Future Directions of Flow Diverter Therapy

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The treatment of intracranial aneurysms has undergone a few very significant paradigm shifts in its history. Needless to say, microsurgery and surgical clipping served as the initial basis for successful treatment of these lesions. The pursuit of endovascular therapy subsequently arose from the desire to reduce the invasiveness of therapy. While the first breakthrough arose with Guido Guglielmi's invention of the detachable platinum coil, commercialized flow diverter therapy represents a disruptive therapy with a completely different paradigm for aneurysmal obliteration. This has not only altered the distribution of aneurysmal management strategies, but also opened the gateway to the treatment of previously inoperable lesions. With the basic flow diverter stent technology now considered an integral part of the neurointerventional armamentarium, we now consider what may lay in the future – including potential directions for research with regards to case selection; the location and type of aneurysms which may become routinely treatable; and modifications to the flow diverter, which may increase its utility and safety in terms of size, structural design, and surface modifications.

KEY WORDS: Brain aneurysm, Flow diversion, Flow diverter therapy, Neuroradiology, Neurosurgery

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The treatment of intracranial aneurysms has undergone a few very significant paradigm shifts in its history. Needless to say, microsurgery and surgical clipping served as the initial basis for successful and robust treatment of these lesions. The pursuit of endovascular therapy arose from the desire to reduce the invasiveness of therapy, given the need for craniotomy with clipping. While attempts at endovascular therapy extend back to Fedor Serbinenko's efforts to occlude aneurysms by use of detachable balloons,[1] the real breakthrough came with Guido Guglielmi's invention of the detachable platinum coil.[2] This represented a significant paradigm change, not only in the endovascular vs open approach, but also in the nature of aneurysmal obliteration – aneurysms were occluded not by the apposition of clip blades preventing ingress of arterial blood, but by presence of coils invoking thrombosis by the action of Virchow's triad. The clinical efficacy of this approach was subsequently borne out in various publications.[3-8] It can be said that while the advent of balloon and stent assistance increased the number of aneurysms that could be treated by coiling, the next significant paradigm shift arises from the pathophysiological understanding that many aneurysms do not in fact need to be completely occluded at the time of treatment – rather a positive disturbance needs to be introduced by the way of reducing flow into and within the aneurysm, so that the aneurysm itself can either thrombose spontaneously or remodel. Given that prototypical flow diversion devices are all, in essence, cylindrical stent devices, additional advantages compared to traditional microsurgical or endovascular therapies is that aneurysms with no neck can be treated efficaciously, and the aneurysm itself, clearly the most fragile part of the vasculature in question, does not need to be manipulated directly.

Although flow diverter stents are now solidly accepted as an integral option in the neurointerventional armamentarium, it can be justified that many of the newer devices, including some bifurcation-specific devices as well as intrasaccular flow disruptor devices all essentially rely on the same "paradigm" of flow disruption, or hemodynamic decoupling, between "normal" vessel and "aneurysmal lumen". This article will briefly explore the history of flow diversion, its current uses worldwide, and what the future may hold for this new paradigm of aneurysmal management.

HISTORY

The realization that alteration of flow can cause aneurysmal thrombosis is not new. In 1962, Mount and Taveras described the placement of a Mayfield clip on the basilar artery to mitigate the water hammer effect on a basilar tip aneurysm, thus precipitating thrombosis.[9] This treatment, however, relied on the presence of significant collateral vessels to the upper posterior circulation, and would not have been suitable for lesions such as a dissecting fusiform aneurysm in a dominant vessel. The effects of flow alteration were explored in animal models in the early 1990s,[10,11] with the premise that hemodynamic decoupling by stent placement obviates the need for intra-aneurysmal manipulation; however, some early attempts were hampered by later realizations that stent porosity influences likelihood of aneurysmal closure,[12] leading to the use of multiple overlapping stent constructs to achieve a higher metal coverage over the aneurysmal neck to reduce intra-aneurysmal flow.[13]

The Silk Device (BALT Extrusion, Montmorency, France) and Pipeline Embolization Device (PED; Medtronic, Dublin, Ireland) are 2 first-generation flow diverting stents of similar design, which respond to the engineering challenge above – to achieve the optimum degree of stent porosity in a single device while being deliverable for the more tortuous intracranial vasculature. The PED has been supported by published clinical trials in peer-reviewed literature; the Pipeline for Intracranial Treatment of Aneurysms Trial (PITA)[14] and the Pipeline for Uncoilable or Failed Aneurysms Trial (PUFS)[15] both demonstrated high complete aneurysmal occlusion rates (93.3% at 180 d and 86.8% at 1 yr, respectively, increasing to 95.2% at 5 yr for PUFS[16]) as well as safety profile (6.4% major ipsilateral stroke in PITA and 5.6% major ipsilateral stroke or death in PUFS). However, both devices have been extensively reported in large case series and published registries,[17] and have proven to be efficacious and safe in the short- and long-term,[16,18-22] with articles also suggesting that the technique requires less fluoroscopic time,[23,24] and have also been documented to have precipitated a significant change in practice pattern, confirming it as a disruptive technological advance.[25]

CURRENT USAGE

Limitations of various jurisdictions and on-label indications aside (for which the 2 FDA-approved devices indicate their use to segments of the intracranial internal carotid artery), conventional flow diverter stent therapy has now been used in a vast number of vessels, from the extracranial neurovasculature to distal intracranial vessels. Reported extracranial usage include carotids to reconstruct dissections extending into the skull base[26] (Figure 1); here, the flexibility of the flow diverter devices have been found to allow placement in tortuous vascular anatomy. The predominant technical issue with this usage is that of relative lack of stent radial force, which can result in residual stenosis. The device can also be used to promote remodelling in extracranial aneurysms,[26-28] acting in a similar fashion to that in the intracranial circulation. One potential advantage in this method is that compared to traditional coiling, a metallic mass of coils is not left, which may become an issue in the more mobile extracranial cervical vasculature.

Intracranially, supraclinoid internal carotid usage in nonruptured aneurysms is the most accepted and is probably the least complication prone, due to the lower number of small eloquent branches with potential for occlusion. Use of flow diverters in vessels smaller than 2.5 mm has been specifically reported in case series,[29,30] as has the use specifically in the middle cerebral,[31] anterior cerebral,[32-34] and posterior cerebral arteries,[35] all with satisfactory safety profiles, though there is some suggestion that perforator occlusion rates may be higher, and there may be a higher risk of stent occlusion, given the lower volume flow rate and high metal-to-cross-sectional flow area ratio.[20] Delivery of the devices in smaller vessels can also be difficult due to the requirement for larger caliber microcatheters of the current generation of devices, which can cause poor visibility to plan placement from proximal spasm and, potentially, inability to deliver the devices to the required location (Figure 2). Use in the basilar artery has been studied however unlike the supraclinoid carotid, due to the higher risks of causing symptomatic perforator occlusion,[36-39] flow diversion should be reserved for cases where other potential options are considered nonviable.

NEWER GENERATION TECHNOLOGY AND THE FUTURE

Three areas present themselves as potential directions of improvement in this rapidly developing field. The first is that of case selection. It is well reported that certain aneurysms do not appear to thrombose despite long follow-up periods. Certain potential geometric, and thus, hemodynamic factors related to the aneurysm may play a role in this,[20,40-43] but these have not been entirely elucidated. These changes may also have a role to play in the development of delayed aneurysmal rupture[44] as well as spontaneous distant hemorrhage.[45] Future research may shed more light and, thus, allow better case selection in the future. Also pertaining to case selection is whether certain aneurysms, which are treatable by other techniques, may benefit from a lower procedural risk profile and greater therapeutic success through flow diverter therapy. The current literature has explored essentially all subgroups of aneurysms, including small[46] and tiny aneurysms,[47] large and giant aneurysms,[48] tandem aneurysms along dysplastic segments,[49] noncomplex aneurysms,[50] wide necked but theoretically balloon- and/or stent-assisted coilable aneurysms,[48,51,52] bifurcation aneurysms, cavernous aneurysms,[53] paraclinoid aneurysms,[51] recurrent aneurysms,[54] and even ruptured aneurysms.[55] In many cases, the selection of therapeutic technique may be dependent on operator familiarity with each technique and patient suitability for antiplatelet therapy, but as experience and technology, as well

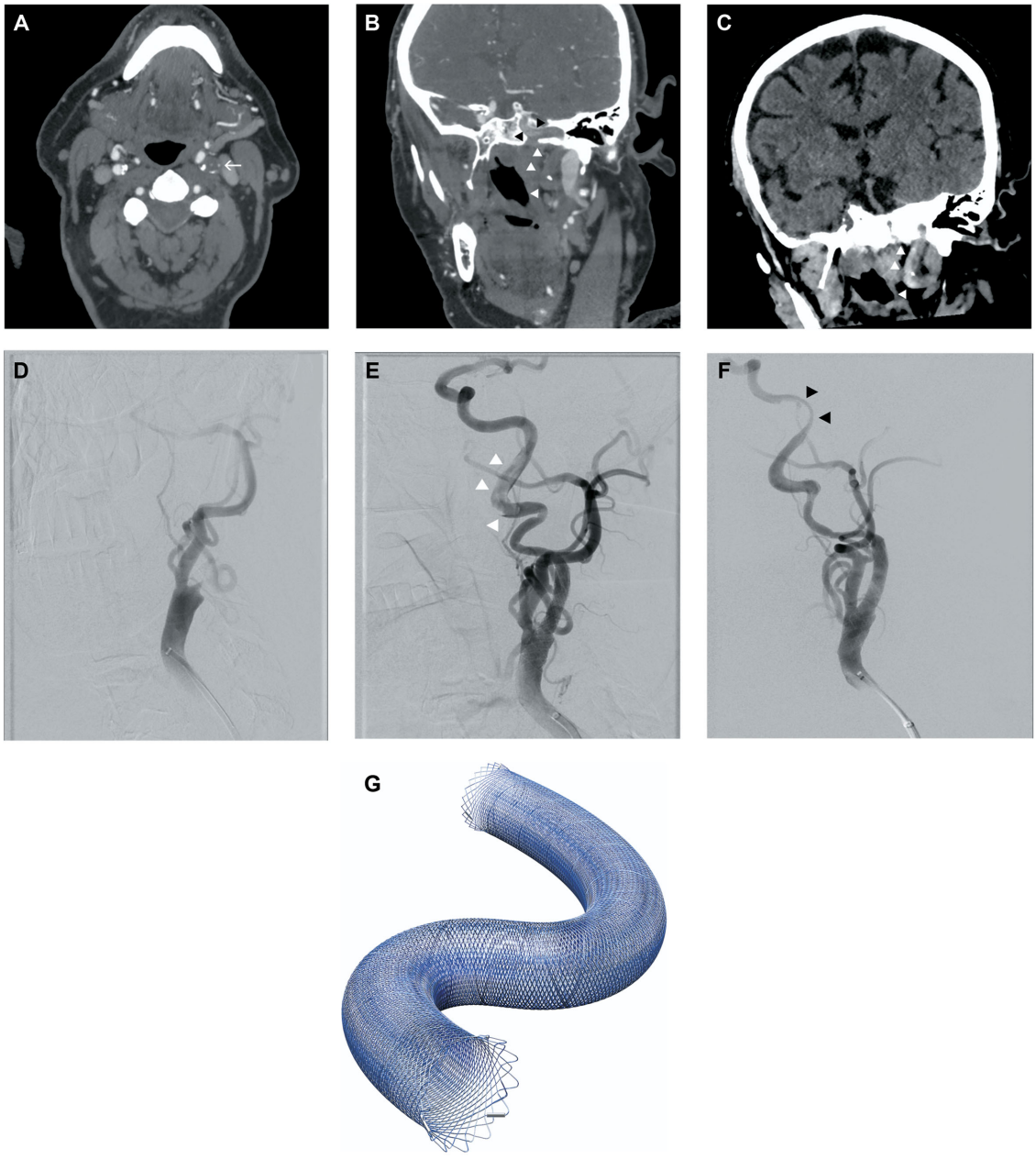

FIGURE 1. **A**, *Computed tomography (CT) angiography axial average intensity projection at the level of the carotid bulb in a man in his 60s who presented with a left hemispheric stroke. It was felt his critical left internal carotid artery (ICA) bulb stenosis, secondary to atheroma (white arrow), was likely the cause of his symptoms.* **B**, *Poor flow was noted distal to the stenosis on CT angiography (white arrowheads), with reconstitution in the petrous carotid canal (black arrowheads).* **C**, *However, noncontrast CT head, coronal oblique average intensity projection demonstrates mural hyperdensity in the distal cervical left internal carotid artery (white arrowheads), concerning for thrombus within false lumen. Carotid revascularization was initially performed awake via a right radial approach. Left common carotid artery (CCA) digital subtraction angiogram (DSA), right posterior oblique projection immediately before,* **D**, *and after,* **E**, *stenting of the bulb stenosis. With increased contrast opacification of the high ICA, appearances suggestive of dissection are noted (white arrowheads). This went on to occlude.* **F**, *The patient was placed under GA, thrombectomy performed with complete reperfusion, and the dissection extending from the tortuous cervical ICA into the petrous segment was covered with a DERIVO Embolisation Device and postangioplastied, resulting in restoration of flow, albeit with some residual stent stenosis (black arrowheads). The patient made a good recovery and was discharged 2 d post procedure with minimal deficit.* **G**, *The DERIVO Embolization Device. Images reprinted with permission of Penumbra/Accandis GmbH.*

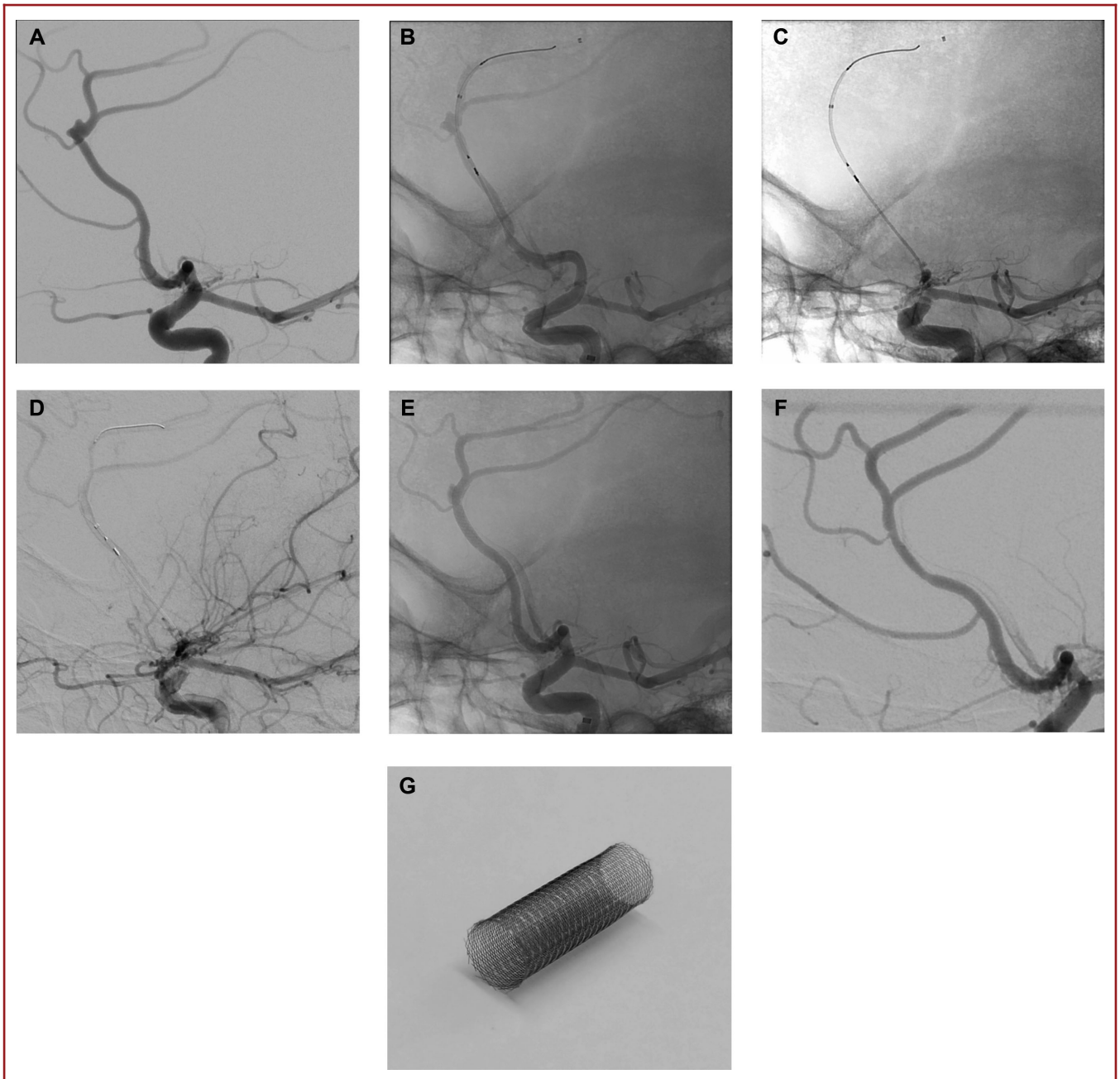

FIGURE 2. **A**, *Left ICA DSA, lateral projection demonstrates an incidentally discovered 5.5 mm lobulated fusiform aneurysm of the distal A2 segment of the left anterior cerebral artery (ACA) in the context of an asymptomatically absent middle cerebral artery in a female in her 50s; the territory is supplied by pial collaterals. It was felt in this abnormally high flow context the ACA aneurysm should be treated, and was admitted for elective treatment under dual antiplatelet therapy.* **B**, *Left ICA unsubtracted angiogram demonstrates the undeployed Pipeline Flex Embolization Device with Shield Technology within the microcatheter positioned across the aneurysm.* **C**, *Left ICA unsubtracted angiogram demonstrates as the ACA was straightened by the microcatheter in preparation for deployment, spasm caused complete occlusion.* **D**, *Left ICA DSA demonstrates partial deployment of the flow diverter, and with forward loading and some restoration of the anatomical course of the proximal ACA, some flow penetrates into the A2 to demonstrate the distal stent margin relative to the pericallosal–callosomarginal branch point.* **E**, *Left ICA unsubtracted angiogram demonstrates immediate post deployment appearances. The patient awoke with no deficit.* **F**, *Six-month follow-up left ICA DSA demonstrating complete aneurysmal occlusion and minimal narrowing of stent lumen.* **G**, *The Pipeline Flex Embolization Device with Shield Technology. Copyright © 2019 Medtronic. All rights reserved. Reprinted with permission.*

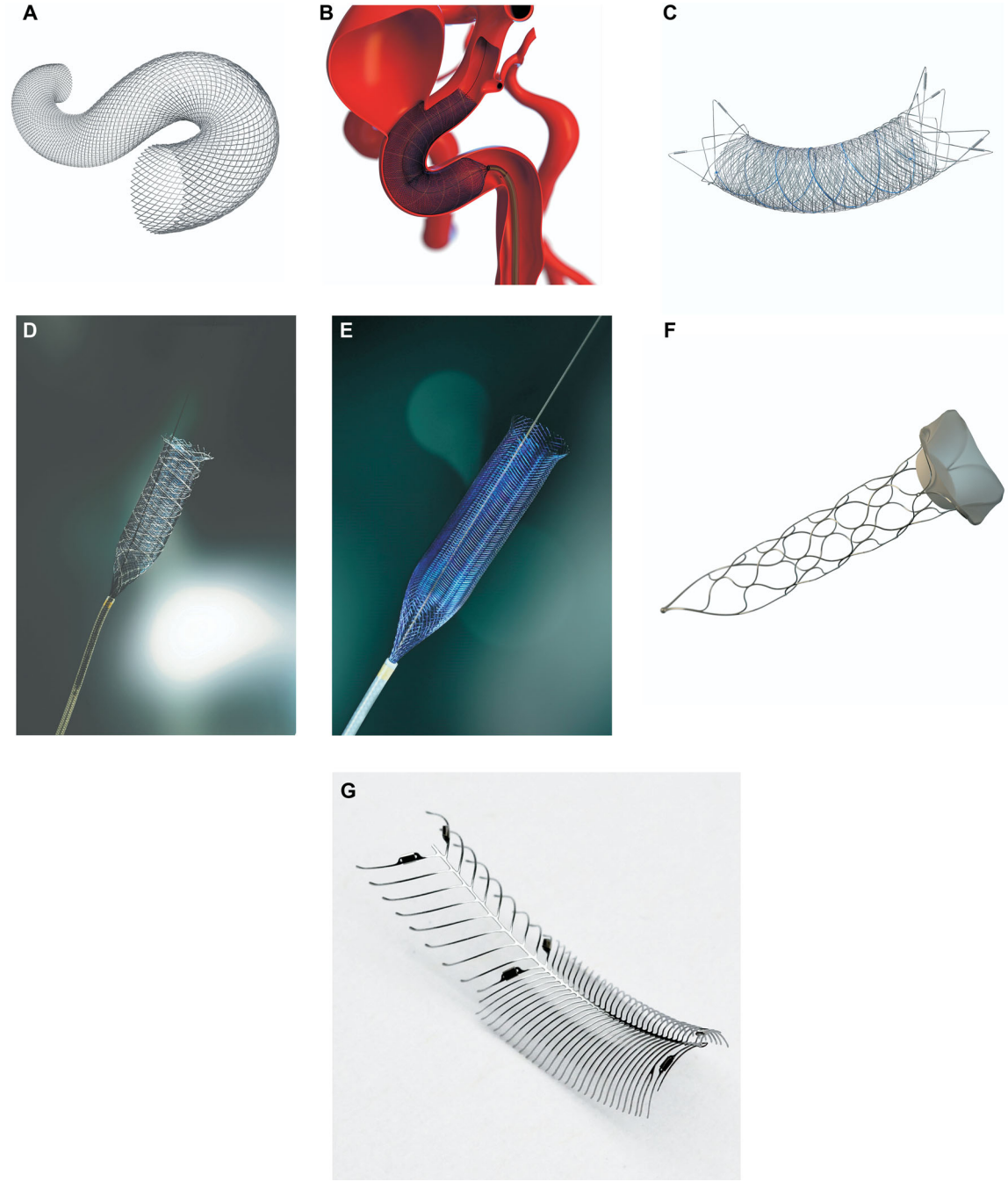

FIGURE 3. *A representative collage of different flow diverter devices.* **A**, *The Surpass Streamline Flow Diverter. Image supplied and approved for use by Stryker Neurovascular.* **B**, *Fully deployed but undetached p64 Flow Modulation Device. Pictures supplied and approved for publication by phenox GmbH.* **C**, *The FRED, demonstrating its dual-layer design, allowing a longer proximal and distal landing zone compared to its flow-diverting segment. Images courtesy of Microvention, Inc.* **D**, *The SILK+ Flow Diverter, deliverable through 0.021″ and 0.025″ microcatheters.* **E**, *The SILK Vista Baby, deliverable through a 0.017″ microcatheter. Pictures supplied and approved for use by Balt International Marketing Department, Montmorency, France.* **F**, *The pCANVAS Device, which lies in the parent vessel and deploys a flow-diverting membrane across the aneurysm neck. Pictures supplied and approved for publication by phenox GmbH.* **G**, *The eCLIPs Bifurcation Remodelling System, which sequesters support struts to half the wall of one side branch, deploying a dense leaf segment across the aneurysmal orifice while leaving the main vessel and side branches free of bridging metallic struts. Images reprinted with permission of Evasc Neurovascular Enterprises.*

as the body of evidence for use in different circumstances grow, the pattern of technique usage in different aneurysmal types may change, especially if flow diversion is more financially favorable as has been demonstrated by some publications.[56,57]

Second, since the initial introduction of flow diverters as a therapeutic option, a number of manufacturers have introduced variants and new iterations of the stent-type flow diverter to the market, and these present potentially important improvements in the type and caliber of vessel that is able to be treated by this technique. While this is neither intended to be a direct comparison of the efficacies of each device nor a comprehensive catalogue of all devices currently in development or available to the market, the discussion uses examples to highlight how different alterations to devices attempt to address a different aspect of flow diverter therapy, which may improve its utility and/or efficacy. To this end, we can divide the attempts into optimization of porosity, deliverability, radial force, and nonthrombogenicity; some examples of different designs are shown in Figure 3.

Addressing the problem of altered porosity and potential reduced occlusion rates is the Surpass Streamline Flow Diverter (Stryker Neurovascular, Fremont, California), which employs increasing numbers of wires within its weave to maintain porosity over different diameter sizes; its delivery system over a microwire of choice also addresses potential concerns with delivery wire forward migration that comes into play with stents that come with its own wire.[58] The p64 Flow Modulation Device (phenox, Bochum, Germany) also has a higher wire count compared to earlier flow diverter designs, and hence, lower porosity, theoretically increasing aneurysmal hemodynamic decoupling, as well as a different, dedicated stent detachment system that allows retrieval after full deployment.[59] Conversely, the Flow Redirection Endoluminal Device (FRED; MicroVention Terumo, Tustin, California) is a 2-layer design that allows the essential delivering of a high-porosity stent and a low-porosity flow diverter in 1 deployment. With the external high-porosity stent extending further proximally and distally compared to the internal flow diverting component, it has theoretical advantage of allowing more stable stent placement around vessels that the operator does not wish to jail, and thus, flow divert by increasing the length of the landing zones.[60]

Addressing deliverability, the Silk Vista Baby (BALT Extrusion, Montmorency, France), given its deliverability through a smaller 0.017″ catheter, suggests that the treatment of distal fusiform and wide necked aneurysms may be more feasible; the same theoretically held true, to a lesser extent, for the earlier Silk+ (BALT Extrusion, Montmorency, France) (Table). Addressing concerns regarding potential poor stent opening in certain cases, such as aneurysms that impinge on their in- and out-flow vessels, as well as extracranial applications, such as dissections that enter the skull base, is the DERIVO Embolization Device (Acandis, Pforzheim, Germany), which has a much higher radial force than first-generation devices due to its braid angle.[61] The dual-layer stent design of the FRED is also intended to address deliverability and stent apposition, given its lower contact area with the microcatheter during delivery and higher radial force of its external layer.[60]

TABLE. Delivery Catheter Sizes for Flow Diverter Devices

Delivery catheter size (inches)	Devices deliverable (specified if device size specific)
0.017	SILK Vista Baby[75] Woven EndoBridge (2-7 mm SL, 4-7 mm SLS)[76]
0.021	Medina Embolization Device[70] p48 Flow Modulation Device[77] SILK+ (2-4.5 mm)[78] Woven Endobridge (4-7 mm)[79]
0.025	SILK+ (4.5-5.5 mm diameter)[80]
0.027	Contour Neurovascular System[69] DERIVO Embolization Device[81] Flow Redirection Endoluminal Device[60] p64 Flow Modulation Device[59] pCANvas[82] Pipeline Embolization Device[83] Woven Endobridge (8-9 mm)[79]
0.033	Woven Endobridge (10-11 mm)[79]
0.034	eCLIPS[84]
0.040	Surpass Streamline[85]

With regards to nonthrombogenicity, long marketed in some areas of the world is the Pipeline Embolization Device with SHIELD Technology (PED-SHIELD, Medtronic), which employs a phosphorylcholine coating on its struts, which has been proven to reduce thrombogenicity in vitro.[62-64] It may be potentially justifiable to use this device with a reduced antithrombotic regimen in certain cases where the concern for hemorrhage is high and other methods of treatment prove impossible, such as dissecting aneurysms in nonsacrificable vessels[65,66] (Figure 4). Other manufacturers have also explored forms of stent surface treatment and/or coating with similar intent, including DERIVO's BlueXide finish,[64] and phenox's HPC coating,[67,68] which has been incorporated into their p48 Flow Modulation Device (phenox). In the future the application of even less thrombogenic coatings may revolutionize intracranial stent therapy in general.

Lastly, modifications to the nature and position of the components of the implanted device which hold the flow diverting surface across the aneurysm orifice, itself may present new advantages and open new subsets of aneurysms for treatment. One ground breaking development is the introduction of intrasaccular flow disruptor devices, such as the Woven EndoBridge (WEB; Sequent Medical, Aliso Viejo, California). Arguably this device is also a flow diverter in that its treatment effect is produced by the flow diversion surface across the neck of the aneurysm being treated. While having its own set of limitations (namely requiring intra-aneurysmal deployment of the device and in some device sizes, requirement for larger 0.033″ delivery catheters), it essentially consigns all foreign bodies to the aneurysmal neck or fundus – thus, theoretically reducing the risk of thromboembolic complications (Figure 5). Similar themes are explored by devices

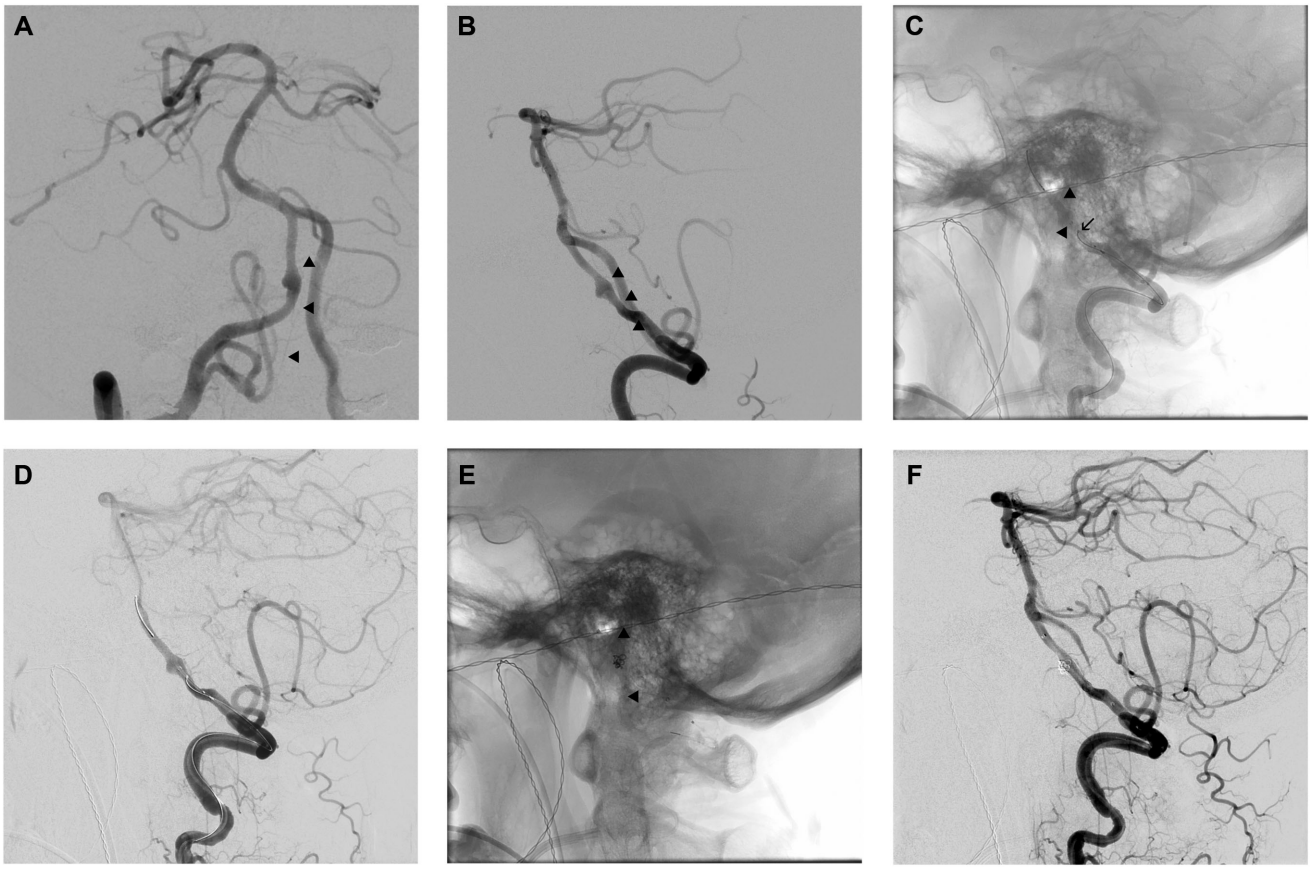

FIGURE 4. **A**, *Right vertebral artery (RVA) DSA, transfacial projection, demonstrating the intradural dissecting aneurysm in context of a WFNS grade 5 subarachnoid hemorrhage in a male in his 50s. An anterior spinal artery (ASA) can be seen arising from the superomedial margin of the fusiform aneurysm (black arrowheads).* **B**, *RVA DSA, lateral projection, demonstrating the likely anterior rupture point of the fusiform aneurysm, with the origin of the ASA tending posteriorly. Due to the presence of this ASA (black arrowheads) the segment was felt to not be suitable for sacrifice.* **C**, *RVA unsubtracted angiogram demonstrates partial deployment of a flow diverter (black arrowheads) down to the level of the fusiform aneurysm, intended to be used as a temporary intravascular buttress for coiling with the adjacent microcatheter (black arrow) before complete deployment. Treatment was performed with intravenous aspirin and heparin cover.* **D**, *RVA DSA demonstrating the same as* **C**. **E**, *RVA unsubtracted angiogram demonstrating anterior placement of a single fibred detachable coil jailed by the now completely deployed flow diverter (black arrowheads). Coils have not been placed posteriorly so as to not impinge on the ASA origin.* **F**, *RVA DSA demonstrating the same as* **E**. *He was maintained on aspirin cover only during the course of his admission. Subsequent DSA demonstrated persistent patency of the construct and the patient was started on clopidogrel on discharge 20 d after admission. He subsequently made a modified Rankin Score 1 recovery at 1 mo post ictus.*

on the horizon or in development but not yet in routine clinical use. Some examples are the Contour Neurovascular System and the Neqstent (both Cerus Endovascular, Fremont, California), with reducing degrees of intra-aneurysmal mural contact by deploying across the lower aspect of the aneurysm and neck only in a disc-like format.[69] Continuing the theme of intrasaccular placement of flow disrupting surfaces but deviating towards a more conventional coil-like delivery is the Medina Embolization Device (Medtronic), which combines braided mesh petals to loops of core wire, allowing sequential delivery of the petals into the aneurysm.[70] Moving further away are the extrasaccular noncylindrical-stent designs, such as the pCANVAS device (phenox), which represents an evolution of bifurcation devices, such as the pCONus (phenox) and Pulserider (Pulsar Vascular, Los Gatos, California), in that an additional flow diverting membrane is deployed across the waffle-cone-like aneurysmal neck interface with the bifurcation. While the pCONus itself has not been demonstrated to cause flow alteration within the aneurysm, the effect has been demonstrated in the pCANVAS device.[71,72] The eCLIPs device (Evasc, Vancouver, Canada) is another design which may be more suitable for wide necked bifurcation aneurysms, given the traditional flow diverter stent design necessitates the jailing of 1 of the 2 bifurcation branches. Its design, sequestering support struts to half the wall of one side branch, deploys a dense leaf design across the aneurysmal orifice while leaving the main vessel and side branches free of

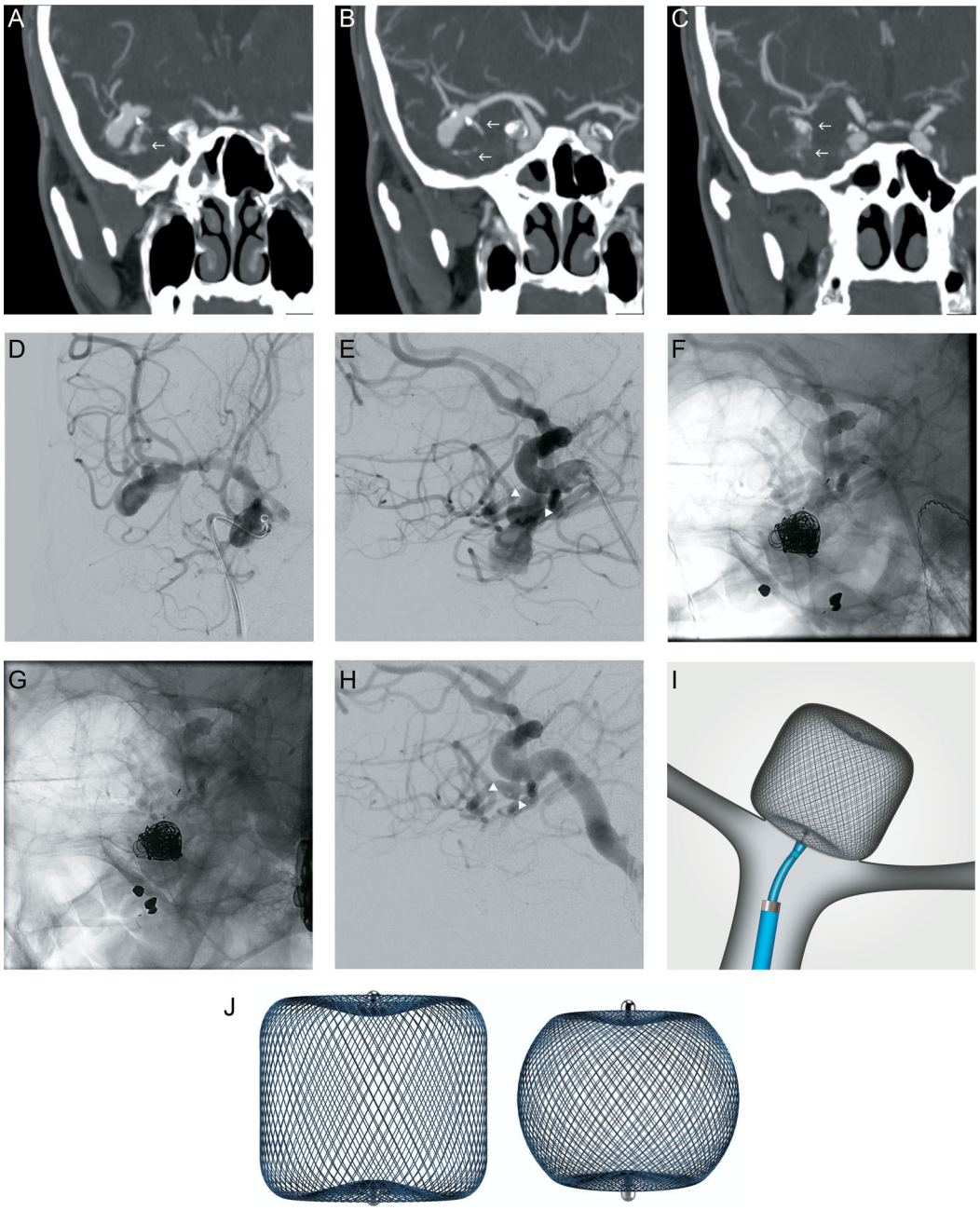

FIGURE 5. **A** *to* **C**, *Sequential anterior to posterior 5 mm coronal maximum intensity projections of a CT brain angiogram. These demonstrate the partly thrombosed lumen of a heavily calcified (white arrows) 28 mm giant right M2 aneurysm in a male in his 30s presenting with headache.* **D**, *Right ICA DSA, frontal oblique projection demonstrating the perfused component of the giant M2 aneurysm.* **E**, *Right ICA DSA, lateral oblique demonstrates the neck of the aneurysm, marked by white arrowheads.* **F**, *Right ICA unsubtracted angiogram, lateral oblique projection demonstrates the distal coiled component of the perfused lumen and the neck component occluded with an intrasaccular flow disruptor (Woven EndoBridge). It was felt that compaction would be less likely with the device in context of the large volume of intra-aneurysmal thrombus. He awoke without deficit.* **G**, *Six-month follow-up right ICA unsubtracted angiogram, lateral oblique projection demonstrates the complete occlusion of the aneurysm save for the tiny 2 mm neck remnant. There has essentially been no compaction of the disruptor into the aneurysm.* **H**, *Right ICA DSA demonstrating the same as* **G**, *with the neck remnant marked by white arrowheads.* **I**, *The WEB. Image courtesy of MicroVention Inc.* **J**, *Side profile of the WEB SL (left) and WEB SLS (right). Images courtesy of MicroVention Inc.*

bridging metallic struts. There is suggestion on animal studies that the dense leaf segment not only allows coil retention but may disrupt flow away from the aneurysm and serve as a platform for endothelial growth.[73] Its unique deployment technique, however, may introduce a learning curve compared to other devices that are closer to more traditionally and commonly used techniques, such as stent deployment.[74]

With the above in mind, it is worth noting that given the rapid innovation and progress in device design and technology, there are a vast number of devices in today's neurointerventional armamentarium which can be used. Most devices are supported by a number of observational studies and registry data,[17] but save for the PED, clinical trials are still lacking. However, a number of trials are close to peer-reviewed publication, including the Prospective Study on Embolization of Intracranial Aneurysms with Pipeline Embolization Device (PREMIER) trial for the PED and the Safety and Effectiveness of an Intracranial Aneurysm Embolization System for Treating Large or Giant Wide Neck Aneurysms (SCENT) trial for the Surpass Streamline Flow Diverter. Others are progress, with one of the most interesting being the Flow Diversion in Intracranial Aneurysm Treatment (FIAT) trial, which aims to compare flow diversion with coiling and clipping, but single arm interventional trials on other conventional flow diverters, such as the Pivotal Study of the FRED Stent System in the Treatment of Intracranial Aneurysms, as well as newer generation devices, such as the Contour Neurovascular System – European Pre-Market Unruptured Aneurysm Study (CERUS), the European eCLIPS Safety, Feasibility and Efficacy Study (EESIS) the WEB Intrasaccular Therapy (WEB-IT) trial are also progressing.

CONCLUSION

Similar to other eras during the rapid development of endovascular therapy for intracranial aneurysms, the commercialization of a robust and viable flow diverter technology has led to the shift in the types of aneurysms that can be treated with minimal invasiveness. It can be argued that the basic flow diverter stent technology is now mature; however, there is extensive room for further iterative development to increase its areas of potential usage. This conversely can lead to the paradox of choice – in today's neurointerventional armamentarium, there are many devices available, all with some theoretical advantage in one aspect or another. One of the challenges of any operator is to become adept in the tools of his or her trade and yet progress as the technology and techniques do, and using too many variations of the flow diverter device may reduce his or her expertise in each individual device. However, the counterargument also holds true that such a philosophy may hold back progress. The same arguments, of course, can be applied to detachable coils, albeit coils being a much more mature technology. Such issues aside, should certain current technological restrictions be overcome – probably most importantly of stent thrombogenicity and whether dual antiplatelets will be required, we may yet see a further dramatic shift in the pattern of intracranial aneurysm treatment in the future.

Disclosures

Outside of publication in this supplement, the authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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