Inflammation Not Behind Depression/CHD Link

BY SUSAN LONDON

FROM THE WORLD CONGRESS ON HEART DISEASE

VANCOUVER, B.C. – Depression increases the risk of coronary heart disease, but it does not do so through proinflammatory mechanisms, a study has shown.

In 1,794 healthy Nova Scotians randomly selected from the general population, those with higher levels of depressive symptoms did indeed have higher levels of inflammatory biomarkers.

But after these markers and traditional risk factors were taken into account, depressive symptoms still predicted first coronary heart disease (CHD) events over the next decade, with the risk rising by 26% with each standard deviation increase in Center for Epidemiologic Studies–Depression (CES-D) score.

"Inflammatory biomarkers neither fully nor partially explained the association between depression and CHD," lead investigator Karina W. Davidson, Ph.D., said at the congress.

"We have also looked into recurrent CHD, and we did not find it," she added. "So we are concluding that we need to explore other biological mechanisms, such as platelet aggregation or endothelial dysfunction."

Several scenarios have been proposed to explain associations among depressive symptoms, inflammation, and CHD (Am. J. Cardiol. 2005;96:1016-21), according to Dr. Davidson of the department of medicine at Columbia University Medical Center in New York. In some of these scenarios, depression has effects on physiology or behavior that promote the development of CHD.

These effects could be indirect (for example, nonadherence to cardiac prevention regimens, increased unfavorable lifestyle behaviors, or cardiotoxicity of antidepressants) or direct (for example, increased inflammation, endothelial dysfunction, enhanced platelet aggregation, or autonomic and neuroendocrine perturbations).

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Major Finding: Each standard deviation rise in level of depressive symptoms at baseline, as assessed from CES-D score, was associated with a 26% increase in the risk of a first CHD event after inflammatory markers were taken into account.

Data Source: A population-based study of 1,794 randomly selected Nova Scotians with prospective 10-year follow-up.

Disclosures: Dr. Davidson reported that she had no relevant conflicts of interest.

"Depressive symptoms and inflammatory markers have been highly comorbid in a number of studies, so we felt this was a promising pattern to look at, whether inflammatory markers serve perhaps as the mechanism," she explained.

Dr. Davidson and her colleagues studied apparently healthy adults recruited to the population-based Canadian Nova Scotia Health Survey in 1995.

At baseline, study participants underwent assessment of traditional risk factors such as lipids and smoking, completed the CES-D, and gave a blood sample for measurement of three inflammatory markers: high-sensitivity C-reactive protein (hs-CRP), soluble intercellular adhesion molecule (sICAM), and interleukin-6.

The study population was 46 years old on average and equally divided by sex. Participants' mean body mass index was about 27 kg/m^2, and roughly three-fourths were current smokers. Their total cholesterol level averaged 5.3 mmol/L, and blood pressure averaged 124/77 mm Hg.

Participants had a mean score on the CES-D scale of 7.2 points out of a possible 60, with a standard deviation of 7.7 points. Only 3% of participants were taking antidepressants.

During a prospective 10-year follow-up, 8.5% of participants had a first CHD event, as ascertained from diagnostic codes on hospital admissions or death certificates, Dr. Davidson reported.

Each standard deviation increase in depressive symptoms was associated with an 8.3% higher hs-CRP level and a 4.7% higher interleukin-6 level.

In analyses adjusted for traditional risk factors, the higher participants' level of depressive symptoms, the greater their risk of CHD events, with a significant 28% greater risk for each standard deviation increase in CES-D score, she said.

The risk of events also rose with hs-CRP level and sICAM level (but not interleukin-6 level) at baseline, independent of traditional risk factors.

When all of the variables were included in a model, a higher level of depressive symptoms still significantly predicted a greater likelihood of CHD events, with a significant 26% greater risk for each standard deviation increase in CES-D score.

Furthermore, this association was consistent across a variety of subgroups: men, current smokers, participants aged 65 years or older, obese participants, those not prescribed any cardiac medications (although statins were not assessed), and those not prescribed antidepressants.

"Depression and inflammation are moderately correlated," commented Dr. Davidson, but "depressive symptoms were independent for CHD, and inflammation was independent for CHD – there did not seem to be any kind of mechanistic association amongst them," she added.

"We still believe in our hearts that there are some patients who have cytokine-induced depression," Dr. Davidson concluded. "We are now trying the hypothesis that there may be a small, intermediary phenotype of depressed persons who actually have very high cytokines, and they may go on to have a higher rate of incident CHD, and we are testing them." ■

Endarterectomy Safer Than Carotid Stenting Past Age 70

BY SHARON WORCESTER

FROM THE LANCET

Carotid stenting may be a safe alternative to endarterectomy in patients under age 70 years with symptomatic carotid stenosis, but stenting should be avoided in those aged 70 years or older, according to findings from a meta-analysis of data from three randomized controlled trials.

While current recommendations restrict the use of stenting to symptomatic patients with contraindications to endarterectomy, carotid stenosis at surgically inaccessible sites, recurrent stenosis after previous endarterectomy, and stenosis after irradiation, the findings of this meta-analysis suggest stenting is also a viable alternative in younger patients in whom surgery could otherwise be undertaken without increased risk, said Dr. Leo H. Bonati of University Hospital Basel, Switzerland, and the Institute of Neurology at University College, London, and his colleagues from the Carotid Stenting Trialists' Collaboration.

They advised, however, that some uncertainty remains about whether recurrent stenosis rates are high after stenting vs. endarterectomy and recommended an approach of offering stenting when "technically feasible as an alternative option to endarterectomy to patients younger than 65-70 years with symptomatic carotid stenosis, in centers in which acceptable periprocedural outcomes have been independently verified … as long as patient are made aware of a possible increase in the risk of restenosis."

Among the 3,433 patients in the trials, overall incidence of any stroke or death in the 120 days after randomization in the three trials was significantly greater in patients who underwent carotid stenting vs. carotid endarterectomy (8.9% vs. 5.8%, respectively; risk ratio 1.53).

However, assessment of multiple subgroup variables showed that age modified the treatment effect; no difference was seen in the estimated 120-day risk of stroke or death in those under age 70 years who underwent stenting vs. endarterectomy, but the risk of stroke or death was doubled in those aged 70 years or older who underwent stenting vs. endarterectomy. (See graph below.)

Similarly, the relative risk estimates for stroke or death at 30 days after treatment were comparable in those under age 70 years who underwent stenting vs. endarterectomy (5.1% and 4.5%, respectively; risk ratio 1.11), but were more than double in those aged 70 years or older for stenting vs. endarterectomy (10.5% and 4.4%, respectively; risk ratio 2.41).

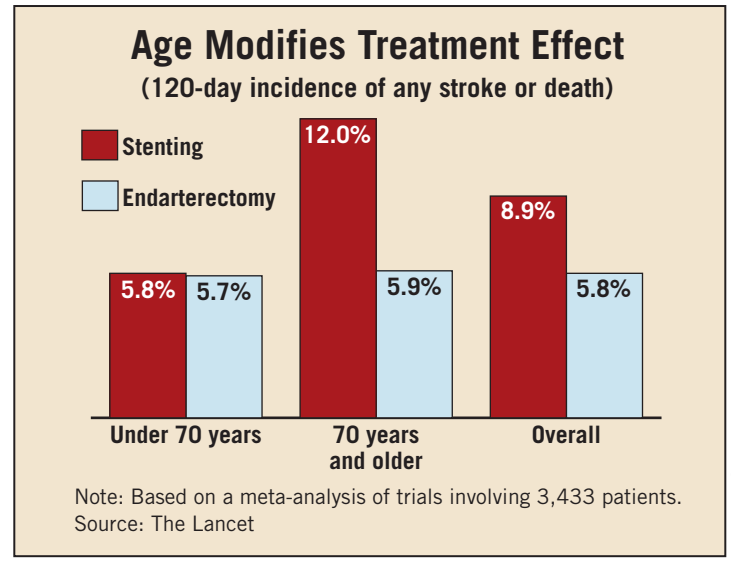
The findings provide "strong evidence that, in the short term, the harm of stenting compared with endarterectomy decreases with younger age," the investigators wrote.

For the meta-analysis, which was funded by the Stroke Association, the investigators analyzed data from Endarterectomy vs. Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S), Stent-Protected Angioplasty vs. Carotid Endarterectomy (SPACE), and the International Carotid Stenting Study (ICSS).

These and other trials have suggested there is a higher periprocedural risk of stroke with stenting vs. endarterectomy, but none of the trials on their own were sufficiently powered to show whether stenting might be a safe alternative in some patients, the investigators noted (Lancet 2010 [doi:10.1016/S0140-6736(10)61009-4]).

Indeed, the risk of stenting remained strongly dependent on age even after additional assessment based on sex, type of recent symptoms, degree of treated carotid stenosis, systolic blood pressure at randomization, and a number of other factors, the investigators noted.

The investigators stated that they have no conflicts of interest. ■



Note: Based on a meta-analysis of trials involving 3,433 patients.
Source: The Lancet

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