

Flow Diverters in the Management of Intracranial Aneurysms: A Review

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Abstract

This review summarises the reported clinical experience with flow diverters for the reconstruction of the parent artery of intracranial aneurysms, since their introduction 5 years ago. Over this period, the literature has documented treatment concepts and initial results. Safety concerns, some of which have proved unwarranted, have limited the use of these devices to the treatment of aneurysms which were likely to fail or had failed to be effectively treated by endosaccular coil embolisation. The emerging data now allows the risks of complications specific to this technology to be quantified and the emerging consensus on its efficacy has extended its use to include aneurysms suitable for conventional coil embolisation, in some centres. The need for antiplatelet prophylaxis will probably limit its use to anatomically complex and dissecting aneurysms in patients after spontaneous intracranial haemorrhage. This extending role highlights the need for systematic retrospective analysis of existing large case series and randomised comparative studies.

Keywords: flow diverters, aneurysm, pipeline embolisation device, silk flow diversion device, stents, intracranial

Background to the Current use of Flow Diverter Stents

Two devices designed to induce aneurysm thrombosis by altering blood flow, commonly called flow diverters (FDs), have been undergoing evaluation for the endovascular treatment of intracranial aneurysms. The evaluation of novel endovascular implants in Stage 2 trials is an ad-hoc process which usually involves the manufacturer recruiting skilled therapists to evaluate their device in largely undefined initial populations of patients. This piecemeal accumulation of data on efficacy, safety and indications is then used to justify the device's wider use. We feel that it is timely to take stock of FDs, and attempt in this review to analyse the published data, highlight areas of concern that remain under investigation and speculate on the future role of these devices.

The need for FDs is based on the rationale that there are a proportion of intracranial aneurysms that are not effectively treated by endovascular 'other means' or that effective treatment using FDs is safer than alternatives. In practice the 'other means' are endosaccular coil embolisation (ECE), conventional high porosity stents and coils (SAC), parent artery occlusion (PAO) or neurosurgical procedures (e.g. clipping, bypass, aneurysm resections). The number of aneurysms best treated with FDs is uncertain; a proportion are due to failure of ECE caused by anatomical constraints or delayed recurrence generally ascribed to the unresolved causative haemodynamic influence. Primary ECE is successful in approximately 90% of patients selected as suitable for this treatment [1] but approximately 10% will undergo retreatment because of delayed recurrence of the aneurysm [2]. High recurrence rates in extremely large aneurysms and

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aneurysms with neck widths greater than 4mm have been recognised for many years [3]. For these reasons large and giant aneurysms have been selected for treatment with FDs. A further group are unsuitable for ECE because of anatomical constraints, i.e. extremes of aneurysm size, fusiform shape, dissecting aneurysms and necks too wide to retain coils. In the past, such aneurysms have been treated by various techniques, e.g. SAC, PAO or neurosurgery.

It is inappropriate to compare the reported results of FD treatments with ECE since they have so far largely comprised aneurysms that are unsuitable for conventional endosaccular packing. Better benchmarks are alternative endovascular techniques, developed to improve the long-term stability of ECE including complex memory geometry and coated coils [4] [5], balloon assisted coiling [6] and the use of alternative packing materials such as Onyx [7]. So far these initiatives have failed to live up to initial enthusiasm and trials have found only modest reductions in recurrence rates [4] [5] [8]. Combining ECE with parent artery stenting, i.e. SAC, has several theoretical advantages (e.g. better coil retention and alterations in the blood flow patterns at the neck) but this technique has yet to demonstrate consistent reductions in recurrence rates. Moreover, they have introduced new complication risks e.g. late in-stent stenosis and delayed thromboembolic events [9]. The literature reporting clinical and anatomical sequelae of aneurysms treated with FDs alone or with endovascular coils has emerged against this background.

Experimental Evidence of Flow Diverters

Over the last 20 years, several researchers have tried to exploit the concept of a single endovascular stent device capable of inducing aneurysm thrombosis whilst maintaining patency of the parent artery. Systematic studies of how stent design features affect local blood flow have been conducted in experimental in-vitro studies using dyes [10] [11] [12] and particles [13] [14] [15] [16] [17] [18]. Particle image velocimetry has become the standard experimental technique of measuring alterations of blood flow in saccular aneurysms and the ability of FD to redirect blood flow within the parent artery [15] [19]. These findings have been supported by in-vivo studies, which demonstrate the potential of stents to disrupt endosaccular blood flow in experimental aneurysms [20] [21] [22] [23] [24] [25]. Using a rabbit model, Kallmes et al. showed that the orifices of side branches remain patent despite general endothelialisation of implanted FDs [26] [27].

Quantification of endosaccular flow on digital subtraction angiography can be performed using time-density curves [28] or washout models [29] and together with computational fluid dynamic simulation techniques [30] have been used to study the haemodynamic effects of stenting [31] [32]. These data have been used to inform the design of flow diverters [33] [34]. Such work has established porosity (defined as the proportion of open area to total area of the stent) and pore density (defined as number of pores per area) as important parameters and a porosity threshold of around 70% as the optimum compromise between stent flexibility and efficient flow diversion [18] [35]. Other important design features are filament size [15] and net design, which influence the implant's effect on side branches. In vitro studies have shown that despite substantial coverage of branch arteries, flow reductions in side branches are modest [18] [36]. However, it is worth remembering that the effective porosity of deployed FD stents depends on other factors such as correct sizing, degrees of opening [37] and position in relation to the geometry of the parent vessel and aneurysm neck.

Stent Assisted Coiling

The principle goal of all aneurysm treatments is exclusion of the aneurysm from the circulation; placing a stent across the aneurysm neck to obstruct blood flow into the sac achieves this objective. Covered stents with zero porosity have been used in cerebral vessels but are generally too stiff for intracranial navigation [38]. Porous stents were used first to treat extra-cranial aneurysms [39] [40] [41] and early reports of their use in intracranial arteries involved aneurysms associated with stenotic arterial disease [42] or fusiform shapes [43] [44]. With the availability of more flexible but high porosity designs, intracranial deployment became possible and several practitioners reported treatments with a combination of stents and coils [45] [46] [47] [48] [49]. There have been reports of successful sole stenting (i.e. without adjuvant endosaccular coils) using conventional high porosity stents [50], [51] but the long-term anatomical results have been inconsistent [52] [53] [54] [55]. These include attempts to decrease the effective porosity of the stent by using double or overlapping stents [53] [56] [57] [58] [59]. To date no comparative trial of these techniques has been reported.

There have been several single centre reports of SAC intracranial aneurysm treatments [60] [50] [9] [61] and one multicentre registry [62]. The larger series of Fiorella et al. [60] and Lylyk et al. [61] reported morbidity rates of 5.3% and 7.4% and mortality of 2.8% and 4.6% respectively. In the report of a multicentre registry concerning 141 patients, the morbidity was 2.8% and mortality 2% [62]. Indications for the use of SAC in early reports were generally similar to those currently applied for FDs but since FDs have been available, stents such Neuroform (Stryker) or Enterprise (Codman), are more often used for other indications. They still represent the endovascular treatment closest to arterial reconstruction with FDs and are therefore the best historic comparator of complication rates and safety.

Aneurysm recurrence rates after SAC treatments have been reported as lower than ECE but, as described above, the reduction has been modest. Sedat et al. [63] reported recurrence on first follow up angiograms in 9.5% of aneurysms in a small series of aneurysms with mean maximum dimensions of 11.3mm and mean neck sizes of 5.33mm. In a larger series, which included dissecting and fusiform aneurysms, Fiorella et al. [64] reported recurrences in 22% which was similar to the residual aneurysm filling reported by Biondi et al., who had an 11% retreatment rate after Neuroform (Stryker) assisted coiling [65]. In a large single series comparing treatments with and without adjuvant stents, Piotin et al. [9] found that recurrence rates were reduced (14.9% SAC versus 33% ECE) and this improvement applied for both small and larger aneurysm groups. However, the use of stents increased procedure related morbidity (7.4% SAC versus 3.8% ECE) and mortality (4.6% SAC versus 1.2% ECE) rates. The HELPS trial also found that SAC increased the risk of untoward events compared to ECE alone [66].

Current Practice

Since 2007, two FDs produced with the aim of uncoupling blood flow between parent artery and aneurysm sac have been available in Europe. They have a woven design of high wire density and low porosity. The treatment goals are: (a) to reconstruct the parent vessel and (b) to redirect blood flow along the longitudinal axis of the parent vessel thereby modifying the haemodynamic forces acting on the aneurysm [67]. Once deployed, the FD creates a physical barrier across the aneurysm neck disrupting blood flow in and out of the sac. The barrier introduced by the FD is subsequently augmented by the growth of endothelium and a neo-intima on its inner surface, consolidating the uncoupling. Endosaccular stagnation

and thrombosis of blood inside the sac may take several weeks to develop. It is best demonstrated by MR or CT scanning. Once achieved, endothelialisation of the FD completes the reconstruction of the parent vessel - aneurysm complex [68].

Instructions of use for both available FDs are broadly similar; the major difference is that adjuvant endosaccular coils are recommended for the SILK flow diverter (SFD) (Balt Extrusion, Montmorency, France). The SFD received European Community approval (i.e., CE marking) for use in January 2008. The Pipeline embolisation device (PED) (Covidien/ev3, Irvine, California) also has a CE mark and was approved by the FDA (Food and Drug Administration, US) in 2011 for the treatment of infra- and supraclinoid internal carotid artery aneurysms without ECE.

The SFD is a flexible, self-expanding, braided mesh stent with flared ends and a pore size of 110 - 250 μm . It is constructed from 48 braided nitinol (nickel-titanium alloy) and 4 platinum microfilaments $\sim 35\mu\text{m}$, which provides 35 - 55% metal coverage when expanded to its nominal diameter. Currently, SFDs are available in a range of diameters (3 - 5.5mm) and lengths (15 - 40 mm). The platinum strands act as radiopaque markers for visualisation under fluoroscopy. Second and third generation devices have been developed with lower porosity and increased the radial force. A SFD (termed SILK-plus) is now available with 8 platinum markers and with the option of tapered diameters to improve the conformity of the device to arteries of varying diameters. The PED is similar and is constructed from 48 microfilaments composed of platinum (25%) and nickel-cobalt-chromium alloy (75%). It is available in sizes similar to SFD (diameters 2.5 - 5 mm, lengths 10 - 35 mm). It is designed to provide 30 - 35% metal coverage of the target vessel's inner surface with a pore size of 0.02 - 0.05 mm^2 at nominal diameter. The PED is attached to a pusher wire, compatible with a 3F (0.027" ID) microcatheter. The pusher wire has a platinum coil tip, which extends 15 mm beyond the distal edge of the PED from which it is detached once deployed.

The devices are delivered via microcatheter (SFD using a 0.023"ID and PED a 0.027"ID microcatheter) requiring 6F guide catheter support. A tri-axial approach, including a 6F, 90 cm long sheath and a 6F distal access catheter is commonly used to provide better support and stability during deployment. Deployment involves positioning the FD's tip distal to the target aneurysm. This is followed by pushing the device, applied to a delivery microwire, to the tip of the delivery microcatheter. The system is then aligned with the selected 'landing position' distal to the aneurysm orifice under x-ray fluoroscopy. The SFD is deployed by unsheathing it from the microcatheter by a combination manoeuvre involving pushing the delivery wire and retrieving the microcatheter to encourage the SFD to expand. The SFD can be retrieved into the microcatheter and removed or repositioned if less than 90% of its length has been extruded from the microcatheter. No retrieval is possible thereafter. For deployment of the PED, the delivery wire is held while the distal 1/3 of the PED is carefully unsheathed. Once the unsheathed segment begins to expand, its distal end is released from the delivery wire either spontaneously or by clockwise rotation of the wire. The proximal segment of the PED is then deployed by gentle advancement of the wire. The PED is not retrievable, but at any point up to final deployment it may be captured and removed from the body [69].

Endosaccular coils can be placed before the FD is deployed or afterwards via a second microcatheter positioned prior to SFD deployment, a technique often referred to as 'jailing' [70]. Multiple overlapping FDs may be needed to cover wide necked or large fusiform aneurysms. In this case, after the first FD is fully deployed, the microcatheter may be re-advanced over the indwelling delivery wire, which is then exchanged for a second FD. The FDs are sometimes deployed within a conventional higher radial force

stent and expanding a balloon within the deployed FD (i.e. stentplasty) can help to ensure that the device is fully expanded and conforms well to the vessel wall. Recently the Surpass device (Surpass, Tel Aviv, Israel) also obtained CE approval (2010) and has now started clinical trials in Europe.

Prophylaxis against Thromboembolism and Parent Artery Thrombosis

Stent implants are likely to cause local vessel thrombosis and thromboembolism and a regimen of prophylaxis with antiplatelet drugs (APDs) is generally recommended. Data of this risk have been translated from stent use in cardiology and interventional radiology and their use for intracranial aneurysm treatment has not been tested in specific randomised trials. In practice, protocols have developed which balance the need to prevent thromboembolic complications against an increased risk of iatrogenic bleeding either intra-cranial or extra-cranial. The risk of the latter is illustrated by reports of serious non-neurological bleeding in up to 4.5% of FD treatments attributed to APDs. APD prophylaxis is best given before the FD is deployed; however, after recent aneurysm rupture there is a natural reluctance to give long acting APDs until the ruptured aneurysm has been secured.

Various pre-treatment regimes have been reported for non-emergency treatments; these vary in length from hours to days. The prescriptions usually involve a combination of aspirin and a thienopyridine (e.g. clopidogrel, ticlopidine or prasugrel). Clopidogrel is a prodrug and activated in the liver by cytochrome P450 enzymes, including CYP2C19. Platelet inhibition can be demonstrated 2h after a single dose of oral clopidogrel, but the onset of action may be slower so a loading dose is usually administered a few hours or days prior to FD placement [71]. The antiplatelet effect of aspirin is faster but given orally its effect increases over time and therefore both drugs are usually prescribed together. Examples of reported pre-treatment prescription protocols are 75 - 300mg aspirin and 75mg of clopidogrel for 3 - 7 days or a short regime of 300mg of both drugs 1 - 2 days prior to FD placement, though a loading dose of 600mg of clopidogrel has been shown to be better than 300mg in coronary arteries [72].

If FDs are used without pre-treatment, e.g. after recent subarachnoid haemorrhage, 500mg of aspirin given intravenously is effective in minutes and can be given with oral loading doses of a thienopyridine. Additional anticoagulation with heparin is used during the deployment procedure but normally not continued afterwards. Some centres also prescribe nimodipine to prevent vessel spasm during FD delivery [73].

Antiplatelet drugs should be given post-treatment for 3 - 6 months. A typical maintenance regime is 75mg - 300mg of aspirin and 75mg clopidogrel per day for 1 - 6 months though exact dosages vary depending on formulations in different countries. Many centres stop clopidogrel before aspirin, e.g. after 3 months, whilst maintaining aspirin for 6 months. Because of individual variations in the effective dose of both aspirin and clopidogrel, testing the patient's platelet activity after giving loading doses is an important precaution. About 15% of patients don't respond to oral clopidogrel [71]. A variety of in vitro platelet activity measurement methods are available. Their sensitivity is influenced by several factors, including the length of time since APDs were first administered. The validation of most tests is controversial which contributes to considerable confusion regarding their role in FD treatment.

Selection of Aneurysms for Treatment with Flow Diverters

The types of aneurysms that have been selected for treatment with FDs are predominantly those considered at high risk of recurrence after ECE, those with complex shapes or aneurysms that have recurred after other treatments. This is largely pragmatic and in theory most saccular aneurysms could be treated. No clear consensus on indications has yet emerged. Reconstruction of the parent artery with FDs is the most elegant solution for all aneurysms, but in practice concerns remain about deploying FDs at arterial bifurcations because of the risk of branch artery occlusion, and for small aneurysms where recurrence after ECE is uncommon. Other outstanding questions are a possible higher rate of complications after treatments of fusiform aneurysms, particularly those in the posterior circulation and the uncertain benefit of adjuvant endosaccular coils. There have been few reports of patients treated after acute SAH [74] [75] and too few for analysis, though SAC is increasingly used in this situation and numbers are likely to increase.

Literature on the use of Pipeline and Silk FDs in practice

There have been several clinical reports of the use of PED; 2 trials [76] [77], case series [78] [79] [80] [69], case reports [81] [82] [83] [84] [85] [86] and abstracts of conference presentations [87] [88] [89] [90] [91]. These involve some duplication of patients in different reports, e.g. 6 patients from Lylyk et al. 2009 [80] and 9 patients from Szikora et al. 2010 [69], were included in the PITA trial [76]. Though all these studies make valid points, the two trials provided much of the data for this review. These trials, called Pipeline Intracranial Treatment of Aneurysms (PITA) [76] and Pipeline for Uncoilable or Failed aneurysms (PUFS) [77] were prospective single arm multicentre trials. The PITA collected data on 31 patients treated in 4 centres for 31 aneurysms selected as unsuitable for ECE. The PUFS study has not been published in a peer review journal but data submitted to the U.S. Food and Drug Administration in 2011 are available [77]. These report details of 108 patients and 110 aneurysms treated in 10 centres. The published data on the SFD comprises a multicentre registry [92], case series [93] [94] [73] [95] [96] [97] and case reports [98] [99] [100] [101].

Reports of Procedures

Descriptions of procedures cover 3 areas; clinical adverse event (CAE), technical adverse event (TAE) and the immediate effect of FDs on flow in aneurysm and parent artery. Published reports only record a minority of treatments because more than 1500 aneurysms had been treated by March 2010 with SFDs but the proportion of these procedures reported in the literature is less than 20%. Byrne et al. [92] conducted the first international multicentre registry (SFD Registry) and Berge J et al. [73] a multicentre retrospective review of patients treated in 6 French centres. Both studies reported data from consecutive treatments over a defined time period. In the SFD Registry, data on 70 patients treated at 18 participating centres worldwide were evaluated for the device's technical performance and safety. In the French study 68 patients were treated for 77 unruptured complex or recurrent aneurysms and followed up at 6 and 12 months. In both studies, the majority of procedures were performed using SFD alone (86% and 78% respectively) and the cohorts contained a higher proportion of fusiform or dissecting aneurysms (37% and 32% respectively) than the PITA. Adjuvant coils were used in a small proportion of aneurysms (14% and 21% respectively). In PITA a single PED was used in 58% of aneurysms, and the aneurysm was covered by multiple PEDs in 42%. Additional coils were used in 52%. In PUFS the aneurysm location was limited to the

internal carotid artery proximal to the origin of the posterior communicating artery. In this study, coils were not allowed but 98% of subjects received more than one PED.

All these studies reported high incidences of successful FD deployment. Successful PED deployment was achieved in 97.9% in PITA and in 99% in PUFs. SFD failure rates were 4% in the SFD Registry and 1.5% in the French study; however, both studies described difficulties in opening the device and suboptimal positioning (17% and 12.3% respectively). These TAE are subjective and their described frequency probably depends on an assessment being mandated on case report forms (CRFs) in study protocols. Any consequent CAEs are likely to be more consistently measured. They were surprisingly infrequently reported in the SFD Registry in which only 1 patient experienced a new stroke despite a high rate of TAEs with inadvertent parent artery occlusion reported after 7 (10%) procedures. In the French study, parent artery occlusions occurred in 6 (9%) procedures but resulted in 4 strokes and one further patient suffered a stroke in the early post procedure period after FD thrombosis (See Table 1). It is probable that this complication is usually caused by poor conformity of the FD with the parent artery wall causing local thrombus and / thromboembolism. Stent conformity can be improved by stentplasty after deployment.

In PITA, two patients (6.4%) suffered a major peri-procedural stroke. One was related to rupture of the target artery during balloon angioplasty that became necessary due to inappropriate PED deployment. In the second case an ischaemic stroke was attributed to potential occlusion of lenticulostriate arteries covered by multiple PEDs and a Neuroform stent [76]. In PUFs the rate of major ipsilateral stroke and death at 180 days was 5.6%. Two of these events occurred peri-procedurally (1.9%); one was ischaemic due to PED thrombosis and the other haemorrhage following administration of a IIb-IIIa inhibitor for suspected minor ischaemic lesions [77]. Szikora et al. reported a major subarachnoid haemorrhage resulting in death, a few hours post procedure that was attributed to rupture of a concurrent small aneurysm located on the same internal carotid artery but distal to the target lesion [69]. No peri-procedural CAEs were reported in the Buenos Aires experience [80]. In a voluntary survey conducted by the European Society of Minimally Invasive Neurological Therapy (ESMINT), peri-procedural thromboembolic events were reported in 6.89% of 697 patients [102]. Peri-procedural parenchymal haemorrhages were found in 1.0% and SAH in 0.86%, totalling an 8.75% procedural complication rate.

The immediate effect of FD deployment on aneurysm filling is described in most reports. Szikora et al. [69] proposed an assessment scheme, which distinguishes complete stasis of contrast media within the sac from flow reduction. Rates for the former were 10% in the SFD Registry and 6.6% in the French study. Thus complete cessation of endosaccular blood flow is not the usual immediate response to FD deployment. Though symptoms generally improve, delayed symptomatic deteriorations may occur. Szikora et al. [69] reported improvement in 68% of patients presented with compression syndromes or headaches and PUFs reported improvement of aneurysm related symptoms in 41% of patients [77].

Delayed Clinical Outcomes

a) Ischaemic and Compression Symptoms

The cause of delayed non-haemorrhagic CAEs is often the subject of speculation because it is sometimes difficult to distinguish ischaemic events due to reductions in parent artery blood flow or small branch artery occlusion from symptoms due to induced aneurysm thrombosis. The latter was reported in early FD

reports [80] [92] and occurred in the first post-treatment 2 weeks in 24/64 (37.5%) of the French study patients [73]. In some cases peri-aneurysmal vasogenic oedema is evident on MRI with gadolinium enhancement around the aneurysm along with evolving signal in the endosaccular thrombus. Berge et al. [103] followed 17 patients treated with FDs and correlated clinical outcomes with such MR imaging findings. Seven patients exhibited emergence of new neurological symptoms or worsening of previous symptoms and MRI showed signs of a peri-aneurysmal brain inflammatory reaction, which was absent for those without clinical deterioration. The symptomatic group had larger aneurysms embedded in brain parenchyma and at least 50% sac thrombosis when new or increased symptoms occurred. These symptoms resolved within 30 days in all but one patient and the abnormal signal on MRI had disappeared at 3 months. The authors concluded that induced thrombosis initiates an inflammatory reaction that spreads to the adjacent parenchyma and may be responsible for post-treatment exacerbation of symptoms. This reaction appears to be worse in larger aneurysms due to a greater thrombus load. It has parallels with the post-implantation syndrome observed after endovascular abdominal aortic aneurysm repair, and this similarly is the basis for treating patients with corticosteroids. Aneurysm swelling alone may cause or exacerbate compression symptoms and has been observed in thrombosed aneurysms after parent artery occlusion due to swelling of endosaccular thrombus [104]. Very late increases in the size of treated aneurysms have also been reported [85] after FD treatments and have raised concerns that endosaccular thrombosis once induced by FDs without ECE may not be stable over time.

Other causes of delayed ischaemic CAEs are late FD thrombosis, thromboembolism, transient ischaemic events (TIA) and narrowing of the vessel lumen (i.e. in-stent stenosis). Post-treatment symptomatic worsening in the Silk Registry (n=70) was attributed to in-stent thrombosis in 1, thromboembolism in 1 and aneurysm swelling or FD-covered branch artery occlusion in 4 patients [92]. These symptoms resolved completely in half of the patients. In PITA no delayed CAEs were recorded [76]. In PUFs, 4 of 6 major ipsilateral stroke events occurred later than the first postoperative day. Two were ischaemic, one was related to significant in-stent stenosis and one was attributed to non-compliance with the antiplatelet protocol. Temporary aggravation of compression related symptoms was not reported but one patient (0.9%) suffered a partial visual field loss attributed to retinal ischaemia. Clinically, 41% of symptomatic patients improved within 180 days [77]. In a study of 54 patients with 57 aneurysms treated with PED, McAuliffe et al. found no permanent morbidity and mortality despite asymptomatic in-stent stenosis at 6 months in two patients [105]. In another case series of 96 aneurysms and 5 dissections, Fisher et al. reported 6 (5.9%) major complications; 2 of which were attributed to FD thrombosis [106].

Post-treatment patency of perforators and sidewall branches arising from the vessel segment covered with high mesh density FDs remains a major theoretical concern despite the evidence from animal models that side branches covered by FDs remain patent, as described above [26, 27]. Kulcsar et al. [94] addressed the issue in a small case series (n 12) of basilar artery aneurysms treated with FDs. They deployed SFD to cover one-third or more of the basilar artery length and subsequent angiograms confirmed patency of angiographically visible vessels covered by the FD in all but 1 patient. In this case, the proximal posterior cerebral artery failed to opacify. The patient was asymptomatic because of adequate collateral blood flow from the posterior communicating artery. In the Budapest experience, of 28 visible side branches covered by PEDs, 1 ophthalmic artery occluded intra-procedurally and 2 in a delayed fashion. These delayed occluded arteries were covered by 3 or 4 PEDs and both were asymptomatic. It is hypothesised that side branches with good collateral supply, such as the ophthalmic artery, have a higher tendency for occlusion due to pressure gradient changes following FD coverage [69]. The issue needs further study,

particularly if the device is, in future, to be used in distal vessels with side branches whose diameters approach those of FD pore sizes.

It is probable that delayed asymptomatic branch artery narrowing or occlusion is underreported. Slow narrowing of arterial origins allows time for collateral blood flow to develop and is thus without clinical sequelae. It may be a 'physiological' response to a chronic flow reduction sufficient to induce collaterals. This effect should be distinguished from thrombosis of the FD, which may be a delayed and sudden event. Fiorella et al. [82] reported stroke due to PED thrombosis at 23 months, and Klisch et al. [83] 12 months after treatments. Klisch et al. reported a patient who developed a fatal infarct and another who suffered no deficit after stopping APDs, illustrating how FD thrombosis may be asymptomatic and missed.

Comparing reports is complicated by variations in protocols for APD prophylaxis against stent thrombosis. There is general agreement among FD users of its value following treatment but peri-procedural prescription protocols vary between centres and studies. In the PITA trial [76] 75mg clopidogrel and 100mg aspirin was required starting 48hrs prior to and continued for 6 weeks following procedures. Aspirin was given indefinitely afterwards. In PUFs, 325mg of aspirin was given for 48hrs and 75mg of clopidogrel for 7 days prior to procedures, but a loading dose of 600mg clopidogrel was allowed the day before procedure. Clopidogrel was required for 3 months, and aspirin for 6 months post procedure, but according to reports most (but not all) centres also used clopidogrel for 6 months [102]. Platelet activity tests were not mandatory in any of these studies. The ESMINT FD related bleeding survey reported delayed thromboembolic events in 4.73% [102] and in some reports, it was unclear whether these patients were adequately anti-aggregated. The effects of APDs on the time-scale of endothelialisation of FDs and whether long fusiform aneurysms take longer to 'heal' and so require longer APD treatment than saccular aneurysms is unknown. So far, no systematic study has addressed this issue.

b) Early and Delayed Intracranial Haemorrhage

Aneurysm bleeding is easily distinguished as a cause of delayed CAEs but its pathophysiology remains uncertain. Both early and delayed post-procedure aneurysmal ruptures have been reported. There have been several small series reports of spontaneous intracranial haemorrhage in the peri-procedural period (i.e. up to 7 days) [81] [88] [89]. These have occurred due to aneurysm or parent artery ruptures or in the brain upstream to FD treatments. Cruz et al. [81], reported parenchymal haemorrhage remote from PED treated aneurysms between 1 - 7 days in 4/47 patients which they were unable to explain on the basis of procedural perforations. Spontaneous haemorrhage may be exacerbated by the aggressive use of APDs. Extra-cranial bleeding has also been reported as a cause of substantial morbidity and this clearly can be attributed to APD use. In the SFD Registry [92] 3 patients suffered complications due to acute extra-cranial bleeding and this contributed to one death.

The ESMINT survey [102] was conducted in 2011 to assess the frequency of FD related bleeding complications. It collected data on 720 aneurysms in 697 patients and investigated the potential reasons for post-FD haemorrhagic complications. Bleeding was classified as intra-cerebral (parenchymal) haemorrhage (ICH) remote from the target aneurysms and SAH related to rupture of the target aneurysm. Delayed ICH was reported in 2.0% and late aneurysm rupture in 1.0% of patients. The reason for remote ICH is unknown. It has been speculated that thrombosis of a giant aneurysm may eliminate the damping effect of the aneurysm sac and subsequently increase the pulsatility of the distal vasculature resulting in

rupture of distal small arterioles. Another theory is that ICH is due to repeated small emboli released from the surface of the yet non-endothelialised FD causing small, clinically silent infarcts, which undergo haemorrhagic transformation exacerbated by APD treatment. In this case, the ICH is primarily related to insufficient anti-aggregation.

There have been several reports of delayed rupture of treated aneurysms. Turowski et al. [98] reported fatal haemorrhage after SFD treatment of a symptomatic, but unruptured, large para-ophthalmic carotid aneurysm which appeared substantially occluded on an initial CT. Acute SAH occurred 20 days post-procedure and a second CT showed recannulation. Late bleeding from treated but incompletely occluded aneurysms has been reported by others [92, 62, 88, 76] and a similar, but much later, reopening of a thrombosed aneurysm was documented in the Silk Registry [92]. In the ESMINT survey, all of the aneurysms which ruptured after FD treatments were larger than 10 mm, and all but one was larger than 18mm, suggesting that this complication is specific to large and giant aneurysms. The delayed aneurysm rupture rate was 2.15% among 511 aneurysms larger than 10mm [102].

To explore the subject of delayed aneurysmal haemorrhage further and to identify putative factors Kulcsar et al. [107] collected 13 cases of post-procedural aneurysmal rupture from 12 centres worldwide and found: (a) 11 of the 13 patients were symptomatic prior to treatment, (b) most patients were hypertensive, (c) all aneurysms were >15mm in size (mean 22±6mm) and (d) all saccular aneurysms had aspect ratio >1.6. Though FDs caused contrast stagnation in all the aneurysms, a persistent in-flow jet was observed in 11 aneurysms. The authors considered this feature to be a contributory factor towards delayed aneurysm rupture. The effects of blood flow dynamics on the risks of late haemorrhage have also been studied by Cebal et al. who used computational fluid dynamics to show that endosaccular pressure increased after FD treatments in aneurysms that ruptured in the peri-operative period (up to 7 days) [108].

Late delayed rupture has raised concern over the stability of endosaccular thrombus after FD treatments. At follow up imaging, all aneurysms in Kulcsar's study [107] except one (for which thrombosis could not be evaluated) were occluded to a significant degree with thrombus (complete occlusion in 2, >90% occlusion in 5, and 50 - 90% occlusion in 5). Post-mortem histopathological examination in 2 patients showed intraluminal thrombi lacking significant organisation or cellular colonisation. Thrombus is known to undergo spontaneous lysis and renewal, and this may have been maintained by persistent low-grade intra-aneurysmal flow through the FD. These unstable thrombi are presumably the result of enzymes (e.g. proteases and elastases) generated within thrombus, which could cause thinning and weakening of the aneurysmal wall. Because aneurysm bleeding is rare after ECE, in which thrombus is generally stable with cicatrization and reverse remodelling of the vessel wall, it has been suggested that larger aneurysms be treated with adjuvant endosaccular coils to increase the flow diverting effect of FDs and improve the stability of induced thrombus.

Angiographic Outcomes

Follow up periods and imaging methods vary considerably between the published studies of FD treatments. Catheter angiography is generally considered the best method of demonstrating the extent of aneurysm and parent artery patency because of the obscuring effect of the FD. CTA and MRA can show vessel patency but are more useful at showing changes in aneurysm size. Large and giant aneurysms

should be considered as stable and completely occluded only after they have lost the initial increase in T1 and T2 signal intensities associated with recent thrombosis and unorganised intra-saccular thrombus. As with APD regimes, no consensus has emerged on imaging follow up protocols and various grading schemes have been described which recognise that residual aneurysm filling is common in the medium-term [69, 90] or are designed for assessing fusiform shape aneurysms [68].

Timing is important and angiographic results appear to be directly related to the interval since treatment and inversely to the use of APDs. In the SFD Registry [92], no follow up protocol was pre-specified and imaging intervals varied between centres. Imaging was performed at various times up to 6 months after treatment in 49 of 70 treated aneurysms and showed complete occlusion in 49%, neck remnants in 26% and saccular filling in 24%. In the PITA study, which specified assessments at 6 months, the rate for complete occlusion was 93.3% [76]. In PUFs, 73% of all study subjects and 80% of those having an angiogram at 6 months had complete occlusion [77]. The rate of complete occlusion increased to 86% among those examined at 1 year. The lowest rate for successful occlusion reported in a substantial series (n = 96) is 69% by O'Kelly et al. [90]. In the single centre report by Lylyk et al. [80], complete occlusion rates were 56% at 3 months and 95% at 12 months. Similarly, Fisher et al reported 52% complete occlusion at 3 months and 74% at 10 months out of 101 aneurysms and arterial dissections [106] and McAuliffe [105] complete occlusion in 62% at 1 month and 86% at 6 months.

Changes in the size of aneurysms after FD-induced thrombosis was studied using CT or MR by Berge et al. [73]. Like Lylyk et al. [80], they observed improving occlusion rates with time (68% complete occlusion at 6 months and 84% at 12 months) and that at 12 months 30% of the completely occluded aneurysm had disappeared, 56% were smaller, 11% were unchanged and 7% larger. Adjuvant endosaccular coils reduced the chance of the aneurysm size reducing; 96% of those treated without coils but only 26% of those treated with adjuvant coils disappeared or reduced in size. None of the reported series have separately reported angiographic outcome for saccular and fusiform aneurysm shapes which is surprising since the parameters generally used, e.g. neck remnant and body filling, are often quite different as pointed out by Kamran et al. [68] and outcomes poorer [92].

There have been no large studies with follow up data beyond 1 year and reports of very late aneurysm rupture have raised concern about the long-term stability of the induced thrombosis. Szikora et al. found no recurrence of 11 aneurysm studied by MR/MRA at 1.5 to 2 years [69]. The PUFs trial is following patients for up to 5 years and the 180 days and 1 year angiographic results are available. Ninety seven percent of aneurysms that were completely occluded at 180 days remained completely occluded on angiograms performed at 1 year without major stenosis or occlusion of the parent artery [77]. These data suggest that angiographic aneurysm occlusion achieved by FD is at least as stable as after ECE but data from long-term studies are still needed to confirm that delayed re-opening is a rare event.

Ongoing randomised clinical trials for flow diverter devices

So far systematic study of the use of FDs is limited to non-comparative cohort studies. Randomised clinical trials have been proposed to compare it with conventional endovascular aneurysm treatments in a rigorous fashion. One prospective randomised controlled trial of the SFD, called MARCO POLO (Multicentre randomised trial on selective endovascular aneurysm occlusion with coils versus parent vessel reconstruction using the SILK flow diverter) is underway. It has been designed to compare SFD treatment

against ECE for efficacy (angiographic outcomes at 12 months post-procedure) and safety (technical problems and clinical complications in a 12 month period post-procedure) [109].

Similar trials of the PED are underway which will evaluate the technical and clinical performance of this device. These include: (a) FIAT trial (Flow diversion in Intracranial Aneurysm Treatment), comparing clinical outcomes between flow diversion and best standard treatment (conservative, coiling, stenting or parent artery occlusion methods) [110] and (b) COCOA trial (Complete Occlusion of COilable intracranial Aneurysms) comparing PED with ECE in small wide neck aneurysms [111]. Clearly, these data are needed before a substantial shift to treat most aneurysms with FDs occurs. The experience of the last 5 years suggests that with improving designs and physician experience, such a shift is now a definite possibility.

Conflict of interest

JVB's department receives research support from Balt Extrusion, and JVB is a paid scientific Consultant advisor for Codman Neurovascular. IS's Department of Neurointervention at the National Institute of Neurosciences has previously received research support from Covidien/ev3, and IS consults for Covidien/ev3 and Stryker Neurovascular.

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Table 1: Summary of published series (n>10) reporting clinical experiences after flow diverter treatments

Study	Patients (P)/ Aneurysms (A)	Aneurysm location and morphology			Procedures abandoned	Deployment difficulty	Thrombo-embolic / Ischaemic events	Haemorrhagic complications or events	Branch occlusion	§ Early neurological morbidity and mortality	Occlusion grade at Follow-up	Delayed neurological morbidity and mortality
		Site	Size	Shape								
Lylyk et al. (2009) [80]	P 53 A 63	AC 56 PC 7	S 33 L 22 G 8	S 55 F 8	0	2	0	0	0	0	OG1 95%** OG2 0 OG3 5%**	0
Szikora et al. (2010) [69]	P 18 A 19	AC 18 PC 1	S 5 L 10 G 4	S 18 F 1	0	3 (15%)	1 (5%)	1 (5%)	1 (5%)	2 (10%)	OG1 94% OG2 0% OG3 6%	0
Byrne et al. (2010) [92]	P 70 A 70	AC 50 PC 20	S 18 L 37 G 15	S 44 F 26	3 (4%)	13 (17%)	7 (10%)	* 4 (3 +1)	0	1 (n 67) 2 (n 67)	OG1 49% OG2 26% OG3 25%	2 (n 50) 4 (n 50)
Lubicz et al. (2010) [93]	P 29 A 34	AC 20 PC 14	S 0 L 20 G 14	S 15 F 14	3 (10%)	1	5	2	2	1 (n 26) 0 (n 26)	OG1 69% OG2 3.5% OG3 27.5%	3 (n 26) 1 (n 26)
Wagner et al. (2011) [95]	P 22 A 26	AC 19 PC 7	S 14 L 11 G 1	S 26 F 0	0	1	2	0	0	0 (n 22) 0 (n 22)	OG1 68% OG2 16% OG3 16%	1 (n 22) 1 (n 22)
Kulcsar et al. (2010) [94]	P 12 A 12	AC 0 PC 12	S 6 L 5 G 1	S 12 F 0	0	1	1	0	1	1 (n12) 0 (n12)	OG1 58% OG2 25% OG3 17%	3 (n12) 0 (n 12)
Berge et al. (2011) [103]	P 17 A 17	AC 12 PC 5	S 4 L 11 G 2	S 7 F 10	0	(12.3%)	4	0	0	NA	NA	7 (n 17) 0 (n 17)
Kulcsar et al. (2011) [107]	P 13 A 13	AC 10 PC 3	S 0 L 9 G 4	S 9 F 4	0	2	4	Occlusion status at follow up: complete in 2, >90% in 5, 50-90% in 5, NA in 1 (n 12) Clinical sequela: 9 deaths, 2 severe disability, 2 CCF and PAO, 1 good recovery				
PITA (2011) [76]	P31 A31	AC 29 PC 2	S 20 L 9 G 2	No info	1	7	1	1	0	2 (6%)	OG1 93% OG2 0 OG3 7%	0
PUFS (2011)[77]	P108 A110	AC 108	S 1 L 85 G 22	No info	1	8	3	2	0	2 (2%)	OG1 84%*** OG2 9% *** OG3 7% ***	4 (n 108) 2 (n 108)
Berge et al (2012) [73]	P65 A77	AC 66 PC 9	S 14 L 35 G 18	S 52 F 25	1 (1.5%)	9	6	4	6	4 (n 65)	OG1 85% OG2/3 15%	5 (n 64) 2 (n 64)
Fischer et al (2012) [106]	P88 A101				1 (1%)	13	2	4 (3+1)	0	3 (3%0 2 (2%)	OG1 52% OG2 36% OG3 12%	1 (2%) 1 (2%)

Legend for Table 1

Abbreviations: P= patients, A = aneurysms, AC = anterior circulation, PC = posterior circulation, OG1 = complete occlusion, OG2 = neck remnant, OG3 = saccular filling.

§ Early (<48 hours post-procedure) outcomes; neurological morbidity and mortality is presented as morbidity n (%) over mortality n (%).

* Of 4 haemorrhagic complications, 3 were extracranial (acute groin haematoma, neck haematoma, and gastrointestinal bleed) and 1 delayed aneurysmal haemorrhage

**angiographic follow up at 12 months

***angiography at 6 months in 92 patients