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Review Article

# A Review of Current Flow Diverters

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Flow diverter (FD) devices are new-generation stents placed in the parent artery at the aneurysmal neck to obstruct intra-aneurysmal blood flow, thus favoring intra-aneurysmal thrombosis. In Japan, about eight years have passed since health insurance approval was granted for FD devices, and FD placement to treat aneurysms has become widespread. Treatment indications have also been expanded with the introduction of novel devices. At present, three types of FD (Pipeline, FRED, and Surpass Streamline) are available in Japan. This report represents a compilation of available FD technologies and describes the current consensus on this treatment.

**Keywords** ▶ intracranial aneurysm, neurointerventional surgery, flow diverter

## Introduction

In the endovascular treatment of wide-necked aneurysms, coiling and stent-assisted coiling are well-established treatment options but are limited by associated morbidity and aneurysm recurrence rates.[1)] Treatment failures with those modalities are related to coil compaction inside the aneurysm pouch, allowing aneurysm recanalization or aneurysmal regrowth. With the need to overcome this phenomenon, the concept of vessel reconstruction using endoluminal implants led to the development of flow diverters (FDs).[2)]

In this review, we highlight the important technical features of FDs currently available in Japan and review the essential clinical literature supporting their use. The research within this submission was approved by the ethics review board of National Cerebral and Cardiovascular Center.

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## Mechanisms of Action for FDs

The mechanisms of action for FDs involve three phases: 1) the hemodynamic phase, 2) the thrombus formation phase, and 3) the endothelialization phase. The hemodynamic phase occurs immediately after the procedure, utilizing obstruction of blood flow into the aneurysm from the parent artery related to the resistance created by the mesh component of the FD. Blood flow velocity inside the aneurysm is then markedly reduced, followed by immediate activation of platelets with progressive formation of a stable thrombus over a period of days to weeks, representing the thrombus formation phase. The endothelialization phase involves the transformation of the thrombus to the final collagen stage over a period of several months to years. The transformation of intra-aneurysmal thrombus to collagen leads to a final reduction in the aneurysmal mass.[3,4)]

## FDs Available in Japan

Three types of FDs are available in Japan: the Pipeline Flex with Shield technology (Pipeline; Medtronic, Irvine, CA, USA), the FRED (TERUMO. Tokyo, Japan), and the Surpass Streamline (Stryker, Fremont, CA, USA). Indications vary between these devices. The Pipeline is indicated for placement in the internal carotid artery (ICA) (petrous to supraclinoid regions) or vertebral artery (VA) for aneurysm sizes ≥5 mm, with length of the aneurysm neck

**Table 1** Flow diverters available in Japan

| FDs | Approved year | Indications | Structure | Material | Surface material |
|---|---|---|---|---|---|
| Pipeline Flex with Shield technology* | 2015 | • ICA (petrous to supraclinoid), VA<br>• Aneurysm size ≥5 mm<br>• Length of neck ≥4 mm or D/N ratio <2 | Mono layer (48 wires) | Cobalt/chromium (36 wires) Platinum/tungsten (12 wires) | MPC polymer |
| FRED** | 2019 | ICA, proximal ACA, proximal MCA, VA, BA<br>• Aneurysm size ≥5 mm<br>• Length of neck ≥4 mm or D/N ratio <2 | Dual layer (66 wires) | Nitinol (64 wires) Tantalum (2 wires) | Bare metal |
| Surpass Streamline*** | 2021 | ICA (petrous to supraclinoid)<br>• Aneurysm size ≥10 mm<br>• Length of neck ≥4 mm or D/N ratio <2 | Mono layer (72 or 96 wires) | Cobalt/chromium Platinum/tungsten | Bare metal |

*Medtronic, **Terumo MicroVention, and *** Stryker.
ACA: anterior cerebral artery; BA: Basilar artery; D/N ratio: dome-to-neck ratio; ICA: internal carotid artery; MCA: middle cerebral artery; MPC: methacryloyloxyethyl phosphorylcholine; VA: vertebral artery

**Table 2** Overview of major prospective clinical trials

| Study | Used FD | Inclusion criteria | Primary efficacy point | | Safety point | | Delayed rupture | Intraparenchymal hemorrhage | Ischemic complication |
|---|---|---|---|---|---|---|---|---|---|
| PUFS | Pipeline Classic | ICA* | CAO with no >50% stenosis of the PA at 6M | 73.6% | MIS or any ND within 6 M | 5.6% | 0.9% | 1.9% | 2.8% |
| PREMIER | Pipeline Classic/ Flex | ICA**, VA | CAO with no >50% stenosis of the PA at 12M | 76.7% | MIS or any ND within 12 M | 2.1% | 0% | 1.4% | 0.7% |
| | Pipeline Shield | ICA, ACA, MCA*** | CAO with no >50% stenosis of the PA at 12M | 71.7% | MIS or any ND within 12 M | 2.9% | 1% | 2.9% | 4.9% |
| SAFE | FRED/ FRED Jr | ICA, ACA, MCA | CAO with no >50% stenosis of the PA at 12M | 73.3% | >2 mRS deterioration and any death | 2.9% | 1% | 1% | 1.9% |
| SCENT | Surpass Streamline | ICA** | CAO with no additional treatment or symptomatic stenosis at 12 M | 62.8% | MIS or any ND within 12 M | 8.3% | 2.2% | 0.6% | 6.1% |

*Petrous to paraclinoid, **petrous to supraclinoid, and ***including ruptured aneurysm.
ACA: anterior cerebral artery; CAO: complete aneurysm occlusion; FD: flow diverter; ICA: internal carotid artery; MCA: middle cerebral artery; MIS: major ipsilateral stroke; ND: neurologic death; PA: parent artery; VA: vertebral artery


**Fig. 1** FDs available in Japan. (**A**) Pipeline (courtesy of Medtronic). (**B**) FRED (courtesy of Terumo). (**C**) Surpass Streamline (courtesy of Stryker). FD: flow diverter

≥4 mm or a dome-to-neck (D/N) ratio <2. The FRED is indicated for the ICA, proximal anterior cerebral artery (ACA), proximal middle cerebral artery (MCA), VA, and basilar artery (BA) for aneurysm size ≥5 mm, length of the aneurysm neck ≥4 mm or D/N ratio <2. The Surpass Streamline is indicated for the ICA (petrous to supraclinoid), for aneurysms size ≥10 mm, length of the aneurysm neck ≥4 mm, or D/N ratio <2. All devices were approved for the treatment of intracranial aneurysms, with the exception of those acutely ruptured. (**Tables 1** and **2**; **Fig. 1**).[5]

## Pipeline

The Pipeline consists of a braided stent of 36 cobalt/chromium wires, together with 12 platinum/tungsten wires serving as marker wires. The FD deployed using a combination of pushing and unsheathing techniques through a 0.027-inch microcatheter. The Pipeline of Uncoilable or Failed Aneurysms (PUFS) trial was the first multicenter study of large and giant (≥10 mm) aneurysms in the petrous to paraclinoid portions of the ICA, reportedly offering complete occlusion rates of 73.6% at 6 months, 86.8% at 1 year, and 95.2% at 5 years.[6] Another recent, long-term follow-up study was reported by Lylyk et al. Based on treatment results from 1000 aneurysms, that study found complete occlusion with no >50% stenosis of the parent artery rates of 75.8% at 1 year, 92.9% at 2–4 years, and 96.4% at ≥5 years. They also reported an in-stent thrombosis rate of 2.5%, an ischemic stroke rate of 3.6%, an aneurysmal rupture rate of 1.4%, an intraparenchymal hemorrhage rate of 0.4%, and a mortality rate of 3.1% during the follow-up period.[7] From Japan, Fujii et al. reported follow-up results for three years after FD treatment using Pipeline for 77 aneurysms. They showed complete occlusion in 60 aneurysms (77.9%), an ischemic stroke rate of 2.4%, and an intraparenchymal hemorrhage rate of 1.2%.[8]

The PREMIER study evaluated the use of Pipeline Flex in the treatment of small to medium-sized (<12 mm) unruptured, wide-necked aneurysms in the petrous to supraclinoid portion of the ICA and VA. The rate of complete aneurysm occlusion with no >50% stenosis of the parent artery at 12 months was reportedly 76.7% and the combined major morbidity and mortality rate was only 2.1%.[9]

The most recent device, the Pipeline Flex with Shield Technology (Pipeline Shield), received CE approval in 2015 and has the same design and configuration as the Pipeline Flex but features a surface modification using methacryloyloxyethyl phosphorylcholine polymer with the aim of reducing thrombogenicity. *In vitro* studies have shown that the Pipeline Shield is less thrombogenic than the previous generation Pipeline Flex.[10] The SHIELD study evaluated the use of Pipeline Shield in the treatment of ICA, ACA, and MCA aneurysms, including ruptured aneurysms. The rate of complete aneurysm occlusion with no >50% stenosis of the parent artery at 12 months was 71.7% and the rate of major ipsilateral stroke or any neurologic death within 12 months was 2.9%.[11]

## FRED

The FRED is a self-expanding, dual-layer, braided stent comprising a low-porosity inner layer (48 nitinol wires) and a high-porosity outer layer (16 nitinol wires). The inner and outer layers are connected with an interwoven tantalum layer. The FD is delivered through a 0.027-inch microcatheter. According to the results of the European FRED study (EuFRED), which retrospectively evaluated the efficacy of FRED for 579 aneurysms from 15 European countries with a median aneurysm size of 7.6 mm and a median neck size of 4.5 mm, complete aneurysm occlusion rates were 20% at 3 months, 82.5% at 6 months, 91.3% at 12 months, and 95.3% at ≥12 months. Transient and permanent morbidity occurred in 3.2% and 0.8%, respectively. The overall mortality rate was 1.5%.[12] The safety and efficacy analysis of the FRED embolic device (SAFE) study reported a rate of complete aneurysm occlusion with no >50% stenosis of the parent artery was 73.3% at 12 months. Permanent morbidity and mortality rates were 2.9% and 1.9%, respectively.[13] According to a recent systematic review of 22 studies including 1729 aneurysms using the FRED, aneurysm occlusion rates were 47.8% at 0–3 months, 73.8% at 4–6 months, 75.1% at 7–12 months, and 86.6% at ≥12 months. The overall morbidity rate was 3.9% and the overall procedure-related mortality rate was 1.4%.[14] As the first large-scale North American multicenter retrospective study with a median aneurysm size of 7.2 mm and a median neck size of 4.1 mm, Khorasanizadeh reported that complete aneurysm occlusion was observed in 55.4% of patients, residual neck in 8.9%, and filling aneurysm in 35.6% at 7 months; among cases with radiological follow-up duration >10 months, these values were 48.8%, 7.0%, 44.2%, respectively. The overall morbidity rate was 8.6% and the overall mortality rate was 0.8%.[15]

## Surpass Streamline

The Surpass Streamline uses braided cobalt–chromium alloy with 12 platinum-tungsten alloy marker wires. The Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT) was a large, prospective, multicenter trial examining the safety and effectiveness of the Surpass. The results showed the rate of complete aneurysm occlusion with no >50% stenosis and no retreatment was 62.8% at 12 months and the rate of major ipsilateral stroke or

any neurologic death at 12 months was 8.3%.[16] The three-year outcomes of the SCENT trial were recently published. The rate of complete aneurysm occlusion with no >50% stenosis and no re-treatment was 71.8% and the rate of disabling stroke or neurological death was 12.2%.[17] From Japan, Teranishi et al. recently reported the short-term follow-up results for FD treatment using Surpass Streamline for 26 aneurysms. Among twenty cases in which angiography was performed, they showed that favorable aneurysm occlusion consisted of complete occlusion, with a residual neck achieved in 16 (80.0%). The rate of major ipsilateral stroke and neurological death at 30 days was 7.7%.[18]

## Antiplatelet Therapy

Dual antiplatelet therapy is required to reduce the risk of thrombotic complications due to the metallic properties of FDs. Aspirin and clopidogrel are the most commonly used antiplatelet agents. However, according to the rising variability in clopidogrel platelet inhibition, platelet aggregation testing is performed to ensure therapeutic inhibition. A meta-analysis by Ajadi et al. reported that platelet hypo- and hyper-responders were associated with thrombotic and hemorrhagic events, respectively, following FD use,[19] meaning that platelet aggregation testing to predict complications may have become more meaningful in recent years. The risk of thrombotic complications among platelet hypo-responders has been lowered with the modification of antiplatelet medication. For example, prasugrel can be substituted for clopidogrel in platelet hypo-responders.[20] Prospective studies are required to clarify the clinical benefits of platelet aggregation testing.

## Future Issues of FD Treatment

Well-known serious complications of FD treatment are delayed rupture of the aneurysm[21] and thromboembolic complications.[22] The rate of delayed rupture varies from report to report, within the range of 0–6.9%.[7,8,13,17,23] Rouchaud reported that 76.6% of delayed ruptures occur within 1 month after treatment and 81.3% show poor prognosis.[24] Based on results from clinicopathological studies, they considered hypothetical mechanisms of delayed rupture. Evolving intra-aneurysmal thrombus may cause transient destabilization of the aneurysmal wall and appears to trigger increased autolysis, which may overload the biological defense mechanisms of the vessel wall and result in aneurysmal rupture.[25,26]. Kulcsár reported four risk factors for delayed rupture: 1) large and giant aneurysm; 2) symptomatic aneurysm; 3) saccular aneurysm with an aspect ratio >1.6; and 4) Inertia-driven flow.[25] With regard to thromboembolic complications, Brinjikji reported in a meta-analysis that the rate of thromboembolic complications was 6%.[22] Risk factors are considered as 1) inadequate inhibition of platelet aggregation; 2) FD malapposition; 3) branch occlusion caused by FD deployment; and 4) in-stent re-stenosis. Further, in cases of incomplete occlusion, stent overlap using the FD can be performed. However, not all incomplete occlusions are treated using that technique. To overcome this problem, FD treatment with adjunctive coil embolization has also been performed, and the effectiveness and safety of this method have been reported, although more clinical evidence is required.[27–29]

## Conclusion

According to the results from the reviewed studies, FDs provide a feasible and effective treatment for unruptured aneurysms. Adequate perioperative management, including anatomical information and results from platelet aggregation tests, is required to avoid complications and minimize the risks of morbidity and mortality. However, experience with these devices remains relatively recent, and the duration of follow-up has thus been short. Further studies with longer follow-up are necessary to clarify rates of complete occlusion.

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