Advances in endovascular aneurysm management: flow modulation techniques with braided mesh devices

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ABSTRACT

Flow diverters and flow disruption technology, alongside nuanced endovascular techniques, have ushered in a new era of treating cerebral aneurysms. Here, we provide an overview of the latest flow modulation devices and highlight their clinical applications and outcomes.

INTRODUCTION

The arrival of the Guglielmi detachable coil system has given rise to the field of neuroendovascular intervention. Multiple randomised controlled trials have demonstrated the efficacy and safety of coil embolisation^{1 2}; however, post-treatment aneurysm recanalisation remained a significant challenge at that time, with rates in some reports up to 50%.^{3 4}

Since then, many technological advancements have been developed to address the shortcomings of endovascular coiling, including significant changes in coil properties.^{3 4} Adjunctive devices such as intracranial stents and balloons were developed to augment coil embolisation. Balloon-assisted coil embolisation reduces the risk of coil prolapse into the parent artery and can provide immediate proximal control with balloon inflation in case of intraprocedural aneurysm rupture. Similarly, stent-assisted coiling allows for increased coil packing density, critical for the treatment of wide-necked, large and giant aneurysms, thereby significantly improving the obliteration rate.^{5–7}

Despite these technological developments, aneurysms with unfavourable parameters such as large diameters (>10 mm), wide necks, small dome-to-neck ratios (<2) and fusiform morphologies remain significant dilemmas, with poor outcomes including aneurysm recurrence as well as treatment-related morbidity and mortality.^{8 9} Flow modulation techniques with braided mesh devices have been designed to tackle these challenges and ushered in a new era of endovascular neurointervention.

FLOW DIVERSION (FD) EMBOLISATION

The concept of FD stems from the lessons learnt in the development of stent-assisted coiling. The association of denser coil packing with better angiographical and clinical outcomes is explained by haemodynamic flow modulation as endovascular stents directly disrupt blood flow into the aneurysmal sac from the parent artery and accelerate intra-aneurysmal thrombosis.^{10 11} FD with braided mesh device is based on two principles: 1) the placement of a high-mesh density device in the parent vessel alters blood flow away from the aneurysm lumen, and 2) the device construct provides a scaffold on which endothelium can grow in a process termed 'neoendothelialisation', thereby isolating the aneurysm from the parent circulation, allowing for gradual intra-aneurysmal thrombosis, and eventually resulting in a curative outcome with complete radiographical occlusion of the aneurysm.¹² The advantage of FD techniques lies in the ability to treat the weakened arterial wall. Neoendothelialisation leads to more resilient aneurysm occlusion, compared with the high rate of recurrence associated with coil embolisation. Additionally, the endoluminal approach in deploying flow diverters (FD) does not require direct access to the aneurysmal sac, thereby removing the risk of intraprocedural aneurysm rupture inherent with coiling.

In 2007, the arrival of the Pipeline Embolization Device (PED; Medtronic Neurovascular, Irvine, California, USA) marked the first clinical application of FD in treating cerebral aneurysms.¹³ Many FDs have since continued to expand the neuroendovascular field, including Surpass (Stryker Neurovascular, Fremont, California, USA), Silk (Balt Extrusion, Montmorency, France), Flow-Redirection Endoluminal Device (FRED; MicroVention, Tustin, California, USA), p64 Flow Modulation Device (Phenox, Bochum, Germany), Derivo Embolization Device (Acandis, Pforzheim, Germany) and

Tubridge (MicroPort Medial, Shanghai, China). In the USA, the Food and Drug Administration (FDA) approved PED in 2011, Surpass in 2018, and FRED in 2019, all for the treatment of large or giant, wide-neck intracranial aneurysms along the internal carotid artery (ICA) (FDA.gov). Comparatively, most FDs are commercially available outside the USA. Table 1 summarises the technical specifications for the more commonly used FDs to date. Table 2 summarises major studies for the different flow diverter devices.

FD indications

On-label large and giant ICA aneurysms

Pipeline Embolization Device (PED)

The efficacy, safety and cost-effectiveness of the initial PED experience was demonstrated in the literature primarily for on-label usage in large and giant ICA aneurysms. Initial experiences from Buenos Aires and Budapest case series showed complete angiographical occlusion rates of 90%–93% at 6 months' follow-up.^{14 15} The Pipeline Embolization Device for the Intracranial Treatment of Aneurysm (PITA) trial and the Pipeline Embolization Device for Uncoilable or Failed Aneurysms (PUFS) trial followed and similarly showed acceptable occlusion rates (81.8%–93.3% at 6 months) with low complication rates reported (5.6%–6.5%).^{13 16} The literature continues to grow as newer generations are released. The pipeline flex with shield technology, with its new phosphorylcholine stent-surface modification aimed at minimising thrombogenicity, was used in two studies, and adequate occlusion rates were achieved with similar morbidity and mortality to previous PED reports.^{17 18}

Surpass

Initial experience from The Netherlands showed a 94% complete neck coverage and aneurysm occlusion with no major periprocedural morbidity or mortality at 6 month of follow-up.¹⁹ A prospective, multicenter study of 165 patients with 190 intracranial aneurysms treated with Surpass was conducted by Wakhloo *et al.* Follow-up angiography available in 158 (86.8%) intracranial aneurysms showed complete occlusion in 75% of cases. Permanent neurological morbidity and mortality were 6.0% and 2.7%, respectively.²⁰

The Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT) trial is a multicenter, prospective, single-arm, non-randomised, interventional trial of the Surpass Flow Diverter for uncoilable or previously treated but failed aneurysms of the intracranial ICA extending from the petrous segment to the carotid terminus at its bifurcation into anterior cerebral artery (ACA) and middle cerebral artery (MCA). Twelve-month primary effectiveness rate was 62.8%, and 12-month major ipsilateral stroke or neurological death rate was 8.3%.²¹ Historically, FD of posterior communication artery (PCoA) aneurysms had been met with concerns for aneurysm persistence and occlusion of the covered (or jailed)

vessel.²² The SCENT trial included the highest percentage of PCoA aneurysms compared with pre-existing FD clinical trials with resulting comparative efficacy, as well as morbidity and mortality rates.²¹

Silk

The Silk and Silk+ are the first-generation and second-generation FDs from Balt (Balt Extrusion, Montmorancy, France). Lubicz and colleagues reported their experience with Silk in treating 29 patients with 34 aneurysms. Angiographical follow-up demonstrated complete occlusion in 20 aneurysms (69%). Morbidity and mortality rates were 15% and 4%, respectively.²³ Several other groups have demonstrated success with Silk, reporting complete occlusion rates of 68% at 6 months to 93.9% at 1 year. Morbidity and mortality rates are comparable to other FDs at 4%–10% and 2%–3%, respectively.^{24 25}

Due to technical complications related to the lower radial force, the second-generation Silk+ was developed. Lubicz *et al.* conducted a retrospective study of 58 patients with 70 aneurysms and found a 73% complete occlusion rate with no recanalisation or retreatment necessary. Permanent neurological morbidity was 5.5% (all within the subgroup of patients treated with the first-generation Silk) with no procedure-related mortality.²⁶

Flow-Redirection Endoluminal Device (FRED)

Safety and Efficacy Analysis of FRED Embolic Device in Aneurysm Treatment (SAFE) is a single-arm, prospective, multicentre, observational study conducted by Pierot *et al.* A total of 103 aneurysms were treated, and at 1 year of follow-up, complete occlusion was observed in 73.3% with no evidence of recurrence. Morbidity and mortality were 2.9% and 1.9%, respectively.²⁷ Several additional case series demonstrate the effectiveness of FRED, each showing excellent radiographical outcomes and low morbidity and mortality.^{28 29}

Derivo

Brazilian Registry of Aneurysms Assigned to Intervention with the Derivo Embolization Device (BRAIDED) is a multicentre, prospective, single-arm trial with 183 aneurysms treated. Trivelato *et al.* reported complete occlusion in 113 of 140 (80.7%) aneurysms with available follow-up at 6 months and 74 of 83 (89.2%) at 12 months. Morbidity was 4.1% and mortality was 1.4%.³⁰ The literature has reported an occlusion rate of 80.7% at 6 months to 89.2% at 1 year with Derivo FD. Morbidity and mortality are comparable to other FDs.^{31 32}

P64

Fischer and colleagues studied 130 aneurysms treated with P64 and reported a 79.6% complete occlusion rate in 106 aneurysms at 9 months of follow-up. Permanent morbidity and mortality were 1.7% and 0.8%, respectively.³³ Complete occlusion has been reported at 66% at 6 months, up to 98.5% at 2 years, with a morbidity of 0%–2.5% and mortality of up to 1%.^{34 35}

Table 1 Technical specifications for flow diverters

Flow diverter	Pipeline (PED)	Pipeline Flex	Pipeline Shield	Surpass	Silk	Silk+	Silk Vista Baby	FRED	FRED Jr.	p64	Derivo	Tubridge	Flowise
CE (Europe) approval	2008	2014	2015	2011	2008	2012	2018	2012	2015	2012	2013	Not reported	Not reported
FDA approval	2011	2015	N/A	2018	N/A	N/A	N/A	2019	2019	N/A	N/A	N/A	N/A
Material	25% platinum-tungsten; 75% cobalt-chromium	25% platinum-tungsten; 75% cobalt-chromium	25% platinum-tungsten; 75% cobalt-chromium-nickel alloy	Cobalt-chromium	92% Nitinol; 8% Platinum	Nitinol; platinum	Nitinol, platinum	Nitinol	Nitinol, tantalum	Nitinol	Nitinol	Nitinol, platinum-iridium	Nitinol, platinum
Number of braids	48	48	48	48-96	48	48	48	64	52	64	48	64	48
Generation	First	Second	Third	First	First	Second	Third	First	Second	First	First	First	First
Delivery system	Empty catheter via 0.027-inch microcatheter	Empty catheter via 0.027-inch microcatheter	Empty catheter via 0.027-inch microcatheter	Preloaded over-the-wire delivery system with a 0.040" inner diameter delivery microcatheter and pusher	Empty catheter via 0.021, 0.023- or 0.025-inch microcatheter	Empty catheter via 0.021-, 0.023- or 0.025-inch microcatheter	Empty catheter via 0.017-inch microcatheter	Empty catheter via 0.027-inch microcatheter	Empty catheter via 0.021-inch microcatheter	Empty catheter via 0.027-inch microcatheter	Empty catheter via 0.027-inch microcatheter	Empty catheter via 0.029-inch microcatheter	Empty catheter via 0.027-inch microcatheter
Resheath feature	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Occlusion rate	81.8-93.3% at 6 months	77% at 12 mo	78.8-90.3% 6-18 mo	62-94% 6-12 mo	68% at 6 mo, up to 93.9% at 12 mo	73% (mean 22 mo)	63% (mean 2.7 mo)	73% 6 mo, up to 96% 12-24 mo	87% (6-24 mo)	66% at 6 mo; up to 98.5% at 24 mo	80.7% at 6 mo; 89.2% at 12 mo	75.34% at 6 mo	66.7% at 6 mo

FDA, Food and Drug Administration; FRED, Flow-Redirection Endoluminal Device; N/A, not applicable; PED, Pipeline Embolization Device.

Table 2 Major studies of flowdiverter devices

Flow diverter	Author, year	Patients, aneurysms (n)	Type of aneurysms treated	Occlusion rate	Morbidity (%), mortality (%)
PED	Lylyk <i>et al</i> , 2009 ¹⁴	53, 63	Wide-necked large and giant aneurysms for which previous treatment attempts failed	93% at 6 months	5; 0
	Szikora <i>et al</i> , 2010 ¹⁵	18, 19	Large, giant, fusiform or wide-necked aneurysms	94.4% at 6 months	5.5, 5.5
	Nelson <i>et al</i> , 2011 (PITA) ¹³	31, 31	Unruptured wide-necked aneurysms or failed previous therapy	93.3% at 6 months	6.5, 0
	Becske <i>et al</i> , 2013 (PUFS) ¹⁶	108, 108	Unruptured large/giant wide-necked aneurysms of proximal ICA	73.6% at 6 months, 86.8% at 1 year, 93.4% at 3 years and 95.2% at 5 years	2.8, 2.8
	Atasoy <i>et al</i> , 2019 (PEDSU) ¹⁷	41, 44	Mostly large/giant, wide-neck, saccular aneurysms	78.8% at 6 months and 90.3% at 18 months	6.8, 2.3
PED Shield	Trivelato <i>et al</i> , 2019 ¹⁸	151, 182	Mostly large and giant aneurysms, mostly saccular	79.7% at 6 months, 85.3% at 1 year	6.0, 0.7
Surpass	De Vries <i>et al</i> , 2013 ¹⁹	37, 49	Unruptured, complex, mostly saccular ICA aneurysms	94% at 6 months	3, 0
	Wakhloo <i>et al</i> , 2015 ²⁰	165, 190	Mostly unruptured, anterior circulation, wide-necked ICA aneurysms	75% at 6 months	6.0, 2.7
	Meyers <i>et al</i> , 2019 (SCENT) ²¹	180, 180	Uncoilable or previously treated but failed ICA aneurysms	62.8% at 1 year	8.3, 2.2
Silk	Lubicz <i>et al</i> , 2010 ²³	29, 34	Fusiform or wide-necked, unruptured aneurysms	69% at 6 months	15, 4
	Berge <i>et al</i> , 2012 ²⁴	65, 77	Unruptured or recanalised, saccular aneurysms	68% at 6 months, 84.3% at 1 year	7.8, 3
	Shankar <i>et al</i> , 2016 ¹⁰³	92, 103	Mostly unruptured saccular ICA aneurysms	83.1% (median 1 year)	8.7, 2.2
	Pumar <i>et al</i> , 2017 ¹⁰⁴	157, 180	Unruptured, saccular ICA aneurysms	78.1% at 1 year	9.6, 3.2
	Foa Torres <i>et al</i> , 2018 ²⁵	246, 293	Unruptured, saccular ICA aneurysms	93.9% at 1 year	4.2, 2.1
Silk+	Lubicz <i>et al</i> , 2015 ²⁶	58, 70	Saccular and fusiform aneurysms	73% (mean follow-up of 22 months)	5.5, 0
FRED	Möhlenbruch <i>et al</i> , 2015 ²⁸	29, 34	Mixture of wide-neck saccular, fusiform/dissecting, large/giant aneurysms	73% at 6 months	3.4, 0
	Pierot <i>et al</i> , 2019 (SAFE) ²⁷	103, 103	Unruptured saccular aneurysms	73.3% at 1 year	2.9; 1.9
	Piano <i>et al</i> , 2019 ²⁹	162, 165	Mostly unruptured, saccular or fusiform/dissecting aneurysms	96% at 12–24 months	7.3 (6.2 related to FRED), 4.3 (2.4 related to FRED)
Derivo	Akgul <i>et al</i> , 2016 ³¹	24, 34	Wide-necked, mostly medium-sized and fusiform aneurysms	71.4% at 3 months, 77.8% at 9 months	8.4, 4.3
	Daglioglu <i>et al</i> , 2019 ³²	146, 182	Mean aneurysm size was 8.3 mm	78.7% at 7.02 months	3.4, 2.7
	Trivelato <i>et al</i> , 2019 ³⁰ (BRAIDED)	146, 183	Mostly saccular and unruptured aneurysms	80.7% at 6 months, 89.2% at 1 year	4.1, 1.4
P64	Fischer <i>et al</i> , 2015 ³³	121, 130	Mostly unruptured, saccular sidewall aneurysms	79.6% at 9 months	1.7, 0.8
	Briganti <i>et al</i> , 2017 ³⁴	40, 50	Mostly unruptured, small, saccular ICA aneurysms	88% at 6–24 months	2.5, 0
	Morais <i>et al</i> , 2017 ⁶⁵	39, 48	Mostly unruptured, saccular aneurysms	66.6% at 6 months, 85.7% at 1 year	0, 0

Table 2 Continued

Flow diverter	Author, year	Patients, aneurysms (n)	Type of aneurysms treated	Occlusion rate	Morbidity (%), mortality (%)
	Sirakov <i>et al</i> , 2019 ³⁵	72, 72	Mostly saccular aneurysms	91.4% at 1 year, 98.5% at 2 years, 100% at 3 years	1.4, 0
Tubridge	Zhou <i>et al</i> , 2014 ³⁷	28, 28	Large or giant ICA aneurysms	72% at mean 9.9 months	0, 0
	Liu <i>et al</i> , 2018 (PARAT) ³⁶	82, 82	Mostly unruptured large/giant aneurysms of ICA	75.3% at 6 months	2.4, 1.6
FloWise	Kim <i>et al</i> , 2019 ³⁸	10, 14	Paraclinoid or ophthalmic ICA aneurysms	66.7% at 6 months, 83.3% at 1 year	0, 0

FRED, Flow-Redirection Endoluminal Device; ICA, internal carotid artery; PARAT, Parent Artery Reconstruction for Large or Giant Cerebral Aneurysms Using the Tubridge Flow Diverter; PEDSU, Pipeline Embolization Device with Shield Technology in Unruptured Aneurysms; PITA, Pipeline Embolization Device for the Intracranial Treatment of Aneurysm; PUFS, Pipeline Embolization Device for Uncoilable or Failed Aneurysms; SAFE, Safety and Efficacy Analysis of FRED Embolic Device in Aneurysm Treatment; SCENT, Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms.

Tubridge

The Parent Artery Reconstruction for Large or Giant Cerebral Aneurysms Using the Tubridge Flow Diverter trial evaluated the safety and efficacy of the Tubridge FD (with and without adjunctive coils) in the treatment of large or giant ICA aneurysms in comparison with stent-assisted coiling. Six-month follow-up imaging showed complete occlusion rates of 75.34%. The procedure-related morbidity and mortality were 2.4% and 3.66%, respectively.³⁶ A similar occlusion rate was shown in a study by Zhou *et al*, with no morbidity or mortality.³⁷

FloWise

In a single-centre prospective pilot study published in 2019, the FloWise flow diverter (Taewoong Medical, Seoul, South Korea) was used to treat 14 ICA aneurysms. There were no treatment-related complications, with complete occlusion of 66.7% of aneurysms at 6 months of follow-up and occlusion of 83.3% aneurysms at 12 month follow-up.³⁸

Small aneurysms

Flow diverters hold unique advantages in treating small aneurysms. Lin *et al* retrospectively reviewed a single-institution aneurysm database of 44 PED cases for small (<10 mm) ICA aneurysms in 41 patients. Angiographical occlusion was observed in 80% at 6 months of follow-up, and mortality was 2.3%.³⁹ Other studies have also established the effectiveness and safety of PED treatment in patients with small intracranial aneurysms, with lower rates of retreatment compared with both simple coiling and stent-assisted techniques.^{40–42} The Prospective Study on Embolization of Intracranial Aneurysms with the Pipeline Device (PREMIER) trial was created to evaluate the safety and efficacy of PED in the treatment of wide-necked aneurysms, measuring ≤12 mm, located along the ICA or the vertebral artery. At 1 year, 76.8% of patients had complete occlusion without parent vessel stenosis (≤50%) or retreatment. The combined major morbidity and mortality rate was 2.1%.⁴³ In 2019, Pipeline Flex

indications were subsequently expanded by the FDA to include treatment of small or medium wide-neck saccular or fusiform brain aneurysms of the ICA. This is important as over 80% of all cerebral aneurysms in the general population are less than 10 mm in size,^{44 45} and the majority of ruptured aneurysms are smaller than 10 mm.⁴⁶ Additionally, prospective 25-year, single-centre studies of 1306 aneurysmal subarachnoid haemorrhage (SAH) has shown that very small ruptured aneurysms (<5 mm) rose from 29% during the initial 5-year period (1991–1996) to 50% in the most recent period (2012–2016).⁴⁷

Aneurysms beyond the ICA

Until recently, there lacked evidence on the effectiveness of FD for aneurysms at the anterior communicating arteries, MCA bifurcation and basilar apex, which collectively account for a majority of aneurysmal SAH. Atallah *et al* reported a complete occlusion rate of 78.3% in 23 distal circulation aneurysms treated with PED (11/23 MCA, 6/23 posterior cerebral artery (PCA), 3/23 ACA (A1/A2, pericallosal artery) and 3/23 PICA) with a good clinical outcome in 95% of patients.⁴⁸ Michelozzi *et al* studied the use of FD in the treatment of 30 aneurysms in 29 patients (21 located in MCA bifurcation, 8 in anterior communicating artery (ACoA) and 1 in pericallosal artery bifurcation). The overall occlusion rate was 82.1% (23/28), with permanent morbidity of 3.4% and no mortality. One recanalisation occurred during the follow-up time.⁴⁹ Colby and colleagues reported a series of 50 cases of ACoA aneurysms treated with PED with 85% complete occlusion at the last follow-up and a permanent neurological morbidity rate of 4%.⁵⁰ Cagnazzo *et al* conducted a systematic review and meta-analysis of 14 studies (published 2009–2018) that included 148 unruptured saccular ACoA aneurysms treated with FD. PED was used in 97/148 (65.6%) cases, FRED in 21/148 (14.2%), Silk in 18/148 (12.1%) and Surpass in 12/148 (8.1%). Long-term complete/near-complete occlusion rate was 87.4%; treatment-related complication rate was 8.6%; and

morbidity and mortality rates of 3.5% and 2.5%, respectively.⁵¹ Pagiola *et al*⁵² analysed 30 ACoA aneurysms in 30 patients treated with PED (8), Surpass (2), Silk (15) and FRED Jr (5) FDs. Follow-up angiography was available for 23/30 patients (76.6%), and total occlusion occurred in 17/23 patients (73.9%) and adequate occlusion in 86.9%. One patient (3.3%) experienced symptomatic ischaemic stroke.⁵²

Initial experiences with FD of MCA aneurysms suggest lower occlusion rates and high rates of covered branch flow modification with unclear symptomatic consequences.³⁴ Cagnazzo *et al* evaluated 244 MCA aneurysms from 12 studies (published from 2008 to May 2017). PED was most commonly used (71%) followed by Silk (11.4%). The authors reported a complete/near-complete occlusion rate of 78.7%. The rupture rate of treated aneurysms during follow-up was 0.4% per aneurysm-year. The rate of treatment-related complications was 20.7%, and approximately 10% of complications were permanent. The mortality rate was close to 2%. Nearly 10% of jailed arteries were occluded during follow-up, whereas 26% had slow flow. Rates of symptoms related to occlusion and slow flow were close to 5%.⁵³

Recent studies further characterise the challenges associated with FD of bifurcation aneurysms and a strategy to improve occlusion outcomes without increasing treatment risk. A single-institution study of occlusion outcomes following 445 anterior circulation PED treatment showed that branch vessel location was a significant predictor of aneurysm persistence on 12-month angiography (OR 2.2, $p=0.035$). Combining FD with adjunctive coiling in a single stage was the only technique that improved occlusion outcomes (OR 0.3, $p=0.036$).^{54 55}

Aneurysms of the pericallosal artery treated with PED were studied by De Macedo Rodrigues *et al*. Of seven aneurysms, five showed a complete aneurysm occlusion at 6–12 months of follow-up with angiography. The two with persistent aneurysm filling showed decreased aneurysm sac volume on follow-up angiograms (96% and 60%). There was no evidence of implant stenosis or intimal hyperplasia. No thromboembolic or haemorrhagic complications were seen during the follow-up period.⁵⁶

Small-diameter vessels

Treatment of aneurysms located beyond the ICA with FD requires technical nuances of managing small-diameter vessels while navigating further into the intracranial vasculature. Advances in vascular access systems and FD deployment have enabled the effective treatment of these aneurysms despite tortuous anatomy and distal intracranial positions. Modern access systems with multiple coaxially introduced catheters of varying stiffness provide proximal support to facilitate navigation of tortuosity within the circle of Willis. Additionally, improved atraumatic catheter tips and catheter tractability reduce the likelihood of vessel injury. Improved modifications in FD systems include the added ability to resheath partially deployed devices, optimised mechanical interaction of the pusher

wire and stent during deployment, and increased stent radiopacity. These technical advances have collectively reduced errors during device deployment and enabled the effective use of FDs for treatment of aneurysms beyond the ICA.

There are numerous FDs whose use in small-vessel case series has been reported widely and are summarised here. Most common is the PED, but also the FRED and SILK series. There is less research supporting the efficacy of Surpass, p64, Derivo and Tubridge stents in small vessels.

Pipeline Embolization Device

Sweid *et al* retrospectively stratified patients receiving a PED or PED FLEX between 2010 and 2019 into small-calibre (devices ≤ 3.0 mm diameter) and large-calibre vessel groups. There were no significant differences between the small-calibre and large-calibre vessel groups in morbidity, mortality or complete aneurysm occlusion. Further, small-calibre vessels were an independent predictor of aneurysm obliteration (2.6 times higher) in multivariate logistic regression.⁵⁷

Bhagal *et al* quantified vessel diameters in a single-centre experience of small vessel (average diameter was 2.1 mm, 1.3–2.5 mm range).⁵⁸ Aneurysm occlusion rates were high, with 94% Raymond-Roy grade 1 occlusion and 6% Raymond-Roy grade 3 (complete filling). Neurological status at 90 days was 2 patients had a modified Rankin Score (mRS) of 6 (one unrelated, one due to enlarging dissecting aneurysm); 27 of 29 patients had $mRS \leq 2$; and 24 of 29 had $mRS=0$.

Bender *et al* reported their experience with 67 aneurysms in 57 patients with even smaller parent vessels, measuring on average 1.93 and 1.70 mm preoperatively at the proximal and distal ends of the stent landing zone, respectively. Complete occlusion was high: 88% at 6 months and 89% at last follow-up. The major morbidity rate of 4.5% and mortality rate of 1.5% compare favourably to both on-label PED and small aneurysm PED series.⁵⁹

Silk Vista Baby (SVB)

The latest in the Silk line of FDs is the SVB, a stent designed specifically deployment in small parent vessels. SVB is the only FD capable of being delivered through a 0.017 ID microcatheter.

Martínez-Galdámez *et al* reviewed the safety and technical feasibility of the SVB in a multicentre, retrospective review of 41 patients with 43 aneurysms treated with SVB.⁶⁰ The average proximal and distal parent vessel diameters were 2.28 and 2.00 mm, respectively (range 0.9–3.6 mm). Immediate occlusion outcomes showed 8 (18.6%) aneurysms showing complete occlusion, 5 (11.6%) aneurysms showing near-complete occlusion, 4 (9.6%) aneurysms showing incomplete filling and 26 cases (60.4%) showing persistent filling. There were five intraprocedural complications which were resolved without clinical consequences, and there were no neurological deficits. Postoperative morbidity was 7.3%.⁶⁰

Schob *et al* presented longer follow-up results on SVB performance in a series of 25 prospectively included patients. There were no technical or clinical complications.⁶¹ Follow-up (average 2.7 months postoperatively) was available for 24/27 aneurysms: 17 (70.8%) aneurysms were completely occluded; 6 (25%) showed decreased influx; and one (4.1%) showed no haemodynamic change. The authors feel that enhanced visibility and radial force likely reduce non-opening issues associated with SILK and SILK+. SVB series reporting long-term clinical and radiographical outcomes are needed and will further characterise the efficacy of SVB as a small-vessel FD.

FRED Jr

FRED Jr, designed specifically for small-vessel aneurysms, has been shown to be safe and effective for treating distal circulation aneurysms. Möhlenbruch *et al* reported a multicentre observational clinical study of 42 patients and 47 aneurysms, all successfully embolised with FRED Jr.⁶² The median parent vessel diameter was 2.4 mm (range 1.4–3.6 mm). There was one disabling ischaemic stroke, one minor stroke with full recovery and one transient ischaemic attack (TIA). Follow-up angiography demonstrated 27/41 aneurysms occluded at 1 month; 21/27 aneurysms occluded at 6 months; and 11/11 aneurysms occluded at 12 months. The author's comment on the stability of this dual-layered FD, its lengthy profile of 41 mm allowing for fewer stent deployments, and only 16 wires in the outer layer reducing stent-to-catheter friction during stent deployment. Rautio *et al* conducted a study of 15 aneurysms and observed a complete occlusion rate of 87%, with no morbidity or mortality.⁶³ In a separate study by Sivansankar *et al*, 12 patients with 15 small aneurysms were treated with FRED Junior. Twelve of 15 aneurysms were unruptured; 1 was treated in an acutely ruptured setting; and 2 (presented with SAH) were initially treated with balloon assisted coiling and then treated with an FD. Complete occlusion was observed 80% of aneurysms. There were no complications in the form of TIAs, stroke or death.⁶⁴

Surpass, p64 and Tubridge

The initial clinical assessment of Surpass, published in 2013, included 11 patients (14 aneurysms) treated with a 2.0 mm diameter Surpass device.¹⁹ Good occlusion outcomes were achieved in seven (64%) of these cases, with procedure-related morbidities in 18%. Literature supports the efficacy of p64 in treating distal circulation aneurysms,^{65,66} but p64 series with quantified parent vessel diameters are scant. There are minimal or no reports to our knowledge describing experiences with Tubridge and Derivo in distal circulation.

Posterior circulation

Posterior circulation aneurysms represent a heterogeneous group with a poor natural history. Non-saccular morphologies are more likely to produce ischaemic or

compressive symptoms,⁶⁷ while saccular aneurysms in the posterior circulation are at higher risk of rupture than their anterior circulation counterparts,⁶⁸ which prompt the desire to treat electively. However, open surgery for posterior circulation aneurysms carries a high morbidity due to the challenging anatomy, and stent-assisted coiling faces high recurrence rates. Bender *et al* reported a series of 59 posterior circulation aneurysms treated with PED in 55 patients with acceptable occlusion rate (78% at 12 month post-PED implantation) and safety (five major complications, 8%). These studies include seven basilar apex aneurysm and an additional seven adjacent aneurysms in which the PED crossed the basilar apex.⁶⁹ Griesenauer and colleagues conducted a multicentre study of 131 posterior circulation aneurysms treated with PED. Twenty-nine (22.1%) dissecting, 53 (40.5%) fusiform and 49 (37.4%) saccular lesions were included. Treatment of 39 aneurysms (29.8%) was performed in the immediate, acute or remote setting of SAH. Complete or near-complete occlusion was 78.1%. Major (≥ 2 points in mRS score change) and minor (< 2 in mRS score change) complications occurred in 10.1% and 14.7% of procedures, respectively. Thromboembolic complications occurred in 22.5% of procedures overall. Mortality within 30 days was 6.3% (eight patients) and after 30 days (six patients) was 4.7%. Major complications were highest in fusiform aneurysms and mortality was highest in dissecting aneurysms.⁷⁰ Dmytriw *et al* studied 16 basilar apex aneurysms treated with either PED or FRED. Five aneurysms (31.3%) were treated in the setting of SAH. Seven aneurysms (43.8%) were treated with FD alone, while nine (56.2%) underwent FD and adjunctive coiling. Complete or near complete occlusion was reported in 11 (68.8%) aneurysms. Retreatment with an additional FD and adjunctive coiling occurred in two aneurysms with wide necks. There was one mortality in a patient (6.3%) who experienced PCA and cerebellar strokes as well as SAH after the placement of an FD. Minor complications occurred in two patients (12.5%).⁷¹ Taschner *et al* reported the safety and efficacy of Surpass in a multicentre, observational study of 52 patients with posterior circulation aneurysms. Angiographical follow-up for 44 patients with a median follow-up of 11.3 months (5.9–12.7 months) showed complete occlusion was in 29 patients (66%). Overall morbidity and mortality rates were 27%. Nine (17.3) patients died, with seven directly related to the procedure. Asymptomatic patients had 5% morbidity and 0% mortality, while symptomatic patients had 44% morbidity and 28% mortality.⁷²

Additional FD advantages

Institutional level studies have continued to establish FD embolisation as an effective and safe treatment, with similarly high angiographical success rates and low rates of morbidity and mortality as reported in previous clinical trials.^{38–41 50 73} In particular, the PED was also shown to be more cost effective than traditional stent-assisted coiling of large anterior circulation aneurysms (27.1%

cost reduction per millimetre of aneurysm treated in the PED arm compared with stent-assisted coiling).⁶ Malhotra *et al* studied the cost effectiveness of PED versus stent-assisted coiling and found that for small unruptured anterior circulation aneurysms, PED embolisation is more cost-effective with stent-assisted coiling and found that for small unruptured anterior circulation aneurysms, PED embolisation is more cost-effective with the main drivers being lower aneurysm recurrence rate and lower morbidity and mortality.⁷⁴ These findings were supported by Twitchell *et al*'s retrospective study on the cost of clipping, coiling and FD. The authors report that coiling (mean total cost $0.25\% \pm 0.20\%$) had a higher cost than FD (mean $0.20\% \pm 0.16\%$) and clipping (mean $0.17\% \pm 0.14\%$, $p < 0.01$).⁷⁵ Using the PED, the treatment of large and giant proximal ICA aneurysms requires less radiation, less fluoroscopy time and less contrast use than traditional coiling techniques.⁷⁶ Average radiation dose with PED treatment is of 2840 mGy, compared with 4010 mGy using traditional coiling techniques.⁷⁶ The increasing body of evidence has firmly established FDs as the standard treatment for large and giant aneurysms, as evidenced by the decrease in use of both coil and stent since their introduction.^{76 77}

Dual-antiplatelet therapy (DAT) and FD

Regular use of DAT consisting of aspirin (ASA) and clopidogrel in the neurointerventional field was inherited from cardiology, where DAT was shown to decrease ischaemic complications after percutaneous coronary intervention. DAT was adopted in neurointerventional practice to address ischaemic complications associated with aneurysm coils and intraluminal implantation such as FDs and vascular reconstruction devices. The efficacy of placing patients undergoing FD embolisation on ASA and clopidogrel has since been widely accepted in preoperative planning.

The biological mechanism of antiplatelet therapy is slightly altered, depending on the combination of drugs administered. ASA is commonly paired with either clopidogrel (Plavix), prasugrel (Effient) or ticagrelor (Brilinta). Clopidogrel and ticagrelor both inhibit P2Y₁₂ receptors, thereby reducing dense granule secretion and subsequent platelet aggregation.⁷⁸ Clopidogrel requires a combination of enteric and hepatic metabolism prior to P2Y₁₂ receptor binding. Perhaps due to this complex metabolic pathway, approximately 30% of patients exhibit clopidogrel hyporesponse (<30% P2Y₁₂ receptor inhibition on routine dosing) due to heterozygosity in the CYP2C19 gene. In contrast, ticagrelor binds directly to the P2Y₁₂ receptor. Ticagrelor and prasugrel have been shown to have more favourable pharmacokinetics than clopidogrel and correspondingly elicit a more timely and potent antiplatelet effect.⁷⁹

DAT consisting of ASA and clopidogrel is the gold standard. However, the aforementioned interindividual variability in clopidogrel response has prompted research into adoption of prasugrel or ticagrelor as alternatives.

Studies indicate no difference in morbidity, mortality or angiographical outcome when comparing clopidogrel/ASA and ticagrelor/ASA.^{78 80} Though ticagrelor has been shown to be more potent and reliable than clopidogrel, its use is largely limited to clopidogrel hyporesponders because of its expense.⁷⁸

Prasugrel has also been shown to safely replace clopidogrel in DAT for clopidogrel hyporesponders. Of 22 patients receiving ASA and prasugrel, 4.5% demonstrated in-stent stenosis (ISS) compared with 6.1% for the ASA and clopidogrel group.⁷⁹ There were no long-term recurrences among the prasugrel group, and the post-procedural complication rate of the prasugrel group was statistically insignificantly lower than that of the clopidogrel group. Some centres have fully adopted prasugrel as the efficacy of this antiplatelet agent is further explored.

Platelet Function Testing

Lack of predictability in a patient's response to DAT added to the need for accurate and convenient platelet function tests to personalise DAT regimens. Lab-based methods include Light Transmission Aggregometry (LTA), Impedance Aggregometry, and Thromboelastography (TEG). While LTA is traditionally the gold standard, it is a time-consuming process calling for centrifugation of blood samples. The VerifyNow P2Y₁₂ clopidogrel assessment is a convenient point-of-care method of assessing clopidogrel response. Kim *et al* suggest use of routine platelet function in patients at high risk for thrombosis to identify clopidogrel non-responders and provide alternate DAT regimens as previously discussed, including ticagrelor, prasugrel, or cilostazol.⁸¹ However, Bender *et al* reported on this assay's imprecision in their experience with PED patients: they observed that 24% of patients shifted between the categories of hypo-response, therapeutic, and hyper-response within a 24 hours period. The authors suggest that this high variability in the VerifyNow P2Y₁₂ clopidogrel response assessment may reflect assay or biological imprecision, and suggest caution when guiding clinical decision based on P2Y₁₂ levels.⁸²

In-stent stenosis (ISS) and acute stent thrombosis

ISS refers to the gradual occlusion of the stented arterial segment in part from intimal hyperplasia and platelet interactions with FD wires and may be observed in short-term angiographical follow-up with an incidence of 3.5%–57% with various FDs. This wide range is due to the different definitions and grading of ISS used by different authors. A majority of cases show complete resolution or improvement on long-term follow-up with DAT.⁸³ In regard to small-vessel FD, smaller diameter PEDs are less contourable, resulting in a proximal in vivo device diameter that will mirror the distal diameter (mirroring the smallest calibre vessel size of the PED landing zone), which may portend to a higher theoretical risk of ISS. Despite this theoretical risk, only 1 of 66 successful cases described experienced flow delay due to ISS, and this patient remained asymptomatic.⁶⁹

Acute stent thrombosis, another safety concern with small-vessel FD, refers to rapid platelet aggregation on the stent and subsequent ischaemia. Various institutions have reported their experience with stent thrombosis in small-vessel FD. Cagnazzo *et al* reported two strokes due to stent thrombosis from 17 patients treated for distal ACA aneurysms.⁸⁴ Bhogal *et al* reported no stent thrombosis across 29 patients receiving PED in vessels no larger than 2.5 mm.⁵⁸ Martínez-Galdámez *et al* reported no instances of stent thrombosis across 41 patients treated with SVB with an average parent vessel diameter of 2.0 mm.⁶⁰ In a series of 67 small-vessel aneurysms treated with FD, Bender *et al* reported five (7.5%) instances of intraprocedural stent thrombosis, all of which were successfully managed with intraprocedural abciximab dosing according to Lin *et al*'s dosing strategy for the management of acute intraprocedural thromboembolic complications during PED treatment.⁵⁹ Intra-arterial (IA) abciximab (ReoPro) has been shown to be a safe and effective strategy for managing acute intraprocedural thromboembolic complications during PED treatment. Lin *et al* identified 30 cases where thromboembolic complications occurred during PED placement. After using a dosing strategy of either 5 mg increments or a 0.125 mg/kg IA bolus (half cardiac dosing) complete or partial recanalisation was achieved in 100% of cases with a low rate of complications and long-term morbidity.⁸⁵ Heightened vigilance and appropriate perioperative management of stent thrombosis is necessary in small-vessel FD.

INTRASACCULAR FLOW DISRUPTION Woven EndoBridge (WEB) device

Success with FD techniques expanded the neuroendovascular field into creative solutions with flow modulation approaches and braided mesh devices. The WEB intrasaccular flow disrupter (MicroVention/Sequent Medical, Aliso Viejo, California, USA) uses a self-expanding braided mesh implant composed of nitinol and platinum attached to a flexible delivery wire. The WEB device was designed for treatment of wide-neck bifurcation aneurysms (WNBAs). After deployment, the implant is electrothermally detached from the delivery wire.⁸⁶ Dmytriw *et al* reviewed 11 key WEB device trials from articles published between 2014 and 2018.⁸⁷ Adequate occlusion (complete occlusion or residual neck) ranged from 51.7% to 96%, with a mean follow-up time ranging from 1.7 to 39.0 months. Morbidity rates ranged from 0% to 23%, and mortality rates ranged from 0% to 8.5%.

The Woven EndoBridge Intrasaccular Therapy (WEB-IT) Study was the first FDA premarket approval trial for an intrasaccular aneurysm device, and the first trial for a device used to specifically treat WNBAs.⁸⁸ On angiographical follow-up, 53.8% of patients experienced complete occlusion, while 84.6% of patients experienced adequate occlusion (residual neck or complete occlusion). The rate of complete occlusion for WEB device is similar when compared with other endovascular treatments for

wide-necked aneurysms, such as stent-assisted coiling (45.7%, n=70) and Low-profile Visualised Intraluminal Support (LVIS) stent system (62.5%, n=153).^{89,90} However, compared with parent artery stenting and endovascular treatments requiring dual-antiplatelet medication, the results of the WEB-IT study suggest that the WEB device has a superior safety profile up to 1 year after implantation. The safety and effectiveness of the WEB device has been demonstrated in several studies.^{87,91,92}

In a recent publication, Goertz *et al* performed a comparative analysis of a newer generation WEB device (WEB 17) with the predecessor WEB devices. The WEB 17 was designed for smaller aneurysms and a 0.017-inch delivery microcatheter, compared with its predecessor's (WEB 21), which uses a 0.021-inch microcatheter for delivery. The WEB 17 had a lower failure rate, 0% compared with 10.3% in its predecessors devices (p=0.05). The rate of neurological complications and rate of complete occlusion were not significantly different; however, the WEB 17 had a significantly lower thromboembolic event rate (14.3%) compared its predecessors (5.3%).⁹³ The safety and effectiveness of WEB 17 has also been suggested by van Rooji *et al* and Maurer *et al* based on retrospective studies.^{94,95}

Mounting evidence continues to validate the utility and safety of the WEB device for the treatment of wide-necked intracranial aneurysms, and more is being learnt about optimising its use and predicting the potential risk of WEB implantation for patients with varying aneurysm morphologies. A multicentre, retrospective study published by Goertz *et al* focused on risk factors of procedural complications due to WEB endovascular treatment of WNBAs. The authors analysed 120 patients with 120 aneurysms and found that an unfavourable aneurysm height to width ratio significantly increased the risk for procedural complications.⁹⁶ Cagnazzo *et al* sought to predict the factors contributing to adequate intracranial aneurysm occlusion after WEB device implantation. In a single-centre retrospective study with 86 patients with 86 aneurysms with at least a 12-month angiographical follow-up, the authors found using that aneurysms with a neck wider than 4 mm or greater were independently associated with incomplete occlusion.⁹⁷ Recently, Goertz *et al* demonstrated that the WEB device can also be used as an endovascular treatment for ICA sidewall aneurysms and no procedural-related morbidity or mortality⁹⁸. Table 3 summarises the major studies involving WEB.

LUNA/Artisite

The LUNA Aneurysm Embolization System (LUNA AES), also known as Artisite (Medtronic, Irvine, California, USA) is a self-expanding, mechanically detachable, endovascular flow disruption device with a double-layer nitinol mesh with platinum markers.^{87,99,100} This device was evaluated for safety and efficacy in Europe in a prospective multicentre trial, named the LUNA AES Post-Market Clinical Follow-up.¹⁰¹ Adequate occlusion in 78.0% in by 12 months and 79.2% by 36 months. These authors also

Table 3 Summary of intrasaccular flow disruption devices

Intrasaccular flow disruption devices	Author, year	Patients, aneurysms (n)	Aneurysm location	Occlusion rate	Morbidity (%), mortality (%)
WEB device	Klisch <i>et al</i> , 2011 ⁸⁶	2, 2	Unruptured basilar tip and unruptured MCA bifurcation	100% at 8 weeks	0, 0
	Mine <i>et al</i> , 2018 ⁹¹	48, 49	29/49 (59%) located on the MCA, 7/49 on the basilar tip (14%), 5/49 on the ICA (10%), 5/49 ACoA (10%), 2/49 on the PICA (4%) and 1/49 on the vertebral artery (2%)	72.3% 34/47 (range 3–72 months, mean 25 months, median 24 months)	8.3, 0
	Arthur <i>et al</i> , 2019 (WEB-IT Study) ⁸⁸	150, 150 (148 successfully delivered)	Wide-necked bifurcation aneurysms	53.8% complete occlusion, 84.6% complete occlusion/residual neck at 1 year	0.7, 0
	Popielski <i>et al</i> , 2018 ¹⁰⁵	102, 101	86.3% anterior and 13.7% posterior ruptured and unruptured aneurysms	80.7% (63/78) at 3 months and 77.6% (38/49) at 12 months	4, 1
	Kaya <i>et al</i> , 2020 ⁹²	42; 42	MCA bifurcation in 29 (69%), basilar tip in 5 (12%), ACoA in 5 (12%), ICA tip in 2 (5%), and M1 segment of MCA in 1 (2%) patient	Adequate occlusion (complete or neck remnant) in 97.0% (35/36) at 1 year	0, 0
	Goertz <i>et al</i> , 2019 ⁸⁸	20; 20	ICA sidewall aneurysms paraophthalmic segment (n=10), the posterior communicating artery segment (n=9) and the anterior choroidal artery segment (n=1)	76.5% at a mean of 9.6±8.2 months	0, 0
WEB 17	van Rooij <i>et al</i> , 2018 ⁹⁴	40; 46	ACoA in 17, MCA in 13, PICA in 7; pericallosal artery in 3; basilar tip in 3; and the anterior choroidal artery, carotid tip and superior cerebellar artery each in 1	72% at 3 months	0, 0
	Maurer <i>et al</i> , 2019 ⁹⁵	117; 127	26.0% ACoA, 8.6% ACA, 41.0% MCA bifurcation, 1.6% MCA M1, 7.8% ICA PComA, 4.0% ICA bifurcation, 5.4% basilar tip, 0.8% PCA, 2.4% PICA, 2.4% superior cerebellar artery	76.1% (70/92) at 3 months and 78.0% (32/41) 12 months.	1.7, 0
LUNA AES	Piotin <i>et al</i> , 2018 ¹⁰¹	63; 64	23.4% ACoA, 6.3% basilar apex, 29.7 MCA, 12.5% ICA terminus, 4.7% ICA (cavernous), 4.7% ICA (ophthalmic), 4.7% ICA (PComm), 4.7% ICA (hypophyseal), 4.7% PCA, 3.1% ACA, 1.6% PICA	Adequate occlusion in 78.0% in 1 year and 79.2% in 3 years	1.6, 1.6

ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PComm, posterior communicating artery; PICA, posterior inferior cerebellar artery; WEB, Woven EndoBridge.

compare LUNA AES and the WEB device, and discuss the similar occlusion rates and low morbidity and mortality observed in studies of both devices. The WEB has been mostly studied for wide-neck aneurysms, while the LUNA AES has been studied for small and medium aneurysms. More testing is required to validate the use of LUNA AES for large and wide-neck aneurysms. As such, LUNA/Artis has not yet achieved FDA approval for the U.S. [Table 3](#) summarises the literature to date on LUNA AES.

Contour

A newer device to enter the market is the Contour Neurovascular System (Cerus Endovascular, Fremont, California, USA), an electrically detachable endovascular device made of nitinol with radio-opaque markers similar to the WEB device. Early trials are ongoing, and it is being considered for CE mark approval in Europe. It is designed to be deployed at the neck and to avoid the dome. The Contour is meant to act as a flow disruptor and flow redirector for a wider range of aneurysms not limited by size or morphology.¹⁰⁰

CONCLUSION

The use of braided mesh devices in the neuroendovascular space for the treatment of cerebral aneurysms has quickly evolved since the initial introduction of FD technology in 2007. Cerebral aneurysms that are challenging to treat and not previously amenable to endovascular therapy can now be safely and effectively treated with FDs.¹⁰² Over the past decade, adoption of FD techniques has continued to increase with resultant paradigm shift of choosing FDs as first-line treatment for large and giant ICA aneurysms. At present, PED, Surpass, and FRED are the only commercially available devices approved by the FDA for use in the United States. Many other FDs are available in Europe and other countries internationally. With increased adoption of FDs, use of this technique has also expanded with success into small aneurysms, posterior circulation aneurysms, and distal intracranial aneurysms beyond the ICA. Following the evolution of FD techniques, the neuroendovascular space has continued to iterate with additional flow modulation devices such as the intrasaccular flow disrupter.

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