

# Endovascular Treatment of Cerebral Aneurysms

Current devices, emerging therapies, and future technology for the management of cerebral aneurysms.

BY DAVID FIORELLA, MD, PhD; MICHAEL E. KELLY, MD;  
RAYMOND D. TURNER IV, MD; AND PEDRO LYLYK, MD

**D**uring the past 2 decades, the endovascular treatment of cerebral aneurysms has quickly evolved from a nascent technology to a front-line therapy using sophisticated disease and anatomy-specific devices that allow the minimally invasive treatment of even the most complex cerebrovascular lesions. The available devices have transitioned from implantable balloons to embolization coils, to bioactive embolization coils, to adjunctive intracranial stents for use with embolization coils, and ultimately to “stand-alone” stent-like devices. The fundamental basis for treatment is rapidly shifting from techniques that are targeted at occluding the aneurysm sac (endosaccular occlusion) to those designed to achieve a durable physiological reconstruction of the parent vessel that gives rise to the aneurysm (parent vessel reconstruction). In this article, we review the predicate devices, currently available treatments, and finally the status of new and emerging technologies.

## INDICATIONS FOR CEREBRAL ANEURYSM TREATMENT

In general, there are two broad categories of intracranial aneurysms: (1) those that have already ruptured, creating subarachnoid hemorrhage, and (2) those that are unruptured. Typically, unruptured aneurysms are asymptomatic; however, rarely they may become symptomatic—usually due to their size and subsequent mass effect. The management of these two types of lesions differs dramatically.

## Ruptured Aneurysms

These lesions are almost always treated provided that the patient is neurologically and physiologically well enough to undergo therapy, either surgical clipping or endovascular coiling. Subarachnoid hemorrhage from aneurysm rupture is a devastating event with a case-fatality rate of 51% and a 50% rate of significant disability among survivors.<sup>1,2</sup>

Treatment is typically carried out urgently rather than emergently, usually within 24 hours after the arrival of the patient to the hospital. Initially, there was considerable controversy with respect to the treatment modality that was best suited for the right of first refusal for therapy, however, much of this controversy was settled by the International Subarachnoid Aneurysm Trial (ISAT), which demonstrated that for aneurysms amenable to either therapy, patients undergoing coil embolization had better long-term outcomes than those who underwent open surgical clipping.<sup>3,4</sup> Although there were some concerns regarding the durability of coil embolization as a treatment modality, an analysis of the ISAT data demonstrated that the superiority of endovascular coiling was preserved for at least 7 years after treatment.<sup>3</sup> For this reason, at most institutions, endovascular coiling is granted the right of first refusal for ruptured aneurysms amenable to either treatment modality.

## Unruptured Aneurysms

The vast majority of aneurysms discovered incidentally are completely asymptomatic. During the past decade,

with the proliferation of noninvasive cerebrovascular imaging studies ordered by referring physicians, we have begun to diagnose small, unruptured aneurysms with increasing frequency. The diagnosis typically is the cause of great anxiety on the part of the patient and referring physician, resulting in immediate referral to a cerebrovascular interventionist for evaluation. At this point, the decision of whether to treat must be based on the best available evidence regarding the risk of rupture of an incidentally diagnosed cerebral aneurysm. Unfortunately, the available evidence and its interpretation are still actively debated, and these decisions are rarely straightforward. Ultimately, three options are typically provided—conservative management (with or without imaging surveillance), open surgical clipping, and endovascular coil embolization—with the patient making a final decision based on a fair and unbiased presentation of the available data regarding all treatment modalities.

The largest study of the natural history of incidentally discovered unruptured intracranial aneurysms (The International Study of Unruptured Intracranial Aneurysms [ISUIA]) is highly controversial and indicated much lower rates of annual rupture than the majority of previous studies on this topic.<sup>5-13</sup> It is accepted that the risk of rupture of an incidental aneurysm is most closely related to its size. Kotomaru et al,<sup>14</sup> in their recent summary of this available literature, estimated a yearly risk of rupture of approximately 1% for lesions between 7 mm and 10 mm, with the risk being much lower in lesions <5 mm and significantly higher in lesions >10 mm. Whereas small aneurysms (<5 mm) are generally left untreated, larger lesions, particularly in patients younger than 60 years, are considered for treatment with the preference toward treatment increasing with aneurysm size. For lesions >10 mm, treatment is generally recommended in most patients who are without significant other comorbidities and are younger than 70 years of age.<sup>14</sup>

When left untreated, patients are sometimes offered serial imaging for surveillance of the aneurysm, with the idea that any increase in size or change in morphology could represent an indication for treatment. However, as a practical matter, for a small aneurysm (eg, 4 mm), whereas a 1-mm change in the size of the aneurysm might be difficult to detect even with the most advanced noninvasive imaging systems (CTA or MRA), this small change in diameter translates to a doubling of the aneurysm volume. Also, there is no guarantee that an aneurysm will detectably change in size or morphology prior to rupturing. As such, this recommendation of serial imaging follow-up is somewhat controversial, but often provides some piece of mind to the patients (and their physicians), and occasionally might demonstrate significant interval growth of a lesion.

Occasionally, an unruptured aneurysm may become suddenly symptomatic, typically related to either an abrupt increase in size or less frequently acute thrombosis. The most common example is a posterior communicating artery aneurysm that classically produces the acute onset of third nerve palsy. This clinical scenario typically is a harbinger of impending aneurysm rupture and should prompt treatment on an accelerated basis.

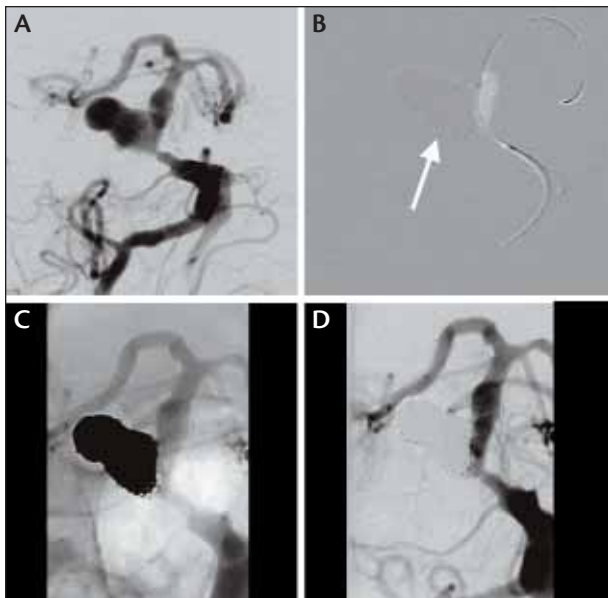
## ANEURYSM TREATMENT

### The Past

A number of strategies for endovascular aneurysm treatment have been employed during the past 3 decades. In 1970, Serbinenko first described the use of implantable latex balloons in the management of cerebral aneurysms.<sup>15</sup> Whereas the technique described by Serbinenko usually involved occlusion or deconstruction of the parent vessel and aneurysm, further development of balloon and catheter technology allowed for the placement of detachable silicone or latex balloons directly into cerebral aneurysms, allowing, in some cases, a constructive occlusion of the aneurysm with preservation of the parent vessel.<sup>16-18</sup> Given the developmental nature of this technology, the lesions treated were generally limited to those that were believed to be of unacceptably high rates of surgical morbidity (ie, giant aneurysms), particularly involving the posterior circulation and aneurysms in patients too ill to undergo surgery. Predictably, these treatments were associated with very high rates (at least 30%) of serious periprocedural morbidity and mortality.<sup>19</sup>

### The Present

*Detachable coils.* The modern era of neuroendovascular aneurysm treatment was heralded by the development of detachable platinum coils in the early 1990s and their subsequent FDA approval in 1995.<sup>20,21</sup> These flexible, soft, detachable coils could be delivered through a microcatheter that could be safely navigated into the targeted aneurysm. Intra-aneurysmal coil placement was also far more atraumatic, controllable, and safer than the manipulation, insufflation, and detachment of the predicate silicone balloons. Once coils were introduced and commercially available, there was a proliferation of reports describing their application in the embolization of intracranial aneurysms. Complex-shaped, three-dimensional coils were developed to facilitate the embolization of wide-necked aneurysms. Coils with faster detachment times were developed to speed the process of embolization and shorten procedure times. As aneurysm embolization with the Guglielmi Detachable Coil (GDC, Boston Scientific Corporation, Natick, MA) became increasingly accepted and more widely performed, com-



**Figure 1. Balloon-assisted technique.** A 64-year-old man presented with a large, ruptured midbasilar trunk aneurysm. An angiogram in the posteroanterior projection performed from a right vertebral catheter position shows that the aneurysm neck is very wide and would allow embolization coils to prolapse into the parent basilar artery if no parent vessel protection technique was used during treatment (A). A subtracted image (B) shows the negative (white) outline of the deflated temporary occlusion balloon that was inflated within the parent artery during placement of the embolization coils. Note that after balloon deflation, the coil mass (arrow) remains completely subtracted out on the map. If there were any coil movement during the balloon deflation, this would become very conspicuous on this subtracted map as a new opacity projecting into the defect left by the balloon. Postcoiling angiography (C= native, D=subtracted) in the PA projection performed from a left vertebral artery catheter position shows a large coil mass in place within the aneurysm (arrow) with coils reconstituting the entire neck defect along the lateral aspect of the parent basilar artery. The subtracted image (D) shows complete coil obliteration of the aneurysm.

petitors emerged, and additional brands of embolization coils became available.

*Adjunctive techniques.* As coil embolization emerged as a viable alternative to surgical aneurysm clipping, techniques evolved that allowed the treatment of more complex lesions. The primary anatomic impediment to aneurysm embolization is an unfavorably large neck-to-dome ratio (ie, the wide-necked aneurysm). In these lesions, the wide neck of the aneurysm may allow the detached embolization coils to prolapse from the

aneurysm fundus, through the wide neck and into the parent vessel, giving rise to possible thromboembolic complications or unintentional parent vessel occlusion. Initially, these wide-necked lesions were labeled as inappropriate for endovascular therapy and were largely referred for open surgical treatment.

### Balloon Remodeling

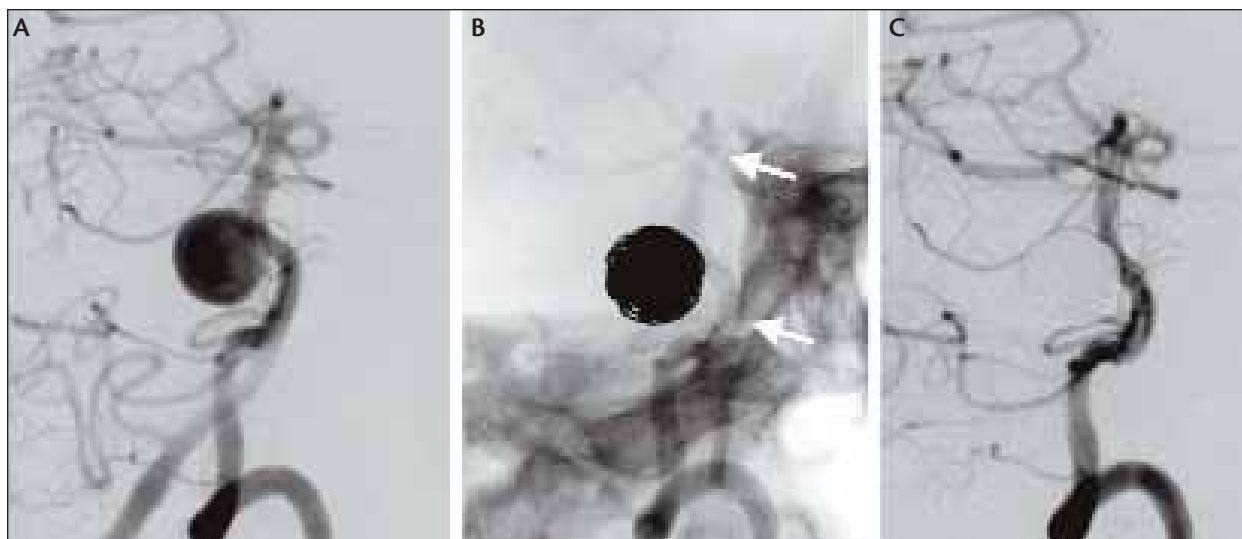
In the late 1990s, the technique of balloon remodeling was developed for the treatment of wide-necked aneurysms.<sup>22,23</sup> With the balloon remodeling technique, a temporary occlusion balloon is inflated across the neck of the aneurysm while embolization coils are introduced. The balloon functions to prevent the prolapse of coils into the parent vessel. After the introduction of a coil under balloon protection, the occlusion balloon is traditionally deflated, and the coil is observed for prolapse into the parent vessel. If the coil appears stable, it is detached, and the balloon is reinflated for the introduction of the next coil. This technique is repeated until occlusion of the aneurysm is achieved (Figure 1).

### Intracranial Stenting

Although the temporary occlusion balloons provide support for coils during their introduction, sometimes the introduced coil can prolapse into the parent artery immediately after balloon deflation, necessitating one or more attempts at coil repositioning. It is also possible that the introduction of a new embolization coil could displace a previously detached coil from the aneurysm sac into the parent vessel. Finally, very wide-necked aneurysms or fusiform/circumferential aneurysms oftentimes lack any neck structure at all, making coil placement, even with a balloon remodeling technique, very tenuous or impossible.

These shortcomings of the traditional method of balloon-assisted coil embolization ultimately led to the development of intracranial microstents. The first report of intracranial stent-supported coil embolization was reported by Higashida et al,<sup>24</sup> who used a balloon-mounted coronary stent to treat a wide-necked, fusiform, basilar artery aneurysm. The rigidity of the commercially available balloon-mounted coronary stents often precluded their delivery and deployment within the tortuous cerebrovascular circulation.

In the early part of this decade, Dr. Peter Kim Nelson and his team at SMART therapeutics developed Neuroform, the first microcatheter-delivered, self-expanding, intracranial, nitinol microstent designed specifically for application within the intracranial circulation to support the treatment of cerebral aneurysms.<sup>25</sup> This device was much easier to deliver and deploy within the cerebrovasculature than the predicate balloon-mounted stents. The commercial release of Neuroform by Boston Scientific



**Figure 2.** Stent-assisted technique. Fifty-nine-year-old female with a symptomatic basilar aneurysm. Subtracted image in the PA projection shows a large aneurysm projecting laterally from the basilar artery (A). Due to the configuration of the basilar artery and the width of the neck, it was believed that a more complete embolization could be achieved with a stent-supported technique. After placement of an Enterprise 4.5-mm X 20-mm stent (Cordis Neurovascular), coil embolization was performed. The posttreatment native image (B) shows the in situ Neuroform stent, with the proximal and distal ends demarcated by radiopaque marker bands (arrowheads). A coil mass fills the saccular portion of the aneurysm. The posttreatment subtracted image (C) shows near complete occlusion of the aneurysm by the coil mass.

Corporation in the US in 2003 led to a marked increase in the number of complex aneurysms that were amenable to therapy. Neuroform was quickly incorporated into practice, and the embolization of wide-necked aneurysms became more routine. In 2007, the Cordis Enterprise Vascular Reconstruction Device and Delivery System (Cordis Neurovascular, Warren, NJ), a second self-expanding intracranial microstent became available (Figure 2).

As experience with the Neuroform grew, operators began to use the device in novel ways to achieve the embolization of increasingly complex lesions (eg, Y-stent reconstructions, stent placement working across the circle of Willis, and the balloon-in-stent technique).<sup>26-28</sup>

*Shortcomings of coil embolization.* Although essentially still a nascent technology in the later 1990s, endovascular coiling proved superior to open surgical clipping for the treatment of ruptured aneurysms in the ISAT trial.<sup>3,4</sup> During the past decade, coil technology has quickly improved, and technical expertise has grown exponentially as the procedures have become more common and the technology more pervasive. Data from more recent randomized endovascular trials have indicated that the safety of the coiling procedure has improved significantly even in comparison to its track record in ISAT.<sup>29</sup>

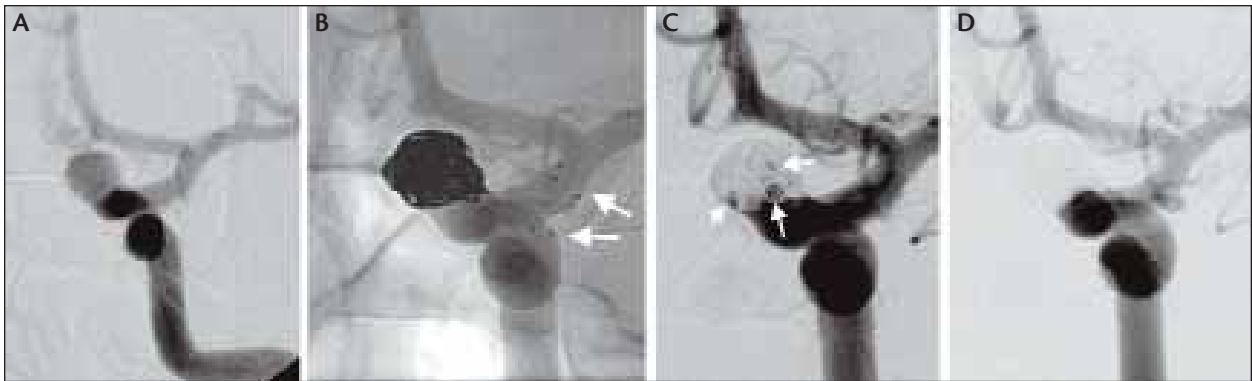
Despite these impressive results, there is still significant room for improvement with respect to the endovascular

treatment of aneurysms. The fundamental shortcoming of coiling technology is that it aims to achieve endosaccular occlusion of cerebral aneurysms without addressing the diseased parent vessel that gave rise to the aneurysm. Although this approach is very effective for many of the small, narrow-necked cerebral aneurysms that are commonly encountered in practice, the technology fails with more complex, difficult lesions.

The failures of coil embolization are manifest in two major ways: (1) incomplete treatment (the inability to achieve complete angiographic occlusion of most lesions), and (2) aneurysm recanalization (interval coil compaction with time [usually over months] leading to a deterioration of the results achieved during the original treatment).

### Incomplete Treatment

Only the minority of aneurysms treated by coil embolization are actually angiographically cured. Raymond et al<sup>30</sup> reviewed their results for a series of 383 aneurysms that were treated by coil embolization. The investigators reported only a 38.3% rate of complete angiographic occlusion at 12-month follow-up. In a more recent series of 182 coiled aneurysms, Rivet et al<sup>31</sup> reported a <50% rate of complete aneurysm occlusion at follow-up angiography. Although the necessity of achieving complete angiographic cure is debated, the recent Cerebral Aneurysm Rerupture After Treatment (CARAT) study pro-



**Figure 3.** Progressive thrombosis and parent vessel remodeling with the Neuroform stent: an asymptomatic, small, unruptured left carotid-ophthalmic artery is demonstrated in an oblique lateral projection (A). This lesion was initially coiled by means of balloon-assisted technique, followed by placement of a Neuroform stent. The immediate posttreatment angiogram in the PA view (B= native) shows the coil mass in place filling the aneurysm, and the end markers of the Neuroform stent (arrowheads), which reconstruct the parent vessel across the region of the aneurysm neck. An immediate posttreatment subtracted angiogram (C) shows small niches of filling within the aneurysm (small arrows) after embolization despite a meticulous coiling with balloon-assisted technique. However, angiographic follow-up at 11 months (D) demonstrates progression to complete occlusion, with all of these tiny niches of residual filling going on to thrombosis. The parent artery appears to be smoothly “remodeled” over the region of the aneurysm neck. This progression to complete occlusion is sometimes seen in aneurysms treated with Neuroform.

vides evidence that it does.<sup>32</sup> In the CARAT study, ruptured aneurysms were followed after either surgical or endovascular treatment to assess the incidence of re-hemorrhage. Although the overall hemorrhage risk was very low after coiling (1.3 re-hemorrhages per 100 person-years), the risk of rebleed increased drastically with decreasing levels of aneurysm occlusion (0.6 re-hemorrhages per 100 person-years for completely occluded aneurysms vs 15 re-hemorrhages per 100 person-years for partially occluded lesions).<sup>32</sup>

Due to the random distribution of coils within an aneurysm and the tendency of the individual strands to break the aneurysm up into multiple small compartments, the best packing densities that can be routinely achieved with conventional embolization coils (with or without adjunctive devices) range between 30% and 40% in experimental silicone and glass aneurysm models and between 20% and 30% in clinical human aneurysm treatments. The rates are much lower for large and giant aneurysms and for aneurysms with wide necks.<sup>33</sup> As such, the majority of the volume (70%–80%) within coiled aneurysms is not filled with metal.

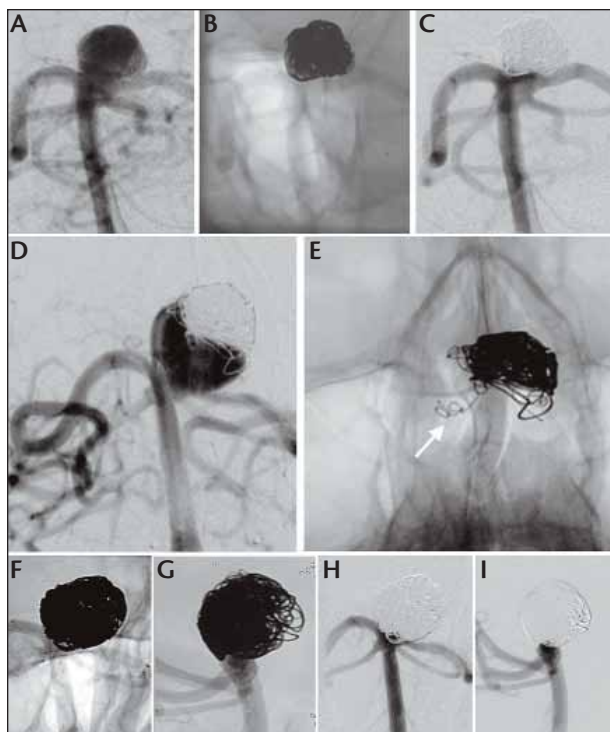
Not only are aneurysms difficult to densely pack with coils, but also contiguously bridging the entire aneurysm neck with coils is extremely difficult, particularly if the aneurysm is wide necked, incorporating a significant percentage of the circumference of the parent vessel. In these situations, even with the most meticulous technique, there are invariably gaps between coils in the region of the aneurysm neck that allow persistent inflow

into the aneurysm neck and probably impair the endothelialization and neointimal growth over the aneurysm neck that is ultimately required to achieve complete angiographic occlusion and durable, curative embolization (Figure 3).

#### Aneurysm Recanalization

The technical limitations with respect to achieving a dense packing of cerebral aneurysms with coils and completely reconstructing the aneurysm neck with coils is also manifest as poor durability of the immediate posttreatment result (Figure 4). Raymond et al<sup>30</sup> observed a recanalization rate of 33.6%, which was considerably higher for large (50.6%) and wide-necked (52.3%) aneurysms. Similarly, Murayama et al<sup>34</sup> reported recanalization rates of 35.3% and 59.1% for large and giant aneurysms, respectively. In addition, once aneurysms recur and require retreatment, they frequently recur a second (or third) time, with a repeat recurrence rate of 48.6%.<sup>30</sup>

These shortcomings of coil embolization have resulted in questions about the long-term durability and, for the more complex and larger aneurysms, the long-term efficacy of the technique. As such, after endovascular aneurysm treatment, the patient is consigned to a schedule of serial imaging follow-up. Although much of this follow-up can now be performed noninvasively with MR imaging examinations specifically designed to assess for aneurysm recurrence, follow-up angiography is often required and, in many cases, one or more retreatments may be necessary to preserve adequate aneurysm occlusion.<sup>35</sup>



**Figure 4. Coiling failure: aneurysm recurrence after treatment.** A 57-year-old woman presented with an 8-mm, wide-necked basilar artery apex aneurysm, demonstrated on this PA view from a right vertebral artery angiogram (A). The aneurysm was coiled to near complete occlusion using balloon-assisted technique. The posttreatment native (B) and subtracted (C) images show a dense coil mass filling the aneurysm with minimal residual filling between the interstices of the coil mass in the region of the aneurysm neck. Follow-up angiography (D=native, E=subtracted) at 6 months shows a large recurrence of the aneurysm with regrowth along the aneurysm neck and compaction of the embolization coils into the fundus. A coil loop (arrow) from the original coiling is left dangling within the recurrent aneurysm fundus and neck. The aneurysm was retreated with a Y-stent supported technique—with one Neuroform stent placed from the basilar artery into the left posterior cerebral artery (PCA) and a second Neuroform stent placed from the basilar artery into the right PCA—followed by aggressive aneurysm coiling. Native PA and lateral images (F, G) show the large coil mass within the recanalized aneurysm. Subtracted PA and lateral images (H, I) confirm complete occlusion of the lesion.

*Bioactive and coated coils.* To address these shortcomings, bioactive coils were developed. Two general categories of modified coils have been introduced: (1) polyglycolic-poly-lactic acid (PGPLA)-containing coils (eg, Matrix, Boston Scientific; Cerecyte, Micrus Endovascular, San Jose, CA) and (2) hydrogel-coated coils (Hydrocoil,

Microvention/Terumo, Alisa Viejo, CA).

The PGPLA-containing coils are designed to stimulate an inflammatory reaction within the aneurysm that induces an accelerated organization of thrombus and ultimately fibrosis and subsequently elicits a faster and more complete neointimal overgrowth of the aneurysm neck. The Matrix coils were the first such PGPLA-containing coils that were commercially available. There is currently a company-sponsored, randomized trial (Matrix and Platinum Science [MAPS]) being conducted to compare these bioactive coils to standard bare platinum coils. The available case series assessing Matrix thus far have been somewhat disappointing, indicating that the angiographic results have been the same (or in some cases worse) than those that have been reported for bare platinum coils. Even fewer data are available for Cerecyte, which is also currently being investigated in a company-sponsored, randomized trial versus bare platinum coils (Cerecyte Coil Trial).

The hydrogel-coated coils are coated with a desiccated hydrogel that absorbs water and swells considerably upon introduction into the blood environment. The -10, -14, and -18 size hydrocoils swell to five, seven, and 11 times the volume of the standard “platinum-10” sized coils. As such, these coils substantially increase the volumetric filling that can be achieved with endosaccular coil embolization, routinely resulting in packing densities between 50% and 100%.<sup>36</sup> Hydrocoil was compared with standard bare platinum coils in a randomized trial (HydroCoil Endovascular Aneurysm Occlusion and Packing Study [HELPS trial]) that was completed in April 2006. The initial blinded safety results have been released; however, the unblinded results are still pending.<sup>29</sup>

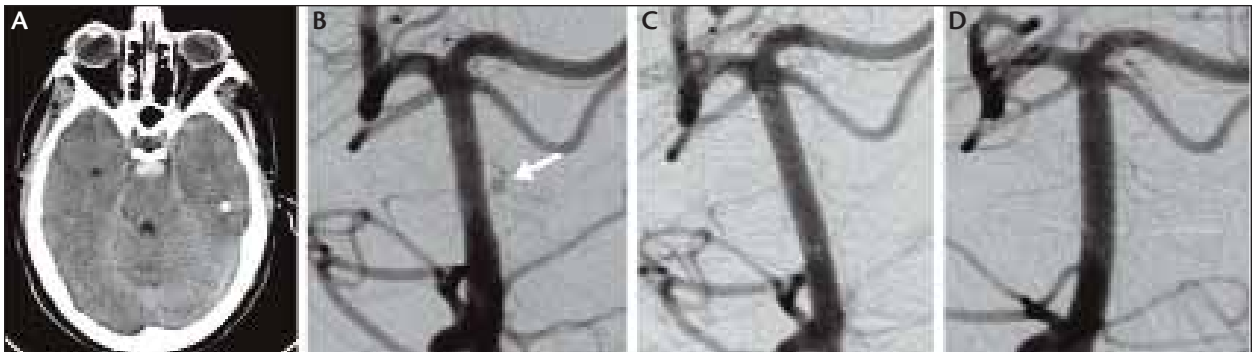
Although bioactive and coated coils may enhance the degree and durability of endosaccular occlusion that can be achieved with coils, they still fail to address the diseased parent vessel and, therefore, still represent largely a solution for the more straightforward small and relatively narrow-necked aneurysms.

## THE FUTURE

### Parent Vessel Reconstruction: Conceptual Basis

Parent vessel reconstruction represents the most physiological treatment of cerebral aneurysms. With this technique, the diseased parent artery that gives rise to the saccular or fusiform aneurysmal outpouching is primarily reconstructed. This procedure is achieved through the implantation of stents or stent-like devices within the parent artery, which function to achieve several important hemodynamic and biological effects:

- Change in parent vessel configuration: The implantation of a stent within a parent artery may straighten the vessel, altering (possibly in a favorable manner) the flow dynamics within the aneurysm. The magnitude of this



**Figure 5.** Neuroform stent monotherapy. A 46-year-old man with subarachnoid hemorrhage (A). Initial angiography (B) was interpreted as normal. However, in retrospect, there may be a tiny bleb (arrow) arising in the region of the midbasilar perforator. Six-week follow-up angiography demonstrated interval growth of a midbasilar trunk aneurysm, which measured slightly less than 2 mm (C). The lesion was too small to accept an embolization coil and was treated with two telescoping Neuroform stents. A follow-up angiogram 14 months after treatment showed complete occlusion of the aneurysm, with maintained patency of the adjacent perforator vessel (D).

effect is affected primarily by the rigidity of the stent.

- **Flow redirection:** The presence of stent tines over the aneurysm neck functions to disrupt the inflow jet, reducing vorticity and shear stress on the aneurysm wall and reducing the “water-hammer” effect of chronic pulsatile blood flow on an intra-aneurysmal coil mass. The magnitude of this effect is affected primarily by the amount of metal surface area coverage provided by the stent.

- **Tissue overgrowth:** The presence of a stent across the neck of the aneurysm provides a scaffolding and stimulus for the overgrowth of endothelial and neointimal tissue across the neck of the aneurysm, creating a “biological remodeling” in the region of the aneurysm neck. The magnitude of this effect is affected by the amount of metal surface area coverage, as well as the structure and composition of the stent material.

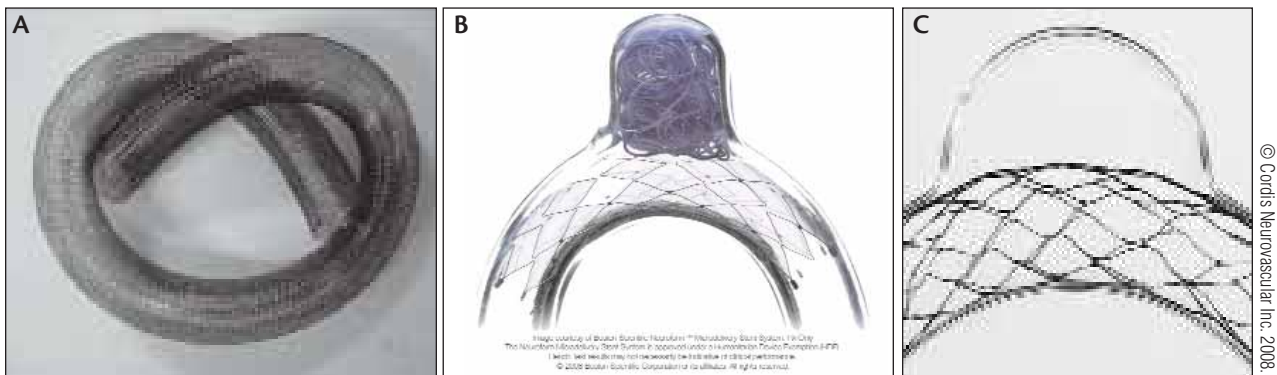
*Parent vessel reconstruction with commercially available self-expanding intracranial microstents.* Initially, self-expanding intracranial microstents (eg, Neuroform, Cordis Enterprise Vascular Reconstruction Device) were marketed and applied as adjunctive devices to facilitate the coil embolization of wide-necked aneurysms. When applied in this context, it became evident that these devices were not only facilitating aneurysm treatment, but they were also potentially increasing the durability of the treatment of wide-necked aneurysms and augmenting the rate and extent of progressive aneurysm thrombosis that occurred after treatment (Figure 3).<sup>37</sup> In addition, in some cases in which uncoilable and unclippable wide-necked “blister-type” aneurysms or pseudoaneurysms were encountered, successful treatment was achieved with the placement of one or more self-expanding microstents, without embolization coils (eg, stent monotherapy). This observation indicated that

parent vessel reconstruction with commercially available stents sometimes represented a viable “stand-alone” technique for the treatment of selected aneurysms that were not amenable to other therapies (Figure 5).<sup>38</sup> Typically, this stent monotherapy strategy was only successful with very small blister aneurysms, the saccular component of which was too small to accommodate an embolization coil.

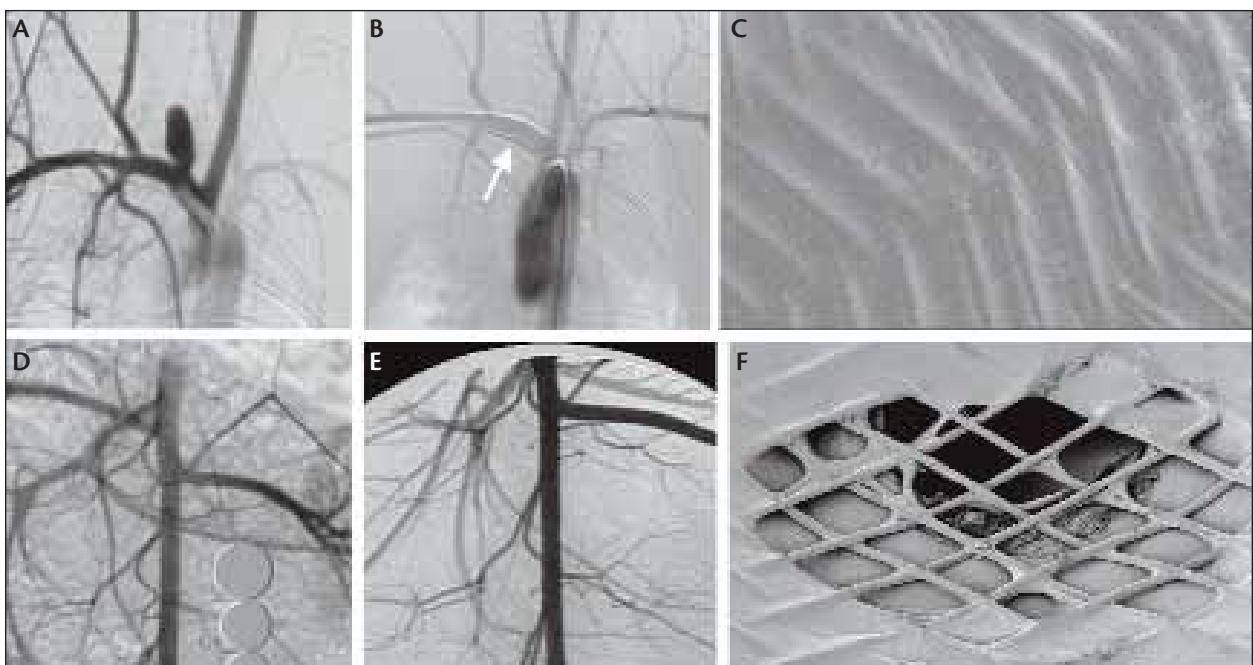
*Parent vessel reconstruction with the Pipeline Embolization Device.* During the past 2 years, a new generation of self-expanding, microcatheter-delivered, intracranial microstents has been specifically engineered to primarily achieve definitive parent vessel reconstruction of the cerebral arteries giving rise to aneurysms. The only such device that has successfully been applied in human patients is the Pipeline Embolization Device (PED, Chestnut Medical, Menlo Park, CA).

The PED is a self-expanding, microcatheter-delivered, cylindrical mesh device composed of 48 individual braided cobalt chromium and platinum strands. The device has a 30% to 35% metal surface area when fully deployed, which is far greater than the 6.5% to 9% metal surface area coverage provided by the commercially available self-expanding intracranial microstents that are routinely used in practice (Figure 6). Multiple devices can be deployed within each other (telescoped) to create a composite endovascular construct. The degree of metal surface area coverage can be manipulated by varying the technique of device deployment, as well as by choosing the number of overlapping devices placed in a particular vascular segment.

Because the PED reconstructs the entire length of the treated parent vessel, the traditional factors that markedly diminish the efficacy of standard endosaccular aneurysm treatments such as neck width, large or giant size, and the

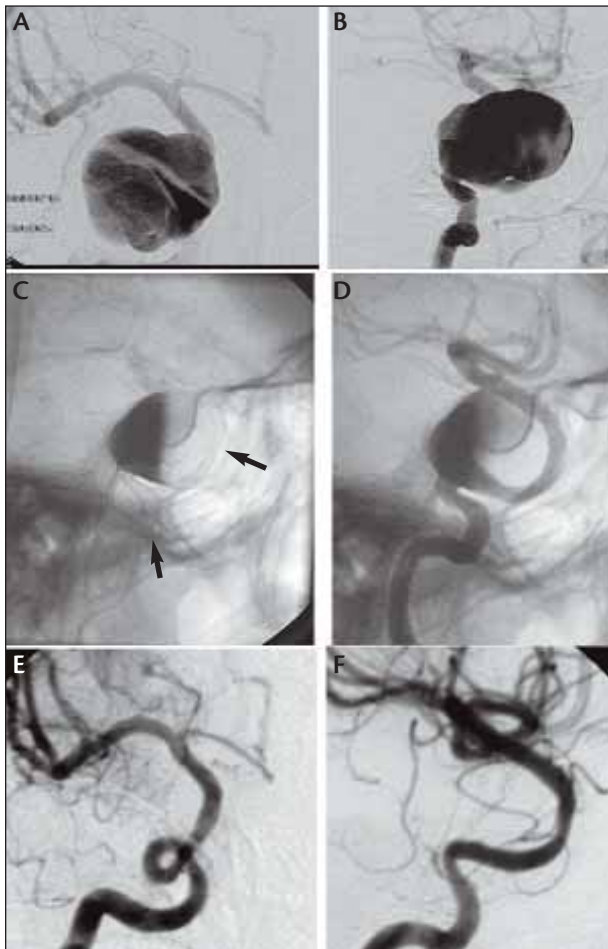


**Figure 6. Pipeline Embolization Device (PED). Construction and difference from other self-expanding intracranial microstents.** The PED (A) is a flexible, microcatheter-delivered, self-expanding, endovascular construct engineered specifically for the treatment of cerebral aneurysms. The device is composed of a braid of individual microfilaments. When fully deployed, the PED provides approximately 30% metal surface coverage at nominal expansion—a much higher percent coverage than that provided by conventional (noncovered) intravascular stents. The Neuroform stent (B) and the Cordis Enterprise Vascular Reconstruction stent (C) are self-expanding, nitinol, microcatheter-delivered microstents. These stents are cut from a nitinol hypotube. When fully deployed, they provide between 6.5% and 9% metal surface area coverage.



**Figure 7. Angiography from an innominate projection shows an experimental aneurysm arising from the proximal innominate artery (A). This experimental aneurysm was treated with a single PED. At 6-month follow-up angiography, the aneurysm has progressed to complete occlusion (B), whereas the adjacent vertebral artery (also covered by the PED) remains patent. Scanning electron micrograph over the region of the aneurysm neck shows a complete layer of tissue coverage (C). Faint striations are visible through the tissue layer, indicative of the strands of the PED that have been covered by neointimal and endothelial tissue (ie, the “steel reinforced artery”). A PA image of the abdominal aorta of the same subject shows numerous small lumbar arteries arising from the vessel (D). Angiography performed 6 months after PED implantation within this vessel shows that all of the lumbar artery side branches covered by the PED remain patent (E). A scanning electron micrograph shows the orifice of one of the lumbar arteries to be widely patent, with the homogenous layer of tissue growth over the PED interrupted by an ovoid gap, which allows perfusion of this side branch (F). (Images from an experiment performed by Kallmes et al. Angiograms and scanning electron micrographs were generously provided by Drs. Kallmes and Dai, Mayo Clinic, Rochester, MN.)**





**Figure 8.** Curative reconstruction of a giant right internal carotid artery aneurysm with PED. A 60-year-old woman presented with right eye vision loss. Conventional angiography (A, B) demonstrates a giant aneurysm arising from the petrocavernous segment of the right internal carotid artery. Mass effect from this lesion is responsible for the decline in vision experienced by the patient. The segmental defect giving rise to the aneurysm was reconstructed using two PEDs. An arterial phase angiographic image (C= native) demonstrates markedly decreased contrast filling within the aneurysm sac after PED reconstruction. A delayed phase native image in the lateral projection (D) shows stasis of contrast material within the aneurysm, layering dependently (ie, the “eclipse sign”) and indicative of markedly reduced flow. Arrows indicate the position of the PED construct. Six-month follow-up conventional angiography in the working angles for PED placement (E, F) demonstrates definitive anatomic reconstruction of the right internal carotid artery, with complete occlusion of the saccular aneurysm.

presence of intra-aneurysmal thrombus would not be expected to have an impact on the efficacy of PED. Hypothetically, the parent vessel reconstruction strategy

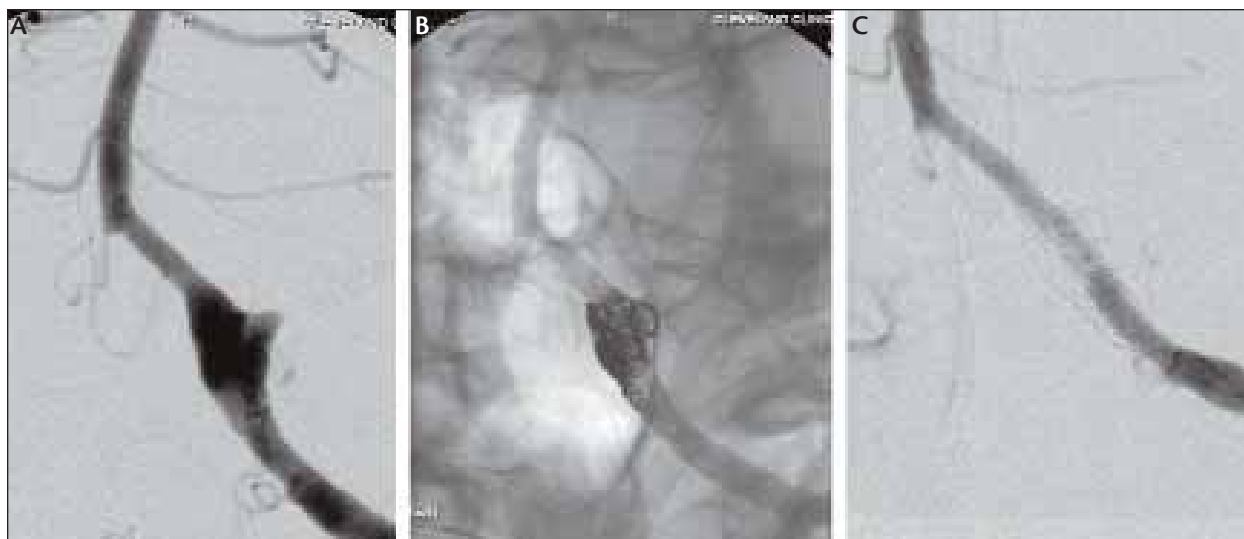
directly addresses those issues that present the greatest impediments to the success of the aneurysm coil embolization. The initial experience with the PED in experimental aneurysm models and human patients has corroborated this hypothesis—the existing data suggest that this technology represents a quantum advance in neuroendovascular aneurysm therapy.

*In vivo experimental data.* Kallmes et al<sup>39</sup> studied the PED in a rabbit elastase animal model and demonstrated that a single construct placed over the orifice of the aneurysms was sufficient to induce aneurysm thrombosis and angiographic occlusion (Figure 7). When these thrombosed aneurysms were harvested and the parent vessel-aneurysm complex was evaluated, the saccular aneurysms were not only thrombosed but often atretic, and the parent vessels were circumferentially reconstructed with the PED structure incorporated into the vessel wall and covered by a lining of well-developed neointima and endothelium. Thus, not only were the aneurysms cured, but the parent vessels from which they arose were essentially reconstructed into a “steel-reinforced” structure. This spectrum of findings would suggest that not only does the PED provide angiographic occlusion of aneurysms, but in these experimental models, effects a durable physiological cure.

In the same series of experimental subjects, Kallmes et al<sup>39</sup> placed a single PED within the abdominal aorta, covering the ostia of the lumbar arteries. The rabbit aorta approximates the caliber of human intracranial vessels, and the lumbar artery branches approximate the perforators. Angiography and histology showed that none of the lumbar arteries covered by the PEDs demonstrated either immediate or delayed occlusion. These data indicate that branch vessels—the patency of which are maintained by a pressure gradient—remain patent, even when their ostia are partially occluded by strands of the PED.

*Human experience.* To date, the PED has been implanted in more than 80 patients for the treatment of intracranial aneurysms; 39 have been in the context of clinical studies (the PED in the Intracranial Treatment of Aneurysms [PITA] trial) or the single-center “Budapest post-PITA study,” whereas the remainder have been performed under provisions for compassionate use for aneurysms that were either untreatable or had failed to respond to previous therapy.

The PITA trial was a single-arm, 31-patient, clinical safety study in which patients with wide-necked saccular aneurysms or aneurysms that had failed to respond to previous endovascular coiling underwent treatment with PED. The average aneurysm size was 11.5 mm, with an average neck width of 5.8 mm; thus, the study was predominantly



**Figure 9.** Curative reconstruction of an otherwise untreatable, circumferential, nonsaccular aneurysm of the left vertebral artery with PED. A 57-year-old man initially presented with acute onset of gait instability and left-sided neck pain. CTA evaluation at that time revealed an acute left PICA territory infarction and mild focal irregularity of the left vertebral artery. The patient was treated with warfarin for 3 months and was then converted to aspirin. A CTA performed 11 months later for recurrent symptoms demonstrated that the right vertebral artery had completely occluded and that the focus of irregularity involving the V4 segment of the left vertebral artery had expanded into a large, nonsaccular, circumferential aneurysm. Conventional left vertebral angiography (A) demonstrated the 14-mm X 7-mm circumferential aneurysm involving a 23-mm length of the parent artery. After parent vessel reconstruction with three PEDs, coil embolization of the saccular component of the aneurysm was performed through a microcatheter, which had been jailed within the aneurysm (outside of the PED construct). An immediate posttreatment native image (B) demonstrates a coil mass distributed circumferentially about the PED construct. Angiography immediately after treatment demonstrated markedly delayed flow into the aneurysm sac, with stasis of contrast around the indwelling coil mass that persisted on delayed imaging. Follow-up angiography performed at 72 hours demonstrated complete cure of the aneurysm. Follow-up angiography performed at 6 months and 1 year (C) has confirmed stable complete occlusion of the aneurysm, with curative reconstruction of the left vertebral parent artery. (Reprinted with permission from Fiorella et al. Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the Pipeline Embolization Device. *Neurosurgery*. 2008; March 11. [Epub ahead of print].)

one of large, wide-necked aneurysms. Overall, the device was delivered successfully in 100% of the cases, with a 6% rate of periprocedural complications (two strokes, no deaths). At 6-month follow-up, 28 of 30 lesions (93%) available for evaluation demonstrated complete angiographic occlusion (Figure 8).<sup>40</sup> This rate of occlusion surpasses any of the reported occlusion rates for aneurysms after endovascular therapy and far exceeds those reported for large or wide-necked lesions. Results for the post-PITA study are not yet available.

The PED has also been used to treat nonsaccular, fusiform or circumferential aneurysms. Three such cases have been performed in North America under an FDA compassionate use exemption. All three lesions, which were judged to be untreatable with existing endovascular or open surgical technologies, were angiographically cured with PED without technical or neurologic complications (Figure 9). In two cases, eloquent perforator or side branch vessels were covered by the PED construct. None of the

covered side branches or angiographically visible perforator vessels went on to occlusion either acutely or at follow-up. Two of these patients now have greater than 1-year clinical and angiographic follow-up and remain cured of their lesions and without neurologic symptoms.<sup>41</sup>

*Limitations.* Although the available data for the PED remains extremely encouraging, there remain several theoretical limitations of the device with respect to its application in the treatment of cerebral aneurysms. First, as with any intracranial stent-like device, a course of dual-antiplatelet medications is required for prophylaxis against thrombosis while the construct is becoming endothelialized and incorporated into the parent artery. The optimal duration of dual-antiplatelet therapy remains uncertain, but the current recommendation is for 6 months of aspirin with clopidogrel with aspirin alone thereafter. For this reason, aneurysmal subarachnoid hemorrhage represents a relative contraindication

to PED placement, given the potential for complications related to the invasive procedures frequently required during the perioperative period in these patients (eg, ventriculostomy catheters, percutaneous gastrostomy tubes, tracheostomies, etc). Second, the efficacy and safety of the device for the treatment of bifurcation aneurysms remains uncertain, considering that this application would require the “jailing” of one limb of a bifurcation. Although this has not been an issue with the current generation of lower-metal-surface-area coverage, self-expanding intracranial microstents, experience with PED is limited in this setting. Finally, the safety of the PED device in vessels rich with eloquent perforators remains to some extent unknown. The available data, both in experimental animal models and in human patients, suggest that single coverage with a PED is safe; however, until a larger data set is available, the amount of coverage (eg, with telescoped or overlapped devices) that can be applied in these anatomic locations remains uncertain.

## SUMMARY

Parent vessel reconstructive devices, such as the PED, represent a new treatment paradigm for intracranial aneurysms. The existing data suggest that these devices may provide a definitive cure of those lesions that have proven to be the most challenging to treat with the standard, more conventional, endosaccular occlusion techniques. Many complex aneurysms that were once thought to be “untreatable” or to require a deconstructive treatment with parent vessel occlusion may be definitively and curatively reconstructed with these new devices. Moreover, the major shortcomings of endosaccular aneurysm therapies—incomplete aneurysm occlusion and aneurysm recurrence—are directly addressed through parent vessel reconstruction.

Currently, the PED is not commercially available and has not yet been approved for use by the FDA. Although the existing data have been very encouraging, our experience with the device in humans remains, to some extent, preliminary. We anticipate that the PED will become available in the US within the context of clinical trials sometime during the upcoming year. ■

*David Fiorella, MD, PhD, is is from the Departments of Neuroradiology and Neurosurgery, Barrow Neurological Institute, in Phoenix, Arizona. He has disclosed that he holds no financial interest in Chestnut Medical; receives research grant funding from Boston Scientific; receives speaking hono-*

*ria from Cordis and Microvention; receives royalty agreement, consulting and speaking honoraria from Micrus; receives group consulting support from ev3; and receives salary support from the NIH: SAMMPRIS as the National Interventional co-Principal Investigator. Dr. Fiorella may be reached at (602) 406-3000; dfiorell@gmail.com.*

*Michael E. Kelly, MD, is Assistant Professor, Division of Neurosurgery, Royal University Hospital, University of Saskatchewan in Canada. He has disclosed that he is a paid consultant to Micrus Endovascular. Dr. Kelly may be reached at (306) 966-8023; mkelly@sasktel.net.*

*Raymond D. Turner IV, MD, is Clinical Instructor, Department of Neurological Surgery and Neuroradiology Neuroscience Institute Medical University of South Carolina in Charleston, South Carolina. He has disclosed that he is a paid consultant to and receives research grants from Microvention and that he is a paid consultant to Micrus. Dr. Turner may be reached at (843) 792-2424; rturnermd@hotmail.com.*

*Pedro Lylyk, MD, is from the Departments of Neurosurgery and Interventional Neuroradiology, Clinica Medica Belgrano, Fundacion para la Lucha contra Las Enfermedades Neurologicas de la Infancia, Buenos Aires, Argentina. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Lylyk may be reached at plylyk@lylyk.com.ar.*

- Hop JW, Rinkel GJ, Algra A, et al. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. *Stroke*. 1997;28:660-664.
- Mayer SA, Kreiter KT, Copeland D, et al. Global and domain-specific cognitive impairment and outcome after subarachnoid hemorrhage. *Neurology*. 2002;59:1750-1758.
- Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. 2005;366:809-817.
- Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet*. 2002;360:1267-1274.
- Wiebers DO, Whisnant JP, Huston J, 3rd, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103-110.
- ISUIA. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. *N Engl J Med*. 1998;339:1725-1733.
- Dippel DW, Habbema JD. Natural history of unruptured aneurysms. *J Neurosurg*. 1994;80:772-774.
- Juvela S, Porras M, Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *J Neurosurg*. 1993;79:174-182.
- Nakagawa T, Hashi K. The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. *J Neurosurg*. 1994;80:217-223.
- Rinkel GJ, Djibuti M, Algra A, et al. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke*. 1998;29:251-256.
- Tomasello F, D'Avella D, Salpietro FM, et al. Asymptomatic aneurysms. Literature meta-analysis and indications for treatment. *J Neurosurg Sci*. 1998;42(suppl 1):47-51.
- Ujije H, Sato K, Onda H, et al. Clinical analysis of incidentally discovered unruptured aneurysms. *Stroke*. 1993;24:1850-1856.
- Yasui N, Suzuki A, Nishimura H, et al. Long-term follow-up study of unruptured intracranial aneurysms. *Neurosurgery*. 1997;40:1155-1159; discussion 9-60.
- Komotar RJ, Mocco J, Solomon RA. Guidelines for the surgical treatment of unruptured intracranial aneurysms: the first annual J. Lawrence pool memorial research symposium—controversies in the management of cerebral aneurysms. *Neurosurgery*. 2008;62:183-193; discussion 93-4.
- Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. *J Neurosurg*. 1974;41:125-145.

16. Debrun G, Fox A, Drake C, et al. Giant unclippable aneurysms: treatment with detachable balloons. *Am J Neuroradiol.* 1981;2:167-173.
17. Berenstein A, Ransohoff J, Kupersmith M, et al. Transvascular treatment of giant aneurysms of the cavernous carotid and vertebral arteries. Functional investigation and embolization. *Surg Neurol.* 1984;21:3-12.
18. Higashida RT, Halbach VV, Barnwell SL, et al. Treatment of intracranial aneurysms with preservation of the parent vessel: results of percutaneous balloon embolization in 84 patients. *Am J Neuroradiol.* 1990;11:633-640.
19. Hieshima GB, Grinnell VS, Mehringer CM. A detachable balloon for therapeutic transcatheter occlusions. *Radiology.* 1981;138:227-228.
20. Guglielmi G, Vinuela F, Dion J, et al. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. *J Neurosurg.* 1991;75:8-14.
21. Guglielmi G, Vinuela F, Sepetka I, et al. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results. *J Neurosurg.* 1991;75:1-7.
22. Moret J, Cognard C, Weill A, et al. Reconstruction technic in the treatment of wide-neck intracranial aneurysms. Long-term angiographic and clinical results. Apropos of 56 cases. *J Neuroradiol.* 1997;24:30-44.
23. Nelson PK, Levy DI. Balloon-assisted coil embolization of wide-necked aneurysms of the internal carotid artery: medium-term angiographic and clinical follow-up in 22 patients. *Am J Neuroradiol.* 2001;22:19-26.
24. Higashida RT, Smith W, Gress D, et al. Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysm of the basilar artery. Case report and review of the literature. *J Neurosurg.* 1997;87:944-949.
25. Fiorella D, Albuquerque FC, Han P, et al. Preliminary experience using the Neuroform stent for the treatment of cerebral aneurysms. *Neurosurgery.* 2004;54:6-16; discussion 7.
26. Chow MM, Woo HH, Masaryk TJ, et al. A novel endovascular treatment of a wide-necked basilar apex aneurysm by using a Y-configuration, double-stent technique. *Am J Neuroradiol.* 2004;25:509-512.
27. Fiorella D, Albuquerque FC, Masaryk TJ, et al. Balloon-in-stent technique for the constructive endovascular treatment of "ultra-wide necked" circumferential aneurysms. *Neurosurgery.* 2005;57:1218-1227; discussion 27.
28. Kelly ME, Turner R, Gonugunta V, et al. Stent reconstruction of wide-necked aneurysms across the circle of Willis. *Neurosurgery.* 2007;61(suppl 2):249-254; discussion 54-55.
29. White PM, Lewis SC, Nahser H, et al. HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS trial): procedural safety and operator-assessed efficacy results. *Am J Neuroradiol.* 2008;29:217-223.
30. Raymond J, Guilbert F, Weill A, et al. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke.* 2003;34:1398-1403.
31. Rivet DJ, Moran CJ, Mazumdar A, et al. Single-institution experience with matrix coils in the treatment of intracranial aneurysms: comparison with same-center outcomes with the use of platinum coils. *Am J Neuroradiol.* 2007;28:1736-1742.
32. Johnston SC, Dowd CF, Higashida RT, et al. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rupture After Treatment (CARAT) study. *Stroke.* 2008;39:120-125.
33. Wehman JC, Hanel RA, Levy EI, et al. Giant cerebral aneurysms: endovascular challenges. *Neurosurgery.* 2006;59(suppl 3):S125-138; discussion S3-13.
34. Murayama Y, Nien YL, Duckwiler G, et al. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg.* 2003;98:959-966.
35. Wallace RC, Karis JP, Partovi S, et al. Noninvasive imaging of treated cerebral aneurysms, part I: MR angiographic follow-up of coiled aneurysms. *Am J Neuroradiol.* 2007;28:1001-1008.
36. Cloft HJ, Kallmes DF. Aneurysm packing with HydroCoil Embolic System versus platinum coils: initial clinical experience. *Am J Neuroradiol.* 2004;25:60-62.
37. Fiorella D, Albuquerque FC, Deshmukh VR, et al. Usefulness of the Neuroform stent for the treatment of cerebral aneurysms: results at initial (3-6-mo) follow-up. *Neurosurgery.* 2005;56:1191-1201; discussion 201-202.
38. Fiorella D, Albuquerque FC, Deshmukh VR, et al. Endovascular reconstruction with the Neuroform stent as monotherapy for the treatment of uncoilable intradural pseudoaneurysms. *Neurosurgery.* 2006;59:291-300; discussion 291-300.
39. Kallmes DF, Ding YH, Dai D, et al. A new endoluminal, flow-disrupting device for treatment of saccular aneurysms. *Stroke.* 2007;38:2346-2352.
40. Nelson PK. PIPELINE Stent for treatment of intracranial aneurysms. Presented at the AANS/CNS Cerebrovascular Section Meeting. New Orleans, LA; 2008.
41. Fiorella D, Woo H, Albuquerque F, et al. Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the Pipeline Embolization Device. *Neurosurgery.* 2008 March 11. [Epub ahead of print].