# Clinical Outcomes and Work Flow Optimisation with Pipeline System and Shield Technology

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**A B S T R A C T**

Endovascular treatment is the treatment of choice for many intracerebral aneurysms (ICAs). However, coiling is probably less effective for giant or wide-necked aneurysms, and retreatment is not uncommon. Flow diversion (FD) is a novel endovascular approach to ICA treatment. A FD-stent is inserted in the parent vessel to disrupt flow into the aneurysmal sac and provide a scaffold for endothelisation. This symposium provided insight into use of the Pipeline Embolization Device (PED). Discussion topics included: results of a new surface modulation to lower the risk of thromboembolic events, pre-procedure use of a simulation model to select the optimal PED size, and clinical experience with PED in the treatment of small aneurysms.

**Key words:** cerebral aneurysm, coiling, flow diversion, Pipeline Embolization Device

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## INTRODUCTION

*Clinical Outcomes and Workflow Optimization with Pipeline System and Shield Technology* was a symposium held at LINNC 2018 in Paris. The symposium incorporated presentations on clinical experience with Pipeline Flex with Shield Technology, including one-year results of the multi-center Pipeline FLEX Embolization Device with Shield Technology (PFLEX) observational study and use in small aneurysms. The symposium also examined the ability of a simulation model to refine size selection of Pipeline to reduce adverse events, including ischemic-related complications.

The prevalence of unruptured ICA is estimated at 2% to 3.2%. ICAs vary in size, location, and morphology. Certain types of ICAs are amenable to endovascular treatment, which historically has consisted of coiling, i.e., "packing" the aneurysms with wires (coils).[1] Clinical trials have demonstrated the safety and efficacy of coiling, with lower morbidity and mortality for coiling compared to surgical "clipping". As a result, medical guidelines indicate that coiling is preferred over clipping in cases for which surgical morbidity is expected to be high (e.g., location of aneurysm, age of patient).[2] However, retreatment is more likely after coiling compared to clipping,[1] underscoring a need for new tools or techniques to reduce the need for reintervention. In addition, giant or wide-necked aneurysms may not be amenable to coiling.[1]

Flow diversion (FD) is a novel endovascular approach to aneurysm treatment. Instead of inserting coils into the aneurysmal sac, a stent is implanted in the parent vessel, disrupting blood flow into the sac and providing a scaffold for endothelialisation.[3] FD was initially conceived as a strategy for treatment of giant, fusiform, or wide-necked aneurysms. The Pipeline Embolization Device (PED) was the first FD endovascular treatment approved for use in ICAs. In clinical trials, PED demonstrated 81.8%-93.3% complete occlusion at six months, with morbidity and mortality rates of 0%-6.5%.[3] PED received CE Mark approval in 2008 and United States Food and Drug Administration (FDA) approval in 2011.[3] Since that time, two iterations of PED have become available: One with a modified delivery system that enables resheathing and redeployment (PED Flex) and one with a new surface treatment (Shield Technology). These iterations strive to reduce adverse events associated with FD, particularly thromboembolic events (Figure 1).

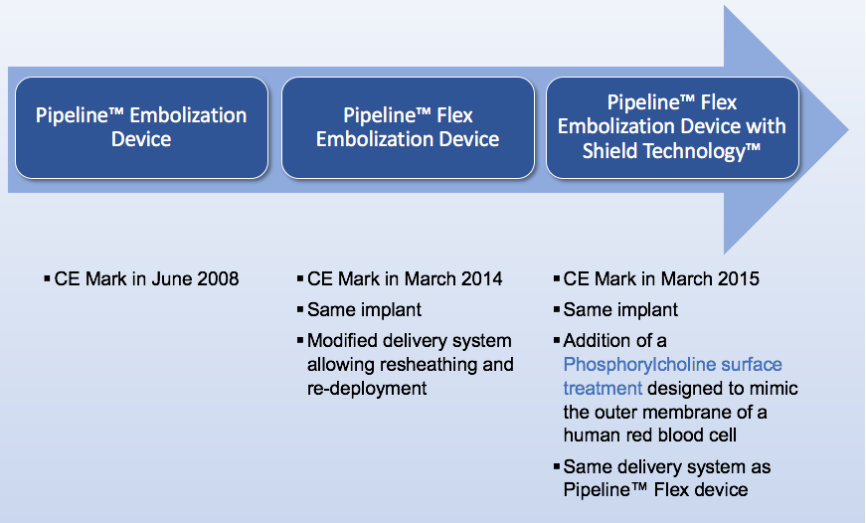
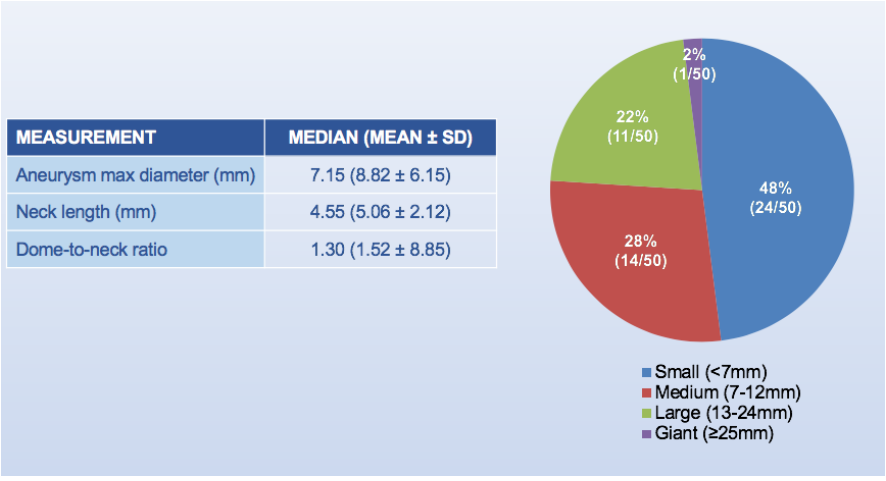



**Figure 1. Evolution of Pipeline Embolisation Device**

## LOWERING COMPLICATION RATES: STENT SURFACE MODULATION

Although PED is associated with a low overall morbidity and mortality rate, serious adverse events can arise. The International Retrospective Study of PED (IntrePED) revealed that 8.5% of patients treated with PED experienced neurological morbidity or mortality, with ischemic stroke comprising the majority of adverse events.[4] As a result, Shield Technology, which uses a phosphorylcholine (PC) polymer to covalently bond to the braids of PED, was developed to reduce the thrombogenicity of the device. The PC polymer creates a layer of "bound water" that shields the substrate from non-specific adhesion of proteins. In vivo testing has shown that the PED Flex with Shield Technology significantly reduced peak thrombin levels compared to other FD devices[5] or neurovascular stents. In addition, the PED Flex with Shield Technology demonstrated a significantly longer time to peak thrombin than other FD devices.[5] Of note, thrombogenicity is not increased when using several PEDs with Shield Technology compared to using a single PED with Shield Technology.

The multi-center Pipeline FLEX Embolization Device with Shield Technology (PFLEX) observational study enrolled 50 patients with an unruptured anterior or posterior ICA that was 1.5-5.0mm distal or proximal to the parent vessel. The primary endpoint was major stroke or neurological death at 12 months. The secondary outcome measure was device-related adverse neurological event rate at one year. Patients were enrolled at seven European centers over a seven-month period (March-October 2015). The average age was 53 years; 82% of patients were female; and 24% had hypertension. Nearly 20% were current smokers, while 30% had smoked in the prior 10 years[4] Approximately half of patients (48%) had an aneurysm <7 mm; 28% of the cohort had a medium-size aneurysm (Figure 2). The median aneurysm size was 7.15 mm. Virtually all aneurysms (98%) had a saccular morphology; 94% were located in the internal carotid artery.[4]



| MEASUREMENT | MEDIAN (MEAN ± SD) |
|---|---|
| Aneurysm max diameter (mm) | 7.15 (8.82 ± 6.15) |
| Neck length (mm) | 4.55 (5.06 ± 2.12) |
| Dome-to-neck ratio | 1.30 (1.52 ± 8.85) |



**Figure 2. PFLEX Study Baseline Aneurysm Size[4]**

Although the study protocol did not mandate antiplatelet reactivity tests, 21 patients underwent testing. The majority of patients (81%) had platelet reactivity within a pre-defined reference range of 60-240 P2Y12 reaction units (PRUs), with 14% of the cohort having a hypo response to clopidogrel (PRU >240) and 5% having a hyper response (PRU <60). Most patients (76%) had a normal response to aspirin, defined as having an aspirin reaction unit (ARU) of ≥ 550. The remainder of the cohort had a hypo response (<550 ARUs).[4]

The technical success rate was 94.6%. The number of PED Flex devices used per patient averaged 1.06. Procedure time averaged 77.3 minutes. Adjunctive devices were not needed for the majority of cases (86%); coils were used for the remainder. Core lab imaging showed complete wall apposition for virtually all implanted cases (96%). All aneurysmal necks were covered by PED Flex.

At one year, 81.8% of treated aneurysms had complete occlusion. There was residual neck in 6.1% of treated cases. There were no aneurysm recurrences or need for re-treatment. For the primary endpoint, no major strokes in the area supplied by the treated artery occurred, and there were no neurological deaths. The 12-month device-related neurological adverse event rate was 14% (Table 1).[4] There were seven events: six instances of asymptomatic in-stent stenosis and one asymptomatic thrombosis in the internal carotid artery. The latter occurred 63 days after the PED FLEX was implanted during treatment of another aneurysm. There were 3 other procedure-related adverse events – headache, double vision, and retroperitoneal hemorrhage – which all resolved.

**Table 1. PFLEX Study Key Measures[4]**

| | | |
|---|---|---|
| Complete aneurysm occlusion | | 81.8% |
| Residual neck | | 6.1% |
| Residual aneurysm | | 12.1% |
| Aneurysm recurrence | | 0% |
| Aneurysm retreatment | | 0% |
| | | |
| **Primary endpoint**:<br>Major stroke in territory supplied by treated parent artery or neurological death | | 0% |
| | | |
| **Secondary endpoint**:<br>Device-related neurological adverse event | | 14% |

The study protocol did not specify a post-procedure antiplatelet regimen. The majority of patients (54%) were placed on double antiplatelet therapy (DAPT) for 4-6 months, followed by single antiplatelet therapy (aspirin) for > 1 year. Twenty percent of patients took DAPT for at least 10 months. Despite 14% of patients having a hypo response to clopidogrel and 24% having a hypo response to aspirin, there was limited adjustment of DAPT or aspirin dosing over the study period. The absence of thromboembolic complications suggests the PC polymer is effective at preventing platelet adhesion to the device. The investigators of the study consider a preoperative PRU of 70-150 as ideal to reduce the risk of hemorrhagic and thromboembolic complications.[4]

Results from the PFLEX study, which was the first study to assess the Shield Technology, are comparable with previous studies of PED. PED Flex has a high technical success rate, and Shield Technology did not adversely affect implantation or procedural complications. The aneurysm occlusion rate was 82% at 12 months, with no major strokes in the territory supplied by the parent artery and no neurological deaths. The device-related neurological adverse event rate was 14%, all of which were asymptomatic.[4]

## LOWERING COMPLICATION RATES: SELECTING THE OPTIMAL STENT SIZE

PED is now used to treat a variety of aneurysms of differing size, morphology, and location, including complex aneurysms (dissecting, wide-necked branch aneurysms, ruptured, recanalized, etc). Particularly with difficult-to-treat aneurysms, inappropriate sizing or placement of an FD stent systems can cause endoleaks, stent shortening or lengthening, problems of stent-opening/deployment, perforation, or ischemic complications.

A meta-analysis of 18 studies evaluating commercially available FD devices, including PED, Silk, Flow Re-direction Endoluminal Device (FRED), and Surpass Flow-Diverter, revealed that stent deployment was the primary cause of peri-procedural thrombosis.[6] In another meta-analysis of 60 studies, the complication rate was 17%, while technical problems occurred in 9.4% of cases, with 8.6% related to stent opening.[7] There are numerous reasons for technical failure, including access or delivery system problems, difficult anatomy, learning curve, and incorrect stent sizing. Most of these potential shortfalls have been ameliorated through better tools and access devices, use of a triaxial technique for stent deployment, and support from company technical staff and neurosurgical teams. As a result, stent sizing seems to be the area where most improvement can be made.

There are several methods to determine the appropriate stent size. Measurements of the distal and proximal parts of the arteries and the arterial length in between can be taken to estimate the diameter and length of the stent. Many bi-plane imaging systems have adjunctive software that calculates a suggested stent size. Some interventionalists perform a visual assessment to determine the stent size to use. These methods do not account for several variables that can affect the stent size. For instance, a vessel's diameter is variable, which can affect stent length. Tortuosity, dysplasia, and stenoses can also affect the stent size after deployment. Another sizing consideration relates to very wide aneurysmal necks, which can cause a stent to bulge at the level of the neck. The common sizing techniques also do not account for the push and pull that is applied during stent deployment. In addition, it is unclear how stent sizing can have an effect on the density of the stent's metal coverage across the aneurysmal neck.

Sim & Size application software was designed to optimize size selection of FD stents. By August 2017, approximately 220 patients had been treated using Sim & Size, which has CE Mark approval and is under regulatory review in the US for a prompt FDA approval. Sim & Size expedites pre-operative planning. 3-D images are imported into the Sim & Size module, which typically takes just a few seconds since the file size of images is generally small. Sim & Size reconstructs the imported image, and the user selects the region of interest. If the reconstruction is satisfactory, the user marks the entrance for the microcatheter and then selects the distal and proximal stent landing zones. Sim & Size reconstructs the images based on the selected parameters and calculates an eventual stent size. A color-coded bar on the left part of the screen indicates whether the proposed stent size allows for good wall apposition, with green representing good apposition and red indicating poor apposition (Figure 3).

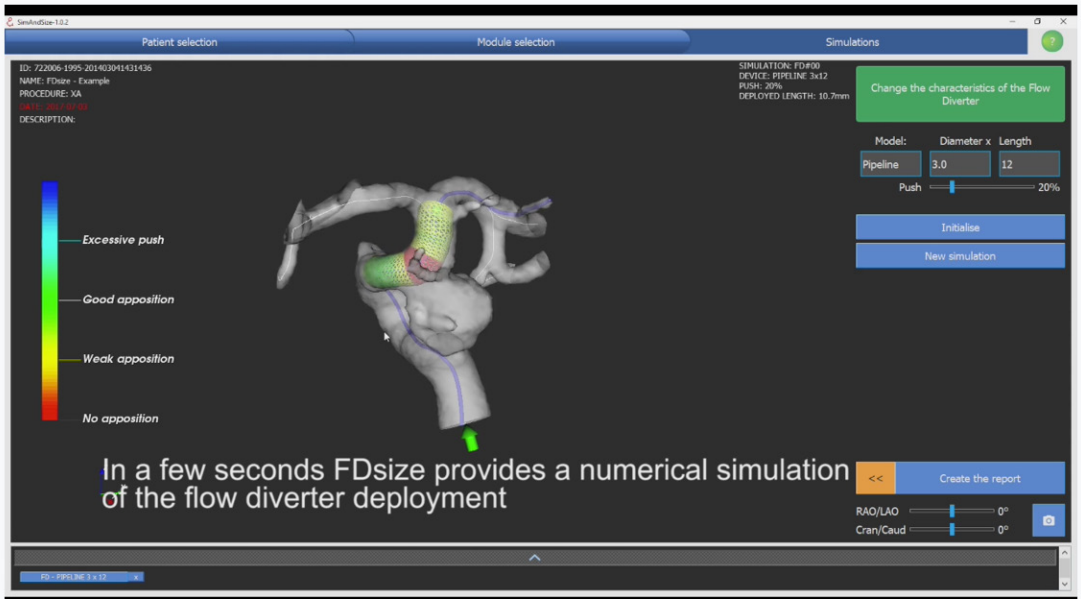



**Figure 3. Sim & Size Screen Showing Distal and Proximal Segments Selected**

A retrospective review of cases performed at the university hospitals of Saint Etienne Saint-Etienne (CHUSE) compared the stent size suggested by Sim & Size to the size of the stent actually deployed and the size proposed by biplane constructor's imaging software. Researchers found a high correlation between the Sim & Size simulation and stent size. Sim & Size enables physicians to know where to land the distal part of the stent before the procedure to ensure perfect stent placement across the aneurysmal neck, which reduces the risk of partial covering of the neck. Pre-operative planning with Sim & Size also allows physicians to anticipate the post-deployment stent length, to avoid protrusions into arterial curves, and has the potential to reduce the number of FD stents (i.e., PED) used in procedures and make PED deployment predictable. It also enables a perfect linear wall apposition of PED all across the treated arterial segment.

Sim & Size also allows users to enter variables to simulate the effect of different stent lengths and diameters. This enables physicians to choose the best stent size for optimal stent placement avoiding the unnecessary coverage of small caliber arteries and perforators. It also allows for optimal prediction of stent placement. The software allows users to modify the assumed "push" to simulate the stent placement technique, which has a direct effect on the length of deployed stents. For instance, the chosen stent length was frequently longer than the target area that needed to be covered (i.e. the chosen diameter was bigger than needed), resulting in elongation of the PED. Sim & Size results in CHUSE interventionalists led to the selection of smaller and shorter PEDs for most cases nowadays. The Sim & Size application can also predict to a high extent the amount of metal coverage across the aneurysmal neck. This has a potentially direct role on the rate of aneurysmal thrombosis and cure.

## TREATING SMALL ANEURYSMS

While advances in endovascular treatment have often focused on the ability to prevent blood flow into giant or wide-necked aneurysms,[3] FD can also be effective for the treatment of smaller aneurysms (<10mm). For instance, a meta-analysis of PED clinical studies showed a lower ischemic complication rate for treatment of small aneurysms compared to larger-sized aneurysms (Table 2).[8] However, given the low morbidity and mortality rates associated with coiling of small aneurysms, FD stents often are not used in this clinical scenario.

**Table 2. Major Ischemic Complication Rate from Meta-Analysis of Three PED Trials[8]**

| | Total | Giant | Large | Small |
|---|---|---|---|---|
| Major ischemic complication rate | 3.7% | 9.4% | 3.3% | 2.4% |

Pooled data from Pipeline for Uncoilable or Failed aneursyms Study (PUFS), International Retrospective Study of the Pipeline Embolization Device (INTREPED), and Aneurysm Study of Pipeline In an observational Registry (ASPIRe) clinical trials

Data were presented from the National Institute of Clinical Neurosciences (NICN), Budapest on the use of PED Flex with Shield Technology for the treatment of small aneurysms (N=25). The average aneurysm size was 6.6mm. The majority (84%) of aneurysms had a berry morphology, and 80% were located in the internal carotid artery (intradural). Coils were used in five cases (20%) and balloon dilatation was applied in three cases. There were two procedural complications—one distal embolus and a cervical internal carotid artery dissection—which did not have clinical sequelae. Post-procedure, there was one small brain stem infraction (modified Rankin scale of 1), and no deaths. Of the 14 patients who had completed six-month follow up, 12 (86%) had complete occlusion. For the seven patients who completed 12-month follow up, all aneurysms were occluded. These results compare favorably to studies of coiling of small aneurysms (Table 3). A meta-analysis of 22 studies (N=1,105) found an average post-coiling occlusion rate of 85%, with a 6% recurrence rate. The morbidity and mortality rates were low at 2% and 3%, respectively. [9]

**Table 3. Comparison of Studies Assessing FD Stent Treatment of Small Aneurysms**

| | No. | Occlusion | Morbidity | Mortality | Recurrence |
|---|---|---|---|---|---|
| Lee, 2016[1] | 150 | 91.3% | 3.3% | 0% | N.A. |
| Feng, 2017[2] | 264 | 73.5% | 2.7% | 0.9% | 5.7% |
| Yamaki, 2016[9] | 1105 | 85% | 2% | 3% | 6% |
| PED Flex with Shield Tech | 25 | 86% - 6 mos.<br>100% - 12 mos. | 4% | 0% | 0% |

NA = Not available

The results at NICN suggest that PED Flex with Shield Technology can safely and effectively treat small aneurysms. Of note, the optimal antiplatelet regimen has not been widely tested. At NICN, DAPT is prescribed for four days prior to the procedure and for three months post-procedure, with aspirin taken for at least one year.

## CONCLUSION

Endovascular treatment is the preferred treatment option for many ICAs. However, coiling is probably less effective for giant or wide-necked aneurysms, and retreatment is not uncommon. PED Flex with Shield Technology, a flow-diverting stent with PC polymer to reduce platelet adhesion, has demonstrated an 82% occlusion rate with no aneurysm recurrence, and no major stroke in the territory supplied by the parent vessel. Compared to coiling, PED Flex with Shield Technology has comparable results for the treatment of small aneurysms. Appropriate sizing and placement of PED Flex with Shield Technology may reduce ischemic complications. By using Sim & Size in pre-operative planning, interventionalists can reliably choose the optimal stent size, which may reduce technical problems, allows the best stent wall-apposition and lower procedural risks.

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