The Off-Label Use of Flow Diverter

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Abstract

The Pipeline embolization device (PED) is the most widely used flow diverter in endovascular treatment of cerebral aneurysms. In 2011, the device received FDA of USA approval for the treatment of large and giant aneurysms in the internal carotid artery (ICA) extending from the petrous to the superior hypophyseal segments. As popularity of the device grew and neurosurgeons gained more experience, its indications were extended to complex wide-necked aneurysms located in the ICA with parent vessels between 2.0 and 5.0 mm in diameter approved by FDA in 2019. However,there are many types of aneurysms ouside this range are considered challenging to treat using the standard surgical and endovascular methods. The PED may be a promising alternative for these otherwise challenging lesions. The off-label uses of flow diverters include blister-like aneurysms, distal circulation aneurysms, posterior circulation aneurysms, previously treated aneurysms, acutely ruptured aneurysms, dissecting aneurysms, and pseudoaneurysms. We will discuss the safety and efficacy of the PED in these off-label uses in this chapter. The off-label use of PED has a reasonable risk-to-benefit profile for appropriately selected aneurysms.

Keywords

Flow diversion · Pipeline embolization device
Off-label uses · Cerebral aneurysms

The treatment of intracranial aneurysms has undergone a few very significant paradigm shifts in its history. Surgical clipping served as the initial basis for successful treatment of these lesions. And then the endovascular therapy arose from the desire to reduce the invasiveness of therapy. The Guglielmi detachable coil (GDC) was developed in the 1990s. This represented a significant paradigm change, aneurysms were occluded not by the clip preventing ingress of arterial blood, but by coils invoking thrombosis by the action of Virchow's triad. The International Subarachnoid Aneurysm Trial (ISAT) began in 1994 found better results with endovascular coiling compared to surgical clipping [1]. The risk of death at 5 years was significantly lower in the coiled group than it was in the clipped group (11% vs. 14%). There was an increased risk of recurrent bleeding from

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X. Lv (ed.), *Endovascular Surgery of Cerebral Aneurysms*,
https://doi.org/10.1007/978-981-16-7102-9_10

a coiled aneurysm compared with a clipped aneurysm, but the risks were small [2]. However, post-treatment aneurysm recanalization remains a major challenge. In one prospective, consecutive, multicenter European study consisting of 404 intracranial aneurysms in 390 patients treated with Nexus detachable coils (ev3-Covidien, Irvine, CA), complete occlusion was seen in 48% of aneurysms with a neck remnant in 22% and an aneurysmal remnant in 30% [3]. Much like in the context of surgical clipping, the morphology of an aneurysm and its proximity to other branches and perforators can pose unique challenges while planning for endovascular coiling. Aneurysms that are large (>10 mm diameter) and/or giant (>25 mm diameter), wide-necked (aneurysms with a dome-to-neck ratio of <2), and fusiform (aneurysms with no distinct neck, consisting of diffuse enlargement of a diseased vessel segment) are difficult to treat either by the endovascular or microsurgical treatment. The next significant paradigm shift after GDC is the remodelling technique by balloon and stent assistance. This technique facilitates improved packing density of the coils, reduces the risk of coil protrusion into the parent vessel, and stent-assisted coil embolization has empowered interventionists to tackle wide-necked/giant aneurysms. Initially, stent-assisted coiling was employed to prevent coil herniation into the parent vessel and allow denser packing of the aneurysm, which is known to correlate with a decreased rate of aneurysm recurrence and better long-term outcomes [4]. Computational fluid dynamics analyses suggested that placement of the stent in the parent vessel itself may alter flow within the aneurysm, potentially accelerating the rate of aneurysm thrombosis [5]. Thus, the idea of flow diversion was established, it was hypothesized that the stent disrupted blood flow from the parent artery into the aneurysm, and the stent provided a scaffold on which endothelial cells could grow, therefore isolating the aneurysm from the parent artery. Flow diverter (FD) needs to have greater metal coverage and decreased porosity, while maintaining pore density. A porosity of 70% is reported to be the ideal porosity for aneurysm occlusion [6]. It changed the pathophysiological understanding that many aneurysms do not in fact need to be completely occluded at the time of treatment. When reducing flow into and within the aneurysm, the aneurysm itself can either thrombose spontaneously or remodel. Advantage of flow diversions compared to traditional microsurgical or endovascular therapies is that aneurysms with no neck can be treated efficaciously, and the aneurysm itself, the most fragile part of the vasculature, does not need to be manipulated directly. As the paradigm of flow disruption, or hemodynamic decoupling, between "normal" vessel and "aneurysmal lumen," FD stents are now accepted as an integral option in the management of cerebral aneurysms.

In the 2010s, a single flow diversion stent was approved by the Food & Drug Administration (FDA) for use in the United States, the Pipeline Embolization Device (PED; ev3-Covidien, Irvine, CA). At the same time, Silk flow diverter (Balt Extrusion, Montmorency, France), Flow-Redirection Endoluminal Device (FRED; MicroVention, Inc., Tustin, CA), Surpass (Stryker Corp., Kalamazoo, MI), and p64R Flow Modulation Device (Phenox, Bochum, Germany) are commercially available in Europe, Asia, and South America. A new flow diverter of Nuva™ (TJWY Medical Company, Beijing, China) in a clinical trial will be launched soon in China (Fig. 10.1).

The PED is the first-generation flow diversion stent to achieve the optimum degree of stent porosity in a single device while being deliverable for the more tortuous intracranial vasculature. The PED has been supported by clinical trials, the Pipeline for Intracranial Treatment of Aneurysms

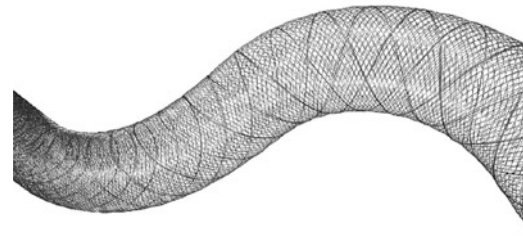

Fig. 10.1 Picture showing the Nuva™ flow diverter (TJWY Medical Company, Beijing, China)

Trial (PITA) [7] and the Pipeline for Uncoilable or Failed Aneurysms Trial (PUFS) [8] both demonstrated high complete aneurysmal occlusion rates (93.3% at 180 days and 86.8% at 1 year, respectively, increasing to 95.2% at 5 years for PUFS) as well as safety profile (6.4% major ipsilateral stroke in PITA and 5.6% major ipsilateral stroke or death in PUFS). In 2011, the FDA approved the PED for endovascular treatment in adults with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segment. After initial experience proved encouraging, it has been documented to have precipitated a significant change in practice pattern, confirming it as a disruptive technological advance [9]. As the popularity of the device grew and neurosurgeons gained more experience, its indications were extended. In 2019, FDA approved PED indications to complex wide-necked aneurysms located in the ICA attached to parent vessels between 2.0 and 5.0 mm in diameter.

PEDs implanted in ICA have been shown a low occlusion rate for the involved branches and the occlusion of side branches were clinically silent [10]. Supraclinoid internal carotid usage in unruptured aneurysms is the most accepted and is probably the least complication prone, due to the lower number of small eloquent branches with potential for occlusion. The flow diverter (FD) has become a separate entity from the stent, with a different purpose and set of indications. Nowadays, FD is being more broadly applied to blister-like aneurysm, distal circulation aneurysm, posterior circulation aneurysm, previously treated aneurysm, acutely ruptured aneurysm, dissecting aneurysm, and pseudoaneurysm.

10.1 Blister-Like Aneurysm

Blister aneurysms are a rare but well-recognized form of cerebral vascular lesions. Comprising less than 2% of all intracranial aneurysms [11], they are typically found on the dorsal or dorsomedial wall of the internal carotid artery (ICA). With a characteristic thorn-like appearance on angiography, blister aneurysms have the fragile wall, which not only reflects the unique pathology of these lesions but also predetermines their high rupture risk, aggressive clinical course, and tendency for rapid growth and progression. In the most common scenario, a blister aneurysm will be diagnosed after an episode of subarachnoid hemorrhage. Being initially small, it will substantially enlarge within days of presentation, reaching finally a shape much similar to that of its saccular counterparts [12]. Commonly, the end result is a rerupture with potentially catastrophic consequences for the patient.

Although most authors agree that blister aneurysms are either dissecting or false lesions, their optimal management remains unknown. The alternative treatment modalities for blister aneurysms are:

1. Reconstructive Techniques
   Surgery: Primary clipping (including encircling clips), wrapping, clip-wrapping, wrap-clipping, and direct suturing.
   Endovascular therapy: Primary coiling, stent-assisted coiling, telescopic stenting (stent-in-stent technique), and flow diverters.
2. Deconstructive Techniques
   Parent artery occlusion (PAO): Surgical or endovascular means with or without bypass surgery.

Management of blister aneurysms is associated with a high overall rate of mortality and morbidity [13]. The main causes for this include the small size and broad neck morphology along with the prominent fragility of such lesions, features that often lead to intra-procedural rupture when traditional surgical or endovascular techniques such as clipping or primary coiling are to be applied [13, 14]. Even if an initial intervention proves successful, subsequent regrowth requiring further treatment has been commonly reported [15]. Other factors contributing to the grim prognosis of blister aneurysms include a commonly grave clinical presentation as well as delays in an appropriate diagnosis.

Traditionally, surgery has been advocated as the first-line treatment. Primary clipping, wrap-

ping, wrap-clipping, or even carotid artery sacrifice (with or without a bypass) have all been tried. However, results have always been far from satisfying, often making neurosurgeons reluctant to operate on such cases. Ogawa et al. described an operative aneurysmal rerupture risk of 38% with direct aneurysm clipping, aneurysmal segment trapping, or aneurysm wrapping. Of this operative rerupture cohort, only 13% had good clinical outcomes, and 53% died as a result of surgery [12]. Other single-center series of open surgical management of ruptured blister aneurysms reported 55% and 41% operative rerupture rates, respectively [14, 16].

A meta-analysis including endovascular deconstructive parent-vessel occlusion treatment of ruptured blister aneurysms found a significantly higher procedural ischemic infarct complication of 29%, versus only 5% for endovascular reconstructive approaches with FD or for other endovascular methods, including stent-assisted coil occlusion, balloon-assisted coil occlusion, or overlapping placement of traditional intracranial stents, with similar rates of perioperative morbidity, and long-term good outcomes [17].

Initial attempts at endovascular reconstructive treatment with primary coiling of blister aneurysms have been disappointed also [18]. A high risk of intra-procedural rupture and coil protrusion or migration were problems commonly encountered due to the small size, their fragile nature, and difficult catheterization access to the sac without perforation [13]. Additionally, the lack of a true wall often allowed for posttreatment progression and rerupture [19]. As a consequence, most authors advocated that blister aneurysms are unsuitable for endovascular treatment and should therefore be left to surgery.

Stent-assisted coiling became the new trend in the field. The procedure is carried out either by first placing the stent and then introducing coils through its struts (trans-stent coiling) or by catheterizing the aneurysm sac and deploying the stent over the microcatheter prior to coiling (jailing technique). Facilitating stable intrasaccular coil deployment while at the same time reinforcing the underlying diseased arterial wall, stent-assisted coiling promised to provide a safe and reliable therapeutic alternative [20]. However, it was soon realized that results, even though better than those of surgery, were far from optimal. Intraoperative complications, mainly bleeding, were encountered in up to 17% of cases, while the risk for recurrence of the lesion, need for further treatment and postoperative repeat hemorrhage were reported at 65, 50, and 13%, respectively [13]. Most authors now use stent-assisted coiling as a preliminary means to achieve a certain degree of protection until definite treatments, in the form of some other techniques, can be instituted.

As blister aneurysms are regarded by many as pseudoaneurysms, FD is the only endovascular technique capable of actually reconstructing the vessel wall and sealing off any underlying defect [21]. This results in thrombosis of the lesion and effect augmented by endothelial proliferation along the length of the implanted stents. However, the off-label use of FD to treat ruptured blister aneurysms is associated with high rates of complete occlusion and good long-term neurological outcomes in most patients. Linfante et al. treated 10 patients with ruptured blister aneurysms of the supraclinoid ICA using a PED, which resulted in the immediate occlusion or near occlusion in 90%, and the follow-up DSA showed the 100% complete occlusion [22]. Of 62 ruptured blister aneurysms treated with FD in a recent meta-analysis, 86% achieved good clinical outcomes, and 17% suffered procedural complications including an almost 8% risk of procedural ICH [17].

Major concerns with the use of FD for the treatment of blister lesions include an even more prominent need for antiplatelets as well as the fact that such an approach does not guarantee protection from postoperative progression and rerupture. Regarding the latter, and despite reports of a marked decrease in intra-aneurysmal flow on the intraoperative already angiogram, hemodynamic stress upon the lesion theoretically remains at least for a few days [19]. The most serious problem that occurs after the placement of FD is the continued existence or growth of blister aneurysms. For example, in the 2016 report by Linfante et al., a blister aneurysm of the

supraclinoid ICA remained patent and tended to grow, despite the placement of three FDs in two procedures, but rerupture did not occur in this patient. However, the patient died of severe vasospasms, despite the administration of a dual antiplatelet regimen and growth of the lesion [22]. A valid alternative possibly addressing the whole issue is the combination of FD with coiling, which is my preference in practice. Figure 10.2 shows an acute ruptured blister aneurysm treated with PED recently. The initial plan was one PED with coiling in the sac. Two PEDs was deployed as the alternative to unstable cathetering in the aneurysm sac during the deployment of PED. Only one antiplatelet drug was used after the procedure since the bleeding existed after two PEDs telescopic stenting which was stopped by reversion of anticoagulation. Kim et al. have

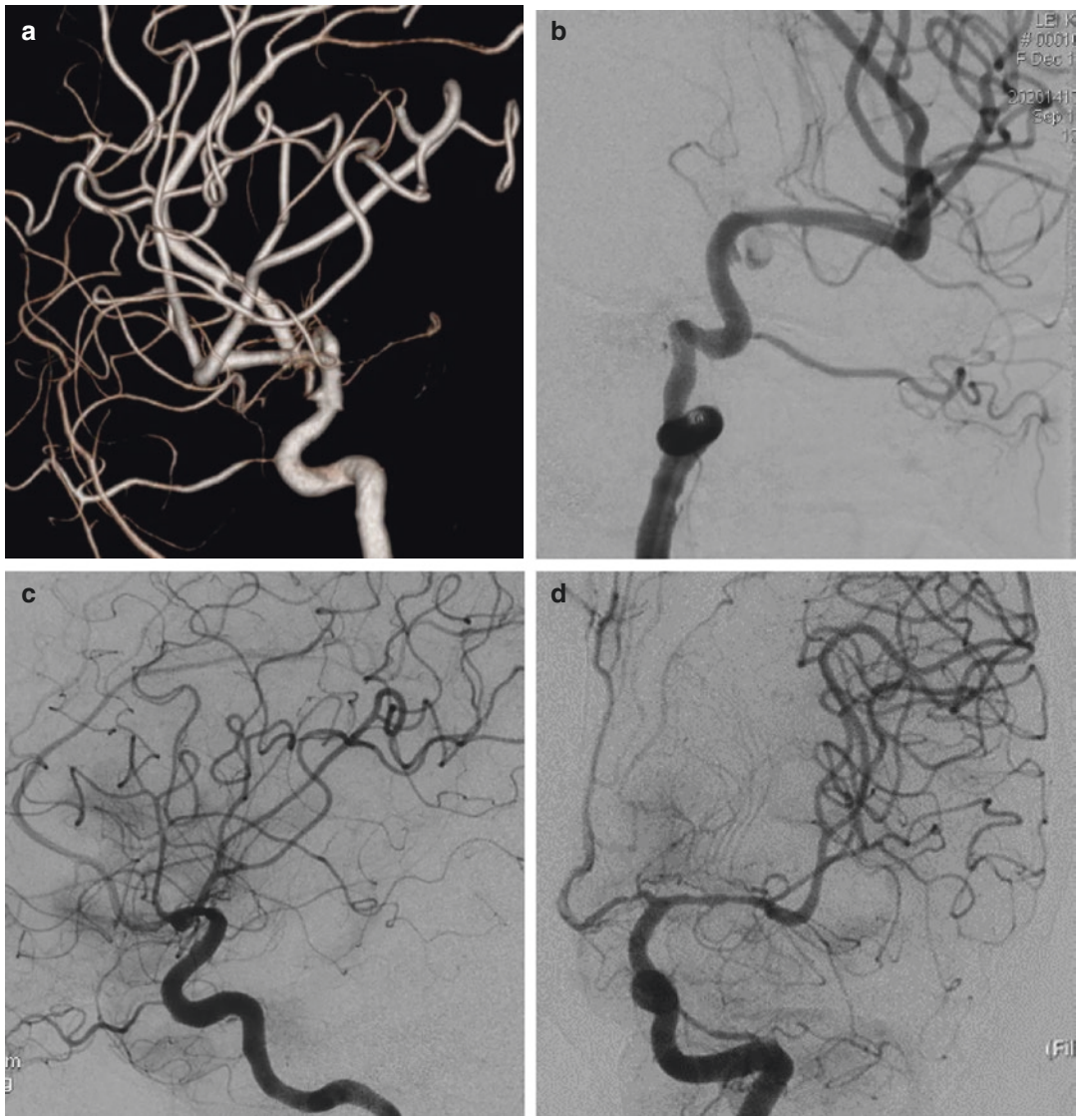

Fig. 10.2 A 27-year-old patient with ICA blister aneurysm ruptured (**a**) in poor grade SAH showed bleeding during treatment with 2 PED shield (**b**) and was stopped after reversion of heparin. Follow-up angiogram 6 days later showed aneurysm occlusion without in-stent thrombosis or occlusion of branch (**c**, **d**), even only a single antiplatelet with ASA was used without inhibitors of IIb/IIIa glycoproteins

reported favorable results with stent-assisted coiling as a primary treatment augmented by deployment of a second flow diverting stent if needed (i.e., postoperative progression of the lesion) [23]. In cases with extremely small lesions where coil deployment is perceived as carrying a significant risk, the reverse route can also be followed: telescopic stenting and subsequent transstent coiling should the lesion further grow to allow that [19].

During the past few years, clinicians' interest in blister aneurysm has been renewed with the introduction of endovascular modalities in everyday practice. Among all the different available approaches, FD seems lately to be gaining ground, showing promising results. Of course, until consensus has been reached, blister aneurysms are still to be treated on a case-by-case basis.

10.2 Distal Circulation Aneurysm

Distal cerebral circulation aneurysms may be defined as those located beyond the circle of Willis. They may be either saccular (at the level of bifurcations mainly), fusiform, or dissecting aneurysms. They are rare, representing approximately 1–9% of all intracranial aneurysms. Ruptured distal anterior cerebral aneurysms (DACA) cause intracerebral hemorrhage (in addition to SAH) in more than one-half of cases and are associated with worse outcome after rupture when compared with aneurysms in other locations [24]. Both microsurgical clipping and endovascular coiling of aneurysms of the distal cerebral circulation can be associated with high morbidity. Lahaska treated 258 ruptured DACA by clipping with 15% morbidity and 84 unruptured DACA clipping with 12% morbidity [24]. Meanwhile, complications associated with endovascular treatment of these aneurysms are not rare and probably related to a higher level of technical difficulty because of distal location, morphology (with frequent partial incorporation of the parent artery in the neck), and higher association with anatomic variations. These challenges may explain the relatively higher procedure-related complication rates compared with aneurysms in more common locations. Sturiale et al. reviewed 16 studies with 279 distal cerebral circulation aneurysms (185 ruptured) treated by coiling, procedure-related morbidity rate was 8% and mortality rate was 9% [25]. Thus, making FD a potentially attractive alternative. However, off-label use of FD in vessels smaller than 2.5 mm may be technically challenging, as these systems are stiffer and have a higher profile than conventional stents, and require larger caliber microcatheters, which can cause proximal spasm and inability to deliver the devices to the required distal location. The other potential concerns are vessel injury, acute stent thrombosis, delayed branch vessels occlusion, and in-stent stenosis.

Successful delivery of FD needs more robust and versatile catheter support systems. From this arose a newer generation of catheters, the distal intracranial catheters (DICs) or intermediate catheters (ICs), which are designed with the flexibility to safely travel further into the cranial circulation. Initial versions of these catheters, including Neuron (Penumbra, San Leandro, California, USA), helped move support systems from the proximal cervical circulation to the distal cervical vessels and proximal intracranial vessels [26]. The Navien (Medtronic, Minneapolis, MN, USA), with additional advances in catheter technology, allowed for the placement of 5-Fr and 6-Fr support catheters distal into the intracranial anterior and posterior circulations [27]. Further improvements in catheter technology have focused on atraumatic distal tracking, stability in distal position, and resistance to catheter deformation. The AXS Catalyst 5 distal access catheter (Cat5; Stryker, Freemont, CA, USA) is a novel multi-durometer intracranial support catheter [28]. And Syphontrak (Codman Neuro, Raynham, MA, USA) is the newest. Colby et al. have a series reports of their institutional experience with the DICs. Compared to earlier experiences with the Navien, both the Catalyst 5 and the Syphontrak cases utilized statistically significantly less fluoroscopy time, despite similar

numbers and sizes of PED. The last 2 DICs were routinely positioned in the distal cavernous ICA and even tracked the catheter to the supraclinoid ICA and M1 without evidence of vessel injury or significant flow-limiting vasospasm. In addition to serving as a support system, the DIC can also be used as an instrument or advanced technique for augmenting PED Flex deployment with the ability of tracking and pushing. DICs can be tracked over the 0.027″ microcatheter with ease to bump and foreshorten the proximal end of the PED Flex in order to improve vessel wall apposition if needed. The DIC also can be tracked over the microcatheter into the PED Flex for endoluminal access in cases needing multi-device deployments or balloon angioplasty. The use of verapamil was their institutional practice patterns to utilize IA vasodilation prophylactically rather than as a reactive measure to vasospasm [29]. And they used the Via (Sequent Medical/MicroVention; Terumo, Tustin, California, USA) microcatheter with its increased column strength and stiffness facilitated bringing the PED through regions of vessel tortuosity and deploying it predictably without the accordion effect of the Marksman in distal locations [30]. After successful delivery, PED can be deployed by more unsheathing rather than pushing to minimize the force buildup during deployment and mitigate the possibility of translating push force into wire perforation [31]. Another choice to improve delivery and deployment is low-profile FD, dedicated to small vessels, which have been lately developed. The first has been the small-sized version of the dual-layer Flow Direction Endoluminal Device (FRED) (MicroVention, Aliso Viejo, California), called FRED Jr. More recently, the P48MW Flow Modulation Device (Phenox GmbH, Bochum, Germany) has been launched. Both FRED Jr. and P48MW are delivered through a 0.021-inch microcatheter. Very recently, the Silk Baby Vista (Balt Extrusion, Montmorency, France) has been launched in Europe; this is the only FD delivered through a 0.017-inch microcatheter. During PED deployment, extreme attention has to be paid not to perforate small, distal branches with the inner wire as it is pushed forward while unsheathing the stent. FRED Jr. delivery wire is shorter and it remains inside the stent during its deployment, thus minimizing the risk of perforation; however, the drawback of this system probably is the inferior stability. Interestingly, the P48 inner wire can be moved independently from the implant, potentially improving safety and stability during deployment.

Heightened concern for acute stent thrombosis associated with PED deployments in small caliber vessels is justified. In the series of 67 PEDs deployed in 57 patients, Bender et al. found 5 cases (7.5%) of intra-procedural thrombosis in the stent, higher than in their overall experience with anterior circulation PED (4%), and treated successfully with escalating doses of intra-arterial abciximab [31]. The other institutions prefer alternative glycoprotein IIb/IIIa inhibitors such as eptifibatide or tirofiban because of their shorter half-lives [32]. The experience of Bender also suggests that platelet plugging may be more difficult to reverse in small caliber vessels. In their overall PED series of 30 patients treated with intra-arterial abciximab, only 4 (13%) went on to experience symptomatic ischemic infarcts. In the distal series, 2 of 5 patients (40%) had major strokes [31]. In Ravindran series, 5 patients (10%) experienced a transient parent artery occlusion immediately after FD deployment, resolved with intra-arterial glycoprotein IIb/IIIa inhibitor, with no clinical deficits experienced [33].

Heightened concern for symptomatic delayed stent thrombosis in distal small vessels is not justified. Several studies reveal asymptomatic in-stent stenosis with mild associated flow limitation in small vessels aneurysms treated with PED [31, 33, 34]. Significant reduction in parent vessel caliber at the proximal end of the stent but not the distal end of the stent was found in Bender series. They believed that there was a tendency for the device to adopt a similar diameter across its length in small vessels, and was restricted by the smaller (typically distal) vessel diameter and results in a greater reduction in the larger (typically proximal) diameter [31].

However, the risk of perforator stroke secondary to FD coverage of perforator-rich arterial seg-

ments, particularly the A1 and M1, has thus largely dissuaded the use of FD for aneurysms at these locations. In Ravindran series [33], 76.1% aneurysms had associated perforator vessel coverage by the FD, and 88.9% bifurcation aneurysms with side branch coverage. Despite this situation, there were only 3 complications related to perforator or side branch coverage, and all neurologic deficits were transient. These results suggest that it is safe to cross side branches with the FD. In MCA bifurcation aneurysms treated with FD, the risk of cortical infarction secondary to bifurcation branch coverage seems to be subclinical. In Iosif et al.'s study of MCA bifurcation aneurysms, although angiographic narrowing or occlusion of covered branches was observed in 29 of 63 patients at 6-month follow-up, only 2 cases of branch occlusion were symptomatic. Furthermore, at 12-month follow-up, only 10 cases of branch narrowing were observed, all of which were asymptomatic [35]. In my practice on distal aneurysm treated with PED, only one case was found late occlusion of the covered branch (Fig. 10.3) but no symptom.

With the 4.5% major stroke and 1.5% mortality, complete occlusion was observed in 42 (89%) cases of Bender's study at on average 10 months after embolization [31]. Occlusion outcomes of other studies from 77.8% to 100%, are similar to the aforementioned small-caliber vessel series [33, 36, 37].

Antiplatelet therapy decisions to balance thromboembolic and hemorrhagic risk are always challenging, perhaps more so when treating aneurysms arising from small vessels. In our institute, P2Y12 test is performed routinely for all patients undergoing PED and adjust antiplatelet regimens based on its results. Meanwhile, some authors do not test P2Y12 routinely. Bender et al. reported the largest series of clopidogrel hyporesponders (P2Y12 > 200) to undergo PED, in which rates of ischemic complications are on a par with the overall PED literature (2/52 cases, 4%) [38]. However, given the increased risks of acute stent thrombosis, this population may be appropriate for clopidogrel alternatives, such as prasugrel and ticagrelor, with more predicable pharmacodynamics.

FD for distal circulation cerebral aneurysms represents a safe and effective application of flow diversion technology. The small-vessel PED delivery and deployment technique differs from its on-label use in ICA. Improvements in robust polyaxial catheter access platforms have facilitated the use of FD in the distal location of cerebral artery. Heightened vigilance for the prevention and management of acute stent and vessel thrombosis is warranted in these cases. Despite the distal location, issues related to vessel trauma and delayed occlusion are uncommon and should not limit use of this technique.

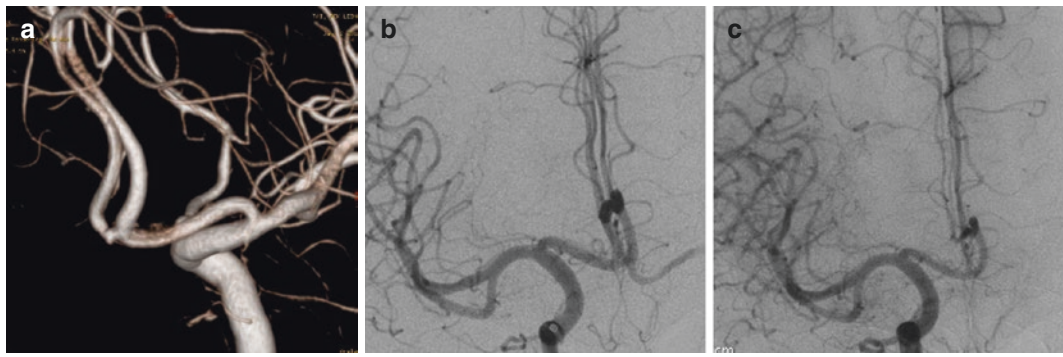

Fig. 10.3 A 66-year-old patient presented with SAH and the first angiogram negative, follow-up angiogram 2 weeks later revealed anterior communicating artery blister aneurysm (**a**), which was treated with PED deployed from right A1 to left A2. Aneurysm was occluded immediately with distal ACA patent (**b**). A follow-up angiogram 27 months later revealed the asymptomatic occlusion of right A2 (**c**)

10.3 Previously Treated Aneurysms

Conventional therapies for intracranial aneurysms are microsurgical clipping and endovascular coiling. Two randomized, controlled trials have evaluated these 2 methods and looked at recurrence and retreatment rates. In the International Subarachnoid Hemorrhage Trial (ISAT), 9.0% of patients treated with coiling and 0.85% of patients treated with microsurgical clipping had to be retreated due to recurrence [39]. In the Barrow Ruptured Aneurysm Trial (BRAT), the retreatment rates at the 3-year follow-up were 13% and 5% for coiling and clipping, respectively [40]. To reduce the recurrence associated with conventional treatments, several investigators have studied the safety and efficacy of the FD as a treatment for recurrent aneurysms after previous coiling, stenting, or clipping. Dornbos III et al. reviewed a total of 13 cases in which patients underwent secondary placement of a PED for aneurysm recurrence following prior treatment with another modality. The PEDs were used to treat aneurysm recurrence or residual following endovascular coiling in 7 cases, FD in 2, and microsurgical clipping in 4. The rate of complete occlusion was 80% at 6 months and 100% at 12 months in these patients who underwent PED placement following failed endovascular coiling; there were no adverse clinical sequelae at a mean follow-up of 26.1 months [41].

Daou et al. looked at subsets of patients with recurrent aneurysms that were previously coiled and previously stented [42, 43]. One study followed 32 patients with single lesions who had a recurrence of previously coiled aneurysms, and found a total rate of complete and near-complete occlusion of 86.7%, a complication rate of 3%, and no mortalities [42]. In a series of 21 previously stented aneurysms, the complete occlusion rate after PED placement was found to be 55.6% and the complication rate was 14.3% [43]. In this second study, the authors compared these results with a group of patients who underwent PED placement for aneurysms not previously stented. They concluded that the PED was less effective in managing previously stented aneurysms compared with non-stented aneurysms, and can also be associated with a higher complication rate in the previously treated aneurysms. Similar result was found in a series of 20 patients with recurrent aneurysms successfully treated with PED in the presence of preexisting stents, both FD and reconstructive stent. Cases with in-dwelling stents present additional technical challenges, as evident from the greater number of devices used, longer procedural time, higher radiation exposure, and balloon angioplasty rate. Salvage FD offers a good chance of occlusion (56% complete occlusion at on average 13-month follow-up angiography) with acceptable complication rates (10%), including 1 mortality (5%) [44].

In our institute, FD placement is the first choice for recurrent aneurysms not previously stented (e.g., the case in Fig. 10.4), but re-coiling is a preference to aneurysm treated with stent-assisted coiling previously since technical challenge of a salvage FD case revolves around the indwelling stent. In Fig. 10.5, the recurrent case after 3 times coiling performed the flow diversion and achieved complete occlusion finally.

The indwelling stent poses an obstacle both to delivery and deployment. Given the large cell size and the proximal tines at the parent vessel wall, it can be difficult to stay in the true lumen while navigating across an indwelling stent. A FD deployed through a cell in an indwelling stent will initially appear to have a restricted opening. In addition to hypervigilance for any catching of the wire while crossing the indwelling stent, techniques that can be used to ensure deployment within the lumen of the parent vessel include: crossing with a J-tip wire, compliant balloon inflation following crossing, and visualization on DynaCT after crossing. Crossing an indwelling stent is more difficult when the proximal end/stent tines are located in a vessel bend, such as the anterior genu. The indwelling stent also creates challenges during FD deployment, given the risk of catching on the distal end of the indwelling device and anchoring the device to be implanted, leading to stretching and incomplete opening of the device. It should be deployed directly in its final location and rely more on balloon angioplasty for device opening instead of the drag and drop tech-

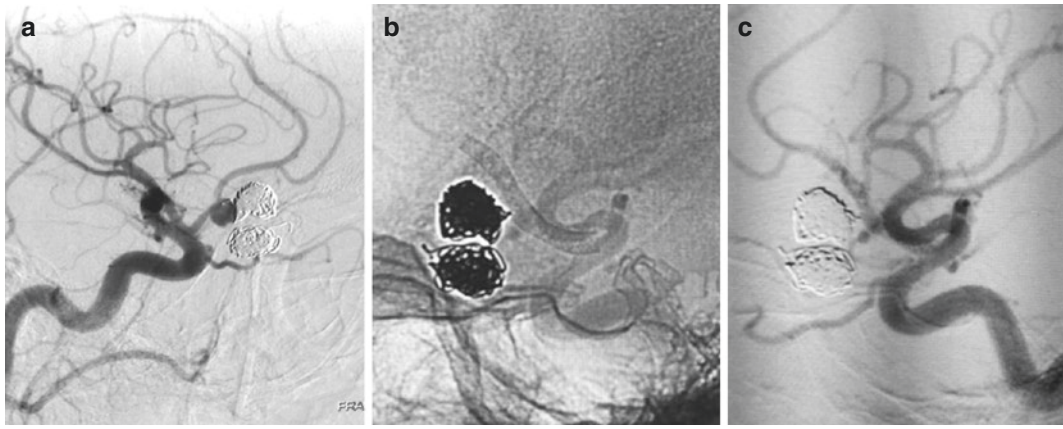

Fig. 10.4 A 40-year-old patient presented with recurrent A1 aneurysm after coiling (**a**), retreated with 1 PED (**b**). Follow-up angiogram showed complete occlusion 6 months later (**c**)

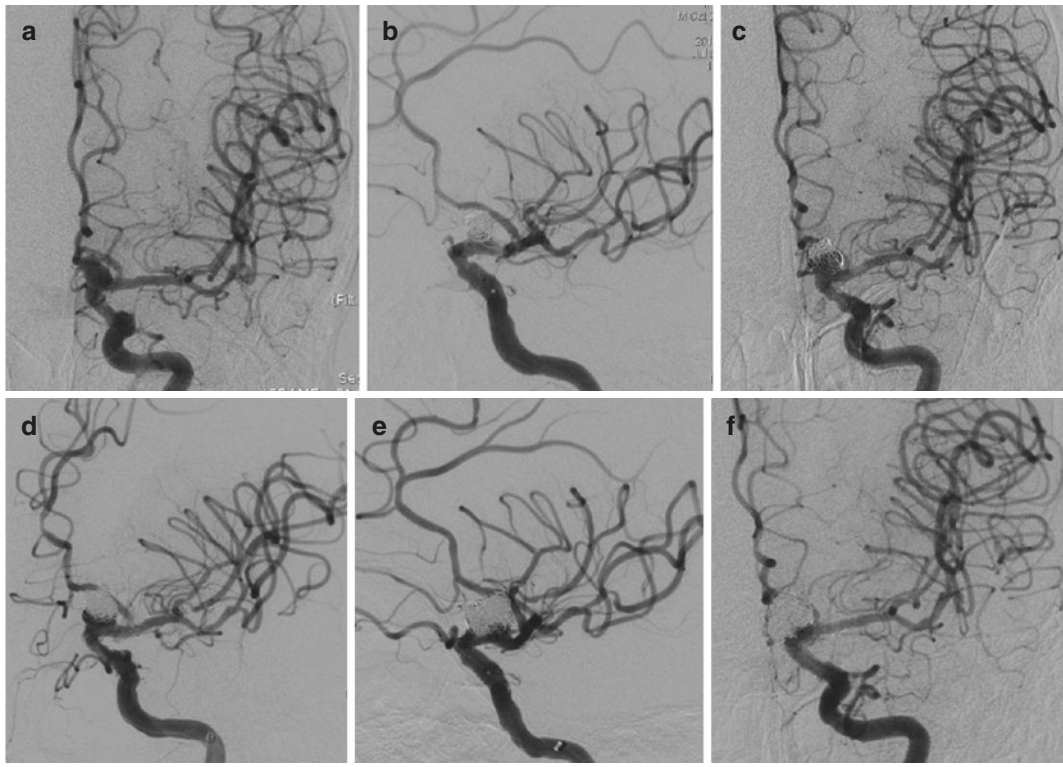

Fig. 10.5 A 73-year-old patient with left ICA asymtomative wide neck aneurysm (**a**), performed stent-assisted coiling first (**b**). Angiogram 9 months later revealed the enlargement of aneurysm, retreatment was performed with coiling (**c**). Follow-up angiogram another 6 months later showed the enlargement again and third coiling performed (**d**). Retreatment with flow diversion 6 months after the third coiling with neck residue (**e**). Final angiogram 27 months from the first treatment showed the complete occlusion (**f**)

nique. The rate of balloon angioplasty in salvage cases was 40% as compared with 13% in all anterior circulation PED cases [44].

A common mechanism of aneurysm persistence after FD is malapposition between the stent and vessel wall, which allows blood flow to insin-

uate between the stent and vessel, continuing to fill the aneurysm, a so-called "endoleak" [45]. The risk of endoleak is greater in salvage FD cases given how a poorly endothelialized preexisting stent may prevent contact between the newly placed FD and vessel endothelium. So the new FD should be deployed to cover the preexisting stent both proximally and distally in salvage cases. Following successful deployment of salvage PED, heightened thrombogenicity of the multi-stent construct is a concern at every follow-up time point. Fischer et al. observed that placing one stent inside another will always delay the endothelialization process and that extended or lifetime DAPT should be considered for these patients [46].

In another more difficult series, PED retreatments were performed for 6 anterior communicating artery region recurrent aneurysms after surgical clipping. Occlusion rate was 83% without complication [47]. Promising results were found in a series of 24 patients who underwent PED placement for previously clipped and coiled aneurysms. The complete or near-complete occlusion rates of previously treated ruptured and unruptured aneurysms were 94.4% at 6 months and 93.3% at 12 months. These investigators also did not observe any severe procedure-related complications [48].

Safety and effectiveness of FD as a salvage treatment following failed coiling or clipping was confirmed in these limited series. Positive results suggest that ruptured complex aneurysms might be deliberately treated 2 times: immediate subtotal coiling (with or without balloon assistance) and planned flow diversion after the acute phase. This strategy will be discussed in detail in the following chapter "Ruptured Aneurysm." FD treatment results for recurrence of previously stented aneurysms are not encouraging, the presence of a stent raises technical challenges. Retreatment is reserved for recanalized stent-coiled aneurysms with a history of prior rupture or progressive symptoms, typically from mass effect. By contrast, retreatment of previously FD treated aneurysms is commonly for persistence or failure to occlude and occasionally for device foreshortening. Continued patency of aneurysm following coverage by FD is dependent on several factors, including the degree of metal coverage, device-to-wall apposition, thrombogenic disposition of the patient, degree of individual intimal reactivity. Given the perceived ease of re-FD some authors have a low threshold for retreatment [45]. Since occlusion outcomes continue to accrue for up to 5 years after PED placement, some authors wait to complete DPAT tapering and have performed re-FD cases at an average of 18 months after the first procedure [44]. There is a need for larger studies to assess the safety and efficacy of the FD in treating such cases.

10.4 Posterior Circulation Aneurysms

Posterior circulation aneurysms are a heterogeneous disease group including sidewall, bifurcation, dissecting, saccular, and fusiform aneurysms. The natural history of the different aneurysm types is not well known. As compared with anterior circulation aneurysms, there is a higher proportion of non-saccular morphologies, which commonly present with a variety of different symptoms ranging from asymptomatic and incidental findings on routine imaging, posterior circulation ischemic strokes, brainstem compression, cranial nerve palsies (most commonly V–VIII), obstructive hydrocephalus, and hemorrhage [49]. The natural history of these lesions is fateful with a review by Shapiro et al. suggesting that mortality could be even higher at 43% [50]. If left untreated they carry significant morbidity with growth of these aneurysms seen in 46% of patients over a median interval period of 8.5 years [49]. Saccular aneurysms of the posterior circulation are at higher risk of rupture than their anterior circulation counterparts and, when ruptured, present in worse clinical grade. In the International Study of Unruptured Intracranial Aneurysms (ISUIA), the rupture rate for posterior circulation aneurysms >7 mm was 3–10% a year [51]. This creates an impetus toward elective treatment, but existing treatments are limited by morbidity and efficacy. Surgery for these lesions—because of the deep exposure and proximity of cranial nerves

and perforating arteries—carries high morbidity [52, 53]. Endovascular coiling has lower morbidity but comparatively inferior occlusion outcomes [54]. Residual posterior circulation aneurysms remain at significant rupture risk and retreatment of these lesions is technically challenging.

The off-label use of FD may be an alternative for these challenging lesions that avoids high morbidity of open surgery while sufficiently excluding the aneurysm. However, overall poor outcome or death was seen in 40% of patients treated for fusiform posterior circulation aneurysms in a large series [55]. A similar trend has been described in a meta-analysis of intracranial FD, which included 29 reports, 1451 patients and 1654 aneurysms. Ischemic strokes and perforator infarctions were significantly higher in the posterior circulation, although there were no difference in subarachnoid hemorrhage and intracranial hemorrhage rates [56].

The main risk factor of the FD treatment in the posterior circulation is due to the unique characteristics of the cerebral vasculature and aneurysms arising in this location. Specifically, numerous unforgiving perforator vessels arise in this area and supply brainstem structures; the occlusion of these perforators can lead to significant disabilities. It is generally believed that covered branch arteries will remain patent provided that flow is maintained through the FD. One theory is that demand phenomena continue to draw blood into the covered branch. Phillips et al. assessed the safety of PED placement in 32 patients with posterior circulation aneurysms. The aneurysm occlusion rate achieved 96% of patients followed up more than 1 year. But perforator infarctions rate was 14% of the 21 patients who had basilar artery aneurysms. Clinical perforator infarction rates may be higher when the PED is placed within the basilar artery compared with the ICA [57]. More recent studies have demonstrated good outcomes with FD. Munich et al. present good outcomes in 12 patients with vertebrobasilar fusiform aneurysms treated with the PED. The complete aneurysm occlusion rate was 90% without thromboembolic complications [58]. None of the patients in Marcus series developed flow restriction of a covered PICA with one PED positioned proximal to the vertebrobasilar junction in 10 of 11 patients. Only 1 patient experienced a PICA occlusion during PED placement and developed an associated region of diffusion restriction on postoperative MRI [59].

The patient shown in Fig. 10.6 presented with right cerebellum infarction, angiogram 1 month later revealed the fusiform aneurysm involved PICA. Flow diversion was achieved with PICA patency at the angiogram after 1 PED was deployed to cover the PICA origin. Dual antiplatelet treatment was stopped 1 year later when angiogram showed complete occlusion of aneurysm with PICA patency. The patient had been follow-up for 3 years without any thromboembolic complications. Strict adherence to adequate platelet inhibition to avoid thromboembolic complications and also vigilant monitoring of patients receiving antiplatelet therapy to avoid hemorrhagic complications.

The other risk factors are multiple overlapped PEDs inserted, clopidogrel resistance, poor apposition of the PED to the aneurysm wall, aneurysm morphology, size, and clinical presentation. Natarajan et al. used an average of 1.7 devices to treat 12 posterior circulation aneurysms with an average size of 13 mm and encountered 1 major complication, a pontomedullary infarct attributed to occlusion of a distal vertebral perforating artery [60]. In contrast, poor result was found in their previous report on 6 patients who underwent PED treatment: 4 (66%) were basilar fusiform aneurysms and 3 had pretreatment strokes as demonstrated by MRI. An average of 5.3 ± 2.9 PEDs without adjunctive coiling were used resulted 83.3% brainstem ischemic events and 33% aneurysms reruptured. During the follow-up period, 4 patients (67%) died, 1 was disabled with mRS score 5, only 1 recovered to mRS score 0 [61]. The author attributed these improved results to the following factors. First, basilar fusiform aneurysms and pretreatment ischemic infarction patient was excluded; second, critical attention to the antiplatelet regimen; third, the number of PED was limited; final, adjunctive

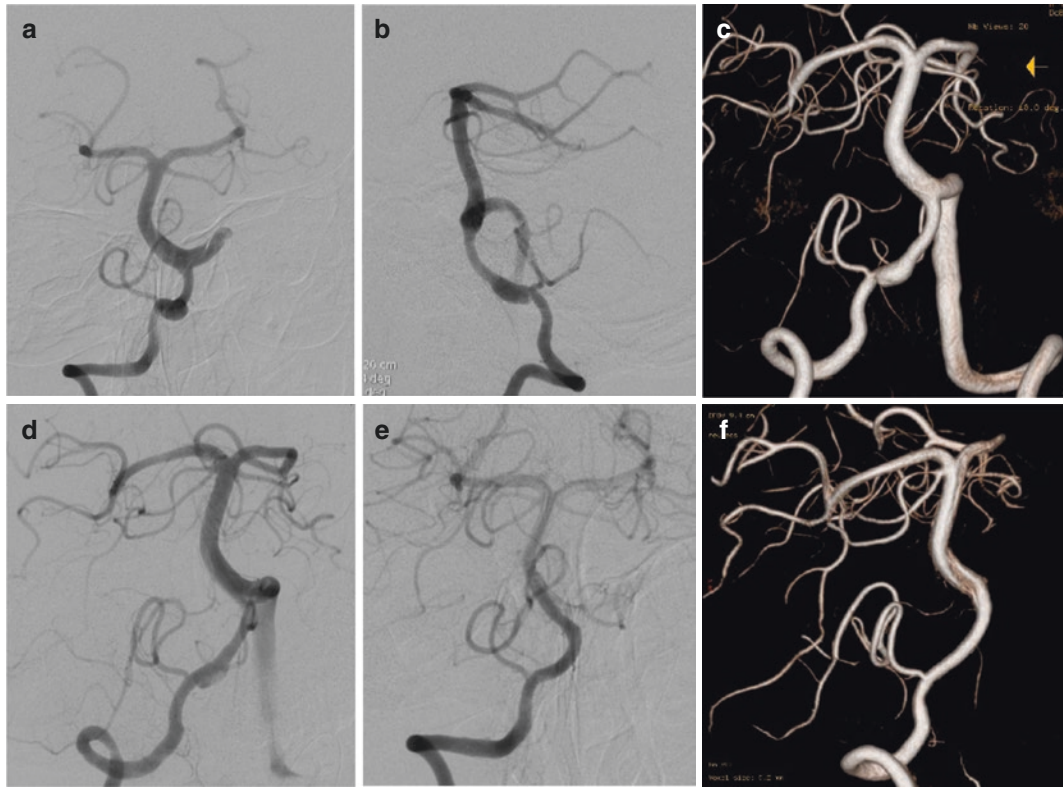

Fig. 10.6 A 43-year-old patient presented with right cerebellum infarction, angiogram 1 month later revealed the fusiform aneurysm involved PICA (**a**–**c**). Flow diversion was achieved with PICA patency at the angiogram after 1 PED was deployed to cover the PICA origin (**d**). Follow-up angiogram 1 year later showed complete occlusion of aneurysm with PICA patency (**e**, **f**)

coiling with FD in the most saccular component of the aneurysm, served as a scaffold to organize thrombi [60]. Bender et al. present the large single-center experience about 59 embolization procedures performed on 55 patients. Morphology was saccular (45%), fusiform (29%), or dissecting/pseudo-aneurysms (25%). Most of the aneurysms (62%) arose along the vertebral artery. 1 PED was placed in 85%; and coiling was performed in 17% of cases. Complete occlusion rate was 78% at 12 months with 8% complications (all stroke). Fusiform or dissecting morphology and large or giant aneurysm size were predictors of aneurysm persistence on multivariate logistic regression. The resolutions of reduced ischemic risk were as follow: first, in the distal basilar artery, the degree of metal coverage was titrated by using devices with relatively short length and oversized diameter to reduce perforator infarction; second, maintain systemically heparinized for 24 h post-embolization and on dual antiplatelet treatment for life (Prasugrel was used rather than Clopidogrel for basilar apex-region aneurysms); Third, single device was used whenever possible, choosing longer and large diameter devices in the fusiform segment, and adjunctive coiling to expedite occlusion rather than telescoping multiple devices [62].

The most difficult and risky morphology in posterior circulation aneurysms with FD treatment is nonsaccular aneurysms. Occlusion rates were lower (57% at last follow-up) in a large single center series focused on the nonsaccular aneurysms [63]. The aneurysms were classified as either dolichoectatic, fusiform, or transitional according to the classification of Flemming et al., with the definition of each subtype based on the following imaging appearance [49]:

1. Fusiform: Dilation >1.5 times normal involving a part of the vertebral or basilar artery, without any discernible neck and with any degree of tortuosity (Fig. 10.7).
2. Dolichoectatic: Uniform dilation >1.5 times normal involving the entire basilar artery, vertebral artery, or both with any degree of tortuosity (Fig. 10.8).
3. Transitional: Uniform dilation of an entire arterial segment >1.5 times normal involving the vertebral artery, basilar artery, or both with a superimposed dilation of a portion of the involved arterial segment (Fig. 10.9).

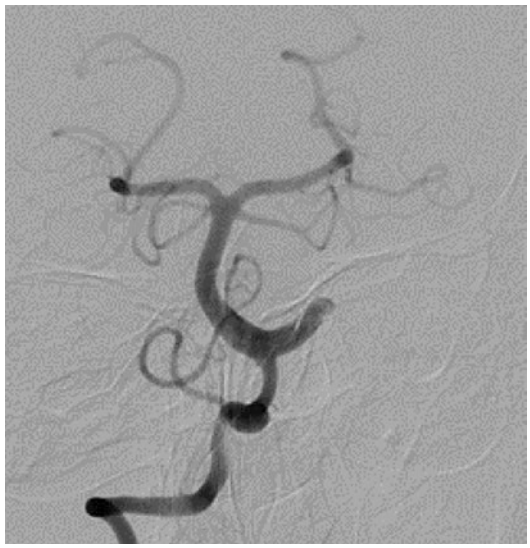

Fig. 10.7 A patient with fusiform aneurysm of the right vertebral artery presented with ischemia attack

In this cohort, the transitional and fusiform types were more likely to be symptomatic and dolichoectatic aneurysms appeared more benign in clinical course. The annual risk of rupture for fusiform and transitional aneurysms was 2.3% while that of dolichoectatic aneurysms was 0.4%. Compressive symptoms were seen in 22% of patients and importantly, 7.5% who did not initially have compressive symptoms developed them. Aneurysm growth was associated with the development of compressive symptoms, which was statistically associated with the transitional and fusiform subtypes, and also affects mortality, with a 5 year 56.6% mortality of enlarging aneurysms compared with 3.7% of stable aneurysms [64]. Given the prognosis, it is no wonder then that management options have been aggressively sought. The author believed that early management prior to infarction or compressive symptoms was extremely important to achieve a good clinical outcome. Strict antiplatelet regimen was also important to avoid in-stent thrombosis or thromboemboli. And direct oral anticoagulants (2 × 100 mg dabigatran daily) were added for patients with large fusiform or transitional type aneurysms involving the basilar trunk. Adjunctive

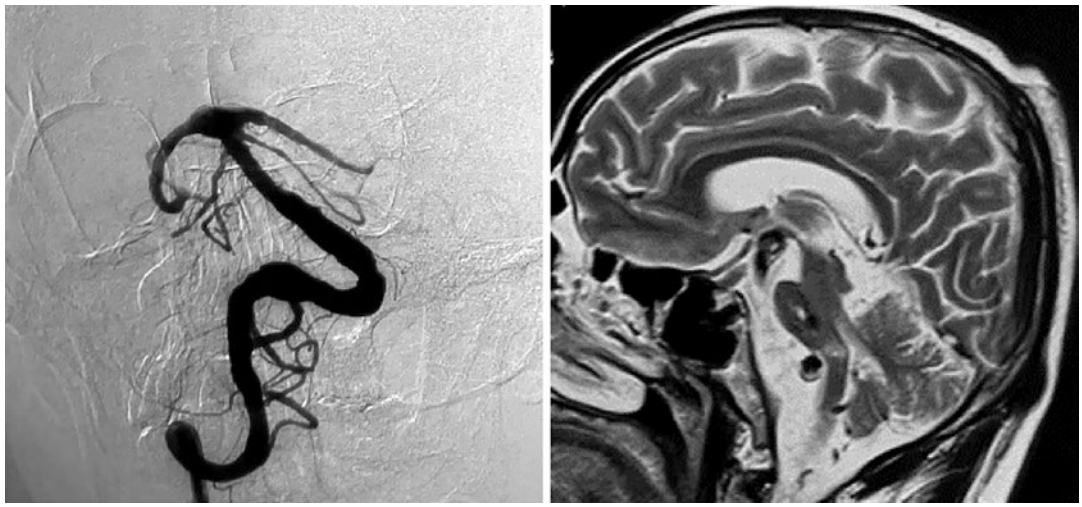

Fig. 10.8 A patient with dolichoectasia of the vertebrobasilar artery presented with symptoms of compression of brain stem. MRI revealed the compression of brain stem without mass

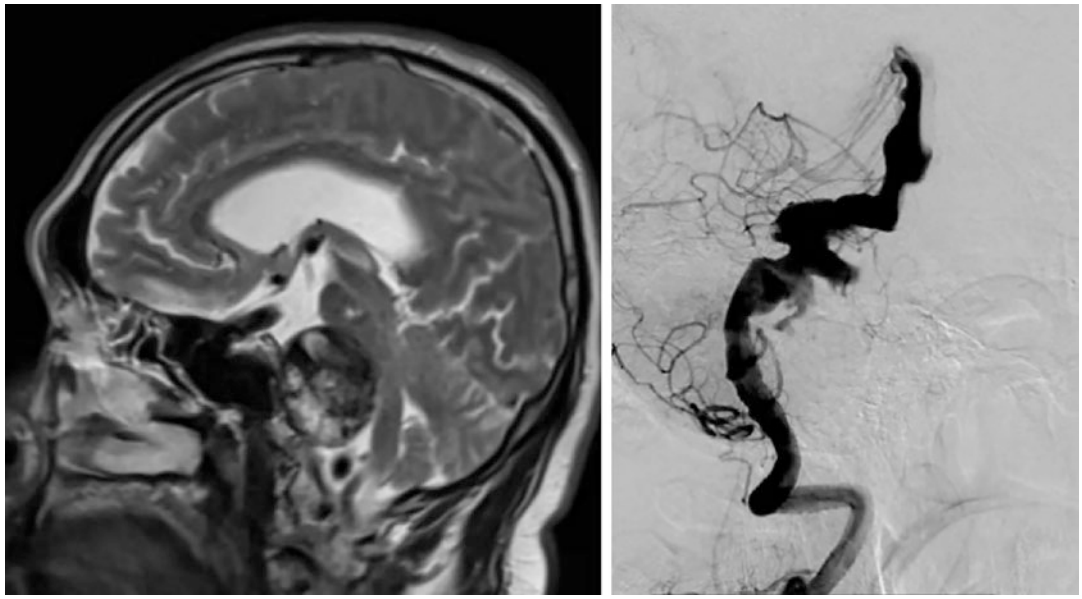

Fig. 10.9 A patient presented with symptoms of mass effect from vertebrobasilar transitional aneurysm. MRI revealed the partially thrombosed and superimposed dilation portion of basilar artery with compression of brain stem

coiling may be useful but did not appear to be necessary and needed to be based on individual anatomy. The number of FD required was based on the longitudinal extent of the disease. Because endothelialization commences from the site of contact with the parent artery, it was important to land the FD in a portion of the vessel that demonstrates a normal appearance, both at the proximal and at the distal end. And longer diseased segments will require a much longer time to endothelialize. This means that a tailored approach is required with some patients likely to require lifelong dual antiplatelet therapy (DAPT). The author prefers telescoping from proximal to distal with about 30% overlap of the implanted FD. The diameter of the most proximal stent should be slightly larger than the diameter of the landing zone. Subsequent FD should have the same or larger but never smaller diameters, since smaller diameters will result in FD displacement. Since the PED for less and p64 for more coverage, a combination of PED and p64, devices with nonmatching braiding patterns, will result in more coverage than telescoping of devices of the same kind. The procedure is usually stopped as soon as a hemodynamic effect becomes visible through repeated catheter angiography. The patient returns for repeat angiography and MRI after approximately 6–12 weeks to observe for flow changes and changes in size of the aneurysm. If no significant flow redirection has occurred compared with the pretreatment angiography, then more FDs are placed inside the construct. Gradual vessel reconstruction obviously allows for the development of collateral brain stem circulation, eventually with no opacification of pontine basilar artery branches but without signs of brain stem ischemia, neither clinically nor MRI. In conclusion, gradual adaption of the local circulation through staged FD implantation, confirmed DPAT, and mild oral anticoagulation is key. Disease of the basilar trunk and disease that crosses the vertebrobasilar junction can be the most difficult to treat. In addition to the FD, coil occlusion of the contralateral vertebral artery is required to prevent a persistent endoleak around the FD. The author proposes early treatment prior to the development of symptoms and when the maximum diameter and length of the diseased segment is minimized. Both transitional and fusiform aneurysmal subtypes should be managed aggressively given their poor prognosis; however, a "watch and wait" strategy could be used for dolichoectatic disease with treatment commenced as soon as enlargement is seen.

As mention above, there is significant variability in mortality, permanent new morbidity, and occlusion rates of posterior circulation aneurysms treated with FD. These studies have several limitations. Interpretation of the results is difficult owing to heterogeneity of the patients and aneurysms, relatively short follow-up, retrospective analysis, and relatively small total numbers. One of the important observations from the overall outcomes is that mortality and morbidity appear to be higher with symptomatic aneurysms. This poses a difficult clinical dilemma, because, reasonably, physicians feel obliged to offer treatment when symptoms are present to prevent further decline. Unfortunately, it is not known what percentage of the incidentally discovered asymptomatic aneurysms would go on to become symptomatic over time. The challenging question is whether it is worth considering treating asymptomatic posterior circulation aneurysms earlier when they may be a lower treatment risk, or waiting to treat until they become symptomatic, less stable, and the risk of intervention is greater. The other finding is in line with prior opinions that fusiform basilar aneurysms have the highest treatment risks, probably owing to extensive involvement of perforators. These aneurysms have unfavorable characteristics for any treatment, including FD. The fate of small perforator arteries is difficult to predict. There is no good understanding of the dynamics of aneurysm thrombosis around FD stent in a large and elongated fusiform vessel segment. In particular, increased distance from the device wall to the perforator vessel origin seems to be very important. The other risk factor is higher number of stents, probably owing to overlapping coverage of the small perforators, more metal and foreign body presence, increased risk of ischemic events, and longer procedure times. An important component of preventing perforator infarcts or other ischemic complications is the strict adherence to the obligatory DAPT. Noncompliance is a rare, but dreaded problem in patients with intravascular stents. Life-threatening consequences should be explicitly discussed with the patient and family before proceeding with FD treatment. The use of antiplatelet inhibition testing appears important and provides guidance about the effect of treatment; however, significant thrombotic or hemorrhagic events may still occur despite adequate testing. Extended follow-up of previously treated patients will be valuable to better understand the long-term risks and benefits of FD.

There is usually a significant dilemma about treatment indications for these challenging aneurysms, which clearly have an unfavorable natural history, and also, an increased risk of treatment. In most large tertiary care centers, intervention is usually considered necessary if new symptoms develop, and/or there is evidence of change in morphology over time, prior hemorrhage, expansion, or progressive posterior circulation mass effect.

Newer-generation devices and computational flow dynamic models may help in tailoring treatment to individual patients in the future. Further prospective data are necessary to assess the role of FD in the posterior circulation.

10.5 Acute Ruptured Aneurysms

Endovascular management of ruptured intracranial aneurysms is well established. However, broad necked or giant saccular, fusiform, or blister aneurysms pose specific challenges for conventional endovascular treatments. These aneurysms may also pose challenges for microsurgical clipping. Few options are available for the safe and effective treatment of this subpopulation of ruptured intracranial aneurysms. In these aneurysms, the use of stent-assisted coiling or FD may be a viable treatment strategy. However, there is understandable resistance to the use of intravascular stents for aneurysmal subarachnoid hemorrhage (aSAH), owing to the risks of thromboembolic and hemorrhagic complications. DAPT reduces the risk of the former at the cost of increasing the risk of the latter. When treating aSAH, multiple additional intracranial procedures may be required, such as external ventricular drain (EVD) placement, ventriculoperitoneal (VP) shunt insertion, or decompressive craniotomy for hematoma evacuation. These subsequent surgeries can be complicated by DAPT that is required in conjunction with FD placement. In addition, placement of FDs like the

PED results in gradual rather than immediate thrombosis of the aneurysm, which may increase the risk of aneurysm rerupture in the acute phase of aSAH.

As mentioned previously in the treatment of ruptured blister aneurysm, flow diverse technique resulted in the immediate occlusion or near occlusion in 90%, and the follow-up DSA showed the 100% complete occlusion [22]. Of 62 ruptured blister aneurysms treated with FD in meta-analysis, 86% achieved good clinical outcomes, and 17% suffered procedural complications including an almost 8% risk of procedural ICH [17]. A recent meta-analysis of 20 studies including 233 patients treated with FDs for acutely ruptured aneurysms reported an almost 90% rate of total or subtotal occlusion at a mean of 9.6 months and although the immediate occlusion rate was only 32%, the rerupture rate was nonetheless low at 4% suggesting that aneurysmal rerupture is not a significant concern with the use of FDs despite the persistent filling. The overall complication rate was 18% with 7% treatment-related morbidities and comparable rates of hemorrhagic and thromboembolic complications [65]. The results suggest an excellent efficacy but higher complication of FD for the management of acutely ruptured aneurysms. VP shunt-related ICH rates of up to 71% have been reported in patients concomitantly treated with dual antiplatelet agents after stent-assisted aneurysm coiling [66]. A matched cohort pilot study by Paisan also found that significantly longer time interval between presentation with aSAH and shunt placement in the DAPT cohort, which reflect the reluctance of practitioners to perform surgical procedures on this subset of patients [67]. However, the same study revealed that patients receiving DAPT after the stent-assisted coiling of acutely ruptured aneurysms did not have an increased risk of shunt-related complications or unfavorable long-term functional outcomes compared to endovascular treatment without DAPT. Another series including 80 aSAH cases with VP shunt found in patients who performed stent-assisted coiling or FD treatment, there was an elevated risk (22% vs 2%) for VP shunt-associated radiographic hemorrhage, but the risk of clinically significant hemorrhage was low (3%) [66].

Given the Iatrogenic hemorrhage complication relative to DAPT, there is considerable debate on the ideal timing of FD placement. Some experts recommend early flow diversion (less than 2 days from SAH ictus) [68, 69], while others advocate for delayed treatment (2–14 days from SAH ictus) [70, 71]. However, the meta-analysis of 13 studies with 142 patients did not show a difference in overall complication rate (primary outcome) between early vs. delayed FD for ruptured aneurysms [72]. Early treatment for blister or dissecting/fusiform aneurysms was associated with a low complication rate in comparison to saccular aneurysms. Given the high risk of rerupture and subsequent mortality from primary FD for large, saccular ruptured aneurysms, acute coiling followed by staged flow diversion, median time of 16 weeks between the coiling and flow diversion, appears to be a safer endovascular option for these ruptured aneurysms. In Brinjikji series, 27 patients with aSAH from large/giant ruptured aneurysms, 18 patients had complete or near-complete aneurysm occlusion, and 25 patients had good performance status [73].

Natarajan et al. present their series [74], despite 18.2% mortality, the patients in the remaining 9 of 11 cases (81.8%) achieved good functional recovery and 100% obliteration of the aneurysm without rebleeding. At their protocol, an EVD was placed before angiogram if needed, followed by primarily dome protection and obliteration of rupture points in aneurysms by coiling or clipping. If the aneurysm morphology was complex (blister or fusiform aneurysms) and/or if the patient was not a good candidate for surgical clipping (elderly patients and/or those with poor Hunt and Hess grades), FD or stent assistance was attempted to achieve aneurysm occlusion.

Despite the importance of antiplatelet therapy on the success of FD-based interventions, there is wide variability in antiplatelet management surrounding the off-label use of FDs in aSAH. Some authors reported performing invasive procedures (EVD or central line placement) 12 h before FD placement or DAPT, administering a loading dose of DPAT before FD placement and continuing DAPT for at least 3 months [68]. Other authors avoided pre-procedural anti-

platelet therapy altogether, instead administering DAPT, and a glycoprotein IIb/IIIa inhibitor during FD placement, followed by a 12-hour maintenance infusion of a glycoprotein IIb/IIIa inhibitor and post-procedural DAPT for 6 months [75]. The inhibitors of IIb/IIIa glycoproteins have a very potent inhibitory effect on platelets, and rapid onset of action, can be used just for short periods of time [76]. The protocol with tirofiban or eptifibatide infusion, drugs with reversible binding to platelets, may be easier to handle than irreversible antagonists (abciximab), was proposed starting immediately after the stent deployment and continuing for 12 h after the procedure, making coagulation better controllable and allowing restoration of coagulation in case of bleeding. The authors reported 17% complications and 2.8% aneurysm rebleeding [75]. One meta-analysis [65] found 4 main groups of antiplatelet therapy administration. There were no statistically significant differences among the analyzed subgroups of antiplatelet therapy, with an overall complication rate ranging from 17% to 23%. The most common drugs were clopidogrel plus ASA, administered intraoperatively and maintained after treatment (19.5% complications and 3% rebleeding). Ticagrelor has an advantage compared with ASA, clopidogrel, and prasugrel in that it binds reversible to platelets and therefore partial platelet activity returns after 12 h and is used for clopidogrel nonresponders.

A promising recent advancement has been surface modification to reduce the inherent thrombogenicity of FD. The PED with Shield Technology (PED Shield, Medtronic) is a phosphorylcholine surface modification of the PED that has shown a reduction in material thrombogenicity in vitro [77]. Manning et al. used the PED with shield technology (with adjunctive coiling in 83%) under single antiplatelet therapy in treating 14 patients with ruptured intracranial aneurysms and reported no hemorrhagic or thromboembolic complications in the subgroup that did not receive post-interventional heparin infusion (heparin infusion postoperatively was associated with all complications combined) [78]. However, PED with shield is not the universal key in the real world. After PED with Shield deployment for the acute ruptured ICA aneurysm, parent artery kept patency in the case of Fig. 10.2 but occlusion in Fig. 10.10 case. Even glycoprotein IIb/IIIa inhibitor (Eptifibatide) was injected immediately with the parent artery reopened, the patient still had minor weakness in the acute phase. Until establishing the efficacy and safety of such coatings in a large clinical trial, the use of FD will remain limited by the need for DAPT.

Flow diversion is not the primary treatment of choice after aSAH, but is a reasonable last option if other, safer options are not available to treat the aneurysm. Careful patient selection, selective use of coiling, timing of flow diversion after dome protection, and timing of heparin and antiplatelet therapy in the periprocedural period improve the safety of flow diversion as a strategy to achieve permanent aneurysm occlusion in the rupture setting. Further development of surface modification technology may allow flow diversion with a single antiplatelet agent, and thus may broaden the use of FD in this setting.

10.6 Intracranial Dissecting Aneurysms

There are relatively few studies of intracranial dissecting aneurysm in the literature, but they seem to have a predilection for young adults and arteries of the posterior circulation [79]. There are numerous mechanisms in the formation of dissections, and each has a different clinical presentation and imaging findings (saccular, fusiform, or pseudoaneurysm). Patients most often present with a nonspecific headache followed by ischemic stroke or SAH. The heterogeneity of this rare condition precludes standardized diagnostic criteria and evidence-based treatment guidelines.

In adults, involvement of the posterior circulation is at least three times more common than the anterior circulation and V4 is the most frequently implicated [79, 80].

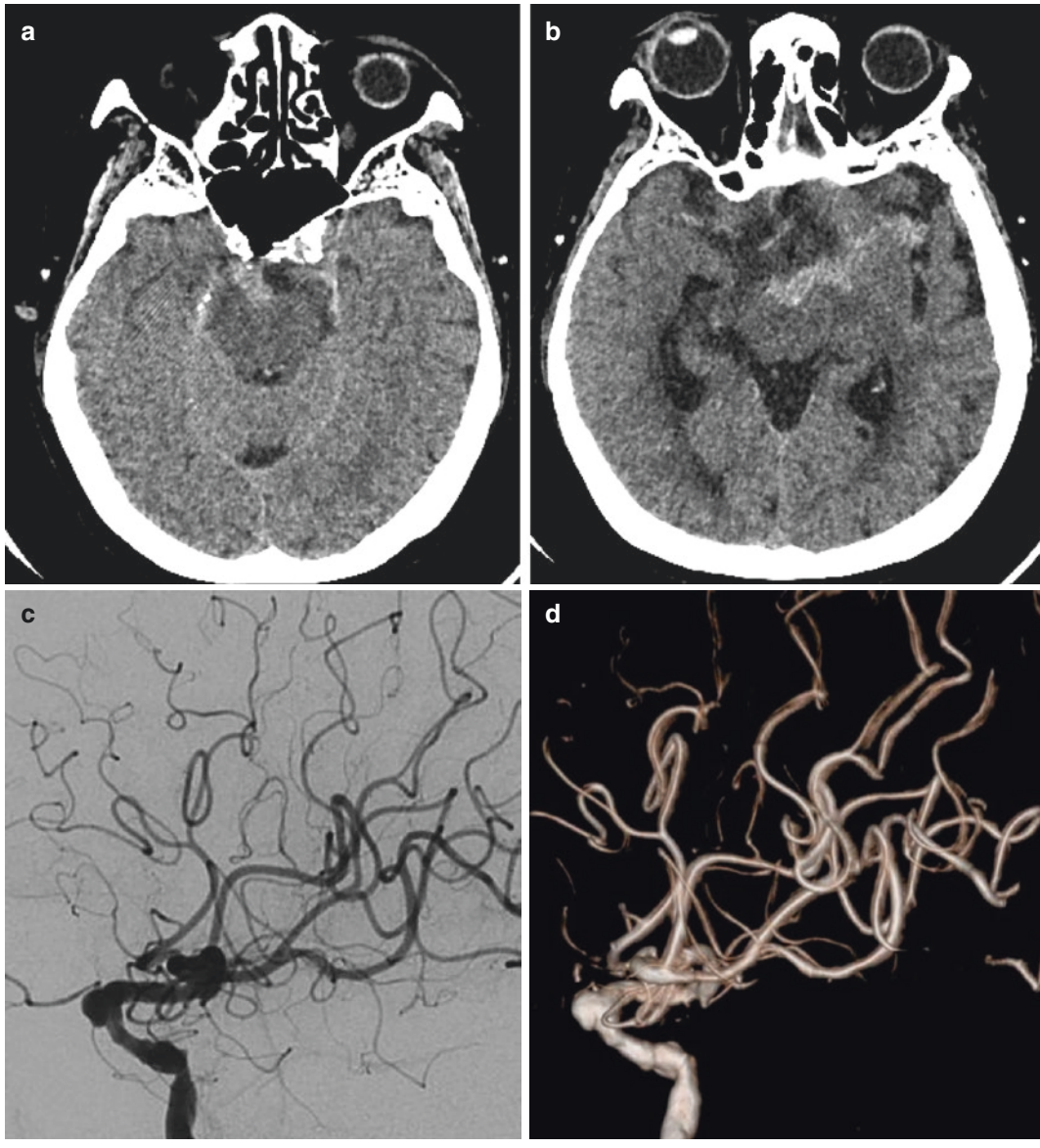

Fig. 10.10 A 76-year-old patient presented with acute headache and vomit, brain CT showed SAH (**a**, **b**), angiogram revealed multiple aneurysms involving both anterior and posterior circulation (**c**–**f**). It was difficult to confirm which one was responsible, so all the aneurysms were treated in one procedure. After loading dose dual antiplatelet drugs was given, the tandem wide-neck aneurysms in left ICA were treated with Pipeline shield stent and coiling at first (**g**) and followed by coiling of the aneurysm in basilar artery (**h**). However, acute thrombosis was found in the flow diverter (**i**). Glycoprotein IIb/IIIa inhibitor (Eptifibatide) was injected immediately and continue to 12 h. Left ICA was reopened at the end (**j**). The patient presented with weakness of right upper limb after the procedure and small infarction was confirmed in day 1 MRI (**k**), limb power recovered well in one week

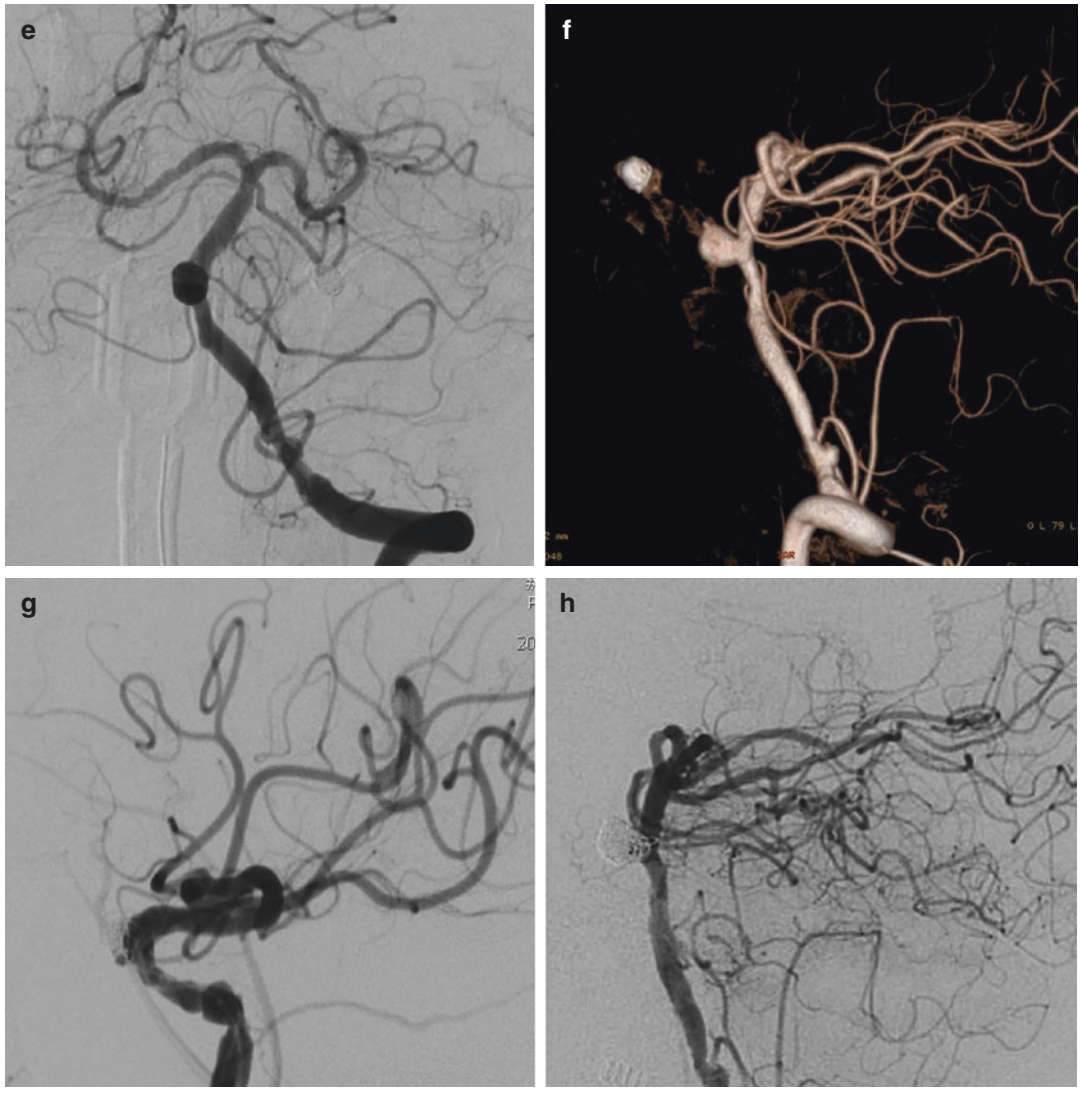

Fig. 10.10 (continued)

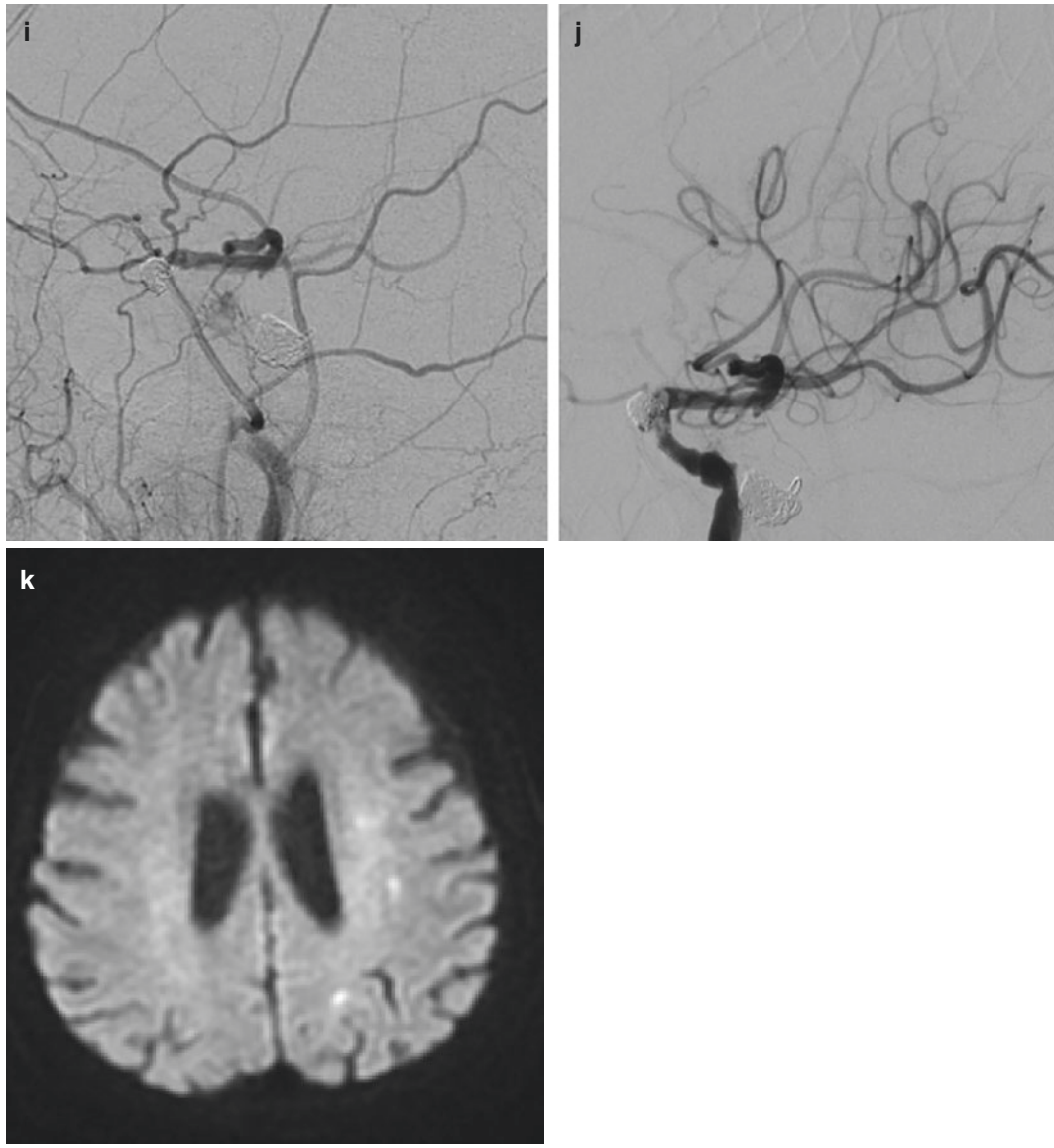

Fig. 10.10 (continued)

The most common location in the anterior circulation of dissection is the supraclinoid internal carotid artery [79].

Approximately 80% of patients with intracranial dissection have a prodromal headache preceding SAH or symptoms of cerebral ischemia, whether it be a stroke or transient ischemic attack [81]. An estimated 50–60% of intracranial dissecting aneurysm patients develop SAH, and 30–78% of patients have ischemic events. Other uncommon presentations include isolated headache or mass effect from brain stem and/or cranial nerve compression [79]. Patients who present with ischemic stroke are at high risk of subsequent ischemic stroke and low risk of SAH while those who present with hemorrhage are at high risk of subsequent hemorrhage but low risk of subsequent ischemic stroke [79]. Mortality is reported to be 19–83% in patients with SAH and 0–3% without SAH [79]. Up to 40% of patients

who present with SAH experience rebleeding, most commonly within the first week. For patients who present with ischemia, recurrent ischemic events have been reported at a rate of 2–38% in numerous studies with widely variable follow-up lengths [82, 83].

When the patient presents with Ischemic, medical management includes antithrombotic or antiplatelet therapy for the prevention of thromboembolic stroke. In patients present with large vessel occlusion, urgent endovascular recanalization should be performed when SAH can be ruled out. In patients with recurrent strokes despite medical therapy, stent reconstruction is reasonable to perform.

In patients present with SAH, there is a significant risk of rebleeding after initial stabilization [83]. As such, surgical or endovascular treatment is often pursued in this population. Various surgical and endovascular treatment methods have been proposed for intracranial dissecting aneurysms. All treatment methods aim to reduce blood flow in the dissected region. Deconstructive techniques sacrifice the parent artery, whereas reconstructive techniques aim to maintain a parent artery. Deconstructive techniques are associated with higher rates of both short-term (90% versus 50%) and long-term complete occlusion (90% versus 80%) [82]. However, there is a trend towards better clinical outcomes in patients treated with reconstructive techniques, likely due to the lower risk of stroke and hypoperfusion due to preservation of the parent artery. Reconstructive techniques are alternative options for patients who are not suitable candidates for parent vessel occlusion [84, 85]. FD and stenting, with or without coiling, selectively occlude the dissection while maintaining patency of the parent vessel. Patients often require treatment with dual antiplatelet therapy after device implantation. There is a risk of rebleeding following reconstructive treatment due to the fact that FD still allows for some blood flow to the aneurysm which is not immediately "protected" against rerupture until vessel wall remodeling and endothelialization of the stent construct. There are also issues surrounding the risks of placing CSF diversion devices while patients are on dual antiplatelet therapy. The timing and technique about additional surgical procedures and antiplatelet treatment have been discussed in the section *Acute ruptured Aneurysms*. Nonetheless, it appears as though reconstructive techniques, especially flow diversion, have become the preferred option for treatment of ruptured intracranial dissections.

The most important consideration in treating unruptured dissecting aneurysms is weighing the risks of treatment with the risks of the natural history of these lesions, especially located in the posterior circulation. It has been discussed in the section *Posterior Circulation Aneurysms*. The Tubridge flow diverter (MicroPort Medical Company, Shanghai, China) was used in Fig. 10.11 case. In Fig. 10.12 case, the small saccular aneurysms maintained patency in portion stented while stenosis improved in portion without stenting after 17 months of antiplatelet treatment. Flow in the false lumen existing with the non-cover proximal portion of dissecting may be the reason.

As expected, treatment with deconstructive techniques (i.e., parent vessel sacrifice) is associated with high rates of complete occlusion in the immediate and postoperative setting (90–100%) while reconstructive techniques including FD require some time to achieve complete occlusion. FD is generally the preferred means of treatment of these lesions due to its high rate of treatment efficacy, high long-term occlusion rates and ability to preserve the parent vessel.

Flow diversion is a new paradigm shift in the treatment of intracranial aneurysms, but, not a universal key. As popularity of the device grew and neurosurgeons gained more experience, its indications were extended. In recent years, off-label use of flow diversion in treatment of intracranial aneurysms has become more and more

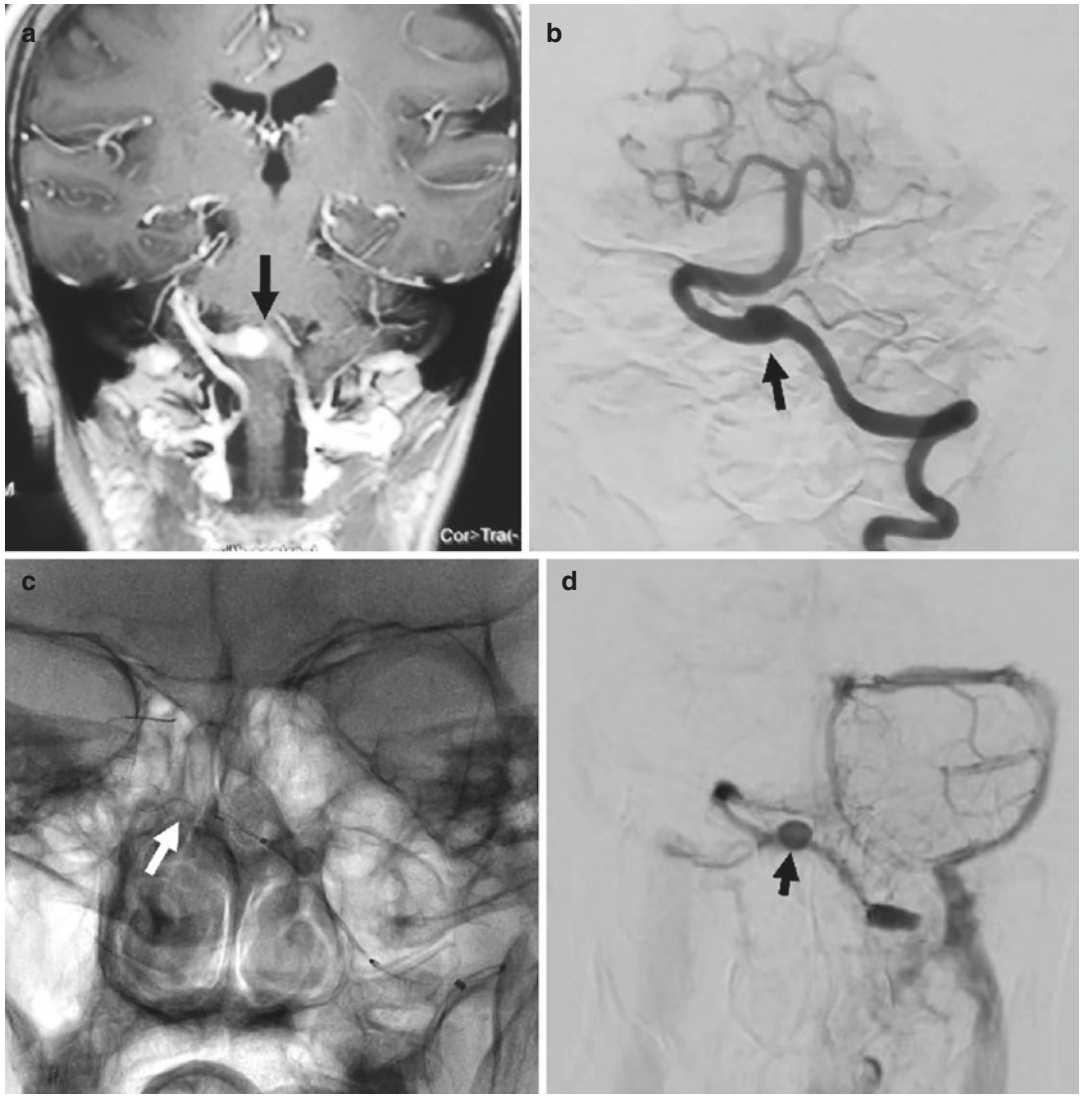

Fig. 10.11 A 58-year-old woman presented with an incidental vertebral artery aneurysm. (**a**) Coronal view of the enhanced MR image showing a fusiform aneurysm of the left vertebral artery (arrow). (**b**) Frontal view of the left vertebral artery injection showing a fusiform aneurysm (arrow). (**c**) Frontal view of unsubtracted image showing the releasing of a 4.0 mm × 50 mm Tubridge flow diversion (Microtherapeutic, Shanghai, China) (arrow). (**d**) Frontal view of the venous phase of the left vertebral artery injection showing intra-aneurysm contrast stagnation (arrow)

popular. It has proven to be a safe and efficacious treatment option for many of these off-label uses, whereas others may still require larger, more extensive studies to draw conclusions. Nevertheless, the FD may be a promising treatment alternative and should be considered when we face the challenge of complex aneurysms that may be deemed difficult to treat by using conventional surgical and endovascular techniques in the real world.

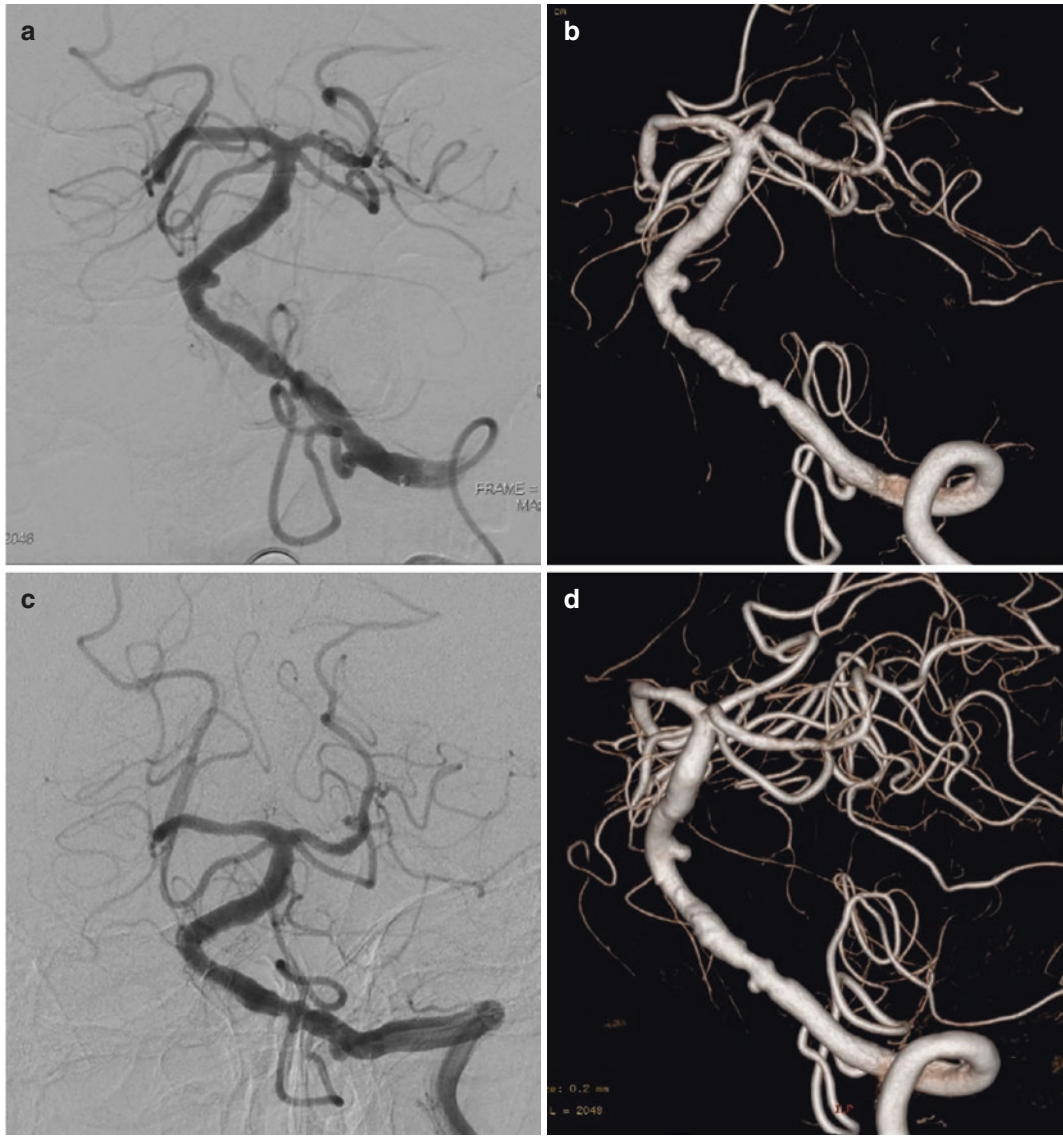

Fig. 10.12 A 63-year-old patient presented with headache was treated left VA dissection (**a**, **b**) with 1 PED covered the saccular portion of vertebrobasilar junction, and kept the focal stenosis and dilation ("string and pearl sign") portion intact. After 17 months of antiplatelet therapy, a follow-up angiogram showed the saccular patency maintained in portion stented while stenosis improved in portion without stenting (**c**, **d**)

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