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.

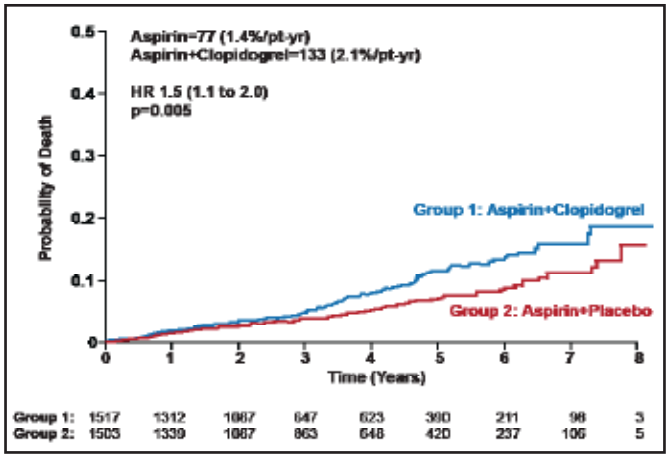

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Table 1. Major Hemorrhages.

	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

female patients who were undergoing endovascular repair of a brain aneurysm to receive 2.6 mg/kg of NA-1 (n=92), a peptide designed to reduce ischemic brain damage, or placebo (n=93) as a 10-minute intravenous infusion after completion of the endovascular procedure on Day 1.

The primary outcome measures were to determine the safety and tolerability of a single IV dose of NA-1 in patients who were undergoing endovascular repair of brain aneurysms and establish the efficacy of NA-1 in reducing the volume of embolic strokes on enrollment and Days 1, 2–4, and 30. Secondary outcome measures were to determine the efficacy of a single IV dose of NA-1 in reducing the number of embolic strokes, procedurally induced vascular cognitive impairment, and frequency of large strokes on enrollment and Days 1, 2–4, and 30.

Other than the number of past smokers (26.9% in controls versus 43.8% in the treatment group), baseline characteristics and treatment factors were similar between the two groups. Except for 2 adverse events of transient (15 minutes) mild hypotension, no serious adverse events were attributable to NA-1.

Compared with baseline, the number and volume reductions of diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) lesions in all subjects were significant (p=0.005 and p=0.026, respectively). In ruptured aneurysm patients, significant reductions in the number of DWI and FLAIR lesions were observed in the treatment and control groups (unadjusted p=0.027 and p=0.46, respectively); similarly, there were significant reductions in the volume of DWI and FLAIR lesions (unadjusted p=0.015 and p=0.023, respectively). In unruptured aneurysm subjects, there were significant reductions between the treatment and control groups in the number of DWI lesions (adjusted p=0.019).

In patients without large stroke, there were significant reductions in the number of DWI and FLAIR lesions (adjusted p=0.002 and p=0.012, respectively) as well as in volume (p=0.009 and p=0.014, respectively). Among proportions of patients with DWI lesions, binned at the 90th percentile, more NA-1 subjects had 0 or 1 lesions; fewer had >15 lesions (p=0.012). Among subjects with ruptured aneurysms, 68.4% of controls and 100% of the treatment group had an NIHSS of 0 to 1 (p=0.020); 73.7% of controls and 94.4% of the treatment group had a modified Rankin scale score of 0 to 2. The relative risk was 1.3 (95% CI, 0.95 to 1.7; p=0.180).

Overall, the trial showed that NA-1 was safe in patients with ruptured and unruptured aneurysms and reduced the number and volume of ischemic stroke lesions in a human model of iatrogenic embolic stroke. The study implies that neuroprotection is possible in older patients and that multiple endovascular procedures may be amenable to NA-1 treatment for stroke.

The authors concluded that testing of NA-1 in human community-acquired stroke is a priority and that it may be a useful treatment for ruptured aneurysm patients.