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THE EXPANDING REALM OF ENDOVASCULAR NEUROSURGERY: FLOW DIVERSION FOR CEREBRAL ANEURYSM MANAGEMENT

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Abstract

The worldwide prevalence of intracranial aneurysms is estimated to be between 5% and 10%, with some demographic variance. Subarachnoid hemorrhage secondary to ruptured intracranial aneurysm results in devastating neurological outcomes, leaving the majority of victims dead or disabled.

Surgical clipping of intracranial aneurysms remained the definitive mode of treatment until Guglielmi detachable coils were introduced in the 1990s. This revolutionary innovation led to the recognition of neurointervention/neuroendovascular surgery as a bona fide option for intracranial aneurysms. Constant evolution of endovascular devices and techniques supported by several prospective randomized trials has catapulted the endovascular treatment of intracranial aneurysms to its current status as the preferred treatment modality for most ruptured and unruptured intracranial aneurysms. We are slowly transitioning from the era of coils to the era of flow diverters. Flow-diversion technology and techniques have revolutionized the treatment of wide-necked, giant, and fusiform aneurysms, where the results of microsurgery or conventional neuroendovascular strategies have traditionally been dismal. Although the Pipeline™ Embolization Device (ev3-Covidien, Irvine, CA) is the only flow-diversion device approved by the Food and Drug Administration for use in the United States, others are commercially available in Europe and South America, including the Silk (Balt Extrusion, Montmorency, France), Flow-Redirection Endoluminal Device (FRED; MicroVention, Tustin, CA), Surpass (Stryker, Kalamazoo, MI), and p64 (Phenox, Bochum, Germany).

Improvements in technology and operator experience and the encouraging results of clinical trials have led to broader acceptance for the use of these devices in cerebral aneurysm management. Continued innovation and refinement of endovascular devices and techniques will inevitably improve technical success rates, reduce procedure-related complications, and broaden the endovascular therapeutic spectrum for varied aneurysm morphology.

Historical Background

The worldwide prevalence of intracranial aneurysms is estimated to be 5% to 10%.[1] More aneurysms are being discovered incidentally while patients are undergoing medical evaluation for unrelated disease processes, in part due to the continuous advances in magnetic resonance angiography and computed tomographic angiography.[2] A relatively small fraction of intracranial aneurysms rupture, leading to atraumatic subarachnoid hemorrhage (SAH), often with devastating consequences. A World Health Organization study found a 10-fold variation in the age-adjusted annual incidence of aneurysmal SAH in countries in Europe and Asia. The incidence ranges from 2.0 cases per 100,000 in China to 22.5 cases per 100,000 in Finland.[3] A more comprehensive systemic review of 58 study populations in 21 countries concluded that the incidences of aneurysmal SAH per one million persons were 22.7 in Japan, 19.7 in Finland, 4.2 in South and Central America, and 9.1 in the other regions.[4] Approximately 30,000 cases of aneurysmal SAH occur in the United States each year, leaving about 60% of victims dead or disabled.[5]

The treatment of intracranial aneurysms has fascinated neurosurgeons since the very inception of the field of neurosurgery. Dott attempted the first surgical intervention for an intracranial aneurysm when he wrapped a ruptured aneurysm in 1933.[6] Dandy in 1937 performed the first described surgical obliteration of an intracranial aneurysm by placing a silver clip across the neck of a posterior communicating artery aneurysm.[7] Since then, neurovascular surgery has continued to evolve with refinements of microsurgical and bypass techniques, microinstruments, operating microscopes, and the application of intraoperative indocyanine green fluorescence angiography along with adjunct anesthesia techniques in the form of hypothermic circulatory arrest and cerebral protection.

Coil Embolization

For many years, surgical clipping of an intracranial aneurysm was considered the definitive mode of treatment. However, in the 1990s, the Guglielmi detachable coil (GDC) was introduced and challenged the effective monopoly that surgical clipping had enjoyed until then.[8-10] GDC technology proved pivotal in establishing neurointervention as a new field. By the dawn of the 21st century, endovascular coiling emerged as a preferred treatment modality for most ruptured and unruptured aneurysms. This trend was largely facilitated by the rapid evolution and ease of use of this technology as well as collectively gained operator experience and comfort with the endovascular approach. The

completion of major randomized clinical trials also bolstered the endovascular field with results of better survival and fewer poor outcomes in patients treated with endovascular coiling compared with surgical clipping.[11,12]

However, post-treatment aneurysm recanalization remains a major challenge. Gory and Turjman[13] recently published the short- and midterm results from a prospective, consecutive, multicenter European study consisting of 404 intracranial aneurysms in 390 patients treated with Nexus detachable coils (ev3-Covidien, Irvine, CA). Complete occlusion was seen in 48% of aneurysms with a neck remnant in 22% and an aneurysmal remnant in 30%. A mean angiographic follow-up obtained at 13.3 months in 64% of the treated patients revealed a recanalization rate of 17.7% and progressive thrombosis in 21.6%. Similarly, a single-center experience with 501 aneurysms treated via endovascular means demonstrated a complete angiographic occlusion rate of only 38.3% at 1 year.[14] Among the patients who required retreatment, approximately half of them required yet more intervention.

Much like in the context of surgical clipping, the morphology of an aneurysm and its proximity to other branches and perforators can pose unique challenges while planning for endovascular coiling. Aneurysms that are large (> 10 mm diameter) and/or giant (> 25 mm diameter), wide-necked (aneurysms with a dome-to-neck ratio of < 2), and fusiform (aneurysms with no distinct neck, consisting of diffuse enlargement of a diseased vessel segment) are difficult to treat either endovascularly or microsurgically. They are associated with a more unfavorable natural history and with higher rupture, morbidity, and mortality rates.[15-21]

Advancements in endovascular techniques and device innovation have alleviated some of the major obstacles faced by earlier operators. The introduction of three-dimensional coils has allowed for more complex framing configurations while reducing the likelihood of coil protrusion into the parent artery. Balloon-assisted coil embolization is yet another important tool in the armamentarium for endovascular treatment of intracranial aneurysms. In this technique, a compliant balloon is positioned and inflated across the neck of an aneurysm as coils are introduced into the aneurysm through a separately placed microcatheter. This technique facilitates improved packing density of the coils, reduces the risk of coil protrusion into the parent vessel, and affords a backup mechanism to arrest blood flow in the parent artery in case of an unfortunate event of intraprocedural aneurysm rupture. Finally, stent-assisted coil embolization has empowered neurointerventionists to tackle wide-necked/giant aneurysms. In this technique, the microcatheter is either navigated through the pores of the stent into the aneurysm or is jailed between the artery wall and the stent, and the coils are delivered into the aneurysm.

Flow Diversion

Initially, stent-assisted coiling was employed primarily to address the challenges posed by geometrically difficult aneurysms by containing the coil mass within the aneurysmal dome. This prevented coil herniation into the parent vessel and allowed denser packing of the aneurysm, which is known to correlate with a decreased rate of aneurysm recurrence and better long-term outcomes.[22,23] However, computational fluid dynamics analyses suggested that placement of the stent in the parent vessel itself may alter flow within the aneurysm, potentially accelerating the rate of aneurysm thrombosis.[24,25] Flow diversion for the treatment of intracranial aneurysms was conceived through a combination of ingenuity and serendipity. While performing animal studies, researchers discovered that covering an aneurysm with a stent changed the flow dynamic into the aneurysm, in some instances leading to obliteration of the aneurysm.[26,27]

The idea of flow diversion is based on two fundamentally simple concepts: (1) it was hypothesized that the stent disrupted blood flow from the parent artery into the aneurysm, and (2) the stent provided a scaffold on which endothelial cells could grow, therefore isolating the aneurysm from the parent artery. Some pioneers were quick to realize the potential clinical significance of the concept of flow diversion and became early adopters of this novel application. Before flow-diversion devices became available, coronary and intracranial stents were used in attempts to treat intracranial aneurysms that were otherwise not amenable to conventional neuroendovascular treatment.[28-31] In 2001, Benndorf et al.[28] reported treatment of a ruptured, dissecting, right vertebral artery aneurysm with two coronary stents (AVE; Medtronic, Inc., Minneapolis, MN) with complete radiological obliteration of the aneurysm by follow-up at 3 months. Similarly, in 2002, Islak et al.[30] described the treatment of two patients with unruptured giant and fusiform aneurysms with a combination of a coronary stent (AVE; Medtronic, Inc.) and a stent graft (Jostent; Jomed International, Helsingborg, Sweden).

Currently, a single flow-diversion stent is approved by the Food & Drug Administration (FDA) for use in the United States—the Pipeline™ Embolization Device (PED; ev3-Covidien, Irvine, CA), whereas the Silk flow diverter (Balt Extrusion, Montmorency, France), Flow-Redirection Endoluminal Device (FRED; MicroVention, Inc., Tustin, CA), Surpass (Stryker Corp., Kalamazoo, MI), and p64® Flow Modulation Device (Phenox, Bochum, Germany) are commercially available in Europe and South America. The PED was initially developed as a braided mesh tube with 16 strands of stainless steel and 16 strands of platinum, thus providing 30% metallic surface-area coverage when optimally deployed. It evolved into 48 strands consisting of 25% platinum-tungsten and 75% cobalt-chromium-nickel alloy, with 35% metallic surface-area coverage when fully deployed and a pore size of 0.02 to 0.05 mm² at nominal vessel diameter (Figure 1 A, B).[32] A study done on New Zealand white rabbits demonstrated an overall complete occlusion rate of 94% with preservation of the parent artery and small-branch vessels.[33] This result was a substantial improvement over the previous iteration of PED.

The foremost experience that confirmed the PED's clinical prowess came from the Buenos Aires case series, where complete occlusion was observed in approximately 93% of aneurysms on the 6-month follow-up angiograms.[34] Similar evidence came from the Budapest case series, where a nearly 90% rate of complete angiographic occlusion at 6 months was reported. These results laid the foundation of future trials—the Pipeline™ Embolization Device for the Intracranial Treatment of Aneurysms (PITA) trial, and the Pipeline for Uncoilable or Failed Aneurysms (PUFs) trial.[35,36] All of the trials demonstrated relatively high rates of aneurysm occlusion (73.6%-93.3%) with low rates of major morbidity and mortality (0%-6.5%) (Table 1). Subsequently, in 2011, the FDA approved the PED for endovascular treatment in adults with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segment. After initial experience proved encouraging, flow-diverter treatment of aneurysms in other vascular segments gained considerable traction and is now used increasingly for the treatment of wide-necked, large, and giant aneurysms.

According to some estimates, the surface area of metal coverage provided by the PED is approximately three times larger than that of other self-expanding intracranial stents, such as the Neuroform

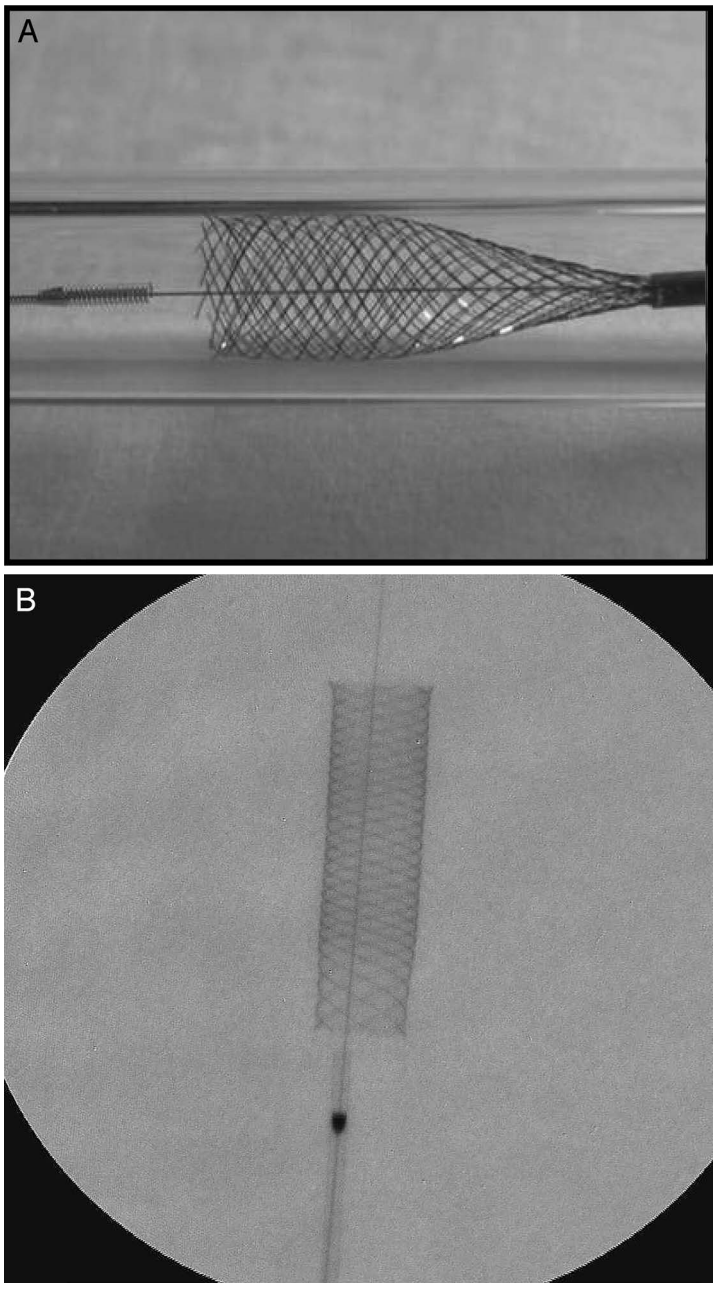

Figure 1. Images of Pipeline Embolization Device (ev3-Covidien, Irvine, CA) (A) being unsheathed inside a glass tube, and (B) deployed on the laboratory bench, under microangiographic fluoroscopic imaging. Image courtesy of Covidien Vascular Therapies. Pipeline is a trademark of a Covidien Company. © Covidien.

(Boston Scientific Corp., Natick, MA) and Enterprise (Codman & Shurtleff , Raynham, MA).[32] The PED is available in sizes ranging from 2.5 mm to 5.0 mm in diameter (in 0.25-mm increments) and 10 mm to 35 mm in length (in 1-mm increments from 10-20 mm and 5-mm increments from 20-35 mm). When fully deployed, the PED remains very flexible and able to conform to tortuous anatomy with little to no distortion. The PED delivery system is analogous to other stent delivery systems. It comes attached to a 0.016-in diameter stainless steel delivery wire, with the segment where it is mounted being 0.008-in thick. It is delivered via a 0.027-in delivery microcatheter, such as the Marksman (ev3-Covidien) or a similar microcatheter. Upon deployment at the nominal vessel diameter, the PED device foreshortens to between 50% and 66% of its constrained length inside the delivery microcatheter, which should be taken into consideration during deployment (Figure 2). The device is thrombogenic, and the risk of thromboembolism or late in-stent stenosis is also important to consider. The rate of PED thrombosis or stenosis was 1.9% in the PUFS trial[35] and approximately 5% in the Buenos Aires series.[34] Although relatively uncommon, these are potentially devastating complications. Therefore, all patients being considered for PED should be pretreated with a dual antiplatelet regimen. At our institution, patients are started on aspirin (325 mg daily) along with clopidogrel (75 mg daily) at least 7 days before the planned intervention. Appropriate therapeutic responses are obtained and dosages are optimized accordingly; clopidogrel nonresponders are placed on alternative agents.

One of the main concerns with flow diversion is related to the patency of side-branch and perforating vessels in the vicinity of treated aneurysms. Despite the low porosity and higher metal content of the flow-diversion device, outflow into perforators is usually maintained as long as there is a pressure gradient from the high-pressure parent artery branch to the low-pressure perforator territory. Existing data suggests that flow through the perforating vessel starts to decline if more than 50% of the perforator orifice is compromised by the flow-diversion device, despite the presence of a flow gradient.[27,37] Puffer et al.[38] surmised that up to 25% of ophthalmic arteries will undergo thrombosis when covered with the PED. This may be due to competitive collateral flow from the external carotid artery that prevents a pressure gradient from developing, leading to occlusion of the proximal ophthalmic artery when covered by the PED.[38] In a recently published case series of large or giant fusiform vertebrobasilar aneurysms treated with PED, two of the seven patients died secondary to devastating brainstem ischemic strokes.[39] Those deaths may have been secondary to the multiple PEDs used for treatment, leading to occlusion of the perforating vessel branches. One must exercise great caution when using the PED in the posterior circulation and

Study (year of publication)	No. (patients, aneurysms)	Occlusion at 6 months (No., % of aneurysms)	Major stroke or neurological death (No., % of patients)
Buenos Aires, 2009	53, 63	26 of 28, 92.8%	0 of 53, 0%
Budapest, 2010	18, 19	17 of 19, 89.5%	1 of 19, 5.3%
PITA, 2011	31, 31	28 of 30, 93.3%	2 of 31, 6.5%
PUFS, 2013	108, 108	78 of 106, 73.6%	6 of 108, 5.6%

Table 1. Summary of results of prospective Pipeline Embolization Device studies. No.: number; PITA: Pipeline Embolization Device for the Intracranial Treatment of Aneurysms; PUFS: Pipeline for Uncoilable or Failed Aneurysms.

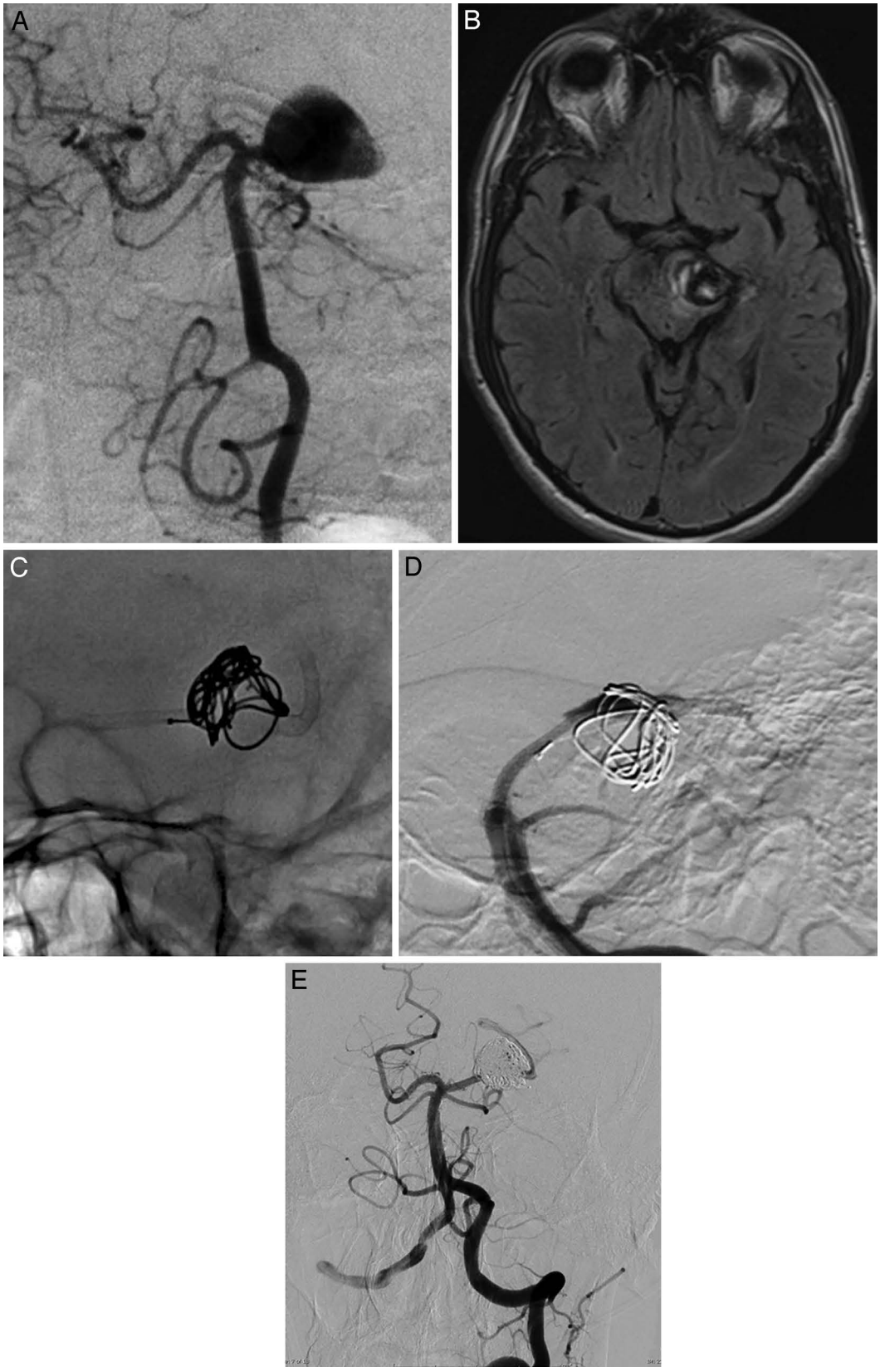

Figure 2. A 37-year-old man experienced pain and weakness of the right arm for approximately 6 months, which he attributed to a pinched nerve. This progressively worsened over the last few weeks before his presentation to our institute; during this time, he also developed a noticeable facial droop and slurred speech and was dragging his right leg. (A) Cerebral angiogram, anteroposterior (AP) view, shows a 15-mm left posterior cerebral artery fusiform aneurysm, with (B) brainstem compression seen on magnetic resonance imaging. Access to the femoral artery was obtained bilaterally. A triaxial system with Neuron™ MAX (Penumbra, Inc., Alameda, CA), 5MAX™ (Penumbra, Inc.), and Marksman™ (ev3-Covidien, Irvine, CA) catheters was advanced into the left vertebral artery for deployment of a Pipeline™ Embolization Device (PED; ev3-Covidien). A 5-Fr Envoy® Guiding Catheter (*Codman* & Shurtleff, Inc., Raynham, MA) with a PX SLIM™ Delivery Microcatheter (Penumbra, Inc.) was used to coil the aneurysm through the right vertebral artery. Angiograms of (C) anteroposterior and (D) lateral views show preliminary deployment of a single coil without detachment and deployment of the PED across the neck of the aneurysm. (E) Angiogram (AP view) at 3-months' follow-up shows complete obliteration of the aneurysm and a patent PED. The patient's symptoms resolved completely.

certainly attempt to place the least number of devices, preferably only one, needed to disrupt aneurysm flow.

Although flow diversion was originally conceived for the treatment of intracranial aneurysms, the use of flow diverters is expanding into visceral and peripheral aneurysms as operators are gaining experience and confidence.[40] Currently, this technology is in a transition period that is leading to second-generation devices, including the next iteration of the PED, the aforementioned FRED[41] and Surpass devices, both of which have been approved for use in other countries.[42] Clinical trials of both devices are currently

underway in the United States. Second-generation devices vary in surface-area coverage and in the mechanism for ease of deployment.[41] Data suggest that a stent with an overall porosity of 50% to 70% (30-50% metallic surface-area coverage) significantly reduces the rate of inflow into an aneurysm.[43] The optimal device porosity and pore density that will spare jailed perforators and small branches while achieving near-perfect aneurysm occlusion remains the "Holy Grail" of flow-diversion devices and is a subject of intense interest for competing industry leaders and researchers alike. Analyzing long-term outcomes of competing devices and understanding flow model dynamics and animal models will likely provide insight towards the optimal balance.

Another novel direction for flow diversion is intra-aneurysmal, with placement into aneurysms that are located at bifurcations and therefore not ideal for conventional flow diversion due to obligatory jailing of a large side branch. Examples of devices approved for use in Europe include the WEB (Sequent Medical, Inc., Aliso Viejo, CA) and the Luna (Covidien). Early data suggests that they may facilitate occlusion similar to their endovascular flow-diverting counterparts without compromising flow or jailing of an essential side branch.

Conclusion

Technologies such as coil embolization and flow diversion are still in their infancy, but early success is rapidly changing the landscape of endovascular options for treatment of aneurysms. Continued innovation and refinement of endovascular devices and techniques will ultimately improve technical success rates, reduce procedure-related complications, and broaden the endovascular therapeutic spectrum for varied aneurysm morphology. We expect further refinement of both indications and tools as more experience is garnered from these initial successes.

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Keywords: flow diverter, intracranial aneurysm, pipeline embolization device, subarachnoid hemorrhage

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