Lipid-Lowering Drugs Reversed Cognitive Decline

At 1 year, active therapy significantly improved patients' memory and speed of data processing.

BY BRUCE JANCIN
Denver Bureau

VIENNA — Potent cholesterol-lowering therapy appears to reverse neurocognitive decline in normolipidemic elderly patients with atrial fibrillation, Dr. Elke Wezenberg said at the annual congress of the European Society of Cardiology.

If this new finding from the small pilot SPACE (Silent Brain Infarction and Cognitive Decline Prevention in Atrial Fibrillation by Cholesterol Lowering in the Elderly) trial is confirmed in a planned larger, more definitive study, then the use of lipid-lowering medications would be warranted in all patients with atrial fibrillation (AF), regardless of their cholesterol level, added Dr. Wezenberg, a psychiatrist at Radboud University, Nijmegen (the Netherlands).

She attributed the positive cognitive effects of the SPACE regimen of 40 mg of atorvastatin/10 mg of ezetimibe daily to the drugs' anti-inflammatory action. Participants had relatively high baseline C-reactive protein (CRP) levels indicative of extensive systemic inflammation. Their CRP levels decreased significantly during 1 year of lipid lowering, and the decline correlated inversely with the observed improvement in cognitive function.

SPACE was a double-blind, placebo-controlled prospective study involving 31 patients, mean age 74, with an average 14-year history of AF. All were on warfarin and adequately anticoagulated, with an international normalized ratio of 2.0-3.0. At baseline and again after 1 year, participants were evaluated for depression using the Montgomery-Asberg Depression Rating Scale (MADRS), by MRI for white matter lesions, as well as by an extensive neuropsychologic test battery for memory, language, executive function, and speed of information processing.

At baseline, participants were free of clinically significant depressive symptoms, showed no indication of impairment on the Mini-Mental State Examination, and were asymptomatic in terms of activities of daily living. However, nearly all patients showed baseline mild neurocognitive impairment, with greater than expected difficulties on specific neurocognitive tests, especially those concerned with speed of information processing, memory, executive function, and psychomotor speed.

At 1 year of follow-up, the placebo group showed continued decline in these neurocognitive domains. In contrast, the AF patients on lipid-lowering therapy demonstrated significant improvement over baseline in speed of information processing, memory, and executive function as assessed by switching tests. The active treatment arm also showed a nonsignificant trend for a reduction in white matter lesions, believed to be of vascular origin.

An estimated 2.2 million Americans have AF, making it the most common cardiac arrhythmia by far. Its prevalence climbs with age, reaching roughly 8% in patients age 80 or older.

It is well established that AF is a risk factor for ischemic strokes, silent brain infarcts, and dementia, even when patients are adequately anticoagulated. The rationale for SPACE comes from prior studies showing that inflammatory markers are increased in patients who have AF, white matter lesions, and/or cognitive impairment—and lipid-lowering drugs are known to decrease inflammation.

The SPACE findings are at odds with the 5,804-patient randomized Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) study, in which 3 years of pravastatin didn't slow cognitive decline (Lancet 2002;360:1623-30).

In an interview, Dr. Wezenberg explained that in her view the main explanation for the disparate results is that PROSPER involved a heterogeneous population with a far lower average risk for stroke and microinfarcts than a population comprised purely of individuals with AF. Moreover, the degree of lipid-lowering achieved with 40 mg/day of pravastatin in PROSPER was considerably less than with the SPACE regimen.

And as the PROSPER investigators noted, pravastatin is a hydrophilic statin that doesn't efficiently cross the blood-brain barrier.

The SPACE study was funded by the departments of psychiatry and cardiology at Radboud University. ■

Small Decline in Each Group

Cognition *from page 1*

lective long-term decline after CABG that cannot be seen in other groups with significant coronary artery disease. We don't think late decline should be an issue in the choice of what procedure you're going to have done," said Dr. McKhann.

The researchers have been studying the issue of neurologic outcomes following coronary surgery since 1992.

"What we set up then was a prospective evaluation of all heart surgery patients within the intensive care unit," said Dr. McKhann.

Starting in 1997, the work that Dr. McKhann and his colleagues were doing with acute-care patients became a four-arm study involving those undergoing conventional CABG, those with off-pump CABG, cardiac controls who received stents, and heart-healthy controls lacking traditional risk factors for heart disease. The researchers looked at cognition at baseline, 3 months, 1 year, 3 years, and 6 years.

In this CAD intervention population, 3%-5% have strokes, 10%-15% have encephalopathies, and about 25% have short-term cognitive problems. In-hospital mortality is 22% following a stroke, 7.5% following encephalopathy, and 12% following both.

"If you have coronary artery disease . . . you're going to be lower at baseline than the heart-healthy controls but not in all cognitive domains," said Dr. McKhann. "In our data we think we see a relative preservation of memory and language, and decreased psychomotor and motor speed and decreased executive function," he added. ■

Little Difference in Cognitive Function After Coronary Artery Bypass Graft or Stents

	CABG (n = 152)	Stents (n = 92)
Age (at enrollment)	64 years	66 years
Death	17%	21%
Statin use	84%	76%
Average MMSE score	27.4	27.9
MMSE score < 24	7%	8%
Average CES-D score	9.5	9.0
CES-D score > 15	13%	15%

Notes: Based on a 6-year follow-up. MMSE stands for Mini-Mental State Examination. CES-D stands for Center for Epidemiologic Studies–Depression.
Source: Dr. McKhann

Elsevier Global Medical News

Lewy Body Pathology Tied to Cerebral Atherosclerosis Severity

BY KERRI WACHTER
Senior Writer

WASHINGTON — Lewy body pathology—the accumulation of α-synuclein protein—appears to be associated with cerebral atherosclerosis.

In a study of 403 preserved brains, those with moderate to severe cerebral atherosclerosis were more than twice as likely to also have Lewy bodies present as were those with no cerebral atherosclerosis.

This association between cerebral atherosclerosis and Lewy body burden was discovered by examining brains from the Columbia University Medical Center databank. The brains were obtained between 1990 and 2007. Neuropathologic evaluation of Lewy bodies involved immunostaining with ubiquitin or α-synuclein. Degree of cerebral atherosclerosis was determined by gross rating of the Circle of Willis, according to Dr. Nikolaos Scarmeas, of the Taub Institute at Columbia University, New York, and his colleagues.

Lewy bodies were present in roughly a quarter of the brains (26%). Patients with Lewy bodies died at an older age on average than did those without the pathology—78 years vs. 75 years. Those with Lewy bodies were also slightly more educated—16 years vs. 14 years. Lewy bodies were more likely to be found in men (66%). Changes associated with Alzheimer's disease (AD) were found in roughly half of those with and without Lewy bodies.

Mild cerebral atherosclerosis raises the risk for Lewy bodies only slightly, while moderate to severe disease was linked to a twofold risk.

Cerebral atherosclerosis was classified as not present, mild, or moderate to severe. No atherosclerosis was found in 31%, mild atherosclerosis in 36%, and moderate to severe in 33%. Atherosclerosis appeared more frequently with increasing age—68 years for those without, 76 years for those with mild, and 82 years for those with moderate to severe.

The presence of AD-related changes increased with increasing cerebral atherosclerosis—44% of those with none, 56% of those with mild, and 64% of those with moderate to severe, they reported.

The researchers used logistic regression analysis to determine if the presence of mild or moderate to severe cerebral atherosclerosis was predictive of the presence of Lewy bodies in the brain. In the unadjusted model, those with both mild (OR 1.25) and moderate to severe (OR 2.38) atherosclerosis were more likely to have Lewy bodies, versus patients without atherosclerosis, as seen in this study presented as a poster at the annual meeting of the American Neurological Association.

After adjustment for gender, age at death, and AD pathologic changes, those with mild atherosclerosis were only slightly more likely to have Lewy bodies (OR 1.07). Those with moderate to severe atherosclerosis were still more than twice as likely to have them (OR 2.20).

In addition, "stratified analyses indicated that the association between Lewy bodies and atherosclerosis was stronger in women and in patients without AD pathological changes," the researchers wrote.

The researchers also examined the effect of restricting their analyses to include only more recent cases—those cases that used α-synuclein immunostaining. However, this restriction did not affect the associations. ■