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Developments on the horizon in the treatment of neurovascular problems

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Abstract

The field of Interventional Neuroradiology and Endovascular Neurosurgery has seen much technical advancement in the past two decades, which has brought the specialty from its infancy as an alternative therapy to the current standing as near standard of care for many complex neurovascular pathologies. This past year is no exception with flow diverting stents and stent retriever devices aiming to make their mark on advanced treatments for intracranial aneurysms and ischemic stroke, respectively. This review article will focus on the development of these technologies, current data supporting their advantages and limitations, and a brief expert opinion on where these technologies may take the field in the next few years.

Key Words: Cerebral aneurysm, flow diversion, ischemic stroke, stent retriever

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CEREBRAL ANEURYSM TREATMENT

Percutaneous treatment of intracranial aneurysms began with electrothrombosis in 1941 and subsequently progressed to the use of various pushable coils and detachable balloons, all of which were difficult to safely control and produced suboptimal, incomplete results.[11,15,19-21,28,36] These factors were significantly improved upon with the development of the electrolytically detachable coil. Clinical testing of the electrolytically detachable coil was approved by the Food and Drug Administration (FDA) in 1995 for high-risk, inoperable, or ruptured intracranial aneurysms and by 2006 over 150,000 patients had been treated with the device.[4,53] Coil technology has increased significantly since the original design, further promoting the ease and effectiveness of its use with advancements including stretch resistance, alternative detachment systems, and biodegradable coating coils (BCCs).[20] Endovascular procedures have been further advanced with the advent of additional devices aimed at assisting the embolization of wide neck intracranial aneurysms including intracranial stents and balloon remodeling.[19]

The most recent development in the field of endovascular therapy for the treatment of intracranial aneurysms in the past several years is the concept of flow diversion. Flow-diverting stents are flexible, self-expanding stents delivered by a standard microcatheter. These stents have significantly expanded metal surface area coverage compared with traditional stents marketed for intracranial use such as Neuroform® (Stryker Neurovascular, Freemont, CA) or Enterprise™ (Cordis, Miami Lakes, Florida). This coverage area gives the device an extremely low porosity, which when placed within a vessel harboring an aneurysm that preferentially redirects flow through the parent vessel, limits aneurysm inflow, and ultimately results in aneurysm thrombosis. In effect these devices create endoluminal parent vessel reconstruction by

altering hemodynamics and by induction of complex biological responses, which result in neointimilization, factors which collectively aim to heal the diseased segment of the vessel and the aneurysm ostia.[37]

Initial experience with these stents has been greatly received as deployment seems to be technically achievable in the majority of cases (although this requires a learning curve above that seen with traditional intracranial stents), they result in a high percentage of complete aneurysm occlusion, and to date have acceptable complication rates. Initially approved and marketed for the treatment of wide necked, complex aneurysms with limited therapeutic options, these devices are increasingly being used for the treatment of more traditional aneurysms.

Two flow diverting stents are currently being used internationally, the Pipeline™ Embolization Device (PED; ev3, Irvine, California, USA) and the Silk stent (BALT Extrusion, Montmorency, France). The PED became the first available device in the United States when it received approval from the FDA on April 6, 2011 for the endovascular treatment of adults (age 22 and above) with large or giant wide-necked intracranial aneurysms of the internal carotid artery (ICA) from the petrous to superior hypophyseal segments.

The PED is composed of 48 braided strands of woven wire mesh containing 25% platinum and 75% cobalt–nickel alloy[49] and when fully expanded provides approximately 30-35% metal surface area coverage, significantly more than that seen with other currently marketed stents for use in the intracranial circulation.[37] The Pipeline Embolization Device for the Intracranial Treatment of Aneurysms Trial (PITA) was the first prospective, multicenter study of this device. Released in December of 2010, this trial demonstrated the device to be highly efficacious, being successfully placed in 96.8% of 31 patients.[37] In addition, complete angiographic occlusion at 6 months was demonstrated in 93% of patients.[37] Further series have confirmed reasonable technical deliverability of the device and that complete aneurysm occlusion is seen in a high percentage of cases on follow-up angiography.[8,12,29,30,39,49]

In PITA only two (6.5%) periprocedural strokes occurred giving the device a similar safety profile to that seen with standard stent-assisted coil embolization of intracranial aneurysms.[37] The periprocedural safety of the device was further supported in the Buenos Aires experience[29] where no major periprocedural stroke or death occurred in 53 patients. As previous authors have noted, the safety profile being achieved with these devices must be considered along with the fact that they are being placed in a population of some of the most difficult intracranial aneurysm morphologies to treat.[37] This fact makes the initial success of these devices all the more exciting.

Not all series have demonstrated as high of a safety profile, however. In the Budapest experience, clinical complications were seen in 4 of 18 (22.2%) patients.[49] Chitale *et al.* reported the results from their series of 36 patients in July of 2012 and demonstrated symptomatic postoperative complications in 13.9% of patients.[8] In addition, a complication being witnessed, which seems somewhat unique to flow diverters in the world of endovascular treatment, is that of delayed aneurysm rupture in an aneurysm, which has presumably been effectively treated. Although the exact mechanism of this peculiar event is uncertain, it seems most likely by limited autopsy data that the rapid aneurysm thrombosis, which occurs following flow diversion, results in a significant inflammatory reaction at the aneurysm dome.[18,39,49] This may result in mural destabilization, and if any residual inflow to the aneurysm remains, delayed rupture may be seen. In addition, flow diverting stents may, by inherent nature of their mechanism of action, inadvertently redirect residual flow into more susceptible areas of the aneurysm dome and promote delayed rupture.[18]

With placement of any intracranial stent, routine antiplatelet therapy is used to prevent peri-procedural thromboembolic complications. Given the increased metal surface of flow diverting stents much attention has been given to the adequate use and monitoring of antiplatelet drugs, although there is no current standard agreement on type, dose, or duration of therapy.[26] In a recent review of 10 studies using the PED, while all patients received dual antiplatelet therapy with both aspirin and clopidogrel, there was wide variance regarding the timing of onset prior to surgery (1-7 days), the dosage used (100-150 mg for aspirin and 75-600 mg for clopidogrel), and the duration of treatment following the procedure with dual therapy continuing for 3 months and aspirin commonly extended for 6 months or even life-long.[26] While clopidogrel has been extensively used as an antithrombotic agent for coronary and carotid stent placement as well as in the neurovascular circulation for stent assisted aneurysm embolization, genetic alterations have been found to result in resistance in a significant percentage of patients.[22,23] Prabhakaran, *et al.* evaluated 76 patients undergoing cerebrovascular stent placement and found that over 50% of patients had a response rate of less than 40% using P2Y12 assays.[40] In addition, a large study of cardiology patients were found to have a 6.3% increase in stent thrombosis in clopidogrel hypo-responders.[6] For these reasons there has been much attention given to therapeutic monitoring although there is no agreement on how to proceed with patients who do not respond to clopidogrel or even what level of "hyporesponsiveness" is clinically relevant.[22] Prasugrel is an alternative agent that is known to achieve higher levels of platelet inhibition more rapidly and more

consistently than clopidogrel, although the drug has been associated with a 30% risk in relative bleeding compared with clopidogrel.[54] This has shown to be an effective alternative agent to be used in flow diversion in select cases,[22] although given the potential increased risk of intracranial hemorrhage, widespread implementation is guarded.[1]

One obvious initial concern of the device given the increased "metal burden" is that significant in-stent stenosis would be observed on follow-up angiograms. PITA demonstrated no evidence of significant in-stent stenosis (≥50%) by conventional angiography at 180 days.[37] Observation of maintained stent patency on follow-up angiography was further supported by the Budapest experience and in other series by Deutschman, *et al.*[12] and McAuliffe, *et al.*[30]

One important concept regarding the mechanism of action of flow diverting stents relies on the idea that branch vessels with outflow will be preserved when the stent covers their ostia while the target aneurysm, which by nature does not have an outflow channel, will undergo progressive thrombosis. In clinical practice to date, this hypothesis seems only partially accurate. In the Budapest experience, a total of 28 visual side branches were covered with at least one PED. One ophthalmic artery was immediately nonvisualized on completion angiography and resulted in retinal branch occlusion. Two additional ophthalmic arteries (each covered by multiple devices) were found to be occluded at 6-month follow-up angiography, although both were clinically silent.[49] In another series looking at ophthalmic artery patency after PED placement, 20 ICA aneurysms in 19 patients were studied in which the ophthalmic ostium was covered with the device. On their follow-up analysis, 21% showed ophthalmic artery occlusion with an additional 11% showing antegrade, though sluggish flow.[41] Although roughly a quarter of ophthalmic arteries were angiographically occluded in this study, no visual symptoms were clinically evident. It is hypothesized that in most circumstances branch vessel patency will be maintained if there is no robust enough collateral flow to support adequate perfusion to the territory of interest.[41] If adequate collateral flow does, however, exist, then the branch vessel may be at risk for occlusion, though the clinical consequence of this may be minimal if any. The hemodynamic effect on branch vessels must be closely observed with time to specifically identify situations in which unfavorable branch occlusion may occur. In addition, it must be noted that the majority of the studies to date have focused mostly on anterior circulation aneurysms of the ICA. The fate of eloquent perforator vessels (such as lenticulostriate vessels or basilar perforators) following flow diverting stent placement has yet to be completely elucidated.[52]

There has been much enthusiasm for the use of flow diverters to treat giant and fusiform aneurysms involving the vertebrobasilar circulation. The natural history of these lesions is dismal with a reported mortality rate of approximately 30% and to date both surgical and endovascular solutions to these lesions remain fraught with potential devastating complications.[27] Initial limited cases reports and single center experiences using flow diversion for these pathologies have not been very promising. In a report by Siddiqui, *et al.*, seven patients were treated with flow diverting stents for symptomatic large or giant fusiform vertebrobasilar aneurysms and four deaths were observed including postreatment aneurysm rupture in two patients.[47] In addition, in one of three remaining patients severe disability was observed.[47] While each of these cases must be observed individually the complication rate from this experienced center has led to a current cessation to treat these lesions with flow diversion.[47] The reasons for apparent poor outcomes, which have been seen following flow diversion for fusiform and giant vertebrobasilar aneurysms remain unclear. We have an incomplete understanding of how flow diversion affects the hemodynamics of brainstem perforators, or what effect stagnant flow within the aneurysm dome has on localized mass effect on the brainstem and adjacent vascular structures.[47] Until these factors are better understood the use of these devices in the posterior circulation is cautioned.

So where do we stand with flow diversion? What is the future? Although many staunch supporters of the device would like to see this to be the cure for all treatments for intracranial aneurysms, it is doubtful this will happen. As with all technical advancements in surgery or the endovascular world each step forward is faced with a smaller step back. It seems likely that flow diverting stents will make a huge impact on the treatment of wide necked large and giant aneurysms of the ICA. These devices seem to work extremely well for these lesions with potentially shorter procedural times and possibly lower costs for the larger aneurysms in which a traditional stent with numerous coils would be required to achieve an acceptable treatment.[10] This may be particularly true in the cavernous and paraophthalmic region where localized mass effect from a traditional coil mass is undesirable, as this may worsen or result in new cranial neuropathies. The device also seems to have great promise for the treatment of multiple aneurysms of the ICA for which traditional endovascular therapy would require lengthy or staged procedures. For example, a patient with three separate paraclinoid aneurysms potentially may be treated with one PED in on procedure, while traditional therapy may have required a stent to be placed in one setting with coil embolization performed in several additional procedures. We have personally found the device to be highly useful for treatment of laterally projecting paraclinoid

aneurysms, which by nature of their anatomic location and geometrical configuration often make obtaining an adequate angiographic working view for traditional stent assisted coiling difficult.

Many positive attributes of flow diverting technology exist. One of the major drawbacks of traditional endovascular therapy as compared to surgical clipping is that complete, durable occlusion is achieved in a significantly lower percentage of patients. Following endovascular therapy many lesions are only partially treated or present later with recurrences. This is particularly true for large (≥10 mm) and wide-necked aneurysms, which often require numerous retreatments and long-term imaging surveillance.[37,52] The significance of small residual aneurysm necks following coil embolization is debatable, although they do have a small potential to grow and subsequently rupture so close surveillance typically remains advised. This requires extensive angiographic or cross sectional imaging follow-up after interventional therapy. This is as opposed to traditional surgical clipping where the aneurysm is presumed to be "cured" and no follow-up necessary. It seems clear from the initial data that for appropriate lesions flow diverting stents are highly efficacious resulting in complete aneurysm thrombosis in potentially over 90% of cases. This may result in a significant shift paradigm over the years where lesions treated with flow diversion can be thought of as "cured" in a more traditional surgical like mindset.

Until we understand the hemodynamic effect of the device on branch and perforating vessels more clearly, use of flow diversion in the vertebrobasilar circulation, the middle cerebral artery bifurcation, and within the anterior communicating artery complex remains to be seen. As of now we have acceptable treatment options both surgically and with endovascular means for these lesions. Until we are sure of the safety profile of the device in these regions, the potential risks seem to outweigh the benefits over established treatments. As with prior technical advancements, it is likely that flow diverting stents will take their place in the interventionalist's armetarium for a specific, albeit potentially large, subset of intracranial aneurysms. This being said traditional endovascular approaches as well as surgical therapies will retain their role. Indeed in our future it is doubtful there will be a "fix all" device for the treatment of intracranial aneurysms.

ISCHEMIC STROKE

The restoration of blood flow by vessel recanalization has been shown in the literature to improve outcome and reduce mortality in the setting of acute ischemic stroke;[42,56] and much technical advancement has been focused on achieving this. Intravenous tissue plasminogen activator (IV rt-PA) was approved for administration within 3 hours of stroke symptom onset over 16 years ago.[50] This has been expanded to 4.5 hours given certain limitations and patient-specific criteria.[17] Despite the success of IV rt-PA there are limitations to its ability, namely the adequate recanalization of large vessel occlusions.[44] Indeed the overall recanalization rate of IV rt-PA may be less than 50%.[42] In an attempt to improve successful reperfusion above that achieved with IV rt-PA, various intraarterial (IA) therapies have been developed and employed. Initial focus was aimed at the IA administration of rt-PA, proven effective for use up to 6 hours postsymptom onset in the Pro-Urokinase for Acute Cerebral Thromboembolism II (PROACT-II) trial.[14] Subsequent developments have primarily centered on various mechanical thrombectomy devices. These devices garnered interest because of their theoretical advantage of improved and timelier recanalization rates in addition to potentially lower rates of hemorrhagic conversion than that seen with both IV and IA thrombolytics. These factors collectively give these devices the advantage of an extended time window for their application.

Attempts to prove the effectiveness and adequacy of IA rt-PA and various mechanical thrombectomy devices as compared to IV therapy for use in acute ischemic stroke has seen many ups and downs in the past decade. The past year has been no different with one potentially major step forward and another backwards with regards to mechanical thrombectomy. On April 18, 2012 the Interventional Management of Stroke (IMS) III independent data monitoring board recommended to place the IMS III trial on hold due to interim analysis showing a very low likelihood of ultimately demonstrating a difference between the two treatment arms. IMS III was a randomized multi-center, open-label clinical trial designed to determine if a combination of intravenous tissue plasminogen activator (IV rt-PA) and an approved IA therapy (an FDA approved mechanical thrombectomy device and/or IA rt-PA) was superior to IV rt-PA alone.[24] The trial was designed to be stopped if it was unlikely that a 10% difference in favorable outcome would be seen at 90 days (modified Rankin Scale score 0-2) between the two groups.[24] The data safety monitoring board stopped the trial after enrollment of 656 of the intended 900 patients as initial data seemed unlikely that the combined treatment was going to show a more favorable outcome than IV rt-PA alone. It is important to note that the monitoring board made it clear that safety concerns were not the reason for halted enrollment (www.ninds.nih.gov/disorders/clinical_trials/NCT00359424.htm).

However, a little over 2 months before halted enrollment in IMS III was announced, the promising preliminary results of the SWIFT (Solitaire with the intention for thrombectomy) trial were presented at the International Stroke Conference in New Orleans on February 3, 2012. SWIFT was an open label, randomized, blinded, multi-center trial evaluating the effectiveness of the

Solitaire™ FR Revascularization Device (ev3 Inc., Irvine, CA, USA) against the Merci Retriever® (Concentric Medical/Stryker Neurovascular, Mountain View, CA, USA) for mechanical revascularization of large vessel occlusions in the setting of acute ischemic stroke. The Solitaire™ FR device is an intracranial stent, initially marketed for use in aneurysm embolization, which demonstrated promising results from preliminary trials abroad for use as a mechanical clot retriever for ischemic stroke.[5,7,13,25,32,33,35,48] This stent is delivered by a standard microcatheter technique; however, has the unique property of being fully retrievable. Thus the stent can be migrated into an occlusive clot and deployed; the radial force of the stent forcing thrombus against the arterial wall allowing immediate, partial restoration of flow and enhancing the effect of thrombolytic agents. Clot also becomes trapped within the interstices, which can be subsequently retrieved along with stent into the base catheter within the carotid or vertebral artery.[25] The stent can be applied repeatedly to remove residual clot and is accessible to small arteries. The hope is that stent retrievers will allow improved and quicker thrombectomy compared with currently available devices, namely the Merci® Retriever and the Penumbra System (Penumbra, Alameda, CA, USA).

The SWIFT trial indeed did support these hopes, showing a significantly higher recanalization rate without symptomatic intracranial hemorrhage (SICH) of the Soltaire™ FR Revascularization Device compared with the Merci® Retriever (61% vs. 24%) in the final report published online August 26, 2012.[45,46] If only successful recanalization is considered (with or without SICH), the Solitaire™ device was able to open 88.9% of occluded vessels compared with 67.3% with Merci®.[45,46] In those patients treated with Solitaire™, 58% had good 3-month neurological outcome (modified Rankin score ≤2) compared with 33% with Merci.[46] In addition, the 3-month mortality rate with the Solitaire device was 17% compared with 38% for Merci®.[45,46]

At least six additional stent retriever devices have entered premarket testing since the early results of high recanalization rates with Solitaire™ were released.[56] The same day the final results of the SWIFT trial were published, results of the Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO 2) were also released.[38] The Trevo Retriever (Stryker Neurovascular, Mountain View, CA, USA) is a stent retriever similar to Solitaire™, which also was able to demonstrate significant superiority to Merci in a randomized, controlled trial. In TREVO 2 the device was able to achieve thrombolysis in cerebral infarction (TICI) scores of 2 or greater in 86% of treated patients compared with 60% in the Merci group.[38] In addition, a 90 day good clinical outcome (modified Rankin score 0-2) was achieved in 40% with Trevo versus 22% with Merci.[38]

So where do we go and what do we do with these conflicting results? The data from IMS III is sound and convincing. With previously available mechanical devices IMS III makes a compelling argument that a combination of IV and IA therapy is not superior to IV therapy alone. However, several main counterpoints must be considered. IMS III was designed to evaluate combination therapy. The trial did not select for IV rt-PA failures, which are often large vessel occlusions for which endovascular therapy is currently considered most useful.[56] In addition, vascular imaging (computed tomographic angiography – CTA or magnetic resonance angiography – MRA) was not required in either arm to access for large vessel occlusions, again for which IV therapy is known to have a lower efficacy.[44] Data has further shown decreased efficacy of IV-rtPA for clot burdens ≥8 mm in the middle cerebral artery.[43] These factors collectively limit the ability of IMS III trial design to focus evaluation of mechanical devices on the disease process to which they are thought to be most useful.

Second, given the recent results of the SWIFT trial it must be noted that the majority of IMS III was completed without the use of stent retriever devices. The Solitaire™ device was incorporated into IMS III as the device was approved; however, this occurred late enough that at the time of interim analysis <1% of interventional cases were performed using the new stent retriever technology.[56] Given recent data suggesting significant superiority of these devices for vessel recanalization, the data from IMS III must be considered with this potential technical limitation. Would stent retrievers have changed the outcome of IMS III? The answer to this question is unknown but it is one that must be answered prior to abandoning mechanical retrieval for all patients except those not eligible for IV therapy.

Stent retrievers will likely positively impact the success of mechanical thrombectomy for acute ischemic stroke. It is doubtful, however, in the author's opinion, that they will truly revolutionize the field, making IA interventions for stroke akin to that seen for acute coronary occlusion. Despite accruing data that mechanical devices give higher rates of recanalization than IV rt-PA there has been difficulty in demonstrating a concurrent improvement in patient outcomes.[2,3,16,51] While SWIFT and Trevo 2 both showed improved patient outcomes compared with Merci, another mechanical device, we still are left with little compelling data that IA mechanical or chemical thrombolysis is superior to IV therapy alone with regard to clinical outcome data. Until this can be shown IA therapies will remain alternative treatment options only for patients who are not candidates for IV rt-PA. These cohorts of patients are often those with severe neurological deficits who present late after onset of symptoms or who have concomitant disease processes which preclude IV therapy. It is not hard to see that if

arterial interventions are always being tested in the most difficult of stroke patients, proving efficacy will remain a challenge.

Indeed the key clinical factor driving the field currently and likely into the future, is the overall poor success of other available treatment options for ischemic stroke, most specifically the relative limited efficacy of IV rt-PA.[16] We continue to search for better treatment options and mechanical devices have been at the forefront of this interest for some time now given their ability to achieve angiographic recanalization in a reasonably high percentage of patients. It is the effect of recanalization, either positive or potentially negative, on patient outcome we still cannot accurately predict. To date we have a limited understanding of and ability to access many of the factors concerning ischemic stroke including the amount of reversibly injured and salvageable brain tissue versus core infarction, collateral flow, as well as clot and patient specific characteristics, which may predict outcomes of intervention.[16] We still do not know exactly which patients will benefit from reperfusion versus those who will have potentially devastating complications from it. With a better understanding of the disease process itself, hopefully we will be able to better predict which patients will likely benefit from these highly advanced technical devices.

As a final point one cannot discuss the current limitations of acute ischemic stroke intervention without addressing patient specific considerations and time window constraints. Although there are roughly 795,000 strokes in the United States each year[55] the number of potentially treatable strokes only represents 7-15% of this total[9] and in most communities only 1-7% of these potentially treatable patients arrive at the hospital in time for stroke revascularization therapies.[31,34] Even in the hospitals with highly active stroke programs <10% of stroke victims receive immediate treatment.[14,31,34] The number of patients potentially qualifying for endovascular therapy is even lower as many present with either small-artery occlusions where endovascular therapy is not beneficial or with devastating large vessel occlusions with severe brain injury where intervention is futile.[31] In comprehensive stroke centers following evidence-based guidelines for intervention on average neurointerventionalists only perform eight procedures per year.[14,31] With these limitations, progression of our understanding of the disease process as well as the ability to develop and appropriately implement technical advancements in IA therapy will be challenged.

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