Society of Vascular and Interventional Neurology

THE CORE

SVIN Newsletter December 2014

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Leah Guzman presented her beautiful *Brain Series* paintings at the 2014 SVIN Annual Meeting and donated **30% of her proceeds** to SVIN. She has offered this promotion again for any purchases generated from the December 2014 Newsletter. To view her artwork and make your purchase, please visit her website: www.leahguzman.com

Leah Guzman, ATR-BC

In This Issue

President's Message

Tudor Jovin, MD
SVIN President

At the crossroads of history: SVIN meeting witnesses news that will forever change acute stroke treatment paradigms

It is a momentous time for patients with acute ischemic stroke, their families and medical professionals who treat them.

SVIN members, its supporters and friends had the privilege to live together moments of historical importance at the SVIN's 8-th annual meeting in Hollywood, Florida, which has just concluded on November 10-th 2014. During the two and a half days event superbly organized by Robin Novakovic MD, meeting chair, together with the rest of the meeting's organizing committee, events have unfolded that have radically shaken the world of acute stroke due to large vessel occlusion and are likely to forever change the treatment of this devastating disease. News transpiring during the meeting will undoubtedly mark a turn-around point for the world of endovascular acute stroke therapy and represent the moment of fulfillment of longstanding hopes by physicians, their patients and family members that proof of effective treatment beyond iv t-PA is finally available within tangible reach.

The stage had been set by the MR CLEAN study whose results were presented at the World Congress of Stroke in Istanbul on the Saturday prior to the start of the SVIN meeting. This study, carried out exclusively in Holland enrolled 500 patients and demonstrated robust benefit of mechanical embolectomy compared to standard medical therapy (including iv t-PA which was administered in about 90% of cases). Treatment group included same standard medical therapy as controls plus additional thrombectomy performed almost entirely with stentrievers. The study, by now published in the New England Journal of Medicine demonstrated a shift in the distribution of the primary-outcome scores in favor of the intervention. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). The shift toward better outcomes in favor of the intervention was consistent for all categories of the modified Rankin scale except for death. This robust benefit was found to be consistent across all analyzed subgroups. The rather unexpected results in terms of magnitude of effect in favor of endovascular therapy exposed by MR CLEAN, triggered enrollment halt with unplanned interim DSMB data analysis of several other ongoing trials including ESCAPE and EXTEND IA. The former, run out of University of Calgary Medical Center in Canada, was stopped at the DSMB's recommendation after the analysis of 243 patients with available 3 months outcomes demonstrated that pre-specified overwhelming efficacy boundaries have been crossed. There are 73 patients excluded out of this analysis whose 90 days outcomes are still pending. Hence, final results are not available for analysis yet. In deference to the investigator's pledge that data are not publicly reproduced until published in a peer review journal, more specific data will not be disclosed in this document. Nonetheless, these news are extremely promising as in

order for the study to have been stopped based on pre-specified criteria, treatment effect has to be even larger than that noted in MR CLEAN. Thus, any concerns that MR CLEAN may have been an outlier have been put aside by ESCAPE. The third, trial EXTEND IA conducted out of Australia was stopped for reasons of overwhelming efficacy after enrollment of 70 patients. The primary endpoints of this trial were reperfusion at 24 hours and favorable clinical response at 3 days, quite different than those of MR CLEAN and ESCAPE and therefore difficult to compare to the other two trials. Nonetheless, having been stopped after 70 patients one can infer that treatment effect must have been quite large.

There are several other randomized trials assessing the efficacy of embolectomy devices in conjunction to t-PA against iv t-PA only, including the Covidien sponsored SWIFT PRIME study using the Solitaire device and THERAPY a Penumbra sponsored trial of aspiration with Penumbra technology that have been placed on hold due to assumed loss of equipoise. Dr. Joe Broderick, MD, a pioneer of acute stroke reperfusion trials illustrated this domino effect by presenting in a slide a line of dominoes falling, sequentially, representing ESCAPE, EXTEND IA, SWIFT PRIME and THERAPY. As a reassurance that results from other ongoing trials are likely to go in the same direction, Jeff Saver, MD, UCLA, another veteran of endovascular stroke trials, stated that given the recent slew of positive trials "it doesn't matter how you design it, it will be positive".

Indeed, in keeping with the previous wave of prematurely halted trials, in early December, one month after the SVIN meeting, REVASCAT another randomized endovascular trial conducted in the province of Catalonia, Spain investigating the benefit of endovascular therapy for stroke due to M1 MCA occlusion with or without accompanying ICA occlusion with best medical therapy (including iv t-PA) versus best medical therapy alone up to 8 hours of symptoms onset was stopped at the recommendation of the DSMB following a pre-planned interim analysis of 174 patients. Specific reasons for this recommendation have not been disclosed by the DSMB due to pending clinical outcome adjudication of another 32 patients enrolled in the study. What was communicated was that there were no safety concerns and that equipoise no longer exists in the patient population studied.

If confirmed by subsequent publications, treatment effects emerging from all these trials may be orders of magnitude higher than the ones demonstrating benefit of percutaneous coronary interventions compared to iv lytics in acute myocardial infarction. At present it is hard to fathom the impact of these studies on overall stroke care but it is likely that the landscape of acute interventional care will be changed forever. If subsequent trials confirm the expected treatment effect and once the data are published, embolectomy for acute stroke will change very quickly from an optional to a mandatory procedure and stroke will be organized akin to trauma, according to levels of care.

Our mission as a Society was stated to represent the advancement of interventional neurology as a field with the ultimate goal of improving clinical care and outcomes of patients with strokes and cerebrovascular diseases.

President's Message: At the Cross Roads of History *continued*

Credit for this great accomplishment must be given to the community of stroke neurologists and neurointerventionalists among which interventional neurologists occupy a prominent role. It was particularity impressive to note the high number of SVIN board members occupying leadership positions in most of the randomized endovascular trials presented. The collective effort put together by the stroke and neurointerventional community is a shining example of perseverance in the face of adversity. It would have been easy to simply disregard endovascular management as a failed experiment after the IMSIII, MR RESCUE and SYNTHESIS studies dealt a near fatal blow to endovascular therapies for acute ischemic stroke. As mentioned at the SVIN meeting, due credit needs also to be given to the ones who have designed and executed trials like IMS3 as the positive results garnered recently could not have been possible without the outstanding preliminary work done by IMS3. This is because IMS3 not only exposed the fundamental flaws in the way endovascular therapy for stroke has been carried out throughout the duration of the trial, thus allowing opportunities for improvement in design and execution of future trials but also created equipoise, enabling randomization of patients that would otherwise never had been enrolled in a randomized trial.

Despite the impressive results there is more work to be done and big opportunities exist to improve outcomes even further. Many remaining questions are yet to be answered; patient selection outside of the 6 hour time window; best imaging modality for timely assessment of the ischemic penumbra and creation of systems of care that will allow this treatment to be carried out in the fastest possible manner thus further increasing its benefit. Combining reperfusion with neuroprotection to mitigate the deleterious effects sometimes seen with reperfusion and also to allow extension of the therapeutic window by transforming "fast progressors" into "slow progressors" is another area worth exploring in the future. . Octogenarians were included in MR CLEAN where the net benefit of intervention in this subgroup was substantial although the relative number of good outcomes when compared to younger patients was less impressive. As octogenarians were excluded from many of the randomized trials mentioned above, the question of benefit in this rapidly growing population segment remains to be settled.

Because the results of all but one of these trials are not yet available in peer reviewed publications, enthusiasm has to remain contained until definitive proof of efficacy is published. It is important to not discourage recruitment in any ongoing trials like THRACE where available evidence has not been considered sufficiently strong to recommend halting. The conundrum however remains that equipoise on a personal level, has, in many cases already, been irretrievably changed yet incontrovertible evidence must still be remains to be published or still accrued in order to win not just a battle but the war in a field where attrition has held sway for far too long.

SVIN leaders among first to be quoted in media on MR CLEAN

Click on the link below to view the NeuroNews article on the MR CLEAN Trial and SVIN leadership's coverage.

NeuroNews

MR CLEAN: expert opinion

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Editor's Corner

In this edition of The CORE, we are very pleased to include several contributions from SVIN members and reviews of the landmark trials that were completed or published recently. We also have a special guest, Dr. Josser Delgado who shares his institutional experience with antiplatelet management in patients undergoing flow diversion with the Pipeline Embolization Device. We thank our newsletter staff and we hope to continue to receive your contributions. We welcome any ideas or interest in writing articles, editorials, or commentary for future SVIN newsletter editions.

Mouhammad A. Jumaa, MD
Ashutosh P. Jadhav, MD, PhD

2014 SVIN Meeting Highlights

Each year SVIN's highly successful annual meeting has grown in an effort to meet the mission statement of the society. To that regard, the pre-conference day focused on elevating SVIN's goal to raise awareness and disseminate knowledge concerning developments in cerebrovascular diseases. In response to society member feedback, an additional day was added to the meeting and increased opportunity for open dialogue through panel discussions and debate -style sessions were provided, including a timely debate on the MR CLEAN trial results and implications for clinical practice. SVIN was honored to feature Mark Alberts, MD, FAHA as the 2014 Keynote Speaker, as well as other leaders in the field who attended and spoke at the meeting. SVIN's commitment to enhance the educational content of the meeting was highlighted by a pre-conference vertebral augmentation course, an acute stroke simulator and the hands-on training opportunities, which were graciously provided by this year's sponsors, for SVIN members to learn and practice new techniques, train with the latest devices and see the advances offered by leading industries in the field. The Abstract Selection Workgroup, chaired by Alicia Castonguay, PhD, met the challenge of choosing the best scientific abstracts from the 100+ excellent submissions. The best of SVIN science was presented in two platform presentation sessions and a poster reception led by professors. It was an exciting meeting with over 250 attendees to these year's SVIN Annual Meeting.

2014 SVIN BOARD ROTATIONS

SVIN would like to thank the following past Board Members for their contributions to the Society.

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The SVIN would like to extend our deepest gratitude for the contributions of our Top Supporter and Exhibitors for helping to make our 2014 Annual Meeting a great success! Their support remains essential to our efforts as a society and interventional neurology as a field.

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Neurointerventional Pioneering Award

Phillip Purdy, MD

For recognition of his outstanding contributions to training and mentoring of Interventional Neurologists.

Neurologist Pioneering Award

Mark Alberts, MD

For recognition of his outstanding contributions to the field of Interventional Neurology.

Innovation Award

Osama Zaidat, MD

For recognition of his innovation in the field of Interventional Neurology.

Distinguished Service Award

Dileep Yavagal, MD

For recognition of his outstanding contributions to the field of Interventional Neurology.

Young Investigator Award

Daniel Korya, MD

(Presented by Siddhart Mehta, MD) for the platform: *Redefining the Gold Standard: Transcranial Doppler Detects More Intra and Extra-Cardiac Right-to-Left Shunts than Trans-Esophageal Echocardiogram*

Best Abstract Award

Yahia Lodi, MD

For the platform presentation: *Primary Thrombectomy within 3 hours of Onset in Acute Ischemic Stroke from Occlusion of Middle Cerebral Artery - A Pilot Study*

Congratulations to the SVIN 2014 Travel Grant Awardees

Mark Alberts, MD, Key Note Speaker

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Tudor Jovin, MD presenting Dileep Yavagal, MD the 2014 Distinguished Service Award.

Raul Nogueira, MD and Robin Novakovic presenting the Fellow Travel Grant Awards.

INTERVENTIONAL STROKE TRIALS

Interventional Stroke Trials in North America

Diogo C. Haussen, MD
Endovascular Surgical Neuroradiologist - Marcus Stroke and Neuroscience Center

In May 1780, a mysterious phenomenon affected New England skies, when the day mysteriously became dark. The darkness was so intense that reading was impossible, requiring candles to be lit during daytime. The abnormality only cleared the following night, and became known as the New England's Dark Day.

In March 2013, three pivotal trials evaluating the interventional management of acute ischemic stroke (AIS) were simultaneously published in the New England Journal of Medicine: Synthesis Expansion, IMS III, and MR RESCUE.[1-3] They failed to demonstrate benefit of endovascular intervention for AIS. The bright hope for an effective approach to intracerebral large vessel occlusion (a disease with high morbidity and fatality rates) attenuated. However, these trials accrued critical knowledge and taught us important lessons.[4-6] After MR– CLEAN, attention has now turned to the ongoing efforts in clarifying the potential benefit of intra-arterial therapy. Currently, several exciting prospective trials are in the final stages of investigating the role of intra-arterial therapy (IAT) for AIS in North America.

The Solitaire™ FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) Clinical Trial was designed considering the substantial clinical advantage of the Solitaire stent-retriever compared to older mechanical thrombectomy technology.[7] SWIFT PRIME is a multi-center, prospective, randomized trial comparing combined IV t-PA and Solitaire FR within 6 hours of AIS onset vs. IV t-PA alone in patients with large vessel occlusion (MCA M1 or carotid terminus confirmed by CTA or MRA). It includes patients between 18-85 years-old with NIH Stroke Scale (NIHSS) ≥8 and <30 at baseline. The trial originally intended to utilize advanced imaging with the RAPID software, which had shown promise in patient selection for interventional stroke cases based on a favorable MRI penumbral pattern.[8] In order to accelerate enrollment, an amendment allowed inclusion of patient with NCCT/CTA or non-contrasted MRI/MRA instead of RAPID (ASPECTS score ≥6). Groin puncture had to be initiated within 90 minutes from imaging. SWIFT PRIME was designed to include 833 individuals by 2018. Enrollment was held after the announcement of MR–CLEAN results. Last month, The SWIFT Prime steering committee voted unanimously to accept the DSMB's recommendations to continue enrollment hold and await 90– day outcome data of all the 196 enrolled patients. Patients have been enrolled in 69 participating sites (40 within US).[9]

The new generation Penumbra thromboaspiration system is represented by the 5 MAX ACE, an easily navigable catheter that generates larger aspiration flow rate, that has been demonstrated in observational studies to lead to very high reperfusion rates.[10] The 3D separator is a stent-like 3D intended to be used as a component of the Penumbra system.[11] The **A Randomized, Concurrent Controlled Trial to Assess the Safety and Effectiveness of the Separator 3D as a Component of the Penumbra System in the Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke (3D SEPARATOR)** is a multicenter trial randomizing anterior circulation AIS patients with symptom onset <8 hours to either the Penumbra thromboaspiration system with or without the use of the Separator 3D. The study includes 18-85 year-old patients with large vessel occlusion that are either ineligible or refractory (persistent occlusion after IV tPA) to IV tPA if presenting within 3 hours and with NIHSS ≥8. There is no advanced imaging requirement. NCCT must confirm lack of mass effect and infarcts <1/3 MCA territory. Enrollment started in 2012 and is expected to achieve a sample size of 230 patients by 2015. No updates regarding enrolment status have been released.

Stroke Trials CONTINUES on page 10

INTERVENTIONAL STROKE TRIALS

The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (The THERAPY Trial is a randomized, multicenter trial designed to assess the safety and effectiveness of the Penumbra thromboaspiration system as an adjunctive treatment to IV tPA in patients with anterior circulation large vessel AIS presenting within 8 hours. It compares IV-tPA vs. dual IV tPA plus Penumbra thromboaspiration system (with or without the utilization of the 3D Separator) in patients between 18-85 years-old with NIHSS >8 or aphasia at the time of neuroimaging. Groin puncture within 12 hours was required. Neuroimaging had to demonstrate large vessel proximal occlusion (distal ICA through MCA M1 bifurcation) and associated large penumbra as defined by physiologic imaging (according to standard of practice at the participating institution). Baseline NCCT with ASPECTS <7 were excluded. The estimated sample size was 750 patients. This trial was halted recently.

The **Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) Trial** is a randomized multicenter trial evaluating if endovascular treatment amongst radiographically selected (small core/proximal occlusion) AIS patients results in improved outcome compared to standard medical treatment. The study enrolled patients presenting within 12 hours of last seen normal with NIHSS >5 and with a confirmed symptomatic intracranial occlusion (Carotid T/L, M1 MCA, or ≥2 M2 MCAs). Patients with NCCT ASPECTS 0-5 were excluded, as well as patients with moderate/large core defined by pre-specified criteria. The groin puncture had to be done within 60 minutes of the end of imaging acquisition. The study was halted recently because of efficacy demonstrated according to the pre-planned interim analysis. Results are expected to be announced in February of 2015.

The **Computed Tomography Perfusion to Predict Response to Recanalization in Ischemic Stroke Project (CRISP)** is a single arm prospective cohort study that aims to demonstrate that the use of a fully automated CTP analysis program (RAPID) can accurately predict response to recanalization in anterior circulation AIS patients undergoing AIT. Individuals ≥18 years old and with NIHSS ≥5 in which IAT can be started within 90 minutes of completion of NCCT/CTA/CTP and within 18 hours of symptom onset were included. IV tPA use was allowed. The NCCT/CTA was used for clinical decision-making, however, the perfusion maps generated by RAPID were used for research purposes only. The planned sample size is 200 patients. The study started enrolling in 2011 and finished enrollment in the end of November..

Other interesting trials include the **Intra-arterial Magnesium Administration for Acute Stroke**, which is a single arm study that will evaluate the safety and feasibility of direct intra-arterial magnesium therapy through endovascular access in AIS patients, as a novel endovascular platform for direct delivery of neuroprotective agents to ischemic tissue. The **Trevo Retriever Registry** is a prospective, open-label, international registry that aims to evaluate the real-world clinical practice performance of the Trevo Retriever. The **Wake up Symptomatic Stroke in Acute Brain Ischemia (WASSABI)** is a randomized trial investigating the safety and effectiveness of the use of CT Perfusion as tool to select patients with unknown time of stroke onset (unknown but <24 hours from last known normal). It includes patients with NIHSS 8-22, NCCT ASPECTS ≥7, and with evidence of penumbra. It aims to enroll 90 patients by November 2014. The **DWI/PWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention (DAWN)** will

Stroke Trials CONTINUES on page 11

study the safety and efficacy of AIT in MR or CT perfusion-selected AIS patients due to a proximal anterior circulation large-vessel occlusion (ICA and/or MCA-M1) who present beyond 8 hours of last seen well (8-24 hours). This applies to both witnessed and un-witnessed (including "wake-up") events. Enrollment started in November with a planned sample size of 500 patients.

Underpowered samples, inclusion of mild stroke severity or distal occlusions, and lack of tissue imaging have been described as significant methodological concerns for future AIS interventional trials.[12] These limitations of prior trials have been addressed, and the new trials included a much larger proportion of "informative" patients.[12] The ongoing investigations will possibly indicate an ideal imaging selection method and, then, further therapy can be accommodated. A brighter day for patients with large vessel occlusion AIS is hopefully very close…

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THE EVOLVING TECHNOLOGY OF FLOW DIVERSION

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While the first pathophysiological correlation between subarachnoid hemorrhage and intracranial aneurysm rupture was appreciated in 1761 by Morgagni, surgical management was not successfully performed until 1937 by Dandy (1). Since then, neurovascular microsurgery has made tremendous strides with smaller craniotomy sites, novel skull-base approaches and complex anastomosis to preserve parent vessel patency. In parallel to these surgical advances in aneurysm management, has been an endovascular neurosurgical revolution. As early as 1931, Moniz was able to use catheter based angiography to visualize a cerebral aneurysm in a living patient. It has seen been increasingly recognized that angiography is essential for excellent visualization and detection of aneurysms.

In 1991, catheter based angiography evolved from a simple diagnostic tool to a therapeutic option. Guglielmi and colleagues demonstrated that placement of coils into an aneurysm would induce thrombosis and ultimately limit the risk of rupture and growth of the aneurysm. A randomized clinical trial comparing clipping and coiling for ruptured aneurysms revealed the superiority of coiling in a majority of patients (2). Since this landmark trial, the endovascular toolset has continued to evolve with the use of adjunctive balloons or stents to prevent coil herniation in the case of wide necked aneurysms. Additional techniques under investigation include the application of liquid embolics (e.g. Onyx HD500) or the investigational intra-saccular flow disrupters (e.g. WEB embolization device) (3).

The principle of isolating the aneurysm from parent artery flow has now been advanced a step further with the development of flow diversion devices (FDD). Endoluminal placement of an FDD in the parent artery and across the aneurismal neck serves to redirect flow away from the aneurysm and promote endothelial growth across the aneurysm neck. While reconstruction is immediate, the ultimate thrombosis of the aneurysm and complete repair of the neck defect may take months. Initial proof of concept was demonstrated with the sequential telescoping placement of several Neuroform stents across an aneurysm flow model with concomitant demonstration of decreased intra-aneurismal flow and shear wall stress (4).

Similar to an intracranial stent, an FDD is intended for placement in the parent artery with emphasis on optimizing porosity (the ratio of metal to surface area) and pore density (number of pores per unit surface area). Optimally, the device functions to occlude the aneurismal neck without occluding branch vessels.

The only low-porosity endoluminal device to achieve FDA approval for use is the Pipeline Embolization Device (PED; Covidien, Irvine, California). The PED is a self-expanding tubular construct, consisting of 48 braided cobalt-chromium and platinum-tungsten wires in a 3:1 ratio. The devices range in size (2.5-5 mm, 10-35 mm) and may expand upto 0.25 mm larger than the nominal diameter. Initial case series and eventually larger studies(5) (6) established the safety and efficacy for PED for the treatment of large aneurysms with specific FDA approval for large or giant wide-necked aneurysms of the internal carotid artery extending from the petrous to the superior hypophyseal segment with success rates of 73.6-93.3% and stroke rates of 5.6-6.5%. Given the need for dual anti-platelets, most early experience has focused on unruptured lesions, although there are now reports of utilization for ruptured lesions. Additional off label applications of the technology have been described for fusiform aneurysms, posterior circulation lesions, blister

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aneurysms and distal anterior circulation aneurysms (7).

The SILK flow-diverting stent (SFD; Balt Extrusion, Montmorency, France) is also a self-expanding device with 48 braided Nitinol strands available in several sizes (2-5 mm, 15-40 mm), currently with clinical approval in Europe but not the US. In contrast to PED, SFD offers the advantage of being resheathable even after 90% of the device has been deployed. Clinical experience in Europe has demonstrated this device to have comparable rates of aneurysm occlusion in relation to PED, although there may be higher rates of complications. At present, there is no head to head comparison of the two devices although a multi-center study(8) of involving 273 patients undergoing either device supports a cumulative risk profile to be reasonable in the anterior circulation (2.3% morbidity, 3.5% mortality). Notably, the posterior circulation lesions continue to be a high risk location for FDD usage (5.4% morbidity, 19% mortality).

To achieve good endoluminal reconstruction and vessel wall apposition, operators have erred on the side of oversizing the construct relative to the parent vessel wall. The optimal construct may be difficult to find, as the parent vessel distal and proximal landing zones may be variable in diameter. Oversizing becomes unavoidable with several unanticipated consequences with both PED and SILK usage. In particular the PED device consists of curved rhomboid cells which will distort in the constrained small vessel with resultant decreased metal coverage. For example while the metal coverage is typically 35%, it can be as low as 18% with an oversized device. To avoid such scenarios, some authors have recommended using multiple PEDs of variable diameter in a telescoping configuration to maintain uniform porosity (9). The use of overlapping devices has to be weighed against the risk of occlusion branch vessel occlusion and the increased procedural complexity of deploying multiple FDDs.

The Surpass flow diverter (Surpass; Stryker Neurovascular, Fremont, CA, USA) is a newer endoluminal construct with the advantage of uniform porosity. The device consists of 48-96 cobalt chromium braided wires and is available in several sizes (2-5 mm x 12-50 mm). Maintaining consistent pore density across the parent vessel and aneurysm neck has the potential of limiting the number of devices necessary to achieve aneurysm occlusion. Indeed, a preliminary study in 37 patients with unruptured intracranial aneurysms treated with the Surpass device revealed that all but 1 patient required more than one device (10). In contrast, the average number of devices required in PUFs was 3.1 devices. Of the 49 total aneurysms, all 35 non-bifurcation aneurysm necks were completely covered with 94% occlusion rate at 6 month follow up of the 31 studied cases. In contrast, bifurcation aneurysms had low rates of neck coverage and occlusion (50% at 6 month followup). The initial results with Surpass for non-bifurcating aneurysms are encouraging and a larger safety and efficacy trial will determine whether these outcomes are generalizable.

The flow redirection endoluminal device system (FRED; MicroVention, Tustin, California, USA) is also a next generation device with a closed cell paired stent design, consisting of 48 braided Nitinol inner strands and 16 outer struts. The outer stent serves as scaffold for the inner stent and is intended to decrease friction during delivery as only 16 wires will be opposed to the microcatheter wall. Re-sheathing is possible even after 50% of partial deployment and sizes include 2.5-5.5 mm diameter and 7-50 mm length. Both the Surpass and FRED include interwoven helical markers for increased visibility. Several small series have reported on the safety and efficacy of the FRED device. The largest series to date consists of 33 patients with 37 aneurysms (11). Only

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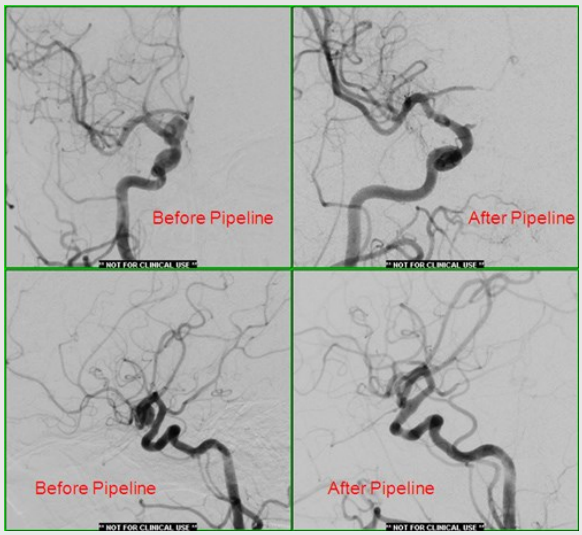
THE EVOLVING TECHNOLOGY OF FLOW DIVERSION

one device was required in all cases. Two patients suffered a TIA, but there were no cases of morbidity or mortality at 12 months follow up with occlusion rates varying from 32% at 0-1 months up to 100% at 7-12 months. A larger trial of safety and efficacy is ongoing.

At present, there is no additional published data available on the p64 Flow Modulation Device (Phenox) but the ability of this device to be fully deployed, recovered and redeployed marks a significant improvement in device safety. The first generation FDDs have dramatically revolutionized the management of intracranial aneurysms, yet the initial successes have highlighted challenges such as delayed hemorrhages and stent thrombosis. Additionally, safety profile can be highly dependent on operator experience. Nonetheless, flow diversion has become an integral part of the therapeutic armamentarium and is becoming the treatment of choice for an increasing number of on - and off-label indications with potential for shorter procedure times and possibly reduced costs. Modifications to the approach with newer devices may help improve the safety and efficacy of this exciting technology.



Current ongoing clinical trials of flow diverter devices:

Trials comparing coiling to flow diversion
A Randomized Trial Comparing Flow Diversion and Best-standard Treatment - the FIAT Trial [NCT01349582]
LARGE Aneurysm Randomized Trial: Flow Diversion Versus Traditional Endovascular Coiling Therapy [NCT01762137]

PIPELINE
Flow Diverter Stent for Endovascular Treatment of Unruptured Saccular Wide-necked Intracranial Aneurysms (EVIDENCE) [NCT01811134]
DIVERT: Diversion of Flow in Intracranial VErtebral and Blood Blister-like Ruptured Aneurysms

Trial: A Randomized Trial Comparing Pipeline Flow Diversion and Best-Standard-Treatment [NCT01976026]

SILK
Multicenter Randomized Trial on Selective Endovascular Aneurysm Occlusion With Coils Versus Parent Vessel Reconstruction Using the SILK Flow Diverter (MARCO POLO Post-Market Clinical Investigation) [NCT01084681]

SURPASS
Safety and Effectiveness of an Intracranial Aneurysm Embolization System for Treating Large or Giant Wide Neck Aneurysms (SCENT) [NCT01716117]

FRED
Pivotal Study of the FRED Stent System in the Treatment of Intracranial Aneurysms [NCT01801007]

The Evolving Technology of Flow Diversion CONTINUES on page 15

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PIPELINE AND ANTIPLATELETS

Evolution in Approach to Dual Anitplatelet Therapy for Endovascular Brain Aneurysm Treatment

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Due to the advent of new endovascular devices requiring to be implanted in the parent artery's lumen for the treatment of brain aneurysms, neurointerventionalists are utilizing increasingly-potent antiplatelet to prevent device thrombosis as it endothelializes. However, with the use of these increasingly-potent drugs, hemorrhagic complications are also being encountered, with parenchymal intracerebral hemorrhage being the most potentially devastating.

While the body of literature specific to neurointerventional procedures has increased in recent years, up to now neurointerventionalists have derived guidance primarily from the interventional cardiology literature. Although these 2 organ systems and clinical scenarios bear some similarities, there are some key differences: the size of the coronary vessels is smaller than the proximal intracranial circulation and the margin of error tolerated by the “downstream organ” is much narrower in the brain than the heart. Hence, while interventional cardiologists are chiefly concerned with reducing thromboembolic complications, neurointerventionalists must manage the risk of thromboembolic as well as hemorrhagic complications.
Clopidogrel, prasugrel & ticagrelor exert their antiplatelet effect by inhibiting the p2y12 receptor on the platelet's surface, which is responsible for platelet activation and aggregation. Clopidogrel & prasugrel cause irreversible inhibition of this receptor, while ticagrelor causes reversible inhibition of the receptor. Clopidogrel is, by far, the p2y12 receptor antagonist most commonly used by neurointerventionalists for neurovascular procedures. However, due to its 2-step hepatic metabolism, there is significant variability in patient response to clopidogrel. Prasugrel undergoes a 1-step hepatic metabolism, thus leading to less patient variability, however, its antiplatelet effect is more potent than clopidogrel. While ticagrelor does not undergo hepatic metabolism and has the potential advantage of its reversibility, this drug is more potent than both clopidogrel & prasugrel and its reversible nature may preclude dose adjustments.

There is considerable debate among neurointerventionalists regarding the validity and clinical utility of p2y12 receptor inhibition testing to assess a patient's response to the p2y12 receptor antagonist administered prior to neurointerventional procedures, with the field being split between "testers" and "non-testers." In general, "non-testers" appear to be more prone to encountering acute device thrombosis requiring emergent treatment with glycoprotein 2b/3a inhibitors, while "testers" may be more prone to major hemorrhagic complications such as ipsilateral parenchymal hemorrhages. Although several assays are commercially available to measure the degree of platelet inhibition, the most commonly-used assay among "neurointerventional testers" is the VerifyNow system (Accumetrics, San Diego, CA). VerifyNow measures the degree of p2y12 receptor inhibition after stimulation with ADP, a p2y12 receptor agonist. Results are reported in "p2y12 reaction units" (PRU), with a higher PRU corresponding to a higher degree of residual platelet reactivity and increased risk of thrombosis, and a lower PRU signaling a lower degree of residual platelet reactivity and increased risk of bleeding. Recently, after the ADAPT-DES study in Europe, an optimal PRU range of 95-207 PRU has been proposed in the interventional cardiology literature. However, to date, no guidelines exist regarding what constitutes an optimal PRU range prior to neurointerventional procedures.

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PIPELINE AND ANTIPLATELETS

Our neurointerventional group at Abbott Northwestern Hospital in Minneapolis was among the "early adopters" of flow diversion technology for treatment of brain aneurysms in the USA. Almost coincidentally, the VerifyNow assay became available in our hospital's laboratory the day before our first Pipeline procedure was performed.

Initially, our approach to PRU testing for Pipeline procedures consisted of initiating clopidogrel administration 7 days before the procedure, testing immediately before the procedure & adjusting the dose "on the fly." After our first 5 cases, we experienced 1 disabling thromboembolic complication in a clopidogrel hypo-responder (PRU 292) & 1 transiently-symptomatic but non-disabling ipsilateral parenchymal hemorrhage in a patient who experienced a delayed hyper-response to the standard 75mg daily clopidogrel dose (PRU 2 on POD 8). Both of these patients had experienced technically-difficult pipeline deployments with prolonged procedure times.

For our subsequent 40 pipeline procedures, we initiated clopidogrel administration 10 days before the procedure, performed our initial testing 1 day before the procedure, and used a “cardiology recommended” 60mg loading dose of prasugrel followed by a 10mg daily prasugrel dose for clopidogrel hypo-responders, using a PRU>200 cut-off. In this time period we did not experience any major thromboembolic complications. However, we experienced 3 major hemorrhagic complications: 2 disabling perioperative ipsilateral basal ganglia parenchymal hemorrhages in patients with a history of hypertension who were on prasugrel (PRUs 0 & 189), and 1 fatal contralateral parenchymal hemorrhage on POD 50 in a patient with autopsy-proven amyloid angiopathy (PRU 58). This experience prompted us to stop using prasugrel for clopidogrel hypo-responders & to increase the PRU cut-off for making a dose adjustment to >240. In addition, we began to realize that p2y12 receptor over-inhibition placed patients at risk of hemorrhagic complications due to any cause, not just those directly related to the Pipeline procedure. For our subsequent 3 pipeline procedures, we returned to using double-dose clopidogrel for hypo-responders and began to reschedule procedures when the initial PRU was markedly-elevated (>250) or markedly-decreased (<40). Our 48th Pipeline procedure was performed in a patient with a recurrent ophthalmic aneurysm. The initial PRU was 246 & the clopidogrel dose was doubled 3 days prior to the procedure, however, per protocol, the procedure was not rescheduled & the PRU was not rechecked until 7 days post-procedure. The patient underwent uncomplicated deployment of a single PED across the aneurysm neck, with a procedure time of 30 minutes. On POD 4, the patient was found unresponsive at home & a fatal ipsilateral intraparenchymal hemorrhage was diagnosed. Her PRU at the time of the hemorrhage was 10.

After these 48 initial Pipeline cases, we conducted a thorough analysis of our post-procedural Pipeline complications and determined that the last-recorded PRU value was the strongest predictor of a post-operative hemorrhagic or thromboembolic complication. Namely, a last recorded PRU>240 was associated with a 50% risk of a major thromboembolic complication, while a last-recorded PRU<60 was associated with a 33% risk of a major hemorrhagic complication. Conversely, when the last-recorded PRU value was in the 60-240 range, the risk of a major thromboembolic or hemorrhagic complication was 2.7%. Additional variables that were associated with perioperative complications were a technically-difficult pipeline deployment and a history of hypertension.

Following our initial experience, we decided that elective Pipeline deployment would not be undertaken unless the PRU value was in the target 60-240 PRU range in pre-procedure testing performed no earlier than 1 day prior to the procedure, blood pressure was to be tightly controlled in the perioperative period, and urgent/emergent

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JOURNAL CORE REVIEW : THE "FAST– MAG" STUDY

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The results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) Phase III were presented in the International Stroke Conference in San Diego, CA, by principle co-investigator, Dr. Jeffrey Saver.

Considering the importance of time in acute stroke care, it is intriguing to consider treatment options in the pre-hospital setting following initial paramedic evaluation as a first medical contact in the field. With revascularization strategies, requiring more advanced clinical and imaging evaluation in the hospital, neuroprotective strategies appear to be the next target in this setting. Delayed delivery has been one of the presumed reasons for prior neuroprotective trials. In the 6 major neuroprotective trials, including 5345 patients, 92.3% of the patients were treated beyond 3 hours of symptom onset; while only 10 patients(0.2%) were treated within 60 minutes.

Magnesium, as a readily available, inexpensive agent, has been extensively studied as a promising neuroprotective agent, with effects on NMDA channel blockade, calcium channel blockade, increasing regional blood flow, enhancing ATP recovery. Its cerebral protection properties has been shown in previous randomized trials

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Pipeline deployment was to be avoided whenever possible. In addition, we began to perform routine post-operative MRIs in all patients on POD 1 to determine if the etiology of post-procedural intracerebral hemorrhages was hemorrhagic conversion of post-procedural DWI abnormalities in the setting of p2y12 receptor over-inhibition. Furthermore, we perform routine follow-up PRU testing 1 -2 weeks post-procedure to determine if the patient has developed a delayed conversion to clopidogrel hyper-response.

Given the intrinsic variability in initial clopidogrel response and the practical need to minimize the rate of rescheduled Pipeline procedures, we currently initiate clopidogrel administration 17 days prior to the planned procedure date, perform an initial PRU test after the 10^{th} 75mg clopidogrel dose, perform dose adjustments - if needed - according to the initial PRU value, and allow 7 days for the dose adjustment to take effect. We then perform a second PRU test the day before the procedure to ensure that the target 60-240 PRU range has been reached prior to Pipeline deployment. Following this protocol, we have managed to reach the target PRU range in pre-procedure - testing in 92.5% of patients and we have not encountered major hemorrhagic or thromboembolic complications following elective Pipeline deployment to date. Overall, in our Pipeline cohort, the major hemorrhagic complication rate when the last-recorded PRU value is <60 stands at 40%, while the major thromboembolic complication rate stands at 50% when the last-recorded PRU value is >240. Conversely, for patients with a last-recorded PRU value within the target 60-240 range, the major thromboembolic or hemorrhagic complication rate currently stands at 1.8%.

In our opinion, careful, active management of dual antiplatelet therapy is crucial to minimize the risk of major thromboembolic and hemorrhagic complications after brain aneurysm treatment with flow diversion or stent assistance.

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IS CILOSTAZOL READY FOR PRIME-TIME?

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Cilostazol is a phosphodiesterase inhibitor that is currently used in reducing the symptoms of intermittent claudication in patients with peripheral arterial disease. It is an anti-platelet, an anti-thrombotic and a vasodilating agent. In addition, it inhibits vascular smooth muscle proliferation, increases HDL cholesterol and reduces serum triglycerides. It also prevents secondary ischemic events in patients with stroke and heart disease.

There have been recent clinical trials showing the efficacy of cilostazol in preventing ischemic

FIELD AMINISTRATION OF STROKE THERAPY-MAGBESIUM, *CONTINUED from page 18*

(ACTOMgSO4 in preterm birth, Brain-CPR in cardiac arrest and IMAGES in stroke) along with favorable safety record in treating pre-eclampsia/ eclampsia and torsades.

The study had two main aims: 1. Specific aim to demonstrate efficacy and safety of magnesium administered by paramedics in the field and 2.Systems aim to demonstrate the feasibility of field enrollment and treatment of acute stroke patients for pivotal phase 3 stroke trials. The study was a placebo-controlled, double blind randomized multicenter, single region trial in Los Angeles and Orange counties. Inclusion criteria included patients suspected of having stroke using Los Angeles Pre-hospital Stroke Scale with ages between 40 to 95 years old, with last known well time within 2 hours. The dose of the administered magnesium was 4-gram load once followed by 16 grams infusion in 24 hours versus placebo. Primary endpoint was the disability at 90 days using modified Rankin Scale distribution.

A total of 1700 patients were included in two magnesium (857 patients) and placebo (843 patients) groups from January 2005 to March 2013. Patients had similar baseline characteristics including age, race and risk factors. Of the included patients in both magnesium and placebo groups, around 73% had ischemic stroke, 23% had intracranial hemorrhage and 3.9% had stroke mimics. Both groups had mean NIHSS of around 11.3, with mean onset to treatment time of around 45 minutes. 74% of patients were treated within 60 minutes, 25% within the second hour, which was well distributed in both magnesium and placebo groups. Intravenous tissue plasminogen activator (IV tPA) was given in 24.9% of all the placebo and 28.2% of magnesium group patients included in each group. Of these patients, in the subset with cerebral ischemia diagnosis, 33.4 % of the placeboand 38.1% of the magnesium group patients received IV tPA. The rate of adverse effects was similar in the two groups. There was no difference in the distribution of disability measured by modified Rankin Scale (p=0.28). Secondary endpoints including mRS 0-1, mRS 0-2, Barthel scores, NIHSS and Stroke impact scale at 90 days were similar in two groups.

Potential reasons for lack of benefit in the treated group can be attributed to potential slow passage of magnesium across the blood brain barrier, insufficiency of the single agent to suppress molecular cascade.

The FAST MAG trial achieved its systems aim by proving feasibility of field enrollment as the first

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IS CILOSTAZOL READY FOR PRIME-TIME?

pre-hospital phase III trial in the stroke field; first randomized controlled pre-hospital trial; first acute neuroprotective phase III trial; first phase III neuroprotective trial before the recanalization; and the first stroke trial in the first golden hour. stroke in comparison with other more commonly used antiplatelet medications like aspirin and clopidogrel. In Japan, cilostazol is used for secondary stroke prevention. Cilostazol Stroke Prevention Study (CSPS) and Cilostazol Stroke Prevention Study-2 (CSPS-2) are two double blinded randomized studies that were conducted in Japan, both demonstrating that cilostazol is safe and effective in stroke prevention. CSPS-2 showed that cilostazol might be superior to aspirin in stroke prevention.

These studies, an increased number of aspirin allergies, and the increase in Plavix resistance appreciated in our practice led us to start a phase I trial in carotid stenting. Our objective was to evaluate the safety and clinical efficacy of Cilostazol and Aspirin therapy following internal carotid angioplasty and stent placement prior to and one month post-procedure. It was a non-randomized single center prospective study. All patients received Aspirin (325 mg/day) and Cilostazol (200 mg/day) for at least 3 days before intra- or extracranial stent placement. The two anti-platelet agents were continued for one month after the procedure and then patients were continued on aspirin daily. The primary efficacy end point was the 30-day composite occurrence of death, cerebral infarction, transient ischemic attack, and unplanned endovascular revascularization procedure. The primary safety end point was bleeding (extracranial or intracranial).

The results were presented at the International Stroke Conference in Honolulu, HI February 2013. Twelve patients (mean age, 66±12 years; 10 men) were enrolled using the study protocol and underwent internal carotid angioplasty and stent placement. One patient discontinued cilostazol after the first dose, prior to stent placement, secondary to non-specific dizziness. Another patient did not follow study protocol and continued anticoagulation dose enoxoparin as well as aspirin and cilostazol resulting in symptomatic intracerebral hemorrhage 15 hours following successful stent placement. A third patient was successfully enrolled in the study but the cilostazol was discontinued by her cardiologist 5 days after the successful and uncomplicated stent placement. None of the patients that successfully completed the study, and followed protocol experienced any complications at one month and three month follow up. We concluded that the use of cilostazol and Aspirin for carotid angioplasty and stent placement appears to be safe but protocol compliance needs to be emphasized.

A few months later a larger study showed the safety of cilostazol and aspirin in extracranial carotid stenting with significant decreased incidence of composite end point (death, stroke, hemorrhage and MI) OR 0.39 p=0.004) compared to aspirin and plavix– (Yamagami et al. IDEALCAST – Scientific Sessions 2013, Dallas, TX).

In the meantime we had received IRB approval for a phase II randomized trial to evaluate the safety, efficacy and clinical outcomes of treatment with cilostazol and aspirin in patients who have had extracranial carotid stent placement for the duration of one month. All patients will receive aspirin (325 mg/day) and be randomized to cilostazol (200 mg/day) or clopidogrel (75mg/day) for at least 3 days before extracranial arterial stenting.

The primary efficacy end point will be the 30-day composite occurrence of death, stroke, transient ischemic attack, and unplanned or urgent surgical intervention, thrombolysis, or subsequent percutaneous revascularization. The primary safety end

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JOURNAL CORE REVIEW:ARUBA

Medical management with or without interventional therapy for un-ruptured brain ateriovenous malformations (ARUBA): A multicenter, non-blinded, randomized trial.

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Summary:

Aruba is a randomized un-blinded trial of un-ruptured brain arteriovenous malformation (AVM) that compared intervention, by mean of neurosurgery, embolization, and/or stereotactic radiotherapy, vs. medical management alone. Results were published in February 2014 in the LANCET The trial had enrolled 223 patients of a planned 400 patients (114 in the interventional group and 109 in the conservative arm). Majority of patients had Spetzler-Martin grades of 1-3. The trial was stopped early, on April 15, 2013, when a data and safety monitoring board recommended halting randomization due to superiority of the medical management group. The average follow-

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point is bleeding (extracranial or intracranial). Bleeding complications are classified as major (hemoglobin decrease >5 g/dl), minor (hemoglobin decrease 3–5 g/dl), or insignificant. The secondary outcome will be the restenosis rate on carotid ultrasound at six months.

We are currently enrolling at two sites (Minneapolis, MN and Harlingen, TX) and our goal is to find an alternative, possibly safer (decreased hemorrhages and decreased re-stenosis rates), therapy to current dual antiplatelet treatment in patients undergoing extracranial carotid stent placement.

Zaid Al Qudah MD, **Ameer E. Hassan DO,** Adnan I Qureshi MD.*Drug Evaluation of Cilostazol in Patients with Ischemic Stroke.* Expert Opinion Pharmacotherapy. 2011 Jun;12(8):1305–1315.
Shinohara Y, Katayama Y, Uchiyama S, Yamaguchi T, Handa S, Matsuoka K, Ohashi Y, Tanahashi N, Yamamoto H, Genka C, Kitagawa Y, Kusuoka H, Nishimaru K, Tsushima M, Koretsune Y, Sawada T, Hamada C; CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. Lancet Neurology. 2010 Oct;9 (10):959-68. doi: 10.1016/S1474-4422(10)70198-8. Epub 2010 Sep 15

Ameer E. Hassan, DO, Haralabos Zacharatos, DO, Mikayel Grigoryan, MD, Saqib A. Chaudhry, MD, Wondwossen G. Tekle, MD, Amir Khan, MD, Farhan Siddiq, MD, Gustavo J. Rodriguez, MD, Ramachandra Tummala, MD, Robert A. Taylor, MD, Bharathi Jagadeesan, MD, M.Fareed K. Suri, MD, Adnan I. Qureshi, MD. Open-label Phase I Clinical Study to Assess the Safety and Efficacy of Cilostazol in Patients Undergoing Carotid Artery Angioplasty and Stent Placement. Abstract presentation at the 2013 International Stroke Conference, Honolulu, HI.

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up was 33.3 months. The primary outcome (death or stroke) had occurred in 11 patients in the conservative group (10.1%) vs. 35 patients (30.7%) in the interventional group. The intention-to- treat analysis showed a significant reduction of the primary outcome in the conservative group, with a hazard ratio of 0.27 (95% confidence interval [CI], 0·14—0·54). The interventional group also had higher modified Rankin scale scores.

Commentary: Is Less Really More?

The core conclusion of the ARUBA trial is that, in the short term, patients with un-ruptured AVMs will have better outcome with conservative management compared to interventional therapy. Multiple concerns were raised about the ARUBA trial though with the lack of long-term follow-up being the most important one. Obviously, interventional therapy carries an increased early risk compared to conservative management. With only short-term follow-up, an average of 3 years in the ARUBA, an inequitable bias against interventional therapy is inevitable and a longer follow-up time might allow for the longer-term benefits of the interventional therapy to become evident. Thus, a long-term analysis model was established by the ARUBA investigators and showed that the outcome curves of the two groups will cross at 20 years. This model was built, however, on the assumption that the interventional group is not having any further events and that the 3-year follow-up represent a true and accurate natural history of the medical group. Both assumptions might be false and not representing the true risk of both arms. Other concerns about the ARUBA trial include selections bias, as only 40% of eligible patients were randomized, and lacking of central lab algorithm in treating these vascular lesions. The ARUBA trial answered very important questions regarding best management of un-ruptured AVMs, but longer-term follow-up is still warranted.

The SVIN Executive Office would like to wish you a very happy holiday season and best wishes for the New Year!

We look forward to new opportunities for the Society in 2015 and thank you for your continued support of SVIN.

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