Complications associated with the use of flow-diverting devices for cerebral aneurysms: a systematic review and meta-analysis

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OBJECTIVE The objective of this study was to review the literature on the use of flow-diverting devices (FDDs) to treat intracranial aneurysms (IAs) and to investigate the safety and complications related to FDD treatment for IAs by performing a meta-analysis of published studies.

METHODS A systematic electronic database search was conducted using the Springer, EBSCO, PubMed, Medline, and Cochrane databases on all accessible articles published up to January 2016, with no restriction on the publication year. Abstracts, full-text manuscripts, and the reference lists of retrieved articles were analyzed. Random-effects meta-analysis was used to pool the complication rates across studies.

RESULTS Sixty studies were included, which involved retrospectively collected data on 3125 patients. The use of FDDs was associated with an overall complication rate of 17.0% (95% confidence interval [CI] 13.6%–20.5%) and a low mortality rate of 2.8% (95% CI 1.2%–4.4%). The neurological morbidity rate was 4.5% (95% CI 3.2%–5.8%). No significant difference in the complication or mortality rate was observed between 2 commonly used devices (the Pipeline embolization device and the Silk flow-diverter device). A significantly higher overall complication rate was found in the case of ruptured IAs than in unruptured IA (odds ratio 2.3, 95% CI 1.2–4.3).

CONCLUSIONS The use of FDDs in the treatment of IAs yielded satisfactory results with regard to complications and the mortality rate. The risk of complications should be considered when deciding on treatment with FDDs. Further studies on the mechanism underlying the occurrence of adverse events are required.

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KEY WORDS intracranial aneurysm; flow-diverting device; complication; delayed rupture

FLOW-DIVERTING devices (FDDs) are a groundbreaking invention in the treatment of intracranial aneurysms (IAs). Since their inception in 2007, FDDs have revolutionized the treatment of IAs by replacing the earlier endosaccular approach with an endoluminal strategy.⁴⁴ Currently, parent vessel reconstruction with FDDs is rapidly becoming the preferred endovascular modality for giant and complex IAs.⁷ In some areas, FDD application has drastically decreased the rate of coil and stent usage.²¹

Despite the large number of reports on successful treatment of aneurysms with flow diverters, various unpredictable adverse events have also been reported. Moreover, there is a dearth of studies on the complications associated with this technique. To date, the safety issues and compli-

cations related to FDDs have not been fully evaluated. Few studies have comprehensively investigated the clinical and technical events in the use of flow diverters for the treatment of IAs. We therefore performed this meta-analysis to evaluate the overall morbidity and mortality rates associated with this endovascular technique. The purpose of this study is to investigate the overall complication rates for different patient cohorts.

Methods

Literature Search

We used the search strategies recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

ABBREVIATIONS BA = basilar artery; CI = confidence interval; FDD = flow-diverting device; IA = intracranial aneurysm; ISS = in-stent stenosis; MCA = middle cerebral artery; OR = odds ratio; PED = Pipeline embolization device; SAC = stent-assisted coiling; SAH = subarachnoid hemorrhage.

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FIG. 1. Flow diagram of the selection of articles.

Titles, abstracts, key words, and free text were searched using combinations of the following key words: “intracranial aneurysm*,” “cerebral aneurysm*,” “flow divert*,” “complication*,” “morbidity,” and “mortality.” The Springer, EBSCO, MEDLINE, Cochrane, and PubMed databases were searched using the specified key words. We also manually searched the references of review articles for additional studies. The decision on whether a study should be included was made independently by 2 authors (G.Z. and M.S.). Data were obtained from the included articles by 1 investigator and reviewed for accuracy by a second investigator. At each step, disagreements were settled by the senior author (M.-H.L.).

Inclusion and Exclusion Criteria

This analysis included: 1) studies on at least 15 patients undergoing IA treatment with an FDD; 2) studies with data on periprocedural and delayed complications; and 3) English language studies. In addition, the following were excluded: 1) studies that were not published in full; and 2) editorials, letters, review articles, guidelines, case reports, in vitro studies, and studies on animal experimentation.

Data Extraction

Using a prespecified form of data abstraction, 2 investigators (G.Z. and M.S.) independently evaluated all the studies and abstracted the following information: 1) study characteristics; 2) patient characteristics (number of patients, demographics, and clinical characteristics); 3)

eligibility, based on the abovementioned study selection criteria; 4) mortality and morbidity; 5) adverse technical events; 6) treatment devices; and 7) location of the aneurysms. We also categorized adverse procedural events as follows: symptomatic ischemic events, hemorrhagic events, and symptoms derived from mass effect.

Quality Assessment and Statistical Analysis

This meta-analysis was performed using the software package Stata (version 13.0, StataCorp). The pooled data were subjected to a random-effects meta-analysis with 95% confidence intervals (CIs). Dichotomous variables were presented as odds ratios (ORs) with a 95% CI. Significance was set at $p < 0.05$. To assess the heterogeneity in the results of individual studies, we used the I^2 statistic. Funnel plots were used to screen for potential publication bias. The selected cutoff number of 15 patients was based on the assumption that very small study cohorts probably lack statistical power in their outcome analyses. The complications were divided into 3 categories of minor, intermediate, and severe. Minor complications consisted of minor ischemic events (including distal emboli and transient ischemic attack), transient dysphasia, and access site complications without need for transfusion. The intermediate complications comprised visual impairment, dissections, in-stent stenosis (ISS), branch occlusion, poor stent opening, wire perforation, deployment failure, and device migration or poor position. Severe complications consisted of ipsilateral parenchymal hemorrhage, rebleeding, and major stroke.

FIG. 2. Meta-analysis of the reported complication rate of FDDs. A random-effects model was applied. ES = effect size; s.e. = standard error.

Results

Study Selection

A total of 587 articles were obtained from the literature search. After screening the abstracts, we selected 153 complete papers that reported data on the complications associated with FDDs for the treatment of IAs in case se-

ries. Finally, a total of 60 articles^{1–6,8–11,13–15,17,19,20,22–25,27–29,31–33,35–40,42,43,45–48,52,53,55–57,59,61,63,66,67,69,73–77,80,81,84} met all the inclusion criteria and were included and reviewed thoroughly (Figs. 1 and 2). No new studies were found by a manual search of the reference list. In total, 3125 patients and 3427 treated aneurysms were included in the analysis (Table 1).

TABLE 1. Characteristics of studies included in the meta-analysis

Authors & Year	Pts/An	Complication Rate (%)		PMR (%)	Mortality (%)	Site	Status	FDD	Branch Occlusion		ISS	Poor Stent Opening		WP	ICH	Re-bleeding	Migration/ Poor Position	Ischemic Events	ACR (%)
		Overall	P/T (%)																
Albuquerque et al., 2015	17/NA	29.4 (5/17)	5.9 (1/17)	5.9 (1/17)	0	PC	U+R	PED							5.9 (1/17)				17.6 (3/17)
Benaissa et al., 2015	29/29	17.2 (5/29)	—	6.9 (2/29)	0	Recanalized IA	U	PED, Silk			0				6.9 (2/29)	0		6.9 (2/29)	3.4 (1/29)
Berge et al., 2012	65/77	18.6 (12/65)	14.3 (9/63)	7.8 (5/65)	3 (2/64)	IA	U+R	Silk			9.3 (6/64)	12.3 (9/73)				4.7 (3/64)	10.9 (7/64)	6.3 (4/64)	13.6 (9/66)
Briganti et al., 2012	273/295	10.6 (29/273)	11 (30/273)	3.7 (10/273)	5.9 (16/273)	IA	U	PED, Silk	1.1 (3/273)		2.2 (6/273)				5.5 (15/273)			4.8 (13/273)	5.1 (14/273)
Briganti et al., 2014	35/39	14.3 (5/35)	11.4 (4/35)	0	0	IA	U+R	PED, Silk							0	0		0	0
Briganti et al., 2016	14/15	27 (4/14)	0	21 (3/14)	0	MCA	U	PED	7.1 (1/14)		14.3 (2/14)				0	0		27 (4/14)	0
Brinjikji et al., 2015	15/15	6.7 (1/15)	—	0/14	6.7 (1/15)	IA	U+R	PED	7.1 (1/14)						6.7 (1/15)				0
Burrows et al., 2015	93/95	28 (26/93)	35 (33/93)	1 (1/93)	1 (1/93)	IA	U+R	PED	2.2 (2/93)		2.2 (2/93)	9 (9/100)			3.2 (3/93)		12 (12/100)	6.5 (6/93)	0
Byrne et al., 2010	70/70	2.9 (2/70)	21 (15/70)	4 (2/70)	8 (4/70)	IA	U+R	SILK			10 (7/70)	17 (12/70)			0 (1/70)	1.4 (1/70)	20 (14/70)	1.4 (1/70)	14.3 (10/70)
Caroff et al., 2016	14/15	21 (3/14)		14.3 (2/14)	0	MCA	U+R	PED, Silk	7.1 (1/14)							0		43 (6/14)	0
Chalouhi et al., 2013 ^{12,14}	40/NA	7.5 (3/40)	—	5 (2/40)	2.5 (1/40)	IA	U	PED							5 (2/40)			2.5 (1/40)	10 (4/40)
Chalouhi et al., 2014 ¹³	40/NA	5 (2/40)		0	0	IA	U	PED							2.5 (1/40)			2.5 (1/40)	0
Chalouhi et al., 2015 ¹¹	95/NA	8.4 (8/95)	—	—	—	Oph	—	PED	7 (6/95)						1.1 (1/95)			1.1 (1/95)	0
Chalouhi et al., 2015 ¹⁵	100/NA	3 (3/100)	0	0	0	IA	U+R	PED							1 (1/100)		2 (2/100)		2 (2/100)
Chiu et al., 2015	98/119	10.2 (10/98)	7.1 (7/98)	0 (3/98)	0.8 (3/98)	IA	U	PED			7.1 (7/98)				1 (1/98)			8.4 (8/98)	0
Colby et al., 2013	35/41	14.3 (5/35)	5.7 (2/35)	3 (1/35)	3 (1/35)	IA	U	PED			5.7 (2/35)					3 (1/35)		3 (1/35)	0
Colby et al., 2016	42/44	4.5 (2/44)	0	2.3 (1/42)	0	IA	U+R	PED Flex			2.3 (1/42)							2.3 (1/42)	—
Cruz et al., 2012	47/NA	8.5 (4/47)	0	2.1 (1/47)	2.1 (1/47)	AC	—	PED							8.5 (4/47)				0

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TABLE 1. Characteristics of studies included in the meta-analysis

Authors & Year	Pts/An	Complication Rate (%)			PMR (%)	Mortality (%)	Site	Status	FDD	Branch		Poor Stent		Re-bleeding	Migration/ Poor Position		Ischemic Events	ACR (%)
		Overall	P/T (%)							Occlusion	ISS	Opening	WP		ICH			
De Vries et al., 2013	37/49	32.4 (12/37)	10.8 (4/37)	2.7 (1/37)	0	IA	U	Surpass	16.2 (6/37)	3 (1/37)		3 (1/37)	2.7 (1/37)		5.4 (2/37)		5.4 (2/37)	
Deutschmann et al., 2012	12/12	16.7 (2/12)	16.7 (2/12)	0	0	IA	U+R	PED		8.3 (1/12)				0			16.7 (2/12)	
Fischer et al., 2012	88/101	6.8 (6/88)	3 (3/88)	4.5 (4/88)	2 (2/88)	IA	U+R	PED	0	2 (2/88)		1.1 (1/88)	3.4 (3/88)				3.4 (3/88)	
Fischer et al., 2014	65/69	5 (3/65)	9.2 (6/65)	—	8 (5/65)	IA	U	PED+Silk	6.2 (4/65)		1.5 (1/65)	0		0	7.7 (5/65)	6.2 (4/65)	6.2 (4/65)	
Fischer et al., 2015	121/130	6.7 (8/121)	2.3 (3/130)	1.7 (2/121)	0.8 (1/121)	IA	U	p64					0	0		3.3 (4/121)	15.7 (19/121)	
Gascou et al., 2015	59/66	32.3 (19/59)	4.2 (4/59)	5.2 (3/59)	6.9 (4/59)	IA	U+R	PED	3.4 (2/59)	18.6 (11/59)			3.4 (2/59)			3.4 (2/59)	11.9 (7/59)	
Gawlitza et al., 2016	17/18	41.2 (7/17)	0	0	0	AC	U+R	PED, Silk, FRED	10.5 (2/19)				0	0		17.6 (3/17)	5.9 (1/17)	
Heller et al., 2013	23/26	52 (13/23)	—	0	0	AC	—	PED		52 (13/23)							0	
Iosif et al., 2015	38/49	13.2 (5/38)	0	7.8 (3/38)	0	IA	U+R	PED								13.2 (5/38)	0	
Kim et al., 2014	23/24	47.8 (11/23)	8.7 (2/23)	0	0	Cav/Para	U	PED	8 (2/23)		8 (2/23)		4 (1/23)		8 (2/23)	8 (2/23)	0	
Kocer et al., 2014	33/37	3 (1/33)	3 (1/33)	0	0	IA	U	FRED								6.1 (2/33)		
Lanzino et al., 2012	21/22	28.6 (6/21)	14.3 (3/21)	—	—	Para	U	PED		4.5 (1/21)	4.5 (1/21)						0	
Levitt et al., 2013	23/NA	8.7 (2/23)	26.1 (6/23)	0	0	IA	U	PED		8.7 (2/23)			0	0	8.7 (2/23)	13 (3/23)	13 (3/23)	
Lin et al., 2015	26/26	19.2 (5/26)	—	11.5 (3/26)	11.5 (3/26)	IA	R	PED		7.7 (2/26)		3.8 (1/26)			0	7.7 (2/26)	46.2 (12/26)	
Lubicz et al., 2010	29/34	38 (10/26)	11.5 (3/26)	—	4 (1/26)	IA	U	Silk		30.7 (8/26)		3.8 (1/26)			3.8 (1/26)	11.5 (3/26)	0	
Lubicz et al., 2011	20/27	10 (2/20)	36 (9/25)	—	5 (1/20)	IA	U	PED	5 (1/20)	10 (2/20)		10 (1/20)					0	
Lubicz et al., 2015	58/70	15 (8/54)	7 (4/58)	5.5 (3/54)	0	IA	U+R	Silk	12 (7/58)	57 (33/58)							10.3 (6/58)	
Di Maria et al., 2015	77/95	7.8 (6/77)	1.3 (1/77)	3.9 (3/77)	0	Oph	U	PED			1.3 (1/77)	0	2.6 (2/77)				35.1 (27/77)	

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TABLE 1. Characteristics of studies included in the meta-analysis

Authors & Year	Pts/An	Complication Rate (%)			PMR (%)	Mortality (%)	Site	Status	FDD	Branch		Poor Stent		Re-bleeding	ICH	WP	Migration/ Poor Position		Ischemic Events	ACR (%)
		Overall	P/T (%)							Occlusion	FDD	ISS	Opening							
Martinez-Galdamez et al., 2015	25/NA	12 (3/25)	12 (3/25)	—	0	AC	U+R	PED	PED	0	24 (6/25)	4 (1/25)	0	4 (1/25)	4 (1/25)	4 (1/25)	8 (2/25)	0		
Martinez-Galdamez et al., 2016	30/30	13.3 (4/30)	0	6.7 (2/30)	0	IA	U	PED Flex					0	0			6.7 (2/30)	0		
McAuliffe et al., 2012 ⁴⁸	54/57	9.3 (5/54)	7.4 (4/54)	0	0	IA	U	PED	PED	3.5 (2/54)	1.9 (1/54)	0	0	1.9 (1/54)	0	5.6 (3/54)	0			
McAuliffe et al., 2012 ⁴⁷	11/11	27.2 (3/11)	27.2 (3/11)	0	18.2 (2/11)	IA	R	PED	PED	9.1 (1/11)	9.1 (1/11)	9.1 (1/11)	18.2 (2/11)	9.1 (1/11)	0	27.2 (3/11)	0			
Meckel et al., 2013	10/10	60 (6/10)	—		40 (4/10)	VBJ	U+R	PED+Silk							40 (4/10)	70 (7/10)	0			
Möhlenbruch et al., 2015	29/34	13.8 (4/29)	3.4 (1/29)	3.4 (1/29)	0	IA	U+R	FRED	FRED	3.8 (1/26)					10.3 (3/29)	34.5 (10/29)	0			
Monteith et al., 2014	24/24	4.2 (1/24)	—	—	4.2 (1/24)	IA+EA	U	PED	PED							8.3 (2/24)				
Nelson et al., 2011	31/31	9.7 (3/31)	3.2 (1/31)	6.5 (2/31)	0	IA	U	PED	PED	3.2 (1/31)					6.9 (2/29)	51.6 (16/31)	0			
O'Kelly et al., 2013	97/97	4.4 (4/97)	3.1 (3/97)		6.3 (6/97)	IA	U	PED	PED				3.1 (3/97)	4.1 (4/97)	2.1 (2/97)	5.1 (5/97)	0			
Piano et al., 2013	101/104	20 (20/100)	11 (11/101)	0	3 (3/101)	IA	U+R	PED+Silk	PED+Silk	5 (5/101)	3 (3/101)	1 (1/101)			4 (4/101)	14 (14/101)	0			
Pierot, 2016	51/51	17.6 (9/51)	15.7 (8/51)	2 (1/51)	0	IA	U+R	WEB	WEB	17.7 (9/51)			0	9.8 (5/51)	3.9 (2/51)	5.9 (3/51)	0			
Pistocchi et al., 2012	26/30	14.8 (4/27)	3.7 (1/27)	3.7 (1/27)	0	AC	U+R	PED+Silk	PED+Silk	3.7 (1/27)	3.7 (1/27)	3.7 (1/27)	0	0	7.4 (2/27)	23.3 (7/30)	0			
Puffer et al., 2014	44/NA	36 (16/44)	36 (16/44)	0	0	Cav	U	PED+Silk+Surpass	PED+Silk+Surpass	2 (1/44)	2 (1/44)	9 (4/44)				0				
Saatci et al., 2012	191/251	14.1 (27/191)	—	1 (2/191)	0.5 (1/191)	IA	U+R	PED	PED	0.5 (1/191)	4.2 (8/191)		0.5 (1/191)	1 (2/191)	2.1 (4/191)	5.8 (11/191)	0			
Saleme et al., 2014	32/37	8 (3/37)	8 (3/37)	9.4 (3/32)	0	AC	U+R	PED	PED	3.1 (1/32)	3.1 (1/32)		0	0	9.4 (3/32)	50 (7/14)	0			
Shankar et al., 2016	92/103	8.7 (8/92)	4.3 (4/92)	5.4 (5/92)	2.2 (2/92)	IA	U+R	Silk	Silk	2.2 (2/92)	13 (12/92)		4.3 (4/92)	4.3 (4/92)	15.1 (13/92)	23.3 (21/92)	0			
Tähinen et al., 2012	24/24	16.7 (4/24)	13 (3/24)	4.2 (1/24)	0	IA	U+R	Silk	Silk	4.2 (1/24)						16.7 (4/24)	0			

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TABLE 1. Characteristics of studies included in the meta-analysis

Authors & Year	Pts/An	Complication Rate (%)			Mortality (%)	Site	Status	Branch Occlusion		Poor Stent Opening	ICH	Re-bleeding	Migration/ Poor Position	Ischemic Events	ACR (%)
		Overall	P/T (%)	PMR (%)				FDD	ISS						
Tanweer et al., 2014	41/43	2.3 (1/41)		2.3 (1/41)	0	CC	U	PED				2.3 (1/41)			2.4 (1/41)
Vedantam et al., 2015	49/NA	14.3 (7/49)	4.1 (2/49)	6.1 (3/49)	0	Oph	U	PED	6.1 (3/49)	2 (1/49)					20.4 (10/49)
Wagner et al., 2012	22/26	27 (6/22)	0	0	5 (1/22)	AC	U	Silk	4.5 (1/22)	18.1 (4/22)			4.5 (1/22)		9.1 (2/22)
Wakhloo et al., 2015	165/190	12 (18/150)	13 (21/161)	6 (9/150)	2.7 (4/165)	AC+PC	U+R	Surpass	2.7 (4/161)	3.7 (6/165)	3.1 (5/190)	2.5 (4/165)	2.1 (4/190)	3.7 (6/165)	21.8 (36/165)
Yoon et al., 2014	11/12	45.5 (5/11)	9.1 (1/11)	—	9.1 (1/11)	AC	R	PED		9.1 (1/11)		0		9.1 (1/11)	9.1 (1/11)
Zhang et al., 2016	45/NA	8.9 (4/45)	—	4.4 (2/45)	0	IA	U	Tubridge		4.4 (2/45)	0	0		8.9 (4/45)	0
Zhou et al., 2014	28/28	0	3.6 (1/28)	—	0	IA	U	Tubridge	0	0	0	0	0	0	64.3 (18/28)

AC = anterior circulation; ACR = adjunctive coiling ratio; Cav = cavernous; CC = cavernous carotid; EA = extracranial aneurysm; FRED = Flow Re-Direction Endoluminal Device; ICH = intracranial hemorrhage; NA, — = data not available; Oph = ophthalmic; p64 = p64 flow modulation device; Para = paracrine; PC = posterior circulation; PMR = permanent morbidity rate; P/T = procedural/technical; Pts/An = patients/aneurysms; R = ruptured; Surpass = Surpass flow diverter; U = unruptured; VBJ = vertebralbasilar junction; WEB = Woven EndoBridge; WP = wire perforation.

TABLE 2. Summary of complication and mortality rates of FDDs stratified by different categories

Complication	% Type of Device						% (Total) of All Complications
	PED (n = 1570)	Silk (n = 360)	FRED (n = 62)	Surpass (n = 202)	Multiple Devices (n = 614)	Other Devices (n = 317)	
Minor	3.7 (58)	0.2 (1)	4.8 (3)	5.9 (12)	2 (12)	3.2 (10)	16.1 (96/596)
Intermediate	13.7 (215)	15 (54)	0	34.7 (70)	5.7 (35)	12 (38)	69.1 (412/596)
Severe	3.1 (49)	2.2 (8)	4.8 (3)	4 (8)	2.4 (15)	1.6 (5)	14.8 (88/596)
Death	1.8 (29)	2.8 (10)	0	2 (4)	4.6 (28)	0.3 (1)	

Complication Rates

The overall complication rate was 17.0% (95% CI 13.6%–20.5%). The incidence of procedural technical complications was 9.4% (95% CI 6.6%–12.2%). The specific causes of the technical events were poor stent opening (in 8.6% of the cases, 95% CI 4.6%–12.7%) and wire perforation (in 3.8% of the cases, 95% CI 0.73%–6.87%; Table 1). Adverse events were classified and the rates were 14.8% for severe complications, 69.1% for intermediate adverse events, and 16.1% for minor complications (Table 2). The overall complication rate was found to be associated with the rupture status of the aneurysm (Table 3). The complication rate for unruptured IAs was 14.6% (95% CI 9.8%–19.4%), which was significantly lower than that for ruptured IAs (30.6%, $p < 0.05$). A significantly higher overall complication rate was found in the case of ruptured IAs than unruptured IAs (OR 2.3, 95% CI 1.2–4.3). Figure 3 summarizes the complication rates associated with commonly used devices: the Pipeline embolization device (PED; Covidien) was associated with a slightly lower complication rate than the Silk flow-diverter stent (Balt Extrusion; 16.0% vs 18.1%, Table 4). Our present findings indicate the overall complication rate in posterior circulation IAs was 44.7%, which was significantly higher than that for anterior circulation IAs (23.7%, 95% CI 15.4%–31.9%; Table 5). The neurological morbidity rate was 4.5% (95% CI 3.2%–5.8%). The specific causes were ischemia (7.5%, 95% CI 4.9%–10.2%), rebleeding (1.8%, 95% CI 0.5%–3.2%), and intracranial hemorrhages (2.9%, 95% CI 1.9%–3.9%). The permanent morbidity rate and mortality rates were 3.7% (95% CI 2.5%–4.9%) and 2.8% (95% CI 1.2%–4.4%), respectively. Analyses of complications and FDDs were associated with substantial heterogeneity ($I^2 > 50\%$), suggesting unexplained differences in study populations and procedures (Fig. 4).

Discussion

In this paper, we report findings from the largest meta-analysis conducted to date of complications related to FDD

treatment for IAs. Although some heterogeneity was found in the results of the studies that were included, the current published data suggest that aneurysms treated with FDDs have a low complication rate. There is a dearth of studies on the safety and morbidity related to this technique, so the information added by this study will be valuable.

In several recent data analyses, the morbidity and mortality rates were reported as 2.8%–14.1% and 0%–3.7%, respectively, with a permanent morbidity rate of 1.3%–6.3%.^{7,83} Our study has several merits compared with the previously published articles. First, because our study includes all available studies in this important field, it presents a complete overview of all available evidence on the adverse events in FDD strategies. We were able to include a larger number of studies due to the rapid growth of the field. We are therefore able to provide the most conclusive overview currently available. Second, we divided the complications into 3 categories of minor, intermediate, and severe. The presented systematic review and results of the meta-analysis investigating the relationship between FDD placement and adverse events is the most comprehensive assessment of this relationship to date. Our findings demonstrated an overall complication rate of 17%, with a permanent morbidity rate of 3.7% and a mortality rate of 2.8%.

Delayed complications associated with the implantation of FDDs have tempered enthusiasm for their widespread use.¹⁸ Rupture of aneurysms after FDD treatment is rare (1.8%). This probably reflects the balance between complete aneurysm thrombus formation and thrombosis-mediated inflammatory disruption of the aneurysmal wall.³⁰ Xiang et al.⁷⁸ also suggest that stagnant aneurysmal flow and excessively low wall shear stress may promote wall degradation via the inflammatory pathway.

Current reports²⁴ have not shown any evidence suggesting that FDDs may induce a pressure change that could lead to rupture of the aneurysm. Moreover, Schneiders et al.⁶⁸ argue that the wall of the still-perfused aneurysm has to endure hemodynamic stress caused by the cardiac pulse wave, which again might contribute to rupture in a later phase. In our analysis, the reported incidence of delayed ruptures is slightly higher with the Silk FDD than with the PED (3.6% vs 3.3%).

The complication rate for unruptured aneurysms (14.6%) was significantly lower than that for ruptured IAs (30.6%, $p < 0.05$). This result indicated that the aneurysm is not immediately protected after treatment by FDDs, which often leads to complete occlusion in 3–12 months. Patients need antiplatelet medication after FDD insertion,

TABLE 3. Overall complication rates obtained for different types of SAH

SAH Type	Rate (%)	95% CI
Only unruptured IAs	14.6	9.8–19.4
Only ruptured IAs	30.6	—
Unruptured & ruptured IAs	17.4	16.8–22.5

FIG. 3. Forest plot of complication rates comparing different types of FDDs. FRED = Flow Re-Direction Endoluminal Device; WEB = Woven EndoBridge.

TABLE 4. Overall complication rate obtained with commonly used FDDs at last follow-up

FDD	Complication Rate (%)	95% CI
PED	16.0	11.2–20.8
Silk	18.1	7.4–28.8
FRED	8.4	
Surpass	22.2	
PED Flex	29.4	
p64	6.7	
Tubridge	4.45	

potentially increasing the rebleeding risk for ruptured aneurysms. Thus, the use of FDDs in the acute subarachnoid hemorrhage (SAH) stage poses a major clinical challenge. Larger case series are needed to define the safety role of FDD application in these kinds of clinical situations.^{25,54}

In our analysis, the overall ratio of adjunctive coiling was 12.3%. The safety and efficacy of PED placement have to be compared with that of conventional endovascular therapy. Our previous study compared the PED with coil embolization and stent-assisted coiling (SAC), and demonstrated that PED placement did not show a significant difference in morbidity and mortality between the two techniques.⁸³ The complications of coiling and SAC are essentially limited to thromboembolic events and aneurysmal rupture, and the total event rates ranged between 3% and 21%. Most of the complications in the series were asymptomatic, and permanent morbidity rates ranged between 0% and 10%.^{60,65,70,71,75} However, SAC of acutely ruptured aneurysms is associated with significantly higher complication rates (5%–25% vs 0%–16%) than unruptured aneurysms.^{12,42,75} Mortality rates ranged from 0% to 4.6% and 0% to 20% in ruptured cases.^{51,75} Major concerns with

TABLE 5. Relation between overall complication rate and aneurysm location

Site	Rate (%)	95% CI
Anterior circulation	23.7	15.4–31.9
MCA	24	
Ophthalmic segment	8.1	
Supraclinoid segment	21.5	
Cavernous carotid	25.1	
Posterior circulation	44.7	
Vertebrobasilar junction	60	

coiling are coil prolapse into the parent vessel and coil penetration, which is estimated to be 2.5%.⁷² Procedure-related complications were comparable in the SAC group and the coiling-alone group.³⁴ Delayed (30-day) ISS or occlusion following SAC was reported to be 3.4%–5.8%.^{26,50}

At present, the time frame for complete occlusion of an aneurysm is unknown. To prevent complications, aneurysm occlusions need to be stabilized as soon as possible. The process of aneurysm occlusion after FDD placement is also linked in part to the antiplatelet regimen administered.⁷³

Potential occlusion of the side branches or perforating arteries carries the risk of secondary ischemic complications. Further, overlap of FDDs potentially increases the risk of arterial branch or perforator occlusion and may be responsible for ischemic complications.⁷⁶ The branch occlusion rate was found to be 4.9% (95% CI 3.2%–6.6%). Only a few studies have examined the effect of FDDs on side branches. Yavuz et al.⁷⁹ reported that perforators from the middle cerebral artery (MCA) or those from the basilar artery (BA) usually remain patent after FDD placement. However, occlusions may still occur. A previ-

FIG. 4. Funnel plot of the reported rate of complications. Publication biases are evident.

ous report found an alarmingly high correlation between perforator infarction and posterior location of IAs. Most side branch occlusion events have been reported to occur in patients who were treated with more than 2 flow diverters or stents.⁵⁸ Although covering the arterial branch with an FDD may lead to gradual occlusion over time, the vascular territory it supplies could be fed by collateral arterial connections, and most patients were asymptomatic.⁶²

Migration or poor position rate was 5.8% (95% CI 3.7%–8.0%) in the analysis. Fischer et al.²⁸ demonstrated that implantation of an undersized device carries a potential risk of an endoleak-like phenomenon.²⁹ A compliant balloon could be used if the deployed FDD shows poor wall apposition. Moreover, Lubicz et al.⁴¹ recommended a stent diameter that is 0.25–0.5 mm larger than the distal parent vessel diameter. Foreshortening of up to 60% of the flow diverter is possible during implantation, but careful size and length selection is important.^{37,82} Stent placement across a fusiform aneurysm must be performed with more vigilance, as stent anchorage relies on a small surface area for contact with the parent artery.⁶⁴

De Vries et al.²⁴ considered patients with stenosis after device implantation to be at high risk of in-stent thrombosis on discontinuation of clopidogrel. Cohen et al. reported that ISS was observed in 38% of the cases in which the Silk device was used and 39% of the cases in which PEDs were used. ISS was asymptomatic in 12 of 13 patients.¹⁸ No exact duration of treatment, or the best combination for prophylactic platelet inhibition drugs, has been established, which has highlighted the need for better evidence for tailoring antiplatelet therapy.¹⁶ An ISS rate of 10.1% was found in our analysis.

In the case of posterior circulation aneurysms, Meckel et al.⁴⁹ suggested that FDD strategies are associated with significant risk and therefore should be reserved for cases in which alternative approaches are deemed unsafe or ineffective. Our present findings indicate the overall complication rate in posterior circulation aneurysms was 44.7%, which was significantly higher than that for anterior circulation IAs (23.7%).

Our study has several limitations that should be considered. First, the prevalence of risk factors and clinical presentations may differ across participants of various studies, so there is a possibility of a confounding bias. Given this, the overall quality of evidence of this systematic review could be considered as low. We have tried to minimize the effect of such a bias by selecting larger case series with 15 or more patients. Second, most of the selected studies were retrospective. Documentation of complications was collected from medical charts. It is likely that minor complications that did not require event reporting or operative intervention were not taken into account in the published literature.

Conclusions

According to the preliminary series, the complication and mortality rates associated with the use of FDDs appears to be satisfactory, specifically in the context of complex aneurysms. However, the mechanism of delayed rupture after flow diversion must be analyzed so that the

appropriate perioperative medication and optimal method for implantation can be determined. More studies, including randomized trials, are needed to provide accurate data on the safety of the flow diversion technique.

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Disclosures

The authors report no conflict of interest concerning the materi-

als or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Li. Acquisition of data: Zhou, Su. Analysis and interpretation of data: Zhou, Su. Drafting the article: Zhou, Su. Critically revising the article: Li, Yin. Reviewed submitted version of manuscript: Li, Yin. Approved the final version of the manuscript on behalf of all authors: Li. Statistical analysis: Zhou, Su. Administrative/technical/material support: Yin. Study supervision: Li.

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