Cerebral Flow Diverters and Disruptors in 2021: Where Do We Stand?

Key advancements, new devices, landmark trials, treatment strategies by aneurysm type, location, and clinical content, and future directions.

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What is your impression of how cerebral flow diverters (FDs) and their application have evolved over the past 10 years?

Beginning with the PUFS trial of 107 patients, which established safety and efficacy of the Pipeline embolization device (PED; Medtronic) in 2011, flow diversion represents a paradigm change in the treatment of intracranial aneurysms. The mechanism of flow diversion efficacy is twofold, first reducing flow into the aneurysm acutely and then providing a scaffold for neointimal growth, which over time excludes the aneurysm from the parent circulation. This mechanism represents a conceptual shift in aneurysmal treatment from closing or deconstructing the aneurysm to reconstructing the parent vessel.

The PUFS trial established the on-label treatment of “large or giant wide-necked intracranial aneurysms of the internal carotid artery (ICA) from the petrous to superior hypophyseal segments.” Over the last decade, we have seen expansion of the use of FDs for a multiplicity of additional aneurysm types—posterior circulation, blister, fusiform, dissecting, bifurcation, small, distal—and for intra- and extracranial vessel reconstruction (eg, dissections, pseudoaneurysms, cavernous carotid fistulas). Flow diversion allows for treatment of aneurysms with no neck, in addition to treatment without manipulation of the aneurysm itself.

Due to a favorable safety and efficacy profile, more than 100,000 patients have been treated with flow diversion over the last 12 years, and with that experience, our thinking about the types of aneurysms and pathologies that can successfully be treated with FDs has evolved.

In 2011, the PED or PED Classic was the first device approved in the United States, followed by the PED Flex in 2015. The primary improvement of PED Flex over the Classic was the upgrade from capture coil to protective sleeves at the tip, which allows for smoother deployment and, importantly, resheathability. The indication for PED expanded with PREMIER, a prospective trial of PED (including Classic and Flex) in 141 patients with ≤ 12-mm ICA aneurysms (up to the terminus) and vertebral aneurysms up to and including the posterior inferior cerebellar artery, which showed 81.9% occlusion at 1 year. With PREMIER, the label for PED was expanded to include small and medium ICA aneurysms extending to the terminus.

The PED has lead the literature and market space for much of the last decade, with the PED Flex with Shield technology (PED Shield) that is currently available in Europe representing the next generation. Competitor devices have entered including Silk (Balt), Flow Re-direction Endoluminal Device (FRED; MicroVention Terumo), Surpass (Stryker), p64 (phenox GmbH), and Tubridge (MicroPort NeuroTech). Now, operators have more options to treat a specific aneurysm with a specific device or construct.

The devices differ in terms of flow-diverting properties, including porosity, metal coverage, pore density, mechanical properties such as size range and radial forces; and delivery systems, including delivery and guide catheter sizes and device resheathability. Some devices can be layered easily, while others have not been designed or tested for this use. These features impact safety and efficacy in various clinical contexts.

One FD that is gaining usage in the United States is the Surpass Evolve (SE), a second-generation device by Stryker. The first-generation Surpass Streamline (SS) was the second FD to receive FDA approval in the United States after the SCENT trial. SS has 72 or 96 wires depending on diameter and a 3.7-F microcatheter delivery system that is large and cumbersome intracranially, especially distally. Surprisingly,
The ability to safely treat more distal aneurysms is exciting.

The SE is more similar to PED than SS in its design, navigability, and deployment via a 2.7-F microcatheter. Compared with PED Flex’s 48-wire mesh density, SE offers 48 wires for the 2.5-mm device and 64 for the 3.25- to 5-mm sizes. With optimization of higher braided angle, SE maintains rhomboid cell shape and consistent mesh density of 15 to 30 pores/mm². SE may have advantages in easy pushability, reshethability, and recrossability due to the stainless steel push wire and, in theory, consistent opening due to high radial forces. Preliminary experience in patients demonstrates good technical performance and acceptable safety.⁷ Of note, 28% (7/25) of patients in this study were treated with balloon angioplasty postdeployment, compared with 5.6% typical for PED.⁸ A study of 46 aneurysms treated with SE (average of 1.2 devices per aneurysm) reported 75% occlusion at a median 116-day follow-up.⁹ How the design features (including the additional metal) impact conformability, seal, and infarct risk compared with PED Flex are important questions looking forward.

FRED is another device new to the United States market that was studied in the SAFE trial with acceptable safety (2.9% morbidity and 1.9% mortality) and 73.3% efficacy at 1 year.⁸ The FRED is a dual-layer device with 33% to 44% metal surface area—an outer high-porosity braided stent with high radial force around a shorter, low-porosity FD inner layer, which hypothetically improves ease of delivery. FRED cannot be layered into a construct in practice. One concern with FRED is the reports of acute in-stent thrombosis despite dual antiplatelet therapy (DAPT) that may be related to its increased thrombogenicity compared to PED in vitro.⁹ FRED Jr includes the 2.5- and 3-mm sizes, has lower metal surface coverage of 28% to 33%, and can be delivered through a 0.021-inch microcatheter.

The Silk series of FDs was used in Europe first in 2008 and was subsequently updated to the Silk+. Although few early data are available for Silk, efficacy was on par with PED at > 90%, but rates of complications were higher.¹⁰ A recent retrospective review of Silk in 293 sacular ICA aneurysms demonstrated 94% efficacy at 12 months, with 4.2% morbidity and 2.1% mortality.¹¹ The Silk Vista Baby was approved in Europe in 2018; it is designed for the treatment of distal aneurysms arising from a 1.5- to 3.5-mm parent vessel and can be delivered through a 0.017-inch microcatheter. In 2020, the Silk Vista was approved in Europe for use in parent vessels > 3.5 mm and can be delivered through 0.021- and 0.025-inch microcatheters compared with a 0.027-inch delivery for the PED Flex. The ability to safely treat more distal aneurysms is exciting but how the smallest 2.25-mm Silk device compares to a 2.5-mm PED Flex in practice is unknown.

With PED Shield and similar devices with antithrombotic surface modifications, we anticipate safer and expanded application of flow diversion in acutely ruptured aneurysm treatment. PED Shield is expected to gain approval in the United States in 2021. The PED Shield employs phospholipid coating, which reduces thrombogenicity in vitro and has demonstrated safety and efficacy in vivo in a recent study of 182 aneurysms, 175 of which were unruptured, (in patients on DAPT), with a 1-year efficacy of 85.3% and a perioperative complication rate of 7.3%.¹² Other anti-thrombogenic-coated FDs include the Derivo with blueXide surface finishing (Life Medikal) and the p48 (phenox GmbH); however, in vitro data support PED Shield as having the best coating.¹³ Less thrombogenic FDs may prove important in treating ruptured aneurysms where coiling has been shown to be less effective, with many of these patients in practice requiring retreatment.¹⁴ For example, the BRAT trial of acutely ruptured aneurysms treated with coil embolization reported just 40% efficacy at 6-year follow-up.¹⁵ Low thrombogenicity FDs also have potential in patients with bleeding diathesis or who require systemic anticoagulation and, if equivalent to PED, potential to become the new standard more broadly.

What key advancements have there been with flow disruptors since their initial introduction?

Although conventional FDs have continued to evolve, a newer concept of intrasaccular FD or “disruptors” has emerged. The most significant disruptor is the Woven EndoBridge device (WEB, MicroVention Terumo), which treats wide-necked bifurcation aneurysms. WEB is a low-porosity metal mesh cylindrical or spherical construct, which sits within the aneurysm and across its neck to disrupt flow from the parent vessel and provide a scaffold for neointimal growth.

Intrasaccular flow “disruptors” such as the WEB rely on hemodynamic decoupling of the parent vessel and aneurysm lumen. The WEB is indicated for the middle cerebral artery (MCA) bifurcation, ICA terminus, anterior communicating artery complex, or basilar artery apex for saccular, wide-neck bifurcation intracranial aneurysms with dome diameter from 3 to 10 mm and either neck size ≥ 4 mm or dome-to-neck ratio > 1 but < 2.

Unlike the FDs, which are often used off-label, WEB use in practice follows its indication for wide-necked bifurcation aneurysms. The WEB-IT trial of bifurcation aneurysms demonstrated safety of the WEB, with a primary safety endpoint of only 0.7% and 53.8% (77/143) complete occlusion at 1 year. “Adequate occlusion” was achieved in 121/143 (84.6%) of aneurysms in WEB-IT. The long-term implications of “adequate occlusion” in terms of rupture risk is an area of active debate.¹⁶
Being endosaccular, WEB has the disadvantage of requiring catheterization of the aneurysm for delivery but the advantage of faster embolization and less need for long-term antiplatelet therapy, as only the mesh at the neck is exposed to the lumen. Most patients in WEB-IT were on DAPT during the procedure, followed by single antiplatelet therapy in the posttreatment period. WEB has flow-diverting properties, with in vitro data demonstrating better endothelialization across the neck compared to coils. The smaller 4- to 7-mm WEBs can be delivered through 0.017- and 0.021-inch microcatheters, with the larger sizes requiring 0.033-inch delivery catheters.

Recent data on WEB in 48 acute rupture cases demonstrated complete occlusion in 54.2% and “adequate occlusion” in 92.3%, with clinically significant peri-procedural adverse events of 12.5%. For acutely ruptured wide-neck bifurcation aneurysms, WEB may prove as good as coiling or clipping.

Other endosaccular “disruptor” devices include the Contour neurovascular system (Cerus Endovascular), a disc that deploys inside the aneurysm and across its neck, and the Medina embolization device (Medtronic), a three-dimensional mesh implant that delivers like a coil, with mesh petals attached to the primary coil wire into the aneurysm; these devices are primarily in the trial phase in Europe. Extrasaccular flow disruptors include the noncylindrical pCANVAS device (phenox GmbH), which sits in the parent vessels and deploys a membrane across the aneurysm, and is an evolution of the pCONUS (phenox GmbH) and PulseRider (Codman Neurovascular) concepts. The eCLips bifurcation remodeling system (Evasc) applies support struts to half the branch vessel wall and forms a leaf-like segment across the aneurysm. Because the primary benefit of flow disruptors over FDs is that DAPT is not required, if PED Shield performs well with single antiplatelet therapy, it seems unlikely that any of the non-WEB “disruptors” will make a significant impact on practice.

How would you describe the current literature base for these devices?

More than 600 peer-reviewed publications provide a robust base for our understanding of the safety and efficacy of flow diversion in primarily single-arm studies. Across trials of different flow-diverting devices, efficacy is higher than any prior technique (approaching 95%), and safety is good or better than clip reconstruction or coiling. PUFs demonstrated low 4.7% morbidity and 2.8% mortality. Efficacy in PUFs was 74% occlusion at 6 months, 86.8% occlusion at 1 year, and 95.2% occlusion at 5 years.

In terms of safety, a cohort of 598 aneurysms including anterior and posterior circulation treated with FD reported 5.8% morbidity and 2.2% overall mortality. The good safety profile of FDs in part stems from the fact that the aneurysm does not need to be catheterized or manipulated. Reliable deliverability, resheathability, and our understanding of and ability to closely titrate antiplatelet regimens has also enabled low periprocedural morbidity and mortality.

With flow diversion, complications are more often thromboembolically mediated than hemorrhagic. FDs induce endothelial remodeling and a prothrombotic state. In the Swed et al cohort, ischemic stroke occurred at a rate of 3%, with delayed aneurysmal rupture at 1.2% and distal intraparenchymal hemorrhages (IPHs) at 1.5%. IPH often occurs downstream of the FD and is suspected to result from altered flow dynamics or hemorrhagic conversion of embolically mediated infarcts. Predictors of morbidity with FD are posterior circulation aneurysms, increasing aneurysm size, and hypertension. Poor outcome is associated with ruptured aneurysms, increasing aneurysm size, posterior circulation, and patients > 75 years.

One early concern with flow diversion was around covering perforator vessels. We now know that FDs can safely cover most branch vessels, including the ophthalmic, posterior communicating, and anterior choroidal arteries and the anterior communicating artery complex. Branch vessels with poor collaterals tend to stay open, while those with good collaterals may close but typically asymptptomatically. In a meta-analysis of visual outcomes of 520 patients with paraclinoid aneurysms, vision improved more and was less likely to be harmed with FD compared to clipping or coiling.

Efficacy rates with flow diversion are superior to those reported for coiling and clipping; however, no definitive large randomized comparison of flow diversion versus clipping or coiling stands out. The PARAT trial conducted in China compared Tubridge FD to stent-assisted coiling and reported 6-month efficacy of 75.3% for FD compared with 24.5% for stent-assisted coiling.

Safety and efficacy of flow diversion is impacted by aneurysm size, type, and location and by device(s) utilized. In the posterior circulation where aneurysms have a higher chance of causing symptoms and rupturing, there is a breadth of pathology—saccular, basilar tip, and nonsaccular including fusiform, dolichoectatic transitional dissecting—with different natural histories, ability to cause symptoms, and treatment risks. The risk to brainstem perforators with 30% to 35% metal coverage with FDs is always a concern.

Siddiqui’s experience with nonsaccular posterior fossa aneurysms demonstrated varying degrees of success and lessons including careful selection of fusiform or dolichoectatic, use of adjunctive coiling, and reducing number of FDs to reduce perforator infarct risk. In the posterior circulation, flow diversion is superior to other endovascular techniques in efficacy and better than surgery in safety, with the best results demonstrated for saccular and dissecting subtypes.

In the IntrePED subgroup analysis for the posterior circulation, efficacy for complete occlusion was 80%. A multicenter study of posterior circulation aneurysms treated with flow diversion with median follow-up of 11 months
demonstrated an efficacy rate of 79%, with a major morbidity rate of 7.8% and minor complications rate of 19%. Clopidogrel nonresponders had higher complication rates. The occlusion rate for fusiform or dolichoectatic subtypes was 71.2%, with major complications of 11.5%.

Jailing branch vessels has been tolerated as long as the process of closure occurs gradually and there is anatomic potential for collateralization. Jailing a P1 segment was tolerated in a study of 16 basilar tip aneurysms, with 69% aneurysm occlusion at 6 months and major and minor complications of 6% and 13%, respectively. The jailed P1 segment was occluded in four patients, which was asymptomatic in all.

Lower efficacy rates are observed for: (1) nonsaccular or fusiform aneurysms, which are more difficult to treat by any means; (2) patients aged > 70 years, possibly related to reduced ability to endothelialize; and (3) aneurysms with parent vessel incorporated into the aneurysm neck. Parent vessel incorporation, particularly if the branch is “high flow” with poor potential for distal collateralization (eg, fetal posterior communicating artery), represents flow diversion efficacy challenges.

Long term, flow diversion is a stable treatment. Complications 6 months after treatment are rare, approaching 0%. Recanalization after occlusion with flow diversion is exceedingly rare.

With the diversity of cerebral aneurysm locations and presentations, which aneurysms are most likely optimal for treatment via FDs, and which for disruptors?

Compared with intra-aneurysmal flow disruptors, FDs have wider range of utility across aneurysms types, including ruptured, posterior circulation, nonsaccular, blister, anterior communicating, and pericallosal arteries, as well as utility in treating dissections and direct carotid-cavernous fistulas. Data on flow diversion for distal vessels of 1.5 mm demonstrated good efficacy, ranging from 60% to 90%, and variable procedure-related complications of 4% to 17%. A meta-analysis of flow diversion for 148 anterior communicating artery aneurysms demonstrated 87.4% efficacy with a morbidity of 3.5% and mortality of 2.5%.

Extracranial vessel reconstruction and treatment of cavernous sinus fistulas using flow diversion combined with other techniques can be achievable.

For flow disruptors such as WEB, the range of aneurysms appropriate for treatment is narrower. The primary mechanism of efficacy for WEB is endosaccular disruption, which induces thrombogenesis within the dome and secondary flow diversion and neoendothelialization at the neck. Aneurysms for WEB should be wide-necked bifurcation aneurysms with a straight angle of approach for intrasaccular catheter placement. WEB cannot be successfully deployed in side wall aneurysms.

Which cases are still best treated surgically or via coiling or other means?

Open surgical clipping is likely to continue to decline as a percentage of total aneurysms treated. The ISAT trial demonstrated the superiority of endovascular coiling compared with clipping for ruptured aneurysm in independent survival at 1 and 10 years. Surgical clipping in practice is now reserved for aneurysms that cannot be safely flow diverted, disrupted, or coiled or where operator experience may influence this decision. Flow diversion is safer and more efficacious in experienced hands. This is also true for open clipping, and with fewer clipping cases for trainees, open vascular neurosurgery may become a more rarified art. Open surgery will still be needed for complex cases that require both surgical deconstruction and reconstruction of parent anatomy.

Ruptured aneurysms are still primarily being coiled, often with intention for flow diversion for “definitive” treatment after the acute period. A retrospective study on 214 ruptured aneurysms coiled emergently reported 21.5% of aneurysms required retreatment for remnants or recurrence. Although rate of rerupture after emergent coiling is 2.3% to 3%, the authors reported a rerupture risk of 0.9% after retreatment (on par with rates after clipping). No death or neurologic morbidity due to treatment was reported. For incompletely coiled aneurysms, risk of rerupture is estimated at 6% to 16%, which justifies the procedural risk of definitive FD treatment.

Acute ruptured aneurysm treatment is an area of investigation for both FD and disrupters. Investigation of acutely ruptured aneurysm treatment using standard (noncoated) FDs has demonstrated acceptable results. A meta-analysis of 223 ruptured aneurysms treated 4 days from rupture reported 88.9% efficacy at follow-up with a procedural complication rate of 17.8%. Because of the concern of thromboembolic risk in the setting of the hypercoagulable state of acute subarachnoid hemorrhage, many operators await more data on the PED Shield with single antiplatelet therapy in this context. Manning et al treated 14 acutely ruptured aneurysms day 1 postbleed with the PED Shield and single antiplatelet and reported 86% efficacy at 7 days, 21% symptomatic complications, and 7% mortality. More data are needed, specifically best practices around timing postbleed, use of adjunctive coils, device sizing if vasospasm is present, and antiplatelet therapy in setting of ventriculostomy drains.

MCA bifurcation aneurysms is an area where clipping and stent-assisted coiling are highly considered, with the WEB utilized more in this context if anatomy allows. Investigation into the use of FDs for MCA bifurcation aneurysms has demonstrated good efficacy but higher complication rates in some studies. Cagnazzo et al performed a meta-analysis of 244 MCA aneurysms and reported 77% efficacy with 20.7% complications (10.3%
permanent), most of which (16.7%) thrombotically mediated. Antiplatelet therapy and planning of metal coverage is essential to success at the MCA bifurcation.

What is the most significant lesson in pitfall avoidance you share when training colleagues in FD treatment of wide-necked aneurysms?

Treating aneurysms with flow diversion safely and completely on the first attempt is a good general rule. For unruptured aneurysms, performing diagnostic angiography on a separate day from treatment is preferred. Operators should carefully plan antiplatelet therapy, access approach, support catheters, device, or construct, including sizing.

If apposition is not complete, utilize J-wire or balloon angioplasty techniques to ensure a perfect seal of the construct. Rotational cone-beam CTA with contrast after deployment is a tool to confirm neck coverage and device apposition. Retreatment at a later date for issues such as device migration and endoleak can be challenging. The presence of a preexisting stent and incomplete neck coverage is a predictor treatment failure.

If a device is not opening completely, it is acceptable to resheath and attempt to redeploy, but if fishmouthing twists or kinks do not resolve, the device should be recaptured and removed.

Efficacy of FD tends to improve with layered or telescoped devices. That said, layering devices may increase technical difficulty and risk, with some reports of higher complication rates with multiple devices.

The devices with higher metal coverage (eg, FRED) designed for single-device use may achieve acceptable efficacy in many contexts, but some aneurysms will be better treated with customizable constructs that allow for variation in metal density maximized across the neck. Given the difficulties around retreatment, optimizing the number of devices to size, flow dynamics, parent anatomy, and clinical context is ideal.

Similarly, how does one best ensure optimal outcomes when opting for a flow disruptor?

Choosing the right patient and aneurysm for the flow disruptor is the first step. After selection of the aneurysm—wide neck, bifurcation, sufficient height, and straightness of approach for catheterization—sizing is the most important technical decision with WEB treatment. Undersizing of WEB can lead to treatment failure. Other non-WEB “disruptors” should be used by experienced operators, in trial settings, or for aneurysms failed by or unsuitable for better-studied devices.

What pre- and postprocedural medical regimen is typically needed in these cases?

For flow diversion, DAPT is needed pre- and postprocedurally. Preprocedural duration is operator depen-

dent, but 5 to 10 days is typical for electively treated unruptured aneurysms. P2Y12 testing is a reliable method of assessing platelet inhibition and should be used prior to embolization with a target inhibition goal of 40% to 90%. This allows operators to add additional antiplatelet therapy prior, during, and shortly after the procedure. During FD embolization, patients are loaded with intravenous heparin with a goal-activated clotting time of at least two times the baseline. Some operators also administer low-dose intravenous heparin infusions for the first 24 hours postprocedure. After flow diversion, DAPT is maintained for 9 to 12 months.

The data for the safety and efficacy of ticagrelor have become robust in recent years and nonresponders to clopidogrel should be switched to ticagrelor. Intraparenchymal hemorrhagic complications can be the result on small infarcts that bleed with the patient on DAPT. When P2Y12 is very low (< 40), we favor a radial artery approach when feasible. For flow disruptors like the WEB, DAPT during the procedure is typical to allow for salvage stenting, with transition to single antiplatelet therapy postprocedure. The use of DAPT during embolization may evolve to single antiplatelet as our experience with WEB grows.

What is your standard follow-up protocol, and what are you watching for on subsequent visits?

In general, 6 to 12 months post flow diversion is a typical range for most aneurysms for follow-up angiography. Larger aneurysms can take longer to close, so follow-up angiography should be timed to a point when a change in management would be undertaken if the aneurysm is still patent (eg, decision to stop clopidogrel or decision to add FDs). Complex fusiform aneurysms in the posterior fossa sometimes need staggered rounds of flow-diverting treatment, and so follow-up angiography is carefully titrated to clinical context.

What is the most significant as-yet unmet need? What clinical trial would you most like to see next?

As a field, we are always seeking to offer more specificity—the safest and most efficacious treatment for a particular patient, aneurysm type, size, location, and clinical context. More research is needed to continue to optimize our treatment strategies. Theoretically, a trial with matched patients randomized by treatment strategy would help, but in reality, the safety and efficacy of flow diversion is too good and well-established to justify randomization versus clipping or coiling in all but a few scenarios. Bifurcation aneurysms and ruptured aneurysms are two areas with open questions on ideal strategy.

MCA bifurcation aneurysms are an area of interest in comparing flow diversion versus WEB versus stent-assisted coiling or Y-stent—assisted coiling in safety and
efficacy. The anterior communicating artery aneurysm is another "bifurcation" aneurysm type that would be interesting to compare flow diversion versus WEB disruption versus stent-assisted coiling versus open clipping.

For acutely ruptured aneurysms, a trial of flow diversion with antithrombogenic-coated devices versus standard coiling versus WEB with endpoints of safety and occlusion rates at 1-, 5-, and 10-year follow-up would be helpful. In many cases, coiling acutely is followed subacutely by flow diversion given aneurysmal remnants. How coiling plus additional treatment performs versus acute flow diversion with a coated device and single antiplatelet therapy is a clinically important open question.

Another area for investigation is the aneurysm type and location for optimal use of different FDs, in addition to the question of layered versus single-device constructs. A head-to-head comparison of PED Flex versus SV versus FRED using registry and propensity-matched cohorts would assist operators in device selection. How would PED Flex with patients on DAPT versus PED Shield on aspirin alone perform in the medically complex patient?

As safety data approach 1% to 2% for major complications for unruptured aneurysms, an important question is whether to treat smaller aneurysms with a low risk of rupture. For a 45-year-old patient with a 4-mm paraophthalmic aneurysm, the rupture risk accumulates over time to more than the one-time procedural risk of 1% to 2%. Should this aneurysm be treated and at what point?

And as we achieve > 90% efficacy, can we better predict which cases may never occlude with FDs and should be treated in another way? Or, does flow modification without occlusion provide enough protection against rupture in some cases? And similarly for WEB, do neck remnants matter? For other difficult-to-treat categories (the parent vessel arising from the aneurysm, fusiform aneurysms, and older patients), what are technical strategies that can ensure efficacy?