Clin Neuroradiol
DOI 10.1007/s00062-015-0494-8

ORIGINAL ARTICLE

Long-Term Outcome of Tubridge Flow Diverter(S) in Treating Large Vertebral Artery Dissecting Aneurysms—A Pilot Study

Y.-B. Fang · W.-L. Wen · P.-F. Yang · Y. Zhou · Y.-N. Wu · B. Hong · Y. Xu · W.-Y. Zhao · J.-M. Liu · Q.-H. Huang

Received: 22 October 2015 / Accepted: 9 December 2015

Abstract
Background and Purpose The experience of flow diverters (FDs) in treating large vertebral artery-dissecting aneurysms (VADAs) is still limited. This study was conducted to present our long-term outcome of VADAs treated with a Tubridge flow diverter (TFD), a new device developed in China.
Materials and Methods The clinical and angiographic data of six patients harboring large VADAs and treated with TFDs were prospectively collected and analyzed.
Results A total of nine TFDs were successfully implanted in six patients. Angiographic follow-up images were available for all patients at a median of 26.0 (18.5, 37.5) months after treatment. Five of the six VADAs were completely occluded, and the last was improved (near complete occlusion). In-stent stenosis was detected in one case and was handled appropriately by angioplasty and stenting. All covered branches and parent arteries remained patent. There were no complications or new neurological deficits observed in any of the patients. At the latest clinical follow-up (36.5 (26.0, 44.5) months), all patients achieved 0 in the modified Rankin scale score.
Conclusions Our preliminary experience suggests that the Tubridge flow diverter might be an alternative treatment for large and recurrent dissecting aneurysms derived from the vertebral artery.

Keywords Tubridge · Vertebral artery dissecting aneurysm · Endovascular · Flow diverter

Introduction

Vertebral artery dissecting aneurysms (VADAs) contribute to both hemorrhagic and ischemic strokes [1, 2]. They are

Yibin Fang and Wanling Wen are co-first authors.

J.-M. Liu (✉) · Q.-H. Huang (✉) · Y.-B. Fang · W.-L. Wen · P.-F. Yang · Y. Zhou · Y.-N. Wu · B. Hong · Y. Xu · W.-Y. Zhao
Department of Neurosurgery, Changhai Hospital,
Second Military Medical University,
200433 Yangpu District, Shanghai,
No.168 Changhai Road, China
e-mail: chstroke@163.com

Q.-H. Huang
e-mail: ocinhqh@163.com

Y.-B. Fang
e-mail: fangyibin@vip.163.com

W.-L. Wen
e-mail: wwljoy00@hotmail.com

P.-F. Yang
e-mail: 15921196312@163.com

Y. Zhou
e-mail: yzhou_2011@126.com

Y.-N. Wu
e-mail: wuyina0923@163.com

B. Hong
e-mail: hongbosmmu@yeah.net

Y. Xu
e-mail: xuyichyy@163.com

W.-Y. Zhao
e-mail: doczhaowy@163.com

Published online: 15 January 2016

formed following intima rupture and the partial or complete enlargement of the artery wall, the latter of which often leads to a fusiform configuration. The special pathological and morphological features of VADAs make them challenging to treat with traditional modalities. Surgery and endovascular trapping were once used in ruptured VADAs [3, 4]. However, these deconstructive approaches may precipitate severe ischemic complications. Reconstructive techniques, especially flow diverting with Pipeline Embolization Device (PED) or Silk® flow diverter (Silk), have been reported as a potential alternative [5–7].

The Tubridge flow diverter (TFD) is a nickel-titanium braided microfilament, self-expandable stent-like device with flared ends. A TFD has gradient pore size which reaches the lowest in the middle of the device (0.040–0.050 mm^2) to provide high metal coverage (approximately 30.0–35.0 %) at the aneurysmal neck, whereas lower metal coverage at the two ends is designed to avoid perforator infarction as much as possible. The size of TFDs ranges from 2.5 to 6.5 mm in diameter and 12 to 45 mm in length. It had been applied successfully in treating large or giant internal carotid artery (ICA) aneurysms [8].

We aimed to report the preliminary experience and long-term results of TFD in treating large VADAs.

Materials and Methods

Patient Selection and Population

The study was prospectively designed and approved by the institutional Ethics Committee and China Food and Drug Administration. Patients with unruptured or recanalized VADAs being considered for TFD placement should meet all of the following criteria: (1) The subject understood the whole procedure of the trial and provided written informed consent; (2) the patient was willing to be followed up in accordance with the study protocol; (3) the subject was 18–75 years of age; (4) the VADAs were located at V4 segment of vertebral artery; (5) the maximal diameter of the dissection was no less than 10 mm; and (6) the parent artery was 2.0–6.5 mm in diameter.

Procedure and Perioperative Medication

The procedure was performed as described previously [8]. Endovascular treatments were performed by authors of the present article (JML, QHH, BH, and YX), all of whom have more than 10 years of experience in intracranial stent placement. Intensive dual antiplatelet therapy (300 mg/day aspirin plus 75 mg/day clopidogrel) were given for at least 3 days before the procedure and for 6 weeks after the procedure. Clopidogrel was continued at a dose of 75 mg/day for three months, and then discontinued. Aspirin was administered at a dose of 300 mg/day for 6 weeks, followed by 100 mg/day infinitely.

Imaging and Clinical Assessment

For aneurysms treated with the TFD plus coils, the angiographic results obtained immediately after the procedure were classified according to the Raymond classification system and O'Kelly-Marotta Scale [9]. For aneurysms treated with the TFD without coils, flow alterations were defined as either disrupted inflow jet or reduced contrast filling. Angiographic follow-up results were classified into four categories by comparison to the degree of immediate embolization: (1) occluded, with no contrast observed in the aneurysm sac or neck; (2) improved, with decreased contrast filling into the aneurysm sac; (3) stable, with unchanged contrast filling in the aneurysm sac; (4) recanalized, with increased contrast filling in the aneurysm sac or with coil compaction detected. Angiographic results were independently interpreted by two of the authors; differences between raters were solved by discussion with another senior neuro-interventionalist. Images taken immediately after treatment and at follow-up were checked carefully if there were any missing perforators which were initially visible in the baseline angiograph from the same perspective. The clinical outcome was evaluated and recorded according to modified Rankin scale (mRS) through neurologic examination or telephone interview by two experienced neurologists.

Follow-Up Protocol

Catheter-based angiography was required at the 6th month (±1 month) after treatment procedure. Digital subtraction angiography (DSA) follow-up was recommended every year thereafter, and gadolinium-enhanced magnetic resonance angiography (MRA) (1.5 T) follow-up would also be acceptable as long as the result of previous DSA follow-up was satisfactory.

Results

Six patients were recruited in this study from August 2010 to May 2012, including two women and four men ranging from 30 to 58 years old in age. Three of them had a history of subarachnoid hemorrhage (SAH) at least 3 months prior to study entrance and presented because of recanalization from their previous treatment, which included SAC with either Enterprise stent (Codman & Shurtleff, Raynham, Massachusetts, MA, USA) in two patients or Solitaire stent (Covidien/ev3 Inc, Irvine, CA, USA) in one patient.

Table 1 Clinical information of six participants who received Tubridge flow diverter treatment

No.	Age (y)/sex	Symptom at onset	Prior treatment
1	39/M	Infarction	None Major recanalization at 5th month after
2	41/M	SAH	SAC, recanalized again at 6th month after retreatment with SAC
3	49/M	SAH	Recanalized 1 month after SAC
4	30/M	SAH	Recanalized 3 months after SAC
5	58/F	Headache	None
6	48/F	Vertigo	None

y years, *M* male, *F* female, *SAH* subarachnoid hemorrhage, *SAC* stent-assisted coiling

The other three patients presented with ischemic stroke, headache, and vertigo, respectively. The characteristics of the six patients treated with TFDs were summarized in Tables 1 and 2. Another ten patients with large unruptured or recanalized VADAs in the same period refused to participate in the trial.

Immediate Angiographic and Clinical Results

A total of nine TFDs were successfully deployed in six patients. Three of them were treated with single or double TFDs alone and the other three with additional coils. The shape of deployed devices was examined with real-time Dynamic CT to ensure substantial expansion. Immediate angiographic results were neck remnant (Raymond Class II) in 2 VADAs and sac residue (Raymond Class III) in one case treated with additional coils. Disruption of inflow jet and delayed contrast filling was observed in other cases and recorded to be Raymond Class III. None of the PICA were affected, even those covered by the device. No new neurological deficits were observed after the procedure.

Angiographic Follow-up Findings

Long-term angiographic follow-up was available for all patients for a median interval of 26.0 (18.5, 37.5) months (Table 2). Five VADAs (83.3%, 5/6) were completely occluded (Fig. 1 as an illustrative case), and the other one (16.7%, 1/6) was improved in the latest follow-up.

One case of in-stent stenosis occurred in a lesion recanalized after prior SAC. It was detected incidentally at the third month follow-up of subclavian artery stenosis. The stenosis was located proximal to stent and within the TFD. Angioplasty with Gateway 3/15 (Boston scientific, USA) and Enterprise 4.5/28 (Codman, USA) was performed and long-term angiographic results were favorable (Fig. 2).

Table 2 Detailed morphological information of each case and treatment outcome

Case	Side	Dominant VA	Length (mm)	Diameter (mm)	VADA to PICA	Strategy	Instant Raymond score	O'Kelly-Marotta Scale	Perioperative complication	Angiographic follow-ups				mRS score	
										Time (months)	Method	VADA	VA	PICA	AD	FU (months)
1	**R**	Co	22.7	7.5	No PICA or occluded	Overlapping TFDs + coils	2	C3	None	5	DSA	Occluded	Patent	NA	2	0 (49)
										19	MRA	Occluded	Patent	NA		
2	**R**	Co	5.9	10.7	Pre-PICA	TFD	3	B3	None	14	DSA	Occluded	Patent	Patent	1	0 (43)
										45	MRA	Occluded	Patent	Patent		
3	R	Co	13.5	7.9	Involved, middle	TFD	3	B3	None	36	MRA[a]	Improved	Patent	Patent	0	0 (41)
4	**L**	L	15.7	10.6	Pre-PICA	Overlapping TFDs + coils	3	B3	None	3	DSA	Occluded	In-stent stenosis; retreated	Patent	0	0 (32)
										11	DSA	Occluded	Patent	Patent		
										24	DSA	Occluded	Patent	Patent		
5	**L**	Co	9.4	12.6	Post-PICA	TFD + coils	2	C3	None	3	MRA	Occluded	Patent	Patent	1	0 (28)
										7	DSA	Occluded	Patent	Patent		
										28	DSA	Occluded	Patent	Patent		
6	R	Co	13.4	6.0	Involved, distal edge	Overlapping TFDs	3	A3	None	6	DSA	Occluded	Patent	Patent	0	0 (20)
										17	DSA	Occluded	Patent	Patent		

VA vertebral artery, *mm* millimeter, *VADA* vertebral artery dissecting aneurysm, *PICA* posterior inferior cerebellar artery, *AD* at discharge, *FU* follow-up, *R* right, *Co* comparable, *L* left, *TFD* Tubridge flow diverter, *NA* not applicable, *mRS* modified Rankin score, *MRA* magnetic resonance angiography, *DSA* digital subtraction angiography

[a]Case 3 declined to come back for DSA follow-up because of personal financial problem

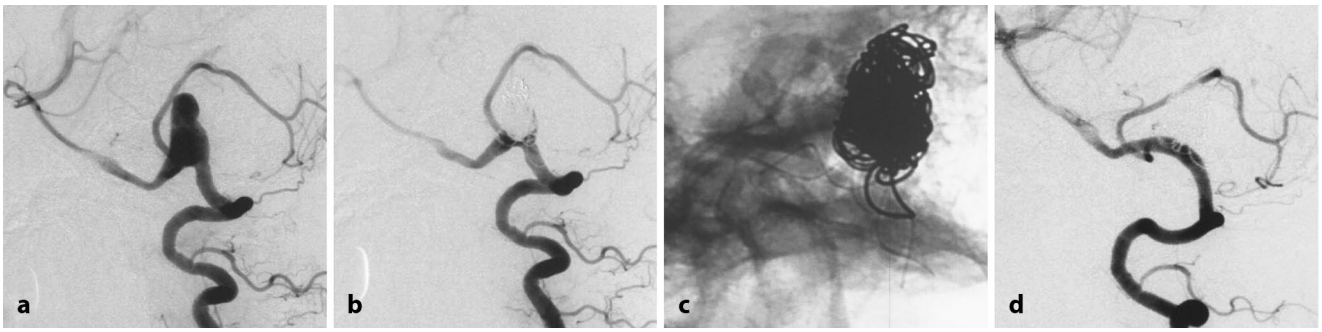

Fig. 1 A large vertebral artery-dissecting aneurysm was detected near the orifice of posterior inferior cerebellar artery (PICA) (**a**) and treated with one Tubridge flow diverter and additional coils; the immediate angiographic outcome was neck remnant, and PICA was perfectly preserved (**b&c**); the 28th month follow-up revealed remodeling of vertebral artery and the aneurysm was no longer visible (**d**)

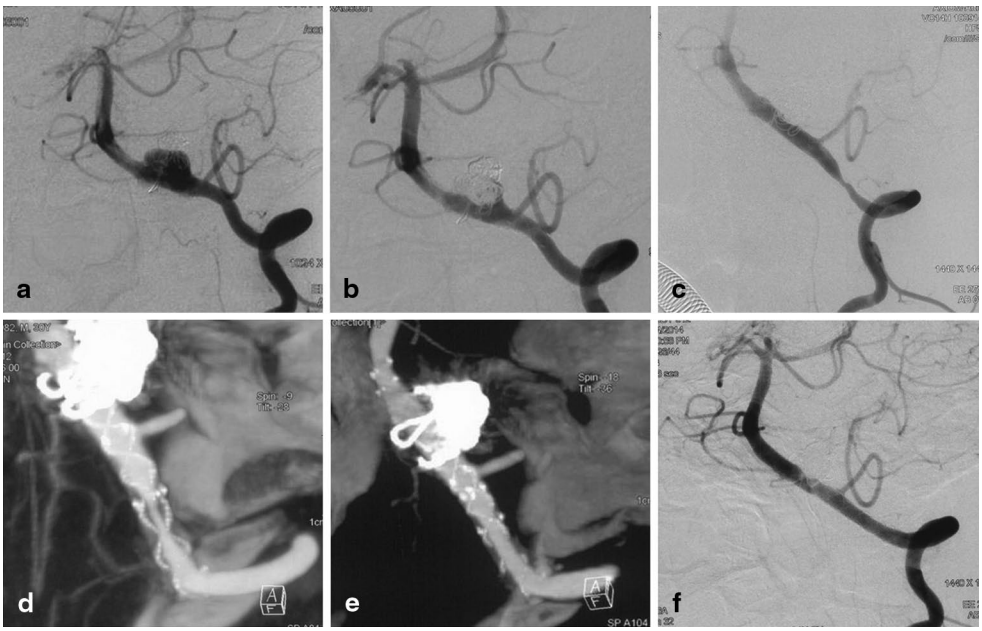

Fig. 2 The 3rd month angiography following stent-assisted coiling revealed major recurrence of a large vertebral artery dissecting aneurysm (**a**), which was partially occluded with a Tubridge flow diverter (TFD) and additional coils (**b**); the 3rd month follow-up revealed in-stent stenosis located at the proximal end of previous stent (**c&d**). Treatment with a Gateway balloon (3 mm/15 mm) and an Enterprise (4.5 mm/28 mm) was performed immediately and the stenosis was greatly resolved (**e**); follow-up imaging at the 21st month after TFD treatment showed no residual stenosis (**f**)

Clinical Outcome

No new symptoms were noted in any of the six patients. The mRS score was 0 in all six patients at a median of 36.5 (26.0, 44.5) months' follow-up.

Discussion

Vertebrobasilar artery-dissecting aneurysms with large diameter; PICA involvement are at high risk of recanalization and are difficult to treat [10, 11]. In our series, five out of six VADAs were completely occluded without recanalization during the mean follow-up period of 28 months, comparable to the obliteration rate of other FDs in treating saccular aneurysms at other locations [12] and TFD in anterior circulation [8], and superior to that of SAC in treating VADAs [13]. The only case that failed to achieve complete occlusion, though substantially improved, was a retreated, ruptured VADA with PICA involvement. Moreover, it is also believed that a preexisting stent in the lumen may have limited the efficacy of FD reconstruction [14].

Use of Additional Coils

SAC is better than conventional stent-only therapy to treat wide-necked aneurysms. However, the benefit of additional coiling with FD implantation in treating unruptured aneurysms remains controversial. It is hypothesized that coils in the aneurismal sac provide extrinsic support for implanted TFDs, thus preventing the TFD from protruding into the aneurismal sac. The support from the coils is beneficial in some degree, especially in VADAs with a fusiform configuration. Additionally, coils may help prevent postoperative SAH, the incidence of which is reported to be as high as 3% [12]. One of the underlying culprits is increased intra-aneurysmal pressure due to blood retention within the sac after FD implantation [15], while additional coils accelerate thrombus

formation, which obstructs inflow. The Balt Extrusion Company also recommends the combination of Silk device and coils. The small sample size of our study may be the main reason why we did not encounter any hemorrhagic complications. However, we believe that additional coiling may help accelerate thrombus formation to prevent aneurysm rupture. The midterm result of Parent artery reconstruction for large or giant cerebral aneurysms using a Tubridge flow diverter (PARAT) [16], a multicenter prospective trial launched by our center to compare TFD treatments with Enterprise SAC in treating big or giant saccular aneurysms, showed that early aneurysm rupture mostly occurred in giant intracranial aneurysms treated with TFD implantation only (unpublished data). However, some studies claimed that additional coils do not decrease the risk of early rupture of aneurysms after FD implantation. The necessity of additional coil embolization is still under evaluation.

Ischemic Complications After TFD Implantation

Ischemic complications, including perforator infarction and infarctions in the downstream region, occur at both acute stage and subacute stages. The overall incidence of ischemic stroke was 4.7% (37/793) and was highest in patients with posterior circulation aneurysms (7.3%, 4/55) [17]. Perforator infarction contributes to nearly half of the ischemic events in FD treatment and is usually explained by coverage of the perforator orifice by stent wires, or migration of disintegrated thrombus formed in the stent [5]. Downstream region infarctions are more likely to be related to in-stent thrombosis or escaped thrombi from the aneurysmal sac, especially in cases of giant, fusiform or dissecting aneurysms.

No ischemic complications were observed in our series. These results are comparable to other studies on VADAs. However, it needs to be noted that people with vertebral–basilar junction aneurysms might be at higher risk of ischemic complications, probably due to the higher density of perforators within this area [11, 18]. None of TFD covered this area in our series, so the safety in treating vertebrobasilar aneurysms needs to be evaluated in the future.

Delayed In-Stent Stenosis After TFD Implantation

In-stent stenosis is detected in 38% (6/16) of patients treated with Silk and 39% (7/18) of patients treated with Pipeline flow diverter [19] and is considered a common reaction of the arterial wall to the device. Early angiographic follow-up is valuable in detecting in-stent stenosis, which tends to occur during the first 2 months after flow-diverter deployment. Most of the stenosis are mild to moderate and can be treated conservatively with enhanced medical therapy. We decided to treat the lesion with an endovascular approach because it was severe and most of the lumen had been occupied by excessively proliferated intima.

Innovations and Limitations

This is the first appraisal of the safety and efficacy of the TFD device in complex VADA treatment, based on long-term follow-up of six case series. The results are encouraging, though some limitations need to be noted. First, the number of cases is limited due to the rarity of indicated cases; second, all patients came from a single center and are highly selected which leads to selection bias; third, there were no proper cases treated with other modalities from which to make a comparison.

Conclusions

The Tubridge flow diverter appears to be a safe and effective treatment alternative for large dissecting aneurysms derived from the VA. Further experience is needed.

Disclosure Statements Author 9 had given some advice about the design of this device and offered some data of our previous hemodynamic studies.

Acknowledgments This work was supported by the National Scitech Support Plan grant number [2011BAI08B14] Shanghai Science and Technology Development Funds grant number [14441904702], National Natural Science Foundation of China grant number [81301004, 81471189] and Shanghai Science and Technology Development Funds grant number [13140903201].

Conflict of Interest The other authors declared they have no competing interests.

References

1. Mizutani T, Aruga T, Kirino T, Miki Y, Saito I, Tsuchida T. Recurrent subarachnoid hemorrhage from untreated ruptured vertebrobasilar dissecting aneurysms. Neurosurgery. 1995;36(5):905–11; discussion 912–3.
2. Yoshimoto Y, Wakai S. Unruptured intracranial vertebral artery dissection. Clinical course and serial radiographic imagings. Stroke. 1997;28(2):370–4.
3. Fukasawa I, Sasaki H, Nukui H. Surgical treatment for ruptured vertebral artery dissecting aneurysms. Neurol Med Chir (Tokyo). 1998;38(Suppl):104–6.
4. Iihara K, Sakai N, Murao K, Sakai H, Higashi T, Kogure S, Takahashi JC, Nagata I. Dissecting aneurysms of the vertebral artery: a management strategy. J Neurosurg. 2002;97(2):259–67.
5. Albuquerque FC, Park MS, Abla AA, Crowley RW, Ducruet AF, McDougall CG. A reappraisal of the Pipeline embolization device for the treatment of posterior circulation aneurysms. J Neurointerv Surg. 2015;7(9):641–5.
6. Murthy SB, Shah S, Shastri A, Venkatasubba RC, Bershad EM, Suarez JI. The SILK flow diverter in the treatment of intracranial aneurysms. J Clin Neurosci. 2014;21(2):203–6.

7. Monteith SJ, Tsimpas A, Dumont AS, Tjoumakaris S, Gonzalez LF, Rosenwasser RH, Jabbour P. Endovascular treatment of fusiform cerebral aneurysms with the Pipeline Embolization Device. J Neurosurg. 2014;120(4):945–54.
8. Zhou Y, Yang PF, Fang YB, Xu Y, Hong B, Zhao WY, Li Q, Zhao R, Huang QH, Liu JM. A novel flow-diverting device (Tubridge) for the treatment of 28 large or giant intracranial aneurysms: a single-center experience. AJNR Am J Neuroradiol. 2014;35(12):2326–33.
9. O'Kelly CJ, Krings T, Fiorella D, Marotta TR. A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents. Interv Neuroradiol. 2010;16(2):133–7.
10. Zhao KJ, Zhao R, Huang QH, Xu Y, Hong B, Fang YB, Li Q, Yang PF, Liu JM, Zhao WY. The interaction between stent(s) implantation, PICA involvement, and immediate occlusion degree affect symptomatic intracranial spontaneous vertebral artery dissection aneurysm (sis-VADA) recurrence after reconstructive treatment with stent(s)-assisted coiling. Eur Radiol. 2014;24(9):2088–96.
11. Ertl L, Holtmannspötter M, Patzig M, Brückmann H, Fesl G. Use of flow-diverting devices in fusiform vertebrobasilar giant aneurysms: a report on periprocedural course and long-term follow-up. AJNR Am J Neuroradiol. 2014;35(7):1346–52.
12. 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.
13. Zhao KJ, Fang YB, Huang QH, Xu Y, Hong B, Li Q, Liu JM, Zhao WY, Deng BQ. Reconstructive treatment of ruptured intracranial spontaneous vertebral artery dissection aneurysms: long-term results and predictors of unfavorable outcomes. PLoS One. 2013;8(6):e67169.
14. Song Y, Wang Y, Li C, Wang Y, Mu S, Yang X. Retreatment and outcomes of recurrent intracranial vertebral artery dissecting aneurysms after stent assisted coiling: a single center experience. PLoS One. 2014;9(11):e113027.
15. Darsaut TE, Rayner-Hartley E, Makoyeva A, Salazkin I, Berthelet F, Raymond J. Aneurysm rupture after endovascular flow diversion: the possible role of persistent flows through the transition zone associated with device deformation. Interv Neuroradiol. 2013;19(2):180–5.
16. Zhou Y, Yang PF, Fang YB, Xu Y, Hong B, Zhao WY, Li Q, Zhao R, Huang QH, Liu JM. 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.
17. Kallmes DF, Hanel R, Lopes D, Boccardi E, Bonafe A, Cekirge S, Fiorella D, Jabbour P, Levy E, McDougall C, Siddiqui A, Szikora I, Woo H, Albuquerque F, Bozorgchami H, Dashti SR, Delgado Almandoz JE, Kelly ME, Turner R 4th, Woodward BK, Brinjikji W, Lanzino G, Lylyk P. International retrospective study of the pipeline embolization device: a multicenter aneurysm treatment study. AJNR Am J Neuroradiol. 2015;36(1):108–15.
18. Meckel S, McAuliffe W, Fiorella D, Taschner CA, Phatouros C, Phillips TJ, Vasak P, Schumacher M, Klisch J. Endovascular treatment of complex aneurysms at the vertebrobasilar junction with flow-diverting stents: initial experience. Neurosurgery. 2013;73(3):386–94.
19. Cohen JE, Gomori JM, Moscovici S, Leker RR, Itshayek E. Delayed complications after flow-diverter stenting: reactive in-stent stenosis and creeping stents. J Clin Neurosci. 2014;21(7):1116–22.