 2019. Gray literature sources, including Web sites of manufacturers, major journals and conferences in interventional neuroradiology, and bibliographies of screened full texts were reviewed to identify additional studies. The following keywords and their combinations and permutations were used in the search: “intracranial aneurysm,” “cerebral aneurysm,” “flow diverter,” “pipeline shield,” “derive,” “p64,” and “p48mw.” Detailed search strategy and results are given in the Online Supplemental Data.

### Eligibility Criteria

Recognizing that most studies on novel neurointerventional devices are nonrandomized, uncontrolled, and observational, we did not limit eligibility by study design.

We included studies meeting the following inclusion criteria:

1. Evaluated use of SM-FDs in intracranial aneurysms in humans
2. Enrolled at least 15 subjects

3. Reported on outcomes described below
4. Followed up subjects for at least 6 months
5. Article published in English.

We excluded studies meeting the following exclusion criteria:

1. Laboratory and cadaveric studies
2. Narrative review or opinion articles
3. Novel series evaluating off-label use in challenging cases not representative of typical clinical scenarios
4. Disaster series highlighting complications
5. Intermixed studies in which outcomes of SM-FD cannot be extracted.

### Data Collection and Analysis

Search results were pooled, and duplicates were removed. The titles and abstracts were screened independently by 2 investigators, and full texts of potentially eligible studies were perused. A list of demographic-, aneurysm-, treatment-, and outcome-related data was extracted. Conflicts were resolved by consensus. We subsequently performed a meta-analysis of the following efficacy and safety outcomes:

Efficacy outcomes:

1. Technical successful rate (%)
2. Aneurysm occlusion rate at 6 months (%)
3. Aneurysm occlusion rate at 12 months (%).

Aneurysm occlusion is defined by cerebral angiography showing Raymond-Roy class I or O’Kelly-Marotta class D results.

Safety outcomes were the following:

1. Mortality rate (%), including any death occurring during the study
2. Morbidity rate (%), including any treatment-related significant clinical symptoms during the study
3. Total ischemia rate (%), including all ischemic events, both clinical and radiologic, during the study

4. Serious ischemia rate (%), including only permanent neurologic deficits attributed to an ischemic mechanism during the study.

### **Result Synthesis and Reporting**

Risk-of-bias assessment was performed by 2 investigators for each study. The National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used, and studies were classified into good, fair, or poor quality.<sup>9</sup>

Random effects model was adopted because neurointerventional procedures were highly variable and the effect was expected to be different depending on the patient, clinical setting, and neurointerventionalist.

Because all the main outcome events were binary and denoted in proportions, they were pooled with results denoted in a summary point estimate with 95% CIs. Outcomes available in less than half of all studies would not undergo pooling. Confidence intervals for individual studies were calculated with the score method. Because the studies included were single-arm with event rates close to 0 or 1, the Freeman-Tukey double arcsine method was used for transformation and pooling.<sup>10</sup>

Subgroup analysis was performed for the type of FD (DED versus SPED) for all outcomes. Heterogeneity was evaluated using the  $I^2$  statistic and the Cochrane Q test. We followed the Cochrane Collaboration's interpretation for statistical heterogeneity.  $P$  values  $< .05$  were considered significant for the Q test. For the  $I^2$  statistic, 0%–40%, 30%–60%, 50%–90%, and 75%–100% were considered little, moderate, substantial, and considerable heterogeneity, respectively.<sup>11</sup>

Meta-regression, funnel plots, and the Egger test were not performed because the results would not be valid if the number of eligible studies was  $< 10$ .<sup>11</sup>

Data entry and review were performed with Excel (Microsoft). Forest plotting and meta-analysis were performed in STATA/IC 16 (StataCorp, 2019) using the metaprop function (Online Supplemental Data).<sup>12</sup>

## **RESULTS**

### **Study Selection and Characteristics**

Our search yielded 2119 entries; 1580 records were screened, and 93 full texts were perused to assess eligibility. After exclusion, 8 studies were eventually included for meta-analysis.<sup>13–24</sup> The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart is given in the Online Supplemental Data.

All 8 studies were single-arm case series, 4 of which studied DED, and 4, SPED. Five were retrospective, and 3 were prospective. There was no eligible study for the p64 and p48 MW HPC. The number of participants per study ranged from 24 to 294, with a total of 911 patients and 1060 aneurysms. Results from individual studies are provided in the Online Supplemental Data.

### **Participant and Aneurysm Characteristics**

Participants ranged from 17 to 82 years of age and were treated in centers in Europe, America, and Australia. The proportion of females in each study ranged from 58.3% to 82%.

The eligible studies evaluated various types of aneurysms, but most were treated in an elective setting. Unruptured aneurysms constituted 66.2%–100% of each study. Most aneurysms were

small ( $< 10$  mm, 75.9%) with a mean sac size ranging from 7.0 to 9.0 mm.

Most aneurysms were in the anterior circulation (90.2%), with the paraophthalmic internal carotid artery being the most common location (50.7%). Distal vessels such as the anterior cerebral artery (5%) and middle cerebral artery (7.5%) accounted for small proportions. Most aneurysms were saccular in morphology (88.1%).

### **Treatment Characteristics**

All interventions were performed with the patient under general anesthesia using transfemoral access with perioperative heparinization. Hemostasis was achieved either by manual compression or a closure device.

The neurointerventional technique was variable, but authors generally adopted a triaxial technique with a long sheath, an intracranial support catheter, and a microcatheter for delivery. The choice of catheter and the use of conebeam CT, balloon angioplasty, resheathing, platelet function testing, or branch artery coverage were not well-reported to allow statistical description.

A total of 1086 flow diverters were placed (1.02 per aneurysm), of which 455 were DED (41.9%) and 631 were SPED (58.1%). The mean proportion of stent-assisted coiling procedures varied greatly from 6.4% to 88.9%.

The periprocedural and postprocedural dual-antiplatelet therapy (DAPT) protocol was poorly documented overall, and statistical analysis was not possible. Compliance with DAPT on follow-up was not reported by all except 1 study.<sup>13,14</sup>

Among those with available data, DAPT was generally prescribed for at least 4 months (aspirin, 75–325 mg daily, plus a second agent, clopidogrel, 75–150 mg daily; prasugrel, 5–10 mg daily; ticagrelor, 90 mg twice daily; or ticlopidine, 250 mg twice daily) followed by variably dosed aspirin for at least 6 months to indefinitely.

### **Risk of Bias Characteristics**

Most studies (6 of 8) received a “good” grade for overall study quality. Two studies scored “fair” because they did not report on consecutive enrollment and used inappropriate outcome measurements and statistical methods.<sup>15,19</sup>

Most studies (6 of 8) lacked adequate follow-up, which was explicable because the devices are novel. Overall, we consider most studies well-conducted with a clearly expressed study question, appropriate case definitions, and consecutive enrollment of comparable subjects. The interventions, outcome measurements, and results were generally clearly described. The overall risk of bias is therefore low. The overall study rating and details are given in the Online Supplemental Data.

### **Results of Meta-Analysis and Subgroup Analysis**

A summary of the results of meta-analysis is given in Table 2.

**Efficacy Outcomes.** The overall technical success rate for device placement was 99.6% (95% CI, 98.6%–99.8%) with no significant difference between DED and SPED ( $P = .33$ ).

Among cases of technical failure, 5 cases of improper DED expansion were seen and solved by angioplasty, device substitution, and placement of an additional overlapping stent. There

**Table 2: Results of meta-analysis<sup>a</sup>**

	Overall	DED	SPED	Intergroup Heterogeneity
<b>Efficacy outcomes</b>				
Technical success	99.6% (98.6%–99.8%) $I^2 = 33.0\%$ $P = .165$	100% (99.2%–100%) $I^2 = 0.00\%$ $P = .487$	99.2% (97.2%–100%) $I^2 = 54.4\%$ $P = .087$	$P = .165$
Aneurysm occlusion rate (6 mo)	80.5% <sup>b</sup> (74.5%–86.0%) $I^2 = 70.8\%$ $P = .000$	78.9% (74.3%–83.1%) $I^2 = 0.00\%$ $P = .559$	82.7% <sup>b</sup> (73.4%–90.4%) $I^2 = 75.3\%$ $P = .000$	$P = .420$
Aneurysm occlusion rate (12 mo)	85.6% (80.6%–90.0%) $I^2 = 0.00\%$ $P = .744$	87.8% (80.9%–93.5%) NA	83.2% (75.8%–89.6%) NA	$P = .329$
<b>Safety outcomes</b>				
Mortality rate	1.0% (0.3%–1.9%) $I^2 = 0.00\%$ $P = .608$	1.3% (0.2%–3.1%) $I^2 = 5.47\%$ $P = .366$	0.8% (0.1%–1.9%) $I^2 = 0.00\%$ $P = .675$	$P = .410$
Morbidity rate	6.0% (4.5%–7.7%) $I^2 = 0.00\%$ $P = .857$	6.3% (3.9%–9.1%) $I^2 = 0.00\%$ $P = .618$	5.8% (3.9%–8.1%) $I^2 = 0.00\%$ $P = .710$	$P = .725$
Total ischemia rate	6.7% <sup>b</sup> (4.1%–10.1%) $I^2 = 61.9\%$ $P = .010$	8.3% <sup>b</sup> (2.9%–15.7%) $I^2 = 75.1\%$ $P = .007$	6.3% (3.2%–10.2%) $I^2 = 50.1\%$ $P = .111$	$P = .548$
Serious ischemia rate	1.8% (0.8%–3.0%) $I^2 = 12.1\%$ $P = .335$	2.5% (1.0%–4.6%) $I^2 = 0.00\%$ $P = .685$	1.2% (0.1%–3.2%) $I^2 = 37.0\%$ $P = .190$	$P = .240$

**Note:**—NA indicates not applicable.

<sup>a</sup> Table shows pooled point estimate, 95% confidence intervals, heterogeneity ( $I^2$  statistic and  $P$  value for the Cochran Q test) and intergroup heterogeneity for all outcomes of the meta-analysis.

<sup>b</sup> Significant heterogeneity.

were 3 cases of incomplete deployment of the SPED, with all stents resheathed without sequelae. There were 3 cases of failed cannulation, including 1 case of off-label use in treating a distal aneurysm.

There was considerable difference in the follow-up period, imaging technique, and imaging scale across studies. To pool data, we discounted longer follow-ups: For example, 9-month follow-up DSA results were pooled under 6 months. As indicated in the protocol, aneurysm obliteration is defined when filling is completely absent in the angiogram (ie, Raymond-Roy I and O’Kelly-Marotta D classification).

The overall median follow-up interval was 8.24 months (interquartile range, 6.67–12 months). Imaging data were available for 825 (90.6%) and 231 (25.4%) patients at 6- and 12-month follow-up, respectively.

The overall pooled aneurysm occlusion rates at 6 and 12 months were 80.5% (95% CI, 74.5%–86.0%) and 85.6% (95% CI, 80.6%–90.0%), respectively, with no significant difference between DED and SPED ( $P = .42$  and  $P = .33$ ).

**Safety Outcomes.** There was considerable heterogeneity in the definition and reporting of complications. The definitions described under Materials and Methods were adopted, and individual events were reclassified when possible. Events with insufficient detail were treated conservatively. For example, an adverse event labelled as “thromboembolism” without further detail was classified under “serious ischemia,” which indicated a permanent neurologic deficit observed in the patient.

The overall pooled morbidity and mortality rates were 6.0% (95% CI, 4.5%–7.7%) and 1.0% (95% CI, 0.3–1.9%), respectively, with no significant difference between DED and SPED ( $P = .73$  and  $P = .41$ ). Among the 10 deaths, 7 were related to early and late rebleeding, 1 patient died of perforation in DED-assisted coiling, and 1 patient died of stent occlusion from self-discontinuation of antiplatelets shortly after the operation. The cause of death in 1 case was not specified.

The overall pooled ischemic and serious ischemic event rates were 6.7% (95% CI, 4.1%–10.1%) and 1.8% (95% CI, 0.8%–3.0%), respectively, with no significant difference between DED and SPED ( $P = .55$  and  $P = .24$ ).

Details of technical challenges during intervention and unsuccessful placements and mortality, morbidity, and ischemic events are listed in the Online Supplemental Data. Forest plots of all meta-analysis outcomes are available in the Online Supplemental Data.

A table showcasing results of the present and previous meta-analyses on older FDs treating different types of aneurysms is shown in the Online Supplemental Data.<sup>3-6,25-30</sup>

## DISCUSSION

This is the first meta-analysis examining clinical outcomes of surface-modified flow diverters since the release of SPED in 2014. As these devices become more available in angiosuites worldwide, it is important for interventionalists to understand their properties, differences, therapeutic efficacy, and safety profile to select the best device for patients.

Surface modifications are designed to reduce platelet activation, adhesion, and clot formation to prevent clinical ischemic events. Our results appear to confirm this claim. Serious ischemic event rates were uniformly low across studies (0.8% to 3.0%) and compare favorably with meta-analyses performed between 2012 and 2017 on older devices including the Pipeline Embolization Device (PED; Medtronic), the Silk flow diverter (Balt Extrusion), the Flow-Redirection Endoluminal Device (FRED; MicroVention), the Surpass stent (Stryker Neurovascular), and the Tubridge flow diverter (MicroPort Medical Company) (4.1%–7.5%).<sup>2,3,5,6</sup>

The significant heterogeneity observed in “total ischemic events” in the present study is accountable by methodologic variation, specifically in 1 study that included ischemic lesions seen on MR imaging immediately postprocedure (Table 2).<sup>23</sup> These lesions are very common and normally not associated with

clinical sequelae.<sup>23</sup> The serious ischemic event rate in that particular study was not inordinately high (4.2%) compared with others.

The overall mortality was low (1.0%) compared with older stents (2.8%–4%), attesting to the *in vivo* safety of these new devices. Cerebral hemorrhage remains the most common cause of mortality in FD treatment of aneurysms (80%) as in a previous meta-analysis.<sup>4</sup> The cause of hemorrhage after flow diversion is not always clear. In patients with ruptured aneurysms, early rebleeds can be explained by the inability of the FD to immediately obliterate the aneurysm. In other patients, bleeding may be facilitated by DAPT. Giant aneurysms are more prone to delayed rupture, and this may be the result of increased intraneurysm pressure after flow diversion.<sup>31,32</sup> Hemodynamic disturbance caused by the FD may explain rare instances of bizarre delayed parenchymal hemorrhage.<sup>33</sup> In our study, surface modifications do not appear to mitigate the risk of bleeding. Three of 8 fatal hemorrhages occurred in patients with giant aneurysms (37.5%). Whether this is causative would require further investigation.

Clinical outcomes of aneurysm treatment are affected by various factors other than the FD, such as aneurysm characteristics. Previous studies have shown higher morbidity and mortality rates in giant, acutely ruptured, blood-blister, posterior circulation, and nonsaccular aneurysms (Online Supplemental Data).<sup>27-30</sup> Because most patients in the present analysis had unruptured (91.6%), anterior circulation (90.8%), and small (<10 mm) aneurysms, perhaps a more appropriate comparison is with the recent studies by Fiorella et al<sup>25</sup> and Bhatia et al,<sup>26</sup> who examined aneurysms with similar characteristics treated by older FDs. They found a 12-month aneurysm occlusion rate of 74.6% compared with our 85.6% and a total morbidity rate of 7.81%–10.1% compared with our 6.0%. While meta-analyses are not meant to be compared directly, this finding would suggest that SM-FDs are noninferior and potentially superior to previous-generation FDs in terms of efficacy and safety.

Our results also corroborate manufacturers' claims of better apposition and improved deliverability. The technical success rate was excellent (99.6%), improved from older stents (90.6%–91.7%), and similar to that of the Pipeline Flex without Shield coating (Medtronic; 99.3%). For cases of technical failure, no significant adverse consequences were seen, with stents resheathed and removed or improper expansion solved with other endovascular techniques. These findings indicate that SM-FDs are robust and highly deliverable devices.

While coiling and clipping may occlude an aneurysm instantly, flow diverters are designed to hemodynamically remodel the parent artery, causing gradual aneurysm occlusion. Hence, occlusion rates at 6 and 12 months may not reflect the eventual obliteration rate, which tends to be higher in the long run. For example, in a study examining long-term outcome for older stents (Silk, PED, and FRED), occlusion rates were found to progress from 76.2% at 6 months to 94.2% at 5 years.<sup>34</sup>

SM-FDs are novel devices, and there are only studies with 6–12 months of follow-up at present. Nevertheless, they appear comparable with older FDs and coiling. The 6-month occlusion is 80.5% compared with 74.5%–77.9% in older FDs<sup>4-6</sup> and slightly

lower than that of coiling (86.1%).<sup>35</sup> Limited data on 12-month occlusion give a pooled estimate of 85.6%, which is slightly lower than that of older FDs (89.6%).<sup>5</sup> Of note, the 6-month aneurysm occlusion rate is significantly higher in the Safety and Clinical Effectiveness of Pipeline Shield Devices for Intracranial Aneurysm (SCOPE-AUS) study than in other studies (90.3% versus pooled estimate of 80.5%,  $I^2 = 75.3%$ ,  $P = .007$ ). Because only intermediate results were presented at the World Federation of Interventional and Therapeutic Neuroradiology conference in 2019, we eagerly anticipate the full article, which may shed more light on its superior results.<sup>20</sup>

Another concern regarding SM-FDs is the effect of neointimal hyperplasia. *In vivo* animal studies using optic coherence tomography showed conflicting results in the early formation of neointimal hyperplasia in the SPED compared with conventional PED, raising concern for in-stent stenosis after FD placement.<sup>7,36</sup> Clinical studies included in this review did not routinely analyze this phenomenon, and its effect on patient outcome remains unclear.

Trivelato et al<sup>21</sup> observed, in their DED cohort, that a branch vessel arising from the aneurysm led to higher rates of persistence, with an odds ratio of 6.36. This finding is consistent with those of previous studies on flow diversion.<sup>37</sup> However, because other authors did not report this detail and the number of studies included was too small, meta-regression was not possible.

Summarizing the present findings, SM-FDs appear to be as efficacious and safe as older FDs and coiling in the early and mid-term results. No significant clinical difference was seen between the SPED and DED.

### **Limitations, Criticisms, and Future Research Directions**

Most included studies were retrospective, uncontrolled, non-randomized case series lacking long-term (>1 year) outcome. Nonetheless, within the limitations of the study design, the authors produced high-quality research. Assessment of aneurysm occlusion was not blinded except for 1 study in which the aneurysm occlusion was determined by an independent radiology laboratory.<sup>13,14</sup> The other studies were prone to performance bias.

Most patients included had unruptured, small, anterior circulation saccular aneurysms, which tend to be the easiest to treat. This feature can cause ecologic bias leading to better outcomes reported than those encountered in real-life clinical practice.

DAPT was a major confounder in ischemic and hemorrhagic events. The regimen, compliance, and platelet function testing were poorly reported for all except 1 study.<sup>13,14</sup> The possibility that the difference in outcome only reflected a variable effect from different antiplatelet therapy cannot be excluded.

There was significant heterogeneity in endovascular techniques, such as the use of stent-assisted coiling, follow-up and imaging protocols, and the definition of treatment success and complications. In particular, adjunctive coiling occurred in 6.0%–47.1% of participants in the included studies. Because some studies did not report this detail and the overall number of studies is small, meta-regression is not feasible. Instead, we adopted the random effects model to minimize the effects of this clinical heterogeneity.

Aneurysm factors such as rupture status, location, branch vessel coverage, and adverse events were not adequately reported to allow analysis. Further individual-patient-data meta-analysis may be helpful in teasing out which patients are more prone to adverse effects.

Because the present findings indicate that SM-FDs are, indeed, less thrombogenic in vivo, future research should be directed to determine the optimal antiplatelet regimen for these stents. There are already initial reports of using a single agent in selected cases.<sup>38,39</sup> If the bleeding risk of DAPT can be mitigated by SM-FD, flow diversion may be posited as an acceptable treatment for ruptured aneurysms, which is currently an off-label use.

Looking forward, 2 prospective observational cohorts on SPED are in progress (Pipeline Flex With Shield Technology Embolization [SHIELD], NCT02719522, and Pipeline Vantage Embolization Device With Shield Technology for Wide-Necked Intracranial Aneurysms [ADVANCE], NCT03873714) as is an Italian registry on DED, and these may add further evidence to this evolving area in the near future.

## CONCLUSIONS

Surface-modified flow diverters appear as efficacious in closing aneurysms as older FDs and coiling in the early- and midterm outcomes. A uniformly high technical success rate is reported for both SPED and DED. Lower mortality and serious ischemic events are observed compared with previous meta-analyses on older FDs. No significant difference was demonstrated between the SPED and DED. Our results may better apply to small, unruptured saccular aneurysms in the anterior circulation. The long-term clinical outcomes of these devices remain to be seen.

Larger scale prospective studies with a standardized DAPT regimen; follow-up protocol; and more detailed reporting of patient, aneurysm, and treatment characteristics can permit further analysis to identify the best fit patients for these newer devices and predict treatment failure.

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