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.

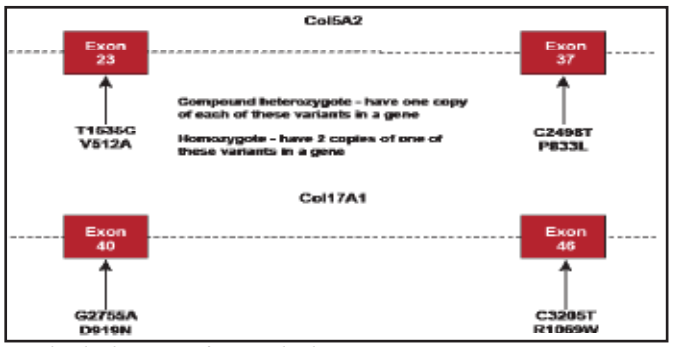

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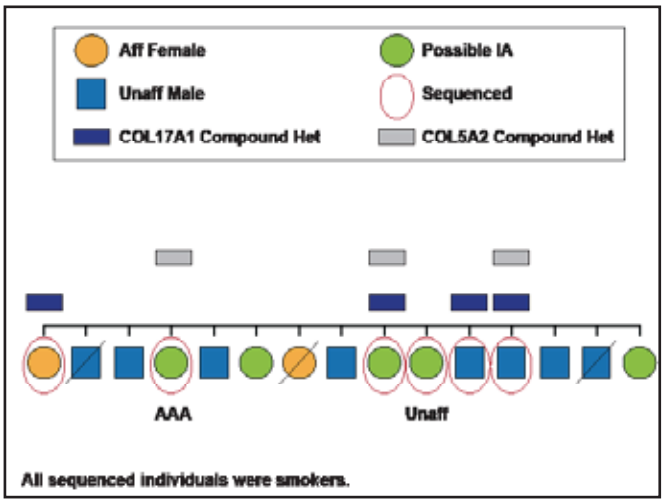
Figure 2. One Family and Collagen.



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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

2 x 2 factorial design to antiplatelet therapy—325 mg aspirin daily plus 75 mg clopidogrel daily versus 325 mg aspirin daily plus placebo—and to one of two levels of open-label blood pressure targets—intensive (130 mm Hg) versus usual (130 to 149 mm Hg). Exclusion criteria included cortical stroke, cardioembolic disease, or carotid stenosis.

SPS3 was a superiority trial that was powered to detect a clinically significant difference in outcomes. The primary outcome was time to recurrent stroke (ischemic or hemorrhagic), analyzed separately for each intervention. The secondary outcomes were rates of cognitive decline and major vascular events. Mean time from index event to randomization was 76 days. Mean follow-up was 3.5 years. Loss to follow-up was 2%. The primary and secondary outcomes were centrally, blindly adjudicated.

Baseline characteristics of patients were similar in both groups, with a mean Mini Mental State Exam score of 28± 2.3. In the aspirin group (n=1503), 66% had a Rankin score of 0 to 1; the figure in the aspirin+clopidogrel group (n=1517) was 67%. The race/ethnicity of participants was 52% white, 31% Hispanic, and 17% black. Baseline medical characteristics, clinical syndromes, and percentage from each region (North America, Latin America, and Spain) were all similar.

The probability of the primary event over time showed no difference between the two groups: aspirin=138 (2.7%/patient-year) compared with aspirin+clopidogrel (n=126; 2.5%/patient-year; HR, 0.92; 0.73 to 1.2; p=0.52). The incidence of ischemic stroke was also nonsignificant: aspirin group (n=125; 2.4%/patient-year) compared with aspirin+clopidogrel (n=105; 2.1%/patient-year; HR, 0.85; 0.66 to 1.1; p=0.21). Major vascular events (stroke, myocardial infarction, or vascular death) were also not significantly different.

Differences in all-cause mortality were significantly different: aspirin (n=77; 1.4%/patient-year) and aspirin +clopidogrel (n=113; 2.1%/patient-year; HR, 1.5; 1.1 to 2.0p=0.005; Figure 1). Differences in probable vascular events (p=0.012), all hemorrhages (p<0.001), and non-CNS hemorrhages were also significant (p<0.001; Table 1).

The antiplatelet intervention was stopped prematurely in July 2011 for reasons of safety and futility. The authors concluded that dual antiplatelet therapy was not more efficacious than aspirin alone. Major bleeds and total mortality were increased. The results do not support the use of combination therapy for stroke prevention in patients with lacunar strokes.

Figure 1. All-Cause Mortality.

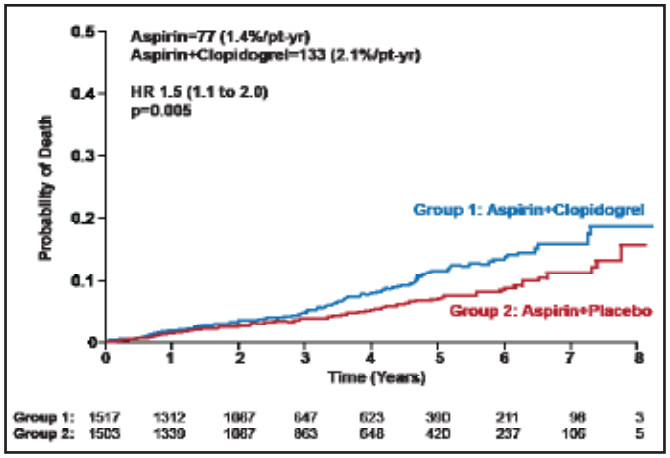

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Table 1. Major Hemorrhages.

	Aspirin		Aspirin+ Clopidogrel		HR (95% CI)	p value
	n	%/pt-yr	n	%/pt-yr		
All hemorrhages	56	1.10	105	2.10	2.0 (1.40-2.70)	<0.001
CNS hemorrhages	15	0.28	22	0.42	1.5 (0.79-2.90)	0.21
intercerebral*	7	0.13	13	0.25	1.9 (0.75-4.70)	0.18
Subdural†	6	0.11	6	0.11	1.0 (0.33-3.20)	0.95
Other‡	3	0.005	2	0.038	0.7 (0.12-4.20)	0.70
Non-CNS hemorrhages	42	0.79	87	1.70	2.2 (1.50-3.10)	<0.001

*Intraparenchymal, spinal; †Subdural, epidural; ‡Subarachnoid, other.

Novel Agent NA-1 Proves that Ischemic Neuroprotection is Possible in Older Patients

Written by Rita Buckley

The Evaluating Neuroprotection in Aneurysm Coiling Therapy trial [ENACT; NCT00728182] showed that the novel agent NA-1 may be a useful treatment for stroke and ruptured aneurysm patients. Michael D. Hill, MD, MSc, FRCPC, University of Calgary, Calgary, Alberta, Canada, reported outcomes from the study.

A randomized, multicenter, double-blind, placebo-controlled, single-dose Phase 2 trial, ENACT randomized 197 male and