SWIFT was a 21-site, blinded endpoint observer, international, active comparator, noninferiority trial that tested the Solitaire™ FR as the initial device against the Merci Retriever® as the initial device. The purpose of the study was to demonstrate substantial equivalence of the Solitaire FR revascularization device with the legally marketed Merci retrieval system.

The primary efficacy endpoint was successful recanalization—TIMI 2 or 3 flow in all treatable vessels—with no symptomatic intracranial hemorrhage, assessed at completion of the first device strategy prior to rescue therapy. Secondary efficacy endpoints were time to recanalization, good neurological outcome at 90 days, and global disability at 90 days. Key inclusion criteria included ability to be treated within 8 hours of onset, National Institute of Health Stroke Scale (NIHSS) 8 to 29, and proximal intracranial occlusion.

Enrollment totaled 144 patients at 18 sites; 113 were randomized 1:1 to receive treatment with the Solitaire FR (n=58) or Merci device (n=55). All baseline demographic features were similar, with no significant differences. Higher rates of atrial fibrillation (p=0.02) was the only significant difference in medical and neurological history (44.8% in the Solitaire group vs 67.3% in the Merci group).

Of the 58 patients who were randomized to Solitaire FR, 60.7% (34/56) achieved the primary trial endpoint versus 24.1% (13/54) with the Merci device (noninferiority p<0.0001; superiority p=0.0001). Rescue therapy was used in 20.7% (12/58) of Solitaire patients versus 43.6% (24/55) of Merci patients (noninferiority p<0.0001; superiority p=0.015).

Good neurological outcomes at 90 days (defined as modified Rankin Scale [mRS] score ≤2 or equal to the prestroke mRS if >2, or NIHSS score improvement ≥10) were achieved by 58.2% (32/55) of Solitaire patients versus 33.3% (16/48) of Merci patients (noninferiority p=0.0001; superiority p=0.017). Mortality at 90 days occurred in 17.2% (10/58) of the Solitaire patients versus 38.2% (21/55) of the Merci patients (noninferiority p=0.0001; superiority p=0.020).

sICH occurred in 1.7% (1/58) of the Solitaire FR patients versus 10.9% (6/55) of the Merci patients (noninferiority p<0.0001; superiority p=0.057). Total intracranial hemorrhage percentages were 17.2% in the Solitaire FR group versus 38.2% in the Merci group (noninferiority p=0.0001; superiority p=0.020). In the Solitaire group, 8.6% of patients suffered study device-related serious adverse events (SAEs) versus 16.4% in the Merci group (p=0.26). The percentages for all procedure-related SAEs were 13.8% in the former versus 16.4% in the latter (p=0.80).

The first patient was enrolled in February 2010. At the end of July 2011, the trial met the interim efficacy stopping rule and was halted by the Data Safety Monitoring Board, Steering Committee, and sponsor for overwhelming efficacy.

FIA II Seeks Genetic Underpinnings of Familial Intracranial Aneurysm

Written by Rita Buckley

Prior studies indicate that genetic factors are important in the formation and rupture of intracranial aneurysms (IAs) [Broderick JP et al. *BMC Med Genet* 2005]. Joseph P. Broderick, MD, University of Cincinnati, Cincinnati, Ohio, USA, presented initial results from the Familial Intracranial Aneurysm Study II [FIA II; NCT00071565].

Most deaths from subarachnoid hemorrhage (SAH) are due to rapid and massive brain injury from the initial bleeding; therefore, prevention of aneurysm formation is of paramount importance. Scientific evidence suggests that a genetic component plays an important role in the development of IAs, but the specific genes that are involved have not been identified.

The purposes of FIA II were to identify genes that may increase the risk of aneurysm development in the brain and to determine the effect of environmental factors, such as cigarette smoking and high blood pressure, on the expression of those genes.

According to Dr. Broderick, approaches to dissect the genetic contribution to IAs have had mixed results. Linkage has been largely unsuccessful and, to this point, has not identified genetic variants that are associated with a risk of IA. Genomewide association studies (GWAS) have been somewhat successful, identifying several replicated genes with modest effect size (OR approximately 1.2 to 1.3), but again have yet to identify specific variants within these genes that are causally related to IA.

Whole exome sequencing (WES) is a promising new approach that focuses on the coding region of the genome (the exome). This method is designed to find variants that affect protein structure or function, which are relatively common in Mendelian disorders. WES complements GWAS but is best suited to the identification of rare (r)

variants of moderate to large effect size, while GWAS finds common variants that are typically of smaller effect size.

The authors reviewed families with a dense history of IA and available DNA. Seven families that met their criteria (two or more affected pairs of siblings, three or more family members with IA, or individuals with a confirmed IA but without a family history) were identified. DNA from affected individuals was sent to the Center for Inherited Disease Research (CIDR) (ie, 32 exomes from 32 individuals who were sequenced).

Quality filtering produced 93,635 single-nucleotide variants (SNVs). Biologic filters, which retain only the variants that meet the biological hypothesis (ie, rare exonic and amino acid-altering alleles that segregate in Mendelian fashion may contribute to IA pathology), reduced that figure to 871 SNVs. Variants were kept if they were observed in at least three affected individuals in a single family if the SNVs were autosomal dominant or recessive. Of the 871 SNVs, 31 were in the gene otology pathways of interest, such as collagen.

Variants in two collagen genes were identified in at least three family members in one of these IA families (Figure 1). These variants are predicted to potentially cause abnormal function in these proteins. Collaborators from Poland have demonstrated that both of these genes are expressed differently in aneurysmal tissue as compared with vascular tissue of the middle meningeal arteries. Figure 2 shows the presence of these variants in affected family members, all of whom were also smokers—the most important environmental risk factor for IA. Further work will need to be done to see whether these gene variants are truly causal in the development of IA. Ultimately, the interplay of three factors—environment (smoking, hypertension), common variants of individual small effects (GWAS), and rare variants with medium to large effects (WES)—likely contributes to disease susceptibility.

Figure 1. Collagen Variants.

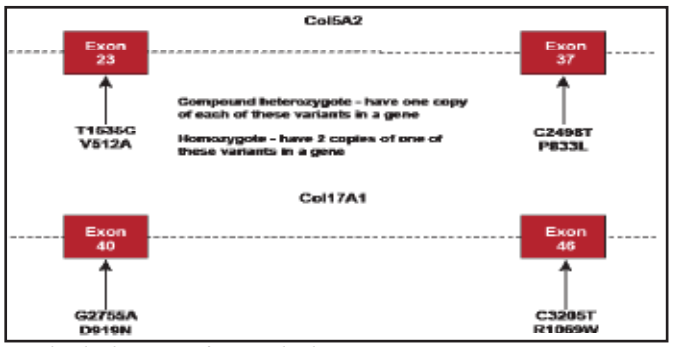

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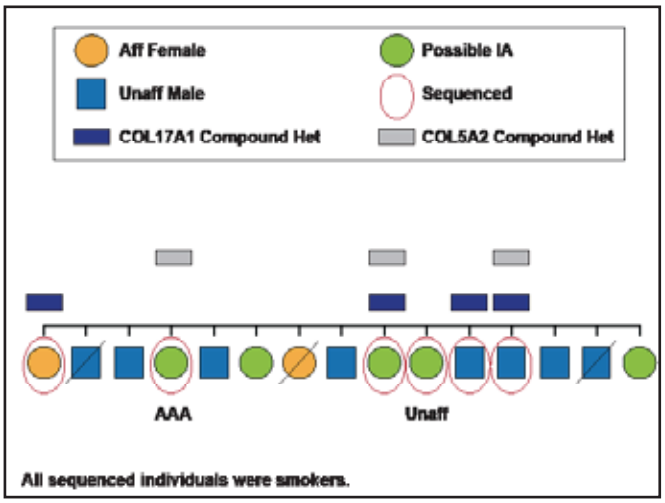
Figure 2. One Family and Collagen.



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The identification of susceptibility genes, along with a better understanding of environmental interactions, such as cigarette smoking, may prevent the development of IAs and IA ruptures in people who are at risk for this condition.

SPS3 Study Does Not Support the Use of Combination Therapy for Stroke Prevention

Written by Rita Buckley

Small subcortical strokes, also known as lacunar strokes, constitute more than 25% of brain infarcts and are the most common cause of vascular cognitive impairment. How to optimally prevent stroke recurrence and cognitive decline in patients with small subcortical stroke is unclear [Benevente OR et al. *Int J Stroke* 2011]. Oscar R. Benavente, MD, FRCP(C), University of British Columbia, Vancouver, British Columbia, Canada, presented results from The Secondary Prevention of Small Subcortical Strokes Study: The Antiplatelet Trial Results [SPS3; NCT00059306].

SPS3 was a randomized, double-blind, multicenter, investigator-initiated, international trial that was conducted at 81 clinical sites in eight countries. From March 2003 to April 2011, 3020 patients with symptomatic lacunar strokes in the prior 6 months verified by magnetic resonance imaging were randomized in a