Flow Diversion for Intracranial Aneurysm Treatment

How this new technology may expand the types of intracranial aneurysms that can be treated.

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The endovascular treatment of intracranial aneurysms has rapidly evolved during the past 2 decades. Until very recently, the primary strategy behind treating aneurysms endovascularly has been focused on filling the aneurysm sac with embolic material (typically embolization coils) and thereby excluding it from the parent artery circulation (ie, endosaccular aneurysm occlusion). With the development of new adjunctive devices (eg, intracranial stents and balloons) and improved embolization materials (eg, three-dimensional coils and liquid embolics), the percentage of lesions amenable to treatment with endovascular techniques has substantially increased. However, our ability to achieve a durable and complete occlusion of aneurysms remains, in some cases, limited. Large and wide-necked aneurysms remain challenging, with recurrence rates approximated at 50% for both of these anatomical subtypes.[1]

During the past 3 years, a new generation of endovascular devices—the flow diverters—has been developed to treat aneurysms through an exclusively endoluminal rather than endosaccular approach. These stent-like devices are designed to reconstruct the parent artery and divert blood flow along the normal anatomical course of

Figure 1. Schematic image of the PED (Chestnut Medical, Menlo Park, CA/ev3 Inc., Plymouth, MN) demonstrates the construct as a conglomerate cylindrical structure composed of 48 individual braided strands of cobalt chromium and platinum.

(Courtesy of ev3 Inc.)

the vessel and away from the aneurysm neck. Ideally, this hemodynamic uncoupling of the parent artery-aneurysm complex creates an intra-aneurysmal environment conducive to thrombosis and provides scaffolding over which neointima and endothelium can grow to ultimately seal off the neck of the aneurysm.[2-4]

The Pipeline Embolization Device (PED) represents the first flow-diversion device used in humans. Although other devices are available, they are earlier in development, the existing data regarding their use in humans are very limited, and we have no experience using these other devices at this point. For these reasons, in this review, we describe the PED, its theoretical mode of action, potential applications and limitations, some of the preliminary data from human use, and its current regulatory status. Finally, we will discuss the potential affect of this new technology on the field of neuroendovascular aneurysm therapy.

THE PED

The PED is a cylindrical, stent-like construct composed of 48 braided strands of cobalt chromium and platinum (Figure 1). The device is packaged within an introducer sheath collapsed upon a delivery wire. The device is loaded into and delivered via the hub of a 0.027-inch internal diameter (ID) microcatheter that has been positioned across the neck of the aneurysm. Initially collapsed within the delivery sheath

or microcatheter, the device is elongated approximately 2.5 times its deployed length when expanded to nominal diameter. As it is deployed, the device foreshortens toward its nominal length (which it achieves only if allowed to expand fully to its nominal diameter). Currently, the available devices range from 2.5 to 5 mm in diameter (in 0.25-mm increments) and 10 to 20 mm in length (in 2-mm increments). The deployed device is very flexible and conforms to the normal parent anatomy, even in very tortuous vascular anatomy.

When fully expanded, the PED provides approximately 30% metal surface area coverage. When deployed in a parent artery smaller than the nominal diameter of the device, the PED cannot fully expand, and as such, it deploys longer than its nominal length and yields a lesser metal surface area coverage. To augment surface area coverage, several devices can be overlapped (Figure 2), or an individual device can be deployed with forward pressure on the microcatheter. To achieve coverage of vessel defects measuring more than 20 mm in length, multiple devices can be telescoped to reconstruct longer segments of the cerebrovascular anatomy (Figure 3). The tremendous versatility of the device essentially allows the operator to achieve reconstructions of most any segment of the cerebrovascular anatomy and allows some control of the metal surface coverage of different regions of the conglomerate construct. This control over the length, shape, and porosity of the final reconstructed vessel allows the operator to build a "customized" implant for each patient treated.

## THEORETICAL BASIS FOR ANEURYSM OCCLUSION

Kallmes et al have characterized the effects of the PED in an experimental rabbit aneurysm model.[5,6] Although there are no human pathological data that demonstrate the evolution of histological changes that occur after PED implantation, clinical data and data from cross-sectional imaging, as well as noninvasive and conventional angiographic studies in human patients, have closely paralleled the findings in these animal models. Our hypothesis (which is described in this arti-

cle) regarding the mechanism of action of the PED in humans is based on these data.

Parent artery reconstruction with the PED is characterized by a gradual transition from flow disruption to aneurysm thrombosis, to endovascular remodeling, and ultimately, to curative anatomical restoration. The stages of this transition are subsequently described.

Mechanical-Anatomical: Flow Disruption

Immediately after the construct is in place, the device coverage over the neck of the aneurysm creates a disrup-
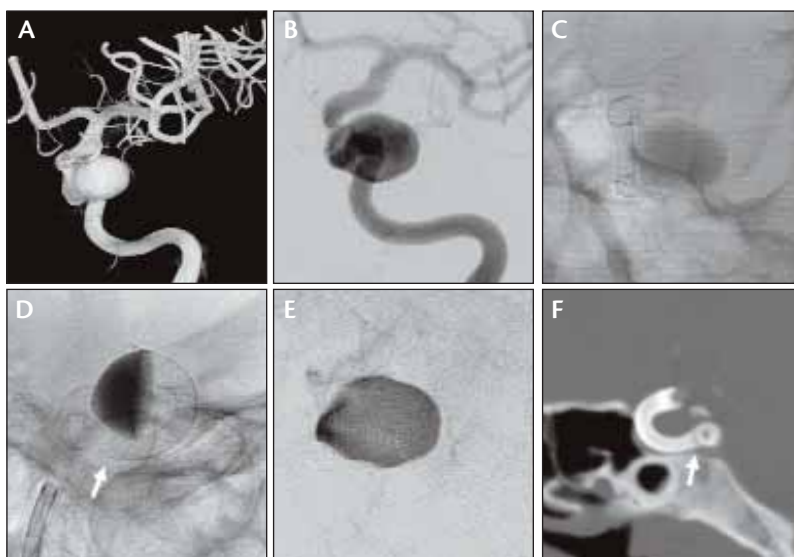
Figure 2. Very large (17 mm) and wide-necked (9 mm) left internal carotid artery (ICA) cavernous segment aneurysm treated with two overlapping PEDs. Rotational angiography (A) shows a large aneurysm arising from an extensive segmental defect in the cavernous segment of the ICA. Left ICA angiography in the frontal working angle (B) for PED reconstruction demonstrates the distal middle cerebral artery into which the delivery wire will ultimately be navigated and which will also serve as the distal landing zone for the PED construct. The lateral working angle was used to visualize the proximal PED landing zone. After treatment, the native frontal (C) and lateral (D) working angles show static contrast within the aneurysm fundus. The lateral image shows the "eclipse" sign with contrast layering dependently within the aneurysm after reconstruction. The differential density of the construct is also seen on the lateral native image. The density of the construct transitions (D, arrow) at the point where the longer 4.25- X 20-mm single-coverage construct overlaps proximally with the 4- X 14-mm construct more distally. Subtracted frontal working angle image after PED reconstruction demonstrates the negative defect of the PED reconstructed parent artery (dotted circle). Contrast rapidly washes out of the reconstructed parent artery, which then stands out in relief against the static contrast that lingers within the aneurysm fundus far into the venous phase of angiography. A reconstructed sagittal image (E) from a CT angiography performed 1 day after the procedure also shows the differential density (F, arrow) of the construct as it transitions from two overlapping devices distally to a single device proximally.

Figure 3. Giant right ICA aneurysm arising from a long-segment parent artery defect reconstructed with a telescoping seven-Pipeline construct. Angiography in the frontal working angle (A) for parent artery reconstruction shows an aneurysm arising from a very long neck defect in the right ICA. A native image in the working angle (B) shows a telescoping construct composed of seven PEDs. The construct spans from the supraclinoid carotid distally to the petrous segment proximally. Early arterial (C) and early venous (D) phase angiography shows that the aneurysm still fills with contrast at the conclusion of the reconstruction; however, the contrast washes out very slowly and is depicted still dribbling into the parent artery (D) during the venous phase of angiography.

tion of both aneurysm inflow and outflow with redirection of the primary vector of blood flow along the course of the reconstructed parent vessel. The disruption of the aneurysm inflow jet would be expected to markedly reduce shear stresses on the aneurysm fundus.

Physiological: Aneurysm Thrombosis

Days to weeks after placement of the construct, the disruption of intra-aneurysmal flow induces thrombosis. Angiographic imaging demonstrates a progression toward complete occlusion, which is usually completed over a period of days to weeks (but can require more time in some cases). The rate at which the lesions progress to complete thrombosis can be difficult to predict (Figure 4).

Biological: Construct Endothelialization and Thrombus Resorption

After flow into the aneurysm is eliminated and the aneurysm is completely thrombosed, the construct becomes incorporated into the wall of the parent artery. Overgrowth of neointima and endothelial tissue forms a permanent biological seal across the segmentally diseased parent artery and bridges the endoluminal surfaces of the normal proximal and distal parent artery segments. At this point, the aneurysm is completely excluded from the circulation. Once this process has been completed, the intra-aneurysmal thrombus mass can begin to resorb, and any mass effect related to the lesion can dissipate. The complete exclusion of the aneurysm from the cerebral vasculature and the subsequent collapse of the aneurysm around the periphery of the construct represent a progression toward the restoration of both normal anatomy and physiology. Cross-sectional imaging may show resolution of the aneurysm mass with the space filled by either relaxation of brain parenchyma or cerebrospinal fluid.

ADJACENT REGIONAL BRANCH VESSELS

The ability of the PED to promote the closure of aneurysms and at the same time allow the patency of the adjacent regional eloquent branch vessels (which are also covered by the construct) is likely based on differences in the physiology that govern blood flow into these two structures.

Aneurysm filling is solely dependent on the geometry of the aneurysm-parent vessel interface that defines the inflow and outflow patterns, the intra-aneurysmal flow velocity, and the shear forces on the aneurysm wall. Once the trajectory of blood flow is redirected along the parent artery and disrupted within the aneurysm, aneurysm filling slows, and the patterns of flow within the aneurysm become disordered; this flow-diversion phenomenon creates an environment that is conducive to thrombosis.

Flow into regional perforator and branch arteries is driven by a pressure gradient that drives flow from the high-pressure parent artery into the lower pressure branches, which perfuse end organs and ultimately drain into the even lower pressure venous system. When such a physiological artery-to-venous pressure gradient exists, some data have suggested that more than 50% occlusion of the surface area of the orifice of the branch vessel is required before flow starts to decline.[7,8] Thus, this pressure gradient drives organized blood flow, which preserves vascular patency and governs device endothelialization. Histological evaluation of Pipeline 6 months after implantation into a rabbit aorta validates this concept, depicting continuous coverage of the construct with neointimal and neoendothelial tissue interrupt-
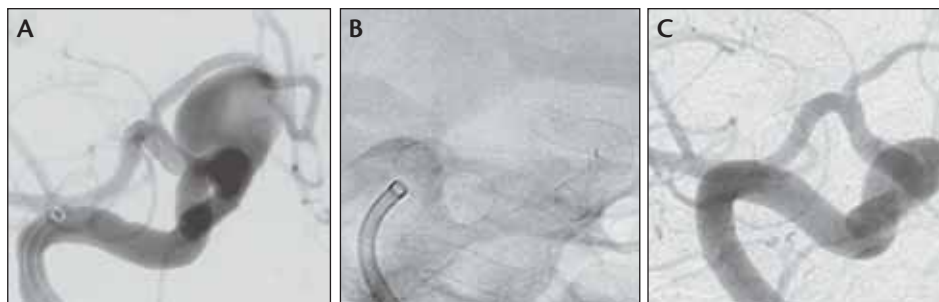
ed only by rounded, funnel-like defects that lead to the orifices of the regional branch vessels.

Theoretically, the porosity of an optimally built PED construct strikes a delicate balance by creating enough flow diversion to cause complete aneurysm thrombosis yet permitting enough flow through the interstices such that the regional eloquent branch vessels may remain patent. This tenuous balance is essential for any flow-

Figure 4. Very large right internal carotid-ophthalmic aneurysm angiographically cured with PED. Original frontal working angle angiogram (A) shows a very large, wide-necked internal carotid-ophthalmic aneurysm arising from a very tortuous segment of the artery. A native image (B) in the frontal working angle shows a single PED in place across the aneurysm neck defect. Angiographic follow-up 1 month in the frontal working angle (C) later shows progression to complete angiographic occlusion with anatomical reconstruction of the ICA.

diverting device to be applied safely and effectively within the cerebral vasculature to treat aneurysms.

ANEURYSM RECONSTRUCTION

The versatility of the PED prohibits a complete discussion of all of the various techniques and strategies behind building an optimized construct. In fact, many of the basic concepts and techniques that are applicable to the endosaccular occlusion of aneurysms are completely different when performing endoluminal reconstruction with Pipeline. These new concepts governing endoluminal reconstruction are essential to pre- and intraprocedural treatment planning and technical success. Important issues include the selection of optimal working angles, device sizing, and the decision as to when an adequate reconstruction has been achieved (and no additional devices are needed). Key technical issues with endoluminal reconstruction that differ from traditional aneurysm coil embolization are:

The working angle does not have to depict the entire aneurysm neck/parent artery relationship. During endosaccular occlusion, the operator determines a working view of the aneurysm that most clearly demonstrates the anatomical relationship of the entire neck defect to the parent artery. During endoluminal reconstruction with Pipeline, this visualization of the parent artery-aneurysm neck interface is much less important than other anatomical features. Although the demands of understanding the aneurysm neck anatomy are equally as important, a constant direct visualization of this interface is not necessary. During endoluminal reconstruction with the PED, the operator must have working views that allow the unambiguous and continuous visualization of a suitable distal branch vessel into which to navigate the tip of the delivery wire during device delivery, as well as the targeted distal and proximal landing zones for the device deployment. Provided that the opera-

tor understands the anatomy of the aneurysm neck, especially the length of the segment of artery that it involves, it is not absolutely necessary that the working angle for PED placement show this to the best advantage.

Visualization of the aneurysm fundus is irrelevant. During the endosaccular occlusion of aneurysms, it is of paramount importance to have an accurate measurement and a complete conceptual understanding of the geometry of the aneurysm fundus. These factors will determine the size, shape, and type of embolization coils selected. Moreover, during coiling, it is critical to have working views that depict the aneurysm fundus clearly, such that the operator can be sure that the coils are not traversing the expected boundaries of the fundus during placement. Visualization of the aneurysm fundus is essentially completely irrelevant during endoluminal reconstruction.

Accurate measurement of the parent artery is critical. During standard endosaccular coil embolization performed without adjunctive devices, the parent artery diameter is unimportant. With few notable exceptions, even in cases in which adjunctive self-expanding nitinol stents are used (eg, Neuroform [Boston Scientific Corporation, Natick, MA] and Enterprise [Codman Neurovascular, Raynham, MA]), the measurement of the parent artery can be performed with a fair degree of latitude on the part of the operator. In contrast, during endoluminal therapy with PED, an accurate measurement of the parent artery landing zones both distal and proximal to the targeted aneurysm is absolutely essential for optimized device sizing.

Complete aneurysm occlusion is not achieved at the time of the procedure. During the endosaccular occlusion of aneurysms, it is the operator's goal to place as much embolic material (typically coils) into the aneurysm as possible, such that complete occlusion is achieved at the time of the original treatment. In contrast, after an adequate PED con-

struct has been built across the neck defect, the aneurysm typically demonstrates persistent filling. At the same time, the dynamics of contrast flow into and out of the aneurysm are often altered after treatment as indicated by new stasis of contrast persisting into the late phases of angiography. This stasis can sometimes be visualized as persistent contrast layering dependently within the aneurysm sac on a lateral image (ie, the eclipse sign) (Figure 2). If the aneurysm is large and circumferential, the PED construct, if visualized in a "down-the-barrel" projection, may create a negative defect within the pool of static contrast filling the aneurysm (Figure 2). This negative defect is best visualized during the venous phase of contrast after the contrast has completely washed out of the recreated parent artery and yet persists within the aneurysm. These signs typically indicate that the construct has provided a level of flow diversion that will be sufficient to induce thrombosis.

DEVICE DEPLOYMENT

The deployment of the flow-diverting devices is likely slightly different. We are experienced only with the PED, and we will only address the delivery and deployment of that device. In terms of the detailed means of PED delivery and deployment, we would defer to the provided instructions for use.

In general, all patients should be pretreated with aspirin and clopidogrel. As much as possible, we attempt to verify that patients are responsive to both agents before proceeding with these elective cases. All cases are performed under general anesthesia. Immediately after evaluation of the femoral access site, patients are administered heparin to achieve an activated clotting time targeted to range between 250 and 300 seconds during device deployment. After conventional angiography (usually including a rotational angiogram), working angles are chosen, and parent vessel measurements are made. The appropriately sized devices are then selected. Accurate control and one-to-one responsiveness of the microcatheter is critical for accurate device deployment, and for this reason, stable guiding catheter access is essential. In the anterior circulation, we have used a coaxial guiding catheter system consisting of a 90-cm KSAW Shuttle Select long sheath (Cook Medical, Bloomington, IN) fitted with a Check-Flow Performer valve (Cook Medical) with an internal 105-cm, 0.07-inch ID Neuron guiding catheter (Penumbra, Inc., Alameda, CA). For anterior circulation lesions, we attempt to place the guiding catheter within the petrous or cavernous segment of the internal carotid artery. For posterior circulation lesions, we favor a standard 6-F, 90-cm, 0.07-inch ID guiding catheter. Once the guiding catheter platform is in place, a 0.027-inch ID microcatheter is manipulated across the lesion under fluoroscopic roadmap control. Once in position, the first PED is introduced into the hub of the microcatheter using the provided loading sheath. The device is advanced through the microcatheter, using a technique that is similar to the introduction of an embolization coil until it is visualized fluoroscopically across the aneurysm neck.

The delivery wire is then stabilized as the microcatheter is gently retracted. Once the distal aspect of the device is exposed, the PED will begin to expand and ultimately come free of the "capture coil" mechanism, which secures the PED to the delivery wire. When the distal aspect of the PED comes off of the delivery wire, the remainder of the device is typically deployed by applying gentle pressure to the delivery wire that gradually "backs out" the microcatheter as the device is deployed. The distal aspect of the PED is then freed from the capture coil, and the delivery wire becomes steerable and can be selectively navigated into a preselected large branch vessel during the final stages of deployment. Once fully deployed, the microcatheter is navigated over the delivery wire to recapture the wire and re-establish microcatheter position through the lumen of the deployed construct and within the normal segment of the parent artery distal to the aneurysm neck defect. At this point, control angiography can be performed, and additional devices can be placed as needed.

REGULATORY STATUS AND CLINICAL DATA

The PED is currently an investigational device in the United States, which is only available within the context of ongoing US Food and Drug Administration (FDA) clinical trials. At present, no data from these clinical trials are available. Individual cases have been performed in the United States outside of the trials under FDA-approved compassionate use exemptions that allow for expanded access to investigational devices in exceptional cases. As such, with the exception of individual case reports from compassionate use cases, very few data from North America are currently available.[2,3]

The PED has received CE Mark approval in Europe on the basis of the Pipeline Embolization Device in the Intracranial Treatment of Aneurysms (PITA) study. Although yet unpublished, the results of the PITA trial were presented at the International Stroke Conference in 2008.[9] Thirty-one patients with intracranial aneurysms were treated within the context of the PITA study at three European centers (Essen, Germany; Graz, Austria; and Budapest, Hungary) and one South American center (Buenos Aires, Argentina). On average, the aneurysms included in PITA were large (average aneurysm size was 11.5 mm) and wide necked (the average neck width was 5.8 mm). Most (28 of 31) were aneurysms of the intracranial ICA. Devices were successfully placed in

all cases. Two major strokes occurred during the periprocedural period. At 6-month angiographic follow-up, 28 of 30 patients (93%) demonstrated complete aneurysm occlusion. This rate of complete angiographic occlusion at 6 months compares very favorably to previously published data describing outcomes after endovascular coil embolization. Raymond et al observed complete aneurysm occlusion in 44.6% of cases at 3 to 12 months and only 38.3% after 12 months.[1] Commercial distribution of the PED is just starting in Europe, and this will likely lead to a proliferation in the amount of available data in the coming months.

In addition to contributing cases to the PITA trial, Dr. Pedro Lylyk and his associates in Buenos Aires, Argentina have continued to treat patients under individual compassionate use provisions.[4] Lylyk et al have recently reported their single-center results for a series of 53 patients treated with the PED, which remains the largest published experience with the device to date. No major procedure-related complications were reported in the series. The angiographic results in the Buenos Aires series mirrored the results in the PITA study, with 93% (n = 28) and 95% (n = 13) rates of complete aneurysm occlusion observed at 6- and 12-month angiographic follow-up, respectively.[4] Recently, in a presentation of an updated version of this data set, a 96% rate of complete aneurysm occlusion was observed for 50 PED-treated aneurysms with 3 months or greater angiographic follow-up.[10]

The Silk stent (Balt Extrusion, Montmorency, France) is a braided, self-expanding, high metal surface area coverage construct that also has CE Mark approval in Europe for the treatment of intracranial aneurysms. Although cases are currently being performed, to our knowledge, no published data are yet available. Other similar flow-diverting constructs are at earlier stages of development and are currently without published clinical data.

PATIENT SELECTION

As with any device, appropriate patient selection is of paramount importance to procedural success. However, it is important to acknowledge that flow-diversion technology is at a very early stage, and in the Unites States, the PED remains an investigational device. As such, the available data do not provide a sufficient foundation on which to make firm recommendations regarding patient selection.

Based on the existing data and our present understanding of the mechanism of action of flow-diversion devices, the following lesion subtypes are likely good candidates for treatment with PED:

Unruptured ICA Aneurysms

The majority of experience using the PED to date has been derived from the treatment of aneurysms involving the intracranial ICA. ICA lesions constitute the majority of cases treated within the PITA trial and all of the aneurysms currently being treated within the context of the ongoing United States trials. The results of the PITA trial suggest that unruptured aneurysms in this location can be treated safely and effectively with PED with high rates of complete occlusion at angiographic follow-up.

Unruptured Fusiform and Circumferential Aneurysms

Data from the existing case reports describing the individual compassionate uses of the device have shown the utility of the PED to achieve a complete angiographic occlusion of fusiform intracranial aneurysms that were not amenable to treatment using commercially available devices or conventional surgical techniques.[2,3] In one of these cases, the device was placed over eloquent perforator vessels arising from the basilar artery without clinical sequelae. This case provides evidence that is in concordance with the existing experimental data in rabbits, that it might be safe, in selected cases, to judiciously place the PED construct across eloquent perforator vessels when necessary.[2]

Large, Giant, and Wide-Necked Aneurysms

Large, giant, and wide-necked aneurysms are the most difficult aneurysms to achieve a safe, complete, and durable treatment result with standard endovascular (and often open neurosurgical) techniques. The constructive treatment of these lesions can be technically challenging and often requires one or more adjunctive devices, which can be associated with higher rates of procedural complications. Numerous aneurysm coils are often required, making these among the most expensive lesions to treat in terms of resource consumption and implantable costs. In addition, biplane fluoroscopy is typically used during the introduction of each embolization coil, resulting in very large accumulated radiation doses during the treatment procedures (and during the commensurate angiographic follow-up examinations and retreatments, if necessary). Complete occlusion of these aneurysms is also very difficult to achieve with embolization coils. Moreover, even when an adequate level of occlusion is achieved, the lesions very frequently recanalize and may require one or more additional retreatments. Because of this high risk of recurrence, these lesions typically require numerous serial follow-up examinations for several years after treatment.[11]

Given the difficulties that these aneurysms pose to conventional endovascular therapies, the emerging data, which have begun to show that the flow-diversion devices may provide a durable and complete occlusion of these lesions during a single treatment session, suggest that this approach might represent a considerably superior treat-

ment option. Moreover, the endoluminal reconstruction of these lesions may obviate the need for a very large number of costly embolization coils and may substantially reduce the amount of radiation exposure required during these procedures. For these reasons, it is likely that many of these lesions could be preferentially treated with the PED (or similar devices) in the future.

Based on the existing data and our present understanding of the mechanism of action of flow-diversion devices, the following lesion subtypes are likely not good candidates for treatment with PED:

Bifurcation Aneurysms

Although these aneurysms represent a significant percentage of all lesions treated using endovascular techniques, the existing data describing the efficacy of PED in this setting are insufficient to support the treatment of most lesions in this location at this time. The treatment of a bifurcation aneurysm with Pipeline results in one limb of the bifurcation being reconstructed while the other limb is necessarily "jailed." If the technique is not effective in achieving complete aneurysm occlusion, in most anatomical configurations, endovascular access to the aneurysm will have been permanently lost. At this point, the only options available for further treatment would be placing additional PEDs over the aneurysm neck (which would place the jailed limb of the bifurcation at further risk of thrombosis) and open surgical clipping.

Ruptured Aneurysms

The coronary stent literature provides evidence that adequate periprocedural dual-antiplatelet medications are required to reduce rates of stent thrombosis after implantation. At the present time, all patients undergoing PED reconstruction are pretreated with both aspirin and clopidogrel and are maintained on these medications for at least 3 to 6 months afterward. This requirement for dual-antiplatelet medications represents a relative contraindication for the application of the PED (or any other intracranial stent or stent-like construct) within the context of acute subarachnoid hemorrhage. Although ruptured aneurysms represent a considerable percentage of the lesions that are treated with endovascular techniques, the risks of dual-antiplatelet therapy in this setting are considerable.[12] In addition, because the PED does not typically elicit complete aneurysm occlusion at the time of placement, it may not provide the immediate protection from rerupture offered by coil embolization or surgical aneurysm clipping. These two factors currently limit the potential applicability of the PED for the treatment of ruptured aneurysms in the vast majority of cases.

IMPORTANT FINAL CONSIDERATIONS

The PED represents an investigational device that is currently unapproved for use outside of clinical trials within the United States and has only recently been approved in Europe. As such, the available data, although very encouraging, remain limited. This is particularly true of midterm (6–12 months) and long-term (> 12 months) follow-up results, which are just starting to become available. Clearly, we will learn a great deal about the flow-diverting devices during the next decade, and it is highly likely that this technology will fundamentally change the endovascular treatment of selected cerebral aneurysms. ■

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