Clinical Neuroradiology
https://doi.org/10.1007/s00062-024-01393-4

ORIGINAL ARTICLE

Clinical Outcomes On Tubridge Flow Diverter in Treatmenting Intracranial Aneurysms: a Retrospective Multicenter Registry Study

Qiang Li[1] · Deyuan Zhu[2] · Nan Lv[1] · Pengfei Yang[1] · Yu Zhou[1] · Rui Zhao[1] · Wenjin Yang[1] · Ming Lv[3] · Tianxiao Li[4] · Wenyuan Zhao[5] · Tiewei Qi[6] · Weixi Jiang[7] · Chuanzhi Duan[8] · Guangyu Zhao[9] · Guoli Duan[1] · Yina Wu[1] · Qian Zheng[1] · Zifu Li[1] · Qiao Zuo[1] · Dongwei Dai[1] · Yibin Fang[2] · Qinghai Huang[1] · Bo Hong[1] · Yi Xu[1] · Yuxiang Gu[10] · Sheng Guan[11] · Jianmin Liu[1]

Received: 11 December 2023 / Accepted: 24 January 2024

Abstract

Purpose In China, the application of nitinol Tubridge flow diverter (TFD) has become popular for treating intracranial aneurysms (IAs). In this study, we investigated the safety outcomes of the application of TFD for treating IAs in real-world scenarios.

Methods We retrospectively analyzed aneurysms treated with TFD in 235 centers throughout China between April 2018 and April 2020. The primary endpoint was the event-free survival rate at 12 months, defined as the occurrence of morbidity (spontaneous rupture, intraparenchymal hemorrhage (IPH), ischemic stroke, and permanent cranial neuropathy) or death. Univariate and multivariate analyses were performed to assess the risk factors. A good outcome was defined as a modified Rankin Score (mRS) of 0–2.

Results We included 1281 unruptured aneurysms treated with TFD. The overall neurological morbidity and death rates after 12 months were 5.4 and 2.8%, respectively. Ischemic strokes were the most common complication (4.2%, $P<0.001$). Cranial neuropathy, IPH, and spontaneous rupture occurred in 0.3%, 0.3%, and 0.5% of aneurysms, respectively. Univariate and multivariate analyses indicated that the male gender, older age, larger aneurysm diameter, and aneurysm located on BA were the independent risk factors for neurologic events. Aneurysm located on BA was the independent risk factor for ischemic strokes. Most patients (1222) had access to the mRS, and 93.2% of them achieved good outcomes.

Conclusion Treatment of IAs with TFD was associated with low morbidity and mortality, most of which were ischemic events. Large posterior aneurysms might be associated with a higher complication rate.

Trial Registration Retrospectively registered.

Keywords Tubridge · Flow diverter · Intracranial aneurysm · Neurological complications

The authors Qiang Li, Deyuan Zhu and Nan Lv contributed equally to the manuscript.

Yuxiang Gu
guyuxiang1972@aliyun.com

Sheng Guan
gsradio@126.com

✉ Jianmin Liu
chstroke@163.com

[1] Neurovascular Center, Changhai Hospital, Naval Medical University, 168 Changhai Road, 200433 Shanghai, China

[2] Department of Neurovascular Disease, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, 200080 Shanghai, China

[3] Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China

[4] Henan Provincial People's Hospital, 463599 Zhengzhou, China

[5] Zhongnan Hospital of Wuhan University, 430071 Wuhan, China

[6] The First Affiliated Hospital, Sun Yat-sen University, 510080 Guangzhou, China

[7] Xiangya Hospital Central South University, 410008 Changsha, China

[8] Zhujiang Hospital of Southern Medical University, 510280 Guangzhou, China

[9] Qilu Hospital of Shandong University, 250012 Jinan, China

[10] Huashan Hospital Affiliated to Fudan University, 200020 Shanghai, China

[11] The First Affiliated Hospital of Zhengzhou University, 450052 Zhengzhou, China

Published online: 15 February 2024

Abbreviations

CEC	Clinical events committee
IA	Intracranial aneurysms
IPH	Intraparenchymal hemorrhage
mRS	Modified Rankin Scored
SAE	Serious adverse events
TFD	Tubridge flow diverter

Introduction

Intracranial aneurysms (IAs) are pathological dilations of cerebral arteries that increase the risk of rupture and might lead to a catastrophic outcome [1–4]. Flow diverter (FD) is an innovative endovascular treatment for IA. It is commonly used for the treatment of IA globally [5–8]. FDs have considerably higher aneurysm occlusion rates than traditional endovascular methods [9]. Recently developed commercialized FDs include a pipeline embolization device (PED, Medtronic, Irvine, California, USA) that is braided using strands of cobalt-chromium, and platinum and silk FDs (Balt Extrusion, Montmorency, France) that are braided using nitinol wires [10–12]. Among the commonly used FDs, PED, silk, FRED, and Surpass have different materials, which makes their characteristics different. The extensive use of PED has shown that it is safe. However, only a few studies have reported the safety of large samples of Nitinol FD, and the largest study on silk FD included only 246 patients with 293 aneurysms [13]. Tubridge FD (TFD, MicroPort Neurotech, Shanghai, China) is a novel, self-expanding, nickel-titanium braided stent-like FD device designed mainly for complex, large, and giant IAs (Fig. 1; [10–12, 14]). The application of TFD was approved by the National Medical Products Administration of China (NMPA) in 2018, and it has been used for treating more than 7000 patients to date.

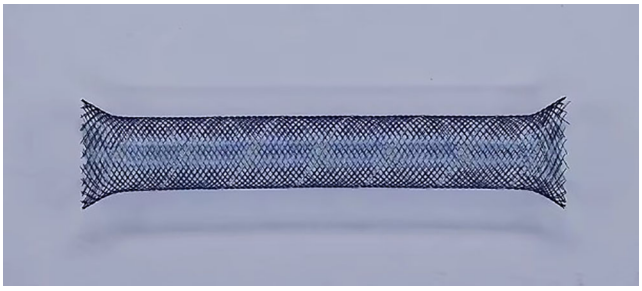

Fig. 1 The Tubridge flow diverter (TFD) is a self-expanding nickel-titanium device with flared ends. A large Tubridge (diameter ≥ 3.5 mm) is braided with 62 nickel-titanium microfilaments and 2 platinum-iridium radiopaque microfilaments, whereas a smaller Tubridge (diameter < 3.5 mm) is composed of 46 nitinol and 2 platinum-iridium microfilaments. The length of Tubridge FD ranges from 10 to 45 mm, and the diameter ranges from 2.5 to 6.5 mm

The reconstruction of the parent artery for large or giant cerebral aneurysms was performed as a part of a recent pre-market, multicenter, and randomized controlled clinical trial for TFD. Several researchers have raised concern about the safety of TFD due to an increase in the complication rate (although non-significant) in the TFD group (17.07% for TFD versus 14.52% for Enterprise) after six months of follow-up [14]. Given the short-term follow-up of the trial, whether the risk of complications for TFD increases or decreases is not clear and requires further investigation. Therefore, in this post-market, retrospective, nationwide, multicenter, registry study, we investigated the incidence of important safety outcomes and the risk factors associated with the complications in patients who underwent TFD treatment for IAs.

Materials and Methods

Study Design and Participants

We retrospectively analyzed all IA cases treated with TFD in 235 centers between April 2018 and April 2020 throughout China. Centers were included in this study if they performed 30 stent-assisted coiling procedures in the previous three years and had a neurosurgical team to make treatment decisions. The study was approved by the local institutional review boards and ethics committees. Written informed consent was obtained from patients when required.

At each center, individuals with intracranial aneurysms were evaluated for study eligibility (including recanalized aneurysms). The inclusion criteria were as follows: (1) patients who received TFD treatment for an intracranial aneurysm after the date of regulatory approval in China, and (2) patients who underwent clinical evaluation following treatment before the institutional review board/ethics committee provided approval. The recommended postoperative antiplatelet regimen was as follows: within six weeks: 300 mg of aspirin and 75 mg of clopidogrel were administered; six weeks to three months: 100 mg of aspirin and 75 mg of clopidogrel were administered; after three months: 100 mg of aspirin was administered indefinitely. And the ultimate antiplatelet regimen was determined by investigators. Patient response testing was performed instead of platelet aggregometry to predict the responsiveness of each patient to clopidogrel.

Follow-ups and Endpoint Events

All patients were followed up by telephone or outpatient review to determine their clinical status and the occurrence of postoperative serious adverse events (SAEs), including procedural success rate, death, stroke, and SAEs during the

Table 1 Baseline characteristics of 1281 patients treated with the TFD ($n = 1281$)

Variable	Modality	n (in %)
Sex	Female	815 (63.62)
	Male	459 (35.83)
	Missing	7 (0.55)
Age, y	< 31	42 (3.28)
	31–50	289 (22.56)
	50–65	643 (50.20)
	> 65	273 (21.31)
	Missing	34 (2.65)
	Mean (SD)	55.07 (11.56)
	Min ~ Max	5 ~ 90
Aneurysm size, mm	< 5 mm	225 (17.56)
	5–10 mm	442 (34.50)
	10–25 mm	562 (43.87)
	> 25 mm	36 (2.81)
	Missing	16 (1.25)
	Mean (SD)	10.55 (6.41)
	Min ~ Max	1.10 ~ 45.00
Aneurysm neck size, mm	< 4 mm	282 (22.01)
	≥ 4 mm	984 (76.81)
	Missing	15 (1.17)
	Mean (SD)	7.11 (4.67)
	Min ~ Max	1.00 ~ 60.00
Location	VA	149 (11.63)
	ICA	1029 (80.33)
	BA	38 (2.96)
	Other distal artery	54 (4.21)
	Missing	11 (8.59)
Aneurysm shape	Fusiform	23 (1.79)
	Saccular	998 (77.91)
	Dissecting	248 (19.36)
	Missing	12 (0.94)
Assisted with coil	No	813 (63.47)
	Yes	457 (35.67)
	Missing	11 (0.86)
Ruptured aneurysm	No	1281 (100)
	Yes	0 (0)
Multiple FD used	No	1278 (99.77)
	Yes	3 (0.23)

perioperative period (within 30 days after stent implantation), death, stroke, and SAEs at six months, one year, two years, three years, and four years after stent implantation. The patients lost to follow-up included those who had three consecutive unsuccessful telephone follow-ups within the telephone follow-up cycle.

The primary endpoint was considered to be the event-free survival rate at 12 months, defined as the occurrence of morbidity (spontaneous rupture of the target aneurysm causing subarachnoid hemorrhage or cavernous carotid fistula),

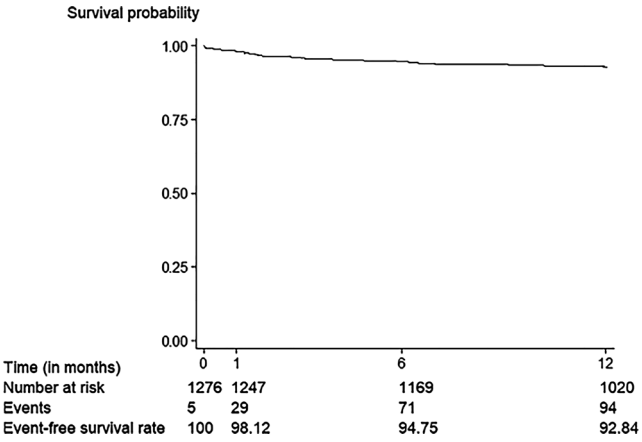

Fig. 2 Survival analysis for the event-free survival rate at 12 months

intraparenchymal hemorrhage (IPH) (both ipsilateral and contralateral), ischemic stroke, and permanent cranial neuropathy, or death within 12 months after treatment. Transient ischemic stroke without clinical adverse events was excluded from the analysis. The secondary endpoints were defined by the modified Rankin Score (mRS) 12 months after aneurysm treatment. A good outcome was defined as a modified Rankin Score (mRS) of 0–2. Neurological deficit was defined as an mRS of ≥ 3 or having a disabling neurological disorder, such as visual deficiency.

Procedures

Due to the retrospective design of this study, the procedural details and periprocedural patient management differed across centers. All centers used a common study protocol for data collection, determining study endpoints and events of interest, and conducting statistical analyses. An independent clinical events committee (CEC) was formed, comprising three physicians who were experts in neurology, neuro intervention, or neurosurgery, and at least one of them had experience in neuro intervention. The CEC investigated all serious adverse events (SAEs), which were then evaluated by the researchers. The case report form (CRF), related medical records, and institutional records were carefully reviewed by the CEC to determine the cause and severity of the SAE and understand the relationship between the SAE and interventional procedures or devices. The status of the SAE was determined by the CEC, while the status of other adverse events was determined by the researchers.

Statistical Analysis

The SPSS package was used for statistical analysis. All statistical data are presented as the mean ± SD for continuous variables. The Chi-squared test/Fisher's exact probability test was used to compare the categorical variables of the

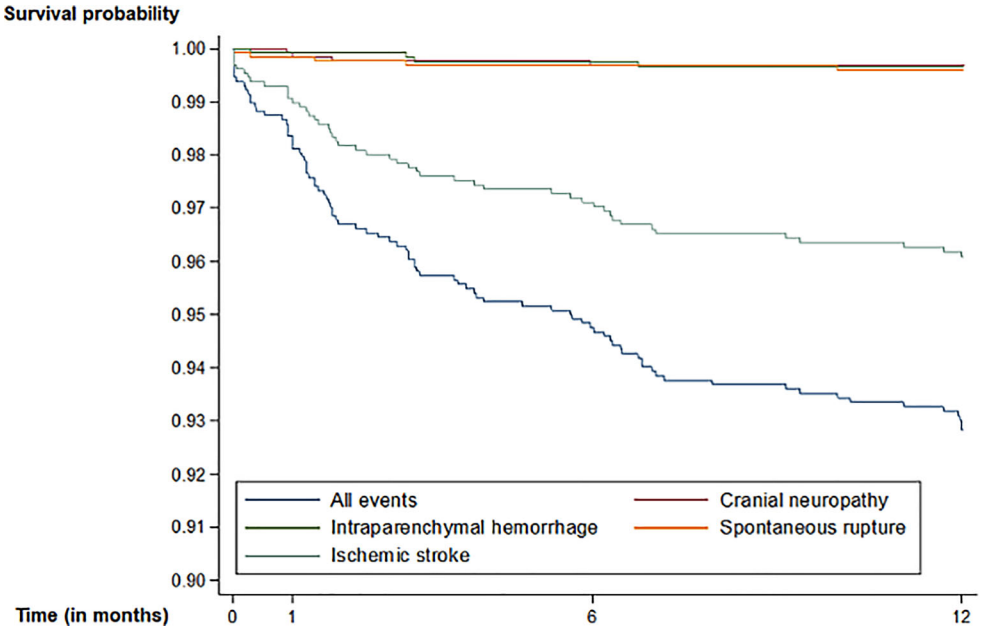

Fig. 3 Survival analysis for all events, ischemic stroke, cranial neuropathy, intraparenchymal hemorrhage, and spontaneous rupture at 12 months

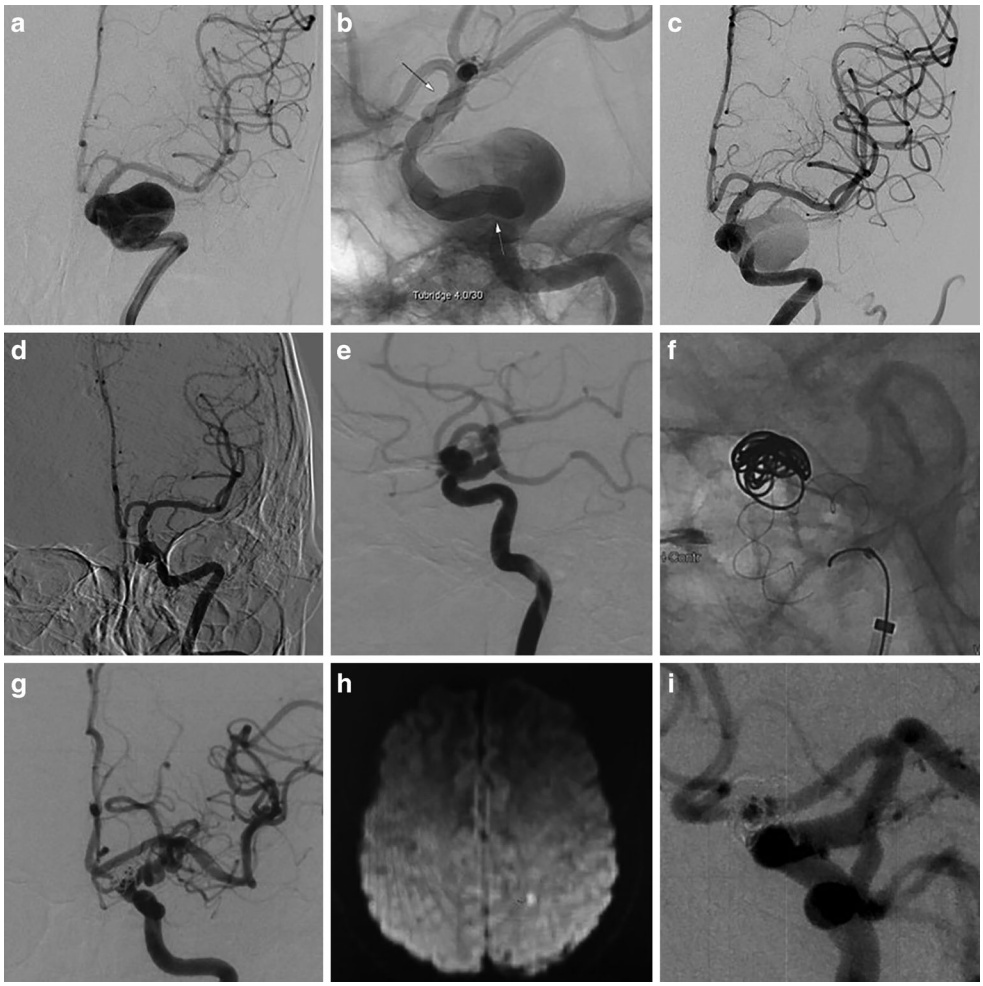

Fig. 4 illustrates two cases, showcasing successful deployment as well as complications. Case 1: **a** DSA image displays a large intracranial aneurysm (22.6 diameter) at the internal carotid artery-Cavernous segment; **b** After the placement of one Tubridge flow diverter (TFD) (size, 4.0* 30 mm); **c** Subsequent frontal DSA image shows partial stasis of contrast media at the dependent part of the aneurysm; **d** Frontal DSA image reveals complete obliteration of the aneurysm 12 months after treatment. Case 2: **e** A 67-year-old woman with an unruptured ICA-Ophthalmic segment aneurysm (8.2*8 mm); **f** A single Axium 8*30 cm 3D coil was inserted into the aneurysm. The aneurysm neck was then covered by a 4.0*35 mm TFD; **g** Immediate control reveals residual filling of the sac; **h** MRI performed one day after the procedure, due to limb weakness, showing ipsilateral ischemic infarction, and the patient subsequently recovered at discharge (mRS 0); **i** 16-month angiogram demonstrating total occlusion of the aneurysm

Table 2 Analysis for Predictors of Events Occurrence ($n = 1281$)

Variable	Modality	Univariate Analysis Hazard Ratio (95% CI)	*P* Value	Multivariate Analysis Hazard Ratio (95% CI)	*P* Value
Sex	Female	1	0.0002	1	**0.02**
	Male	2.12 (1.42,3.18)		1.72 (1.08,2.72)	
Age, y	< 31	1	0.04	–	–
	31–50	2.36 (0.31,17.85)		–	–
	50–65	3.06 (0.42,22.23)		–	–
	> 65	4.84 (0.66,35.49)		–	–
	Continuous	1.03 (1.01,1.05)	0.001	1.03 (1.01,1.05)	**0.001**
Aneurysm size, mm	< 5 mm	1	0.006	–	–
	5–10 mm	1.91 (0.87,4.17)		–	–
	10–25 mm	2.40 (1.13,5.07)		–	–
	> 25 mm	5.95 (2.16,16.42)		–	–
	Continuous	1.04 (1.01,1.07)	0.007	1.04 (1.00,1.08)	**0.0127**
Aneurysm neck size, mm	< 4 mm	1	0.2	–	–
	≥ 4 mm	1.37 (0.79,2.34)		–	–
	Continuous	1.05 (1.03,1.08)	0.0007	0.99 (0.95,1.04)	0.9411
Location	VA	1	< 0.0001	1	–
	ICA	0.56 (0.31,1.02)		0.63 (0.29,1.36)	0.2443
	BA	5.55 (2.71,11.38)		4.81 (2.21,10.44)	**< 0.0001**
	Other distal artery	1.56 (0.65,3.73)		1.74 (0.69,4.38)	0.2403
Aneurysm shape	Fusiform	1	0.02	–	–
	Saccular	0.72 (0.17,2.97)		–	–
	Dissecting	1.39 (0.33,5.84)		–	–
	Non-saccular	1	0.006	1	0.91
	Saccular	0.53 (0.34,0.82)		0.96 (0.52,1.78)	
Assisted with coil	No	1	0.2	–	–
	Yes	1.29 (0.85,1.94)		–	–
Multiple FD used	No	1	0.2	–	–
	Yes	5.02 (0.70,36.06)		–	–

patients. The Kaplan-Meier method was used to perform the survival analysis and estimate the survival rate and 95% confidence interval at each follow-up time point. The survival curve was used to describe the overall process. Our data satisfied the proportional hazards assumption; thus, we used Cox regression analysis to compare the survival analysis. All data were analyzed by two-sided tests. All results were considered to be statistically significant at $P < 0.05$.

Results

In total, 1586 patients with unruptured aneurysms were treated with TFD. Among them, 1281 patients (80.8%) were followed up successfully, while the remaining 305 patients (19.2%) were excluded as they were lost to follow-up. Of the 1281 patients, 815 (63.6%) patients were female, with a mean age of 55.1 years (ranging from 5 to 90 years). The sizes of the aneurysms were as follows: 225 (17.56%), 442 (34.50%), 562 (43.87%), and 36 (2.81%) aneurysms were small (< 5 mm), medium (5–10 mm), large (10–25 mm), and giant (≥ 25 mm) aneurysms, respectively. Most of them were ICA (80.33%) and VA (11.63%) aneurysms; 984 (76.81%) were wide-neck (≥ 4 mm) aneurysms. The shape of the aneurysms included fusiform (1.79%), saccular (77.91%), dissecting (19.36%), and others (0.94%) (Table 1).

The primary outcome measure was evaluated for 1281 patients. During the 12-month follow-up period, at least one morbidity-mortality event occurred in 94 of the 1281 patients, representing an event-free survival rate of 92.84% (95% CI: 91.25–94.14). All patients were available for survival analysis, and the results are presented in Figs. 2 and 3. The follow-up of 12 months showed that the overall neurological morbidity and mortality rates were 5.4 and 2.8%, respectively. Ischemic stroke was the most common complication (4.2%, $P < 0.001$) (Fig. 4).

All patients were included in the analysis for predictors of the occurrence of events, and the results are presented in Tables 2, 3 and 4. The results of the univariate and multivariate analyses indicated that the male sex (HR = 1.72,

Table 3 Analysis for Predictors of Ischemic stroke Occurrence ($n = 1281$)

Variable	Modality	Univariate Analysis Hazard Ratio (95% CI)	P Value	Multivariate Analysis Hazard Ratio (95% CI)	P Value
Sex	Female	1	0.01	1	0.3
	Male	2.07 (1.18,3.62)		1.39 (0.73,2.67)	
Age, y	< 31	1	0.3	–	–
	31–50	1.03 (0.12,8.40)		–	–
	50–65	1.66 (0.22,12.29)		–	–
	> 65	2.42 (0.31,18.31)		–	–
	Continuous	1.02 (0.99,1.05)	0.05	–	–
Aneurysm size, mm	< 5 mm	1	0.1	–	–
	5–10 mm	1.73 (0.64,4.71)		–	–
	10–25 mm	1.67 (0.63,4.54)		–	–
	> 25 mm	5.43 (1.45,20.24)		–	–
	Continuous	1.02 (0.98,1.06)	0.2	–	–
Aneurysm neck size, mm	< 4 mm	1	0.8	–	–
	≥ 4 mm	0.93 (0.47,1.83)		–	–
	Continuous	1.06 (1.02,1.09)	0.008	1.01 (0.97,1.05)	0.35
Location	VA	1	< 0.001	1	–
	ICA	0.54 (0.23,1.25)		0.61 (0.25,1.51)	0.29
	BA	6.84 (2.60,17.99)		6.40 (2.37,17.29)	**0.002**
	Other distal artery	1.56 (0.45,5.34)		1.77 (0.51,6.18)	0.36
Aneurysm shape	Fusiform	1	0.2	–	–
	Saccular	0.37 (0.08,1.56)		–	–
	Dissecting	0.62 (0.14,2.76)		–	–
	Non-saccular	1	0.08	–	–
	Saccular	0.56 (0.30,1.05)		–	–
Assisted with coil	No	1	0.6	–	–
	Yes	1.19 (0.66,2.21)		–	–

95% CI: 1.08–2.72, $P = 0.02$), older age (HR = 1.03, 95% CI: 1.01–1.05, $P = 0.001$), larger aneurysm diameter (HR = 1.04, 95% CI: 1.00–1.08, $P = 0.013$), and aneurysm located on BA (HR = 4.81, 95% CI: 2.21–10.44, $P < 0.001$) were the independent risk factors for neurologic events (Table 2). Aneurysm located on BA (HR = 6.40, 95% CI: 2.37–17.29, $P = 0.002$) was also an independent risk factor for ischemic stroke (Table 3).

We determined the mRS scores of 1222 patients, and 93.2% of them showed good outcomes (Fig. 5). The neurological deficit-free survival rate for the follow-up of 12 months was 94.09% (Fig. 6). The results of the univariate and multivariate analyses indicated that the male sex (HR = 1.98, 95% CI: 1.18–3.29, $P = 0.009$), older age (HR = 1.03, 95% CI: 1.01–1.05, $P = 0.003$), aneurysm located on BA (HR = 4.72, 95% CI: 1.90–11.73, $P < 0.001$), and the use of coil (HR = 2.38, 95% CI: 1.42–3.97, $P < 0.001$) were the independent risk factors for neurological deficit (Table 4).

Discussion

We conducted a post-market, retrospective, and nationwide multicenter registry study of TFD for IA and found overall neurological morbidity and mortality rates of 5.4 and 2.8%. Most of the SAEs were ischemic strokes, and they occurred more frequently in BA aneurysms during the follow-up of 12 months. Cranial neuropathy, intraparenchymal hemorrhage, and spontaneous rupture were rare and occurred in 0.3%, 0.3%, and 0.5% of aneurysms, respectively.

Although a recent international study was conducted that focused on pipeline placement for IA (Intre PED study) [15] and a post-market multicenter cohort study was conducted that investigated the embolization of intracranial aneurysms with a PED in China (PLUS study) [16], this study was the largest clinical study on nitinol TFD to date, where we found the lowest neurological morbidity rate (5.4% for this study versus 7.4% for the Inter PED study versus 8.4% for the PLUS study). The neurological mortality rate recorded in this study was between the values recorded in the previous two studies (2.8% for this study versus 3.8% for the Inter PED study versus 1.5% for the PLUS study) [15, 16].

Table 4 Analysis for Predictors of Neurological Deficit Occurrence ($n = 1281$)

Variable	Modality	Univariate Analysis Hazard Ratio (95% CI)	P Value	Multivariate Analysis Hazard Ratio (95% CI)	P Value
Sex	Female	1	0.0009	1	**0.0091**
	Male	2.14 (1.36,3.67)		1.98 (1.18,3.29)	
Age, y	< 31	1	0.1	–	–
	31–50	2.07 (0.27,15.78)		–	–
	50–65	2.27 (0.31,16.59)		–	–
	> 65	3.88 (0.52,28.70)		–	–
	Continuous	1.03 (1.00,1.05)	0.007	1.03 (1.01,1.05)	**0.0029**
Aneurysm size, mm	< 5 mm	1	0.009	–	–
	5–10 mm	1.82 (0.79,4.22)		–	–
	10–25 mm	2.05 (0.91,4.62)		–	–
	> 25 mm	6.77 (2.37,19.32)		–	–
	Continuous	1.04 (1.01,1.07)	0.009	1.03 (0.99,1.08)	0.0695
Aneurysm neck size, mm	< 4 mm	1	0.4	–	–
	≥ 4 mm	1.24 (0.69,2.22)		–	–
	Continuous	1.05 (1.02,1.08)	0.003	0.99 (0.95,1.04)	0.9257
Location	VA	1	< 0.0001	1	–
	ICA	0.66 (0.33,1.32)		0.57 (0.24,1.36)	0.2082
	BA	5.76 (2.48,13.33)		4.72 (1.90,11.73)	**0.0008**
	Other distal artery	1.92 (0.73,5.04)		1.88 (0.66,5.31)	0.2331
Aneurysm shape	Fusiform	1	0.2	–	–
	Saccular	0.60 (0.14,2.49)		–	–
	Dissecting	1.00 (0.23,4.28)		–	–
	Non-saccular	1	0.05	1	0.8844
	Saccular	0.60 (0.36,0.98)		1.05 (0.52,2.11)	
Assisted with coil	No	1	0.03	1	**0.0008**
	Yes	1.63 (1.04,2.56)		2.38 (1.42,3.97)	
Multiple FD used	No	1	0.2	–	–
	Yes	6.19 (0.86,44.56)		–	–

Compared to the DIVERSION prospective cohort study conducted in France [17], in this study, the primary endpoint rate was considerably higher (92.84% versus 75.7%) and mortality was lower (2.8% versus 3.2%). The results were also better or similar to those of many published studies and meta-analyses [5, 7, 18–20] on the use of FD for the treatment of IA, which indicated that the use of TFD in IA was safe. The results of the univariate analysis indicated that the male gender, older age, larger aneurysm diameter, and aneurysm located on BA were more likely to have neurologic events, which matched our clinical results.

Ischemic strokes, the most common complication of FD, were reported in many studies [5, 7, 21, 22]. They can result from stent wall thrombus formation and occlusion, parent artery occlusion, or distal thromboembolic events[17]. In this study, we found an ischemic stroke rate of 4.2%, which was lower than that in the Intre PED study and the PLUS study (4.7 and 4.4%, respectively) [15, 16]. We found that the ischemic stroke rate was considerably higher in BA aneurysms compared to that in ICA aneurysms (29.0% versus 2.8%, $P = 0.002$). These findings were similar to those of other studies [7, 18]. Although the use of TFD for treating IA is safe, especially for the low incidence of ischemic stroke, ischemic events might still occur after the treatment of IA using TFD. Thus, one needs to be cautious when formulating TFD treatment for patients with BA aneurysms.

The results of the univariate analysis showed that using a coil and multiple TFD was associated with a significantly higher spontaneous rupture rate; however, the occurrences were few, and the confidence interval was wide. For treating patients with large aneurysms, who are more susceptible to delayed postoperative rupture, physicians pack coils in the aneurysm or use more FDs [10]. Most cases of spontaneous rupture occurred in < 30 days of follow-up, indicating that aneurysms tend to spontaneously rupture in the early period after endovascular procedures. Our findings were similar to those of the Intre PED study [15]. Cranial neuropathy was mainly reported for cases of large or giant ICA aneurysms, which might be due to the mass effect, and the occurrence rate decreased after 30 days of follow-up. No occurrence

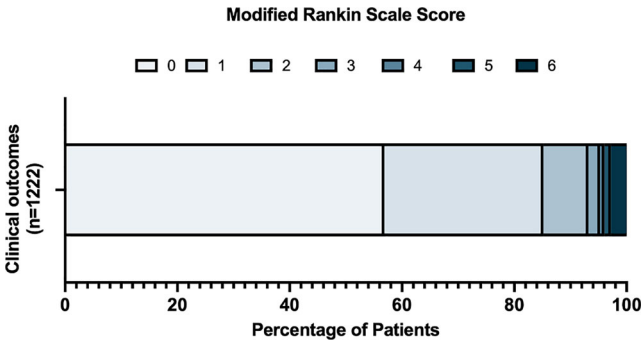

Fig. 5 The distribution of clinical outcomes at 12 months. The scores on the modified Rankin Scale (mRS) are presented for those patients for whom the data of the secondary outcome were available. The scores ranged from 0 to 6; 0 = no symptoms, 1 = no clinically significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death. The mRS scores were available for 1222 patients, and 93.2% of the cases achieved good clinical outcomes (i.e., mRS of 0–2)

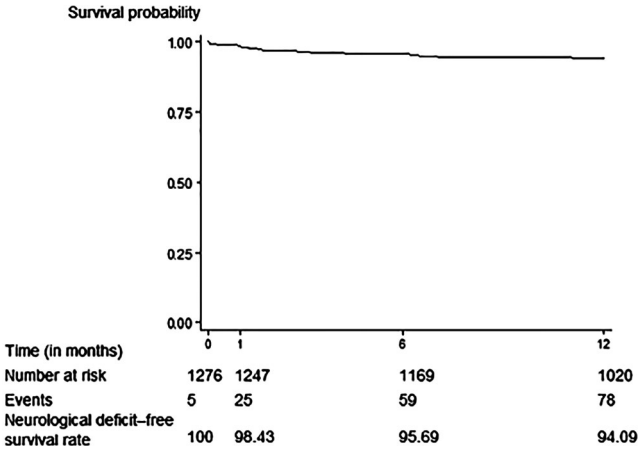

Fig. 6 Survival analysis for the neurological deficit-free survival rate at 12 months

of cranial neuropathy was reported in posterior aneurysms, and the reason was unclear. The intraparenchymal hemorrhage rate in this study was considerably lower than that in the Intre PED study and the PLUS study (0.3% versus 2.4% versus 2.1%) [15, 16], and the results of the univariate analysis showed no significant difference. Unlike the results of the Intre PED study, we did not find that intraparenchymal hemorrhage occurred after treatment of IA with TFD.

Although debatable, adjunctive coiling has become an alternative to FD therapy for IA. Coils within the aneurysm sac might augment the degree of FD and improve the occlusion of the aneurysm [23]. However, adjunctive coil embolization might not improve the already high occlusion rates obtained by using FD alone [24]. Park et al. compared PED with and without coiling for treating IA and found that PED with coiling required a significantly longer procedure time (135.8 versus 96.7 min; $P < 0.0001$) and was associated with higher neurological morbidity (12.5% versus 7.8%; $P = 0.13$) [25]. In the PLUS study, adjunctive coiling was an independent predictor of neurological compression symptoms (OR = 3.105, $P < 0.0001$) and poor functional outcomes (OR = 2.026, $P = 0.005$) [16]. These findings suggested that both strategies had an acceptable risk profile in the treatment of complex cerebral aneurysms and need further investigation.

The characteristics of BA aneurysms include complex neurovascular anatomy with life-sustaining perforating vessels arising from the lesion and an adjacent vessel along the brainstem [26]. The use of FD for the treatment of BA aneurysms needs to be further investigated [27]. Studies on the use of FD for treating BA aneurysms reported highly variable results, with complication rates ranging from 13.3 to 44.8% [28–30]. In this study, we reported 38 (2.96%) BA aneurysms, among which an ischemic stroke was identified in 11 (11/38, 28.9%) aneurysms which were similar to those reported in other studies [28–30]. The FD covers these side branches, which further increases the risk of thromboembolic and ischemic complications [31]. An ischemic stroke is mainly associated with invisible perforator infarction, jailed vessel occlusion, and stent occlusion [32]. The occlusion of an invisible perforator might be the most common cause of ischemia. Several studies have also shown that rapid thrombus formation after FD treatment and subsequent thrombus renewal, instead of thrombus organization, might induce an autolytic and inflammatory cascade, causing edema and further weakening the arterial wall, leading to IA expansion and aggravation of the mass effect [33, 34].

The limitations of this study included its retrospective design with inevitable bias and a shorter follow-up period than that reported in other studies. Another limitation was that 305 of 1586 (19.2%) patients were not followed up adequately throughout the study period, which might have affected the results. A few patients were not enrolled in the subgroup analysis. The imaging studies were not adjudicated by a central core laboratory. Therefore, further prospective studies need to be performed to validate the findings of this study.

Acknowledgements We gratefully acknowledge Professor Xiao yan Yan (Department of Medical Statistics, Peking University, Bei Jing, China) for providing guidance on the various statistical methods used in this study. We are grateful to all principal investigators and delegated physicians who enrolled the required participants in all the participating centers. We also thank the participants, their medical caretakers, and the families who consented to participate in the trial.

Funding This work was supported by the Project of the Shanghai Science and Technology Commission [grant number 19DZ1930300] and the Training Program for Excellent Young Clinical Medical Talents in Hongkou District [grant number HKLCYQ2024-05]; and was sponsored by unrestricted grants from the MicroPort NeuroTech (Shanghai) Co., Ltd. (N/A).

Author Contribution Q. Li: Data curation, Writing—Original draft preparation, Supervision; D. Zhu: Data curation, Writing—Original draft preparation; N. Lv: Data curation, Writing—Original draft preparation; P. Yang: Supervision; Y. Zhou: Supervision; R. Zhao: Supervision; W. Yang: Supervision; M. Lv: Visualization, Investigation; T. Li: Visualization, Investigation; W. Zhao: Visualization, Investigation; T. Qi: Visualization, Investigation; W. Jiang: Visualization, Investigation; C. Duan: Visualization, Investigation; G. Zhao: Visualization, Investigation; G. Duan: Software, Validation; Y. Wu: Software, Validation; Q. Zheng: Software, Validation; Z. Li: Software, Validation; Q. Zuo: Software, Validation; D. Dai: Software, Validation; Y. Fang: Software, Validation; Q. Huang: Visualization, Investigation; B. Hong: Writing—Reviewing and Editing; Y. Xu: Writing—Reviewing and Editing; Y. Gu: Conceptualization, Methodology, Software, Writing—Reviewing and Editing; S. Guan: Conceptualization, Methodology, Software, Writing—Reviewing and Editing; J. Liu: Conceptualization, Methodology, Software, Writing—Reviewing and Editing. All authors read and approved the final manuscript.

Data Availability Statement All data generated or analyzed during this study are included in this article.

Declarations

Conflict of interest Q. Li, D. Zhu, N. Lv, P. Yang, Y. Zhou, R. Zhao, W. Yang, M. Lv, T. Li, W. Zhao, T. Qi, W. Jiang, C. Duan, G. Zhao, G. Duan, Y. Wu, Q. Zheng, Z. Li, Q. Zuo, D. Dai, Y. Fang, Q. Huang, B. Hong, Y. Xu, Y. Gu, S. Guan and J. Liu declare that they have no competing interests.

Ethical standards For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case. This research obtained ethics approval from Shanghai Changhai Hospital Ethics Committee (Approval ID CHEC2022-229). Local institutional review boards or ethics committees authorized the study and retrospective data collection from patients. A waiver of informed consent by an institutional review board or ethics committee. If necessary, written informed consent was obtained from each patient.

References

1. Wu Q, Li L, Shao Q, Xu T, Chang K, Li T, et al. Intracranial aneurysms managed by parent artery reconstruction using Tubridge: Study protocol for a prospective, multicenter, post-market clinical trial. Interv Neuroradiol. 2021;27(4):490–6. https://doi.org/10.1177/1591019920976233.
2. Radaelli AG, Augsburger L, Cebral JR, Ohta M, Rüfenacht DA, Balossino R, et al. Reproducibility of haemodynamical simulations in a subject-specific stented aneurysm model—a report on the Virtual Intracranial Stenting Challenge 2007. J Biomech. 2008;41(10):2069–81. https://doi.org/10.1016/j.jbiomech.2008.04.035.
3. Zhang XJ, Gao BL, Hao WL, Wu SS, Zhang DH. Presence of Anterior Communicating Artery Aneurysm Is Associated With Age, Bifurcation Angle, and Vessel Diameter. Stroke. 2018;49(2):341–7. https://doi.org/10.1161/STROKEAHA.117.019701.
4. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355–69. https://doi.org/10.1016/S1474-4422(09)70025-0.
5. Arrese I, Sarabia R, Pintado R, Delgado-Rodriguez M. Flow-diverter devices for intracranial aneurysms: Systematic review and meta-analysis. Neurosurgery. 2013;73(2):193–200. https://doi.org/10.1227/01.neu.0000430297.17961.f1.
6. Briganti F, Napoli M, Tortora F, Solari D, Bergui M, Boccardi E, et al. Italian multicenter experience with flow-diverter devices for intracranial unruptured aneurysm treatment with periprocedural complications—a retrospective data analysis. Neuroradiology. 2012;54(10):1145–52. https://doi.org/10.1007/s00234-012-1047-3.
7. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke. 2013;44(2):442–7. https://doi.org/10.1161/STROKEAHA.112.678151.
8. Yu SC, Kwok CK, Cheng PW, Chan KY, Lau SS, Lui WM, et al. Intracranial aneurysms: midterm outcome of pipeline embolization device—a prospective study in 143 patients with 178 aneurysms. Radiology. 2012;265(3):893–901. https://doi.org/10.1148/radiol.12120422.
9. Kallmes DF, Brinjikji W, Cekirge S, Fiorella D, Hanel RA, Jabbour P, et al. Safety and efficacy of the Pipeline embolization device for treatment of intracranial aneurysms: a pooled analysis of 3 large studies. J Neurosurg. 2017;127(4):775–80. https://doi.org/10.3171/2016.8.JNS16467.
10. Liu JM, Zhou Y, Li Y, Li T, Leng B, Zhang P, et al. Parent Artery Reconstruction for Large or Giant Cerebral Aneurysms Using the Tubridge Flow Diverter: A Multicenter, Randomized, Controlled Clinical Trial (PARAT). AJNR Am J Neuroradiol. 2018;39(5):807–16. https://doi.org/10.3174/ajnr.A5619.
11. Zhou Y, Yang PF, Fang YB, Xu Y, Hong B, Zhao WY, et al. Parent artery reconstruction for large or giant cerebral aneurysms using a Tubridge flow diverter (PARAT): study protocol for a multicenter, randomized, controlled clinical trial. BMC Neurol. 2014;14:97. https://doi.org/10.1186/1471-2377-14-97.
12. Fang YB, Wen WL, Yang PF, Zhou Y, Wu YN, Hong B, et al. Long-Term Outcome of Tubridge Flow Diverter(S) in Treating Large Vertebral Artery Dissecting Aneurysms—A Pilot Study. Clin Neuroradiol. 2017;27(3):345–50. https://doi.org/10.1007/s00062-015-0494-8.
13. Foa Torres G, Roca F, Noguera A, Godes J, Petrocelli S, Aznar I, et al. Silk flow-diverter stent for the treatment of complex intracranial aneurysms: A one-year follow-up multicenter study. Interv Neuroradiol. 2018;24(4):357–62. https://doi.org/10.1177/1591019918771340.
14. Liang F, Yang Y, Luo L, Liao B, Zhang G, Ou S, et al. Endovascular treatment of complex middle cerebral artery aneurysms using TuBridge flow diverters. Interv Neuroradiol. 2020;26(5):539–46. https://doi.org/10.1177/1591019920946216.
15. Kallmes DF, Hanel R, Lopes D, Boccardi E, Bonafe A, Cekirge S, et al. International retrospective study of the pipeline embolization device: a multicenter aneurysm treatment study. AJNR Am J Neuroradiol. 2015;36(1):108–15. https://doi.org/10.3174/ajnr.A4111.
16. Kang H, Zhou Y, Luo B, Lv N, Zhang H, Li T, et al. Pipeline Embolization Device for Intracranial Aneurysms in a Large Chinese Cohort: Complication Risk Factor Analysis. Neurotherapeutics. 2021;18(2):1198–206. https://doi.org/10.1007/s13311-020-00990-8.
17. Gory B, Berge J, Bonafe A, Pierot L, Spelle L, Piotin M, et al. Flow Diverters for Intracranial Aneurysms: The DIVERSION National Prospective Cohort Study. Stroke. 2019;50(12):3471–80. https://doi.org/10.1161/STROKEAHA.119.024722.
18. Berge J, Biondi A, Machi P, Brunel H, Pierot L, Gabrillargues J, et al. Flow-diverter silk stent for the treatment of intracranial aneurysms: 1-year follow-up in a multicenter study. AJNR Am J Neuroradiol. 2012;33(6):1150–5. https://doi.org/10.3174/ajnr.A2907.
19. Leonardi M, Cirillo L, Toni F, Dall'olio M, Princiotta C, Stafa A, et al. Treatment of intracranial aneurysms using flow-diverting

silk stents (BALT): a single centre experience. Interv Neuroradiol. 2011;17(3):306–15. https://doi.org/10.1177/159101991101700305.
20. Velioglu M, Kizilkilic O, Selcuk H, Kocak B, Tureci E, Islak C, et al. Early and midterm results of complex cerebral aneurysms treated with Silk stent. Neuroradiology. 2012;54(12):1355–65. https://doi.org/10.1007/s00234-012-1051-7.
21. Pierot L. Flow diverter stents in the treatment of intracranial aneurysms: Where are we? J Neuroradiol. 2011;38(1):40–6. https://doi.org/10.1016/j.neurad.2010.12.002.
22. Wong GK, Kwan MC, Ng RY, Yu SC, Poon WS. Flow diverters for treatment of intracranial aneurysms: current status and ongoing clinical trials. J Clin Neurosci. 2011;18(6):737–40. https://doi.org/10.1016/j.jocn.2010.10.011.
23. Fiorella D, Woo HH, Albuquerque FC, Nelson PK. Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the pipeline embolization device. Neurosurgery. 2008;62(5):1115–20. https://doi.org/10.1227/01.neu.0000325873.44881.6e. discussion 20–1.
24. Szikora I, Berentei Z, Kulcsar Z, Marosfoi M, Vajda ZS, Lee W, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. AJNR Am J Neuroradiol. 2010;31(6):1139–47. https://doi.org/10.3174/ajnr.A2023.
25. Park MS, Kilburg C, Taussky P, Albuquerque FC, Kallmes DF, Levy EI, et al. Pipeline Embolization Device with or without Adjunctive Coil Embolization: Analysis of Complications from the IntrePED Registry. AJNR Am J Neuroradiol. 2016;37(6):1127–31. https://doi.org/10.3174/ajnr.A4678.
26. Wang C, Zhu D, Xu X, Zhou Y, Zhao R, Li Q, et al. Use of flow diverter device in basilar artery for aneurysm treatment: Case series and literature review. Front Neurol. 2022;13:990308. https://doi.org/10.3389/fneur.2022.990308.
27. Kiyofuji S, Graffeo CS, Perry A, Murad MH, Flemming KD, Lanzino G, et al. Meta-analysis of treatment outcomes of posterior circulation non-saccular aneurysms by flow diverters. J Neurointerv Surg. 2018;10(5):493–9. https://doi.org/10.1136/neurintsurg-2017-013312.
28. Griessenauer CJ, Enriquez-Marulanda A, Taussky P, Biswas A, Grandhi R, Xiang S, et al. Experience With the Pipeline Embolization Device for Posterior Circulations Aneurysms: A Multicenter Cohort Study. Neurosurgery. 2020;87(6):1252–61. https://doi.org/10.1093/neuros/nyaa277.
29. Ge H, Chen X, Liu K, Zhao Y, Zhang L, Liu P, et al. Endovascular Treatment of Large or Giant Basilar Artery Aneurysms Using the Pipeline Embolization Device: Complications and Outcomes. Front Neurol. 2022;13:843839. https://doi.org/10.3389/fneur.2022.843839.
30. Wallace AN, Madaelil TP, Kamran M, Miller TR, Delgado Almandoz JE, Grossberg JA, et al. Pipeline Embolization of Vertebrobasilar Aneurysms—A Multicenter Case Series. World Neurosurg. 2019; https://doi.org/10.1016/j.wneu.2018.12.116.
31. Adeeb N, Griessenauer CJ, Dmytriw AA, Shallwani H, Gupta R, Foreman PM, et al. Risk of Branch Occlusion and Ischemic Complications with the Pipeline Embolization Device in the Treatment of Posterior Circulation Aneurysms. Ajnr Am J Neuroradiol. 2018;39(7):1303–9. https://doi.org/10.3174/ajnr.A5696.
32. Bender MT, Colby GP, Jiang B, Lin LM, Campos JK, Xu R, et al. Flow Diversion of Posterior Circulation Cerebral Aneurysms: A Single-Institution Series of 59 Cases. Neurosurgery. 2019;84(1):206–16. https://doi.org/10.1093/neuros/nyy076.
33. Kulcsar Z, Houdart E, Bonafe A, Parker G, Millar J, Goddard AJ, et al. Intra-aneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow-diversion treatment. AJNR Am J Neuroradiol. 2011;32(1):20–5. https://doi.org/10.3174/ajnr.A2370.
34. de Korte AM, Aquarius R, Meijer FJA, Boogaarts HD, de Vries J. Intracranial Aneurysm Expansion Might Cause Neurological Deterioration After Flow Diverter Treatment. World Neurosurg. 2018;120:e802–e10. https://doi.org/10.1016/j.wneu.2018.08.169.