Fish Oil Added to Statin Boosts Coronary Benefits

BY BRUCE JANCIN
Denver Bureau

DALLAS — Adding high-dose fish oil to a low-dose statin provided a 19% further reduction in major coronary events, compared with statins alone, Dr. Mitsuhiro Yokoyama reported at the annual scientific sessions of the American Heart Association.

The clinical benefits of fish oil apparently were achieved through lipid-independent mechanisms, since LDL cholesterol levels in the two study arms were reduced by an identical 26% in the 18,645-patient Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS).

JELIS involved nearly 15,000 Japanese patients being treated for primary prevention of coronary heart disease and more than 3,600 others undergoing secondary prevention. All were placed on either 5 mg/day of simvastatin or 10 mg/day of pravastatin and then randomized to 1,800 mg/day of eicosapentaenoic acid (EPA) from high-dose fish oil capsules or not.

The study was open label but featured blinded adjudication of outcomes, explained Dr. Yokoyama, professor and chief of the division of cardiovascular and respiratory medicine at Kobe University.

After a mean of 4.6 years of follow-up, the primary combined study end point—a composite of sudden cardiac death, MI, unstable angina, and/or coronary revascularization—occurred in 2.8% of patients on statin plus fish oil, compared with 3.5% of controls, a highly significant difference.

In the secondary prevention cohort the event rate was 10.7% in controls and 8.7% with dual therapy, a 19% risk reduction. A nearly identical 18% relative risk reduction was seen with dual therapy in the primary prevention cohort; however, this benefit did not achieve statistical significance because event rates were only about one-sixth those in the secondary prevention group.

The high-dose fish oil was well tolerated. The chief side effect—mild GI upset—occurred in 3.8% of recipients, a rate more than twice that in controls. Skin rash and/or itching occurred in 1.7% of the fish oil group and 0.7% of controls. On the other hand, complaints of joint or muscle pain were 20% less common in the fish oil group, Dr. Yokoyama continued.

Discussant Dr. Beatrice Rodriguez observed that the potential mechanisms by which EPA might reduce the risk of cardiovascular events are numerous. They include antithrombotic and anti-inflammatory effects, promotion of endothelial relaxation, and reduced susceptibility to ventricular arrhythmias.

JELIS involved more than 18,000 Japanese patients who were being treated for primary or secondary prevention of CHD.

DR. YOKOYAMA

She encouraged the JELIS investigators to continue follow-up to answer the question of whether fish oil reduces all-cause mortality. Thus far in JELIS it has not, noted Dr. Rodriguez, professor of geriatric medicine, public health science, and epidemiology at University of Hawaii at Manoa.

She added that a secondary analysis of the effects of fish oil in smokers versus nonsmokers in JELIS would be illuminating. Heavy smoking is common in Japan; indeed, roughly 80% of patients in the primary prevention arm and 26% in the secondary prevention arm of JELIS were smokers, averaging 22 cigarettes per day.

Of potential relevance is the finding in the 23-year follow-up of the Honolulu Heart Study, in which Dr. Rodriguez is a coinvestigator, that age-adjusted coronary mortality among current heavy smokers who ate fish at least twice weekly was significantly less than in smokers who ate fish less frequently. "It's possible that the benefits of EPA observed in JELIS are substantially greater among the heavy smokers," she said.

Dr. Rodriguez said the clinical applicability of JELIS to Western populations is unclear because background fish consumption in Japan is so great that even the control group had quite high plasma EPA levels by American or European standards.

That's not the only reason JELIS may have limited applicability, Dr. Lawrence J. Appel said in an interview. Most fish oil supplements available over the counter in the United States contain just 0.18 g of EPA per capsule, meaning Americans would need to take 10 per day to replicate the JELIS dosing.

It could also be argued that the statin doses used in the trial were suboptimal, added Dr. Appel, vice chair of the AHA Nutrition Committee and professor of medicine at Johns Hopkins University, Baltimore.

JELIS was funded by Mochida Pharmaceutical Co. ■

Museum Features 'Healthy Heart'

The National Museum of Health and Medicine at Walter Reed Army Medical Center, Washington, is featuring an exhibit, "A Healthy Heart," through 2006. The exhibit examines human cardiovascular anatomy for both scientific and lay audiences.

For more information, go to www.nmhm.washingtondc.museum, or call 202-782-2200.

Decreased Blood Pressure May Reduce Coronary Atheroma Load

BY MITCHEL L. ZOLER
Philadelphia Bureau

DALLAS — Regression of coronary atheroma load was linked with cuts in systolic blood pressure and pulse pressure in an analysis of data from 274 patients.

Patients whose average systolic pressure fell below 120 mm Hg or those whose pulse pressure dropped below about 46 mm Hg had a significant regression in their coronary atheroma load during 2 years of follow-up, Dr. Ilke Sipahi reported at the annual Scientific Sessions of the American Heart Association. Among patients whose average pressures were above these levels, higher pressure was directly associated with increased atheroma load during follow-up, said Dr. Sipahi, a cardiologist at the Cleveland Clinic Foundation.

"Hypertension is involved in initiating atheroma by damaging endothelial cells and making them more permeable to lipids," explained Dr. Steven E. Nissen, medical director of the Cleveland Clinic Cardiovascular Coordinating Center and a coinvestigator on the study. "In blood vessels there's a battle between the forces that drive oxidized cholesterol into vessel walls and the forces that are trying to pull it out. Everyone focuses on lipids, but we need to think more about blood pressure."

The analysis used data collected in the CAMELOT study, which compared the ability of amlodipine or enalapril with placebo to prevent cardiovascular events in patients with coronary artery disease and hypertension (JAMA 2004;292:2217-25). The primary finding of the CAMELOT study was that amlodipine was more effective than enalapril for preventing cardiovascular events.

In a substudy, 274 patients who required coronary angiography for clinical indications underwent intravascular ultrasound assessment at baseline and 24 months later. Atheroma burden in a representative segment of the coronary artery of each patient was calculated by summing the atheroma areas in a series of cross-sectional ultrasound images taken at 1-mm intervals. Blood pressures were measured in each patient at 3-month intervals, and each patient's average pressures during follow-up were used for this analysis.

In a multivariate analysis that controlled for several clinical and demographic variables, including the ratio of total cholesterol to HDL cholesterol and atheroma burden at baseline, systolic blood pressure and pulse pressure were the only variables that were significantly associated with changes in atheroma burden, Dr. Sipahi said.

"The relationship between systolic blood pressure and pulse pressure and atheroma volume was independent of the treatment that patients received, and was independent of their lipid levels," he said. The analysis showed no link between changes in diastolic pressure and changes in atheroma volume. ■

Higher Glucose Levels in Women Tied to Atherosclerosis Progression

BY MITCHEL L. ZOLER
Philadelphia Bureau

DALLAS — Postmenopausal women with coronary artery disease and no diabetes who had a high-normal response to an oral glucose tolerance test had faster progression of atherosclerosis, compared with women who have lower glucose levels following an oral challenge.

This finding in a total of 51 patients suggests that an oral glucose tolerance test may help identify women who have an increased risk for progression of atherosclerosis, Dr. Philip B. Mellen and his associate reported in a poster presented at the annual scientific sessions of the American Heart Association.

The results also raise questions about optimal glucose levels in women with coronary artery disease who undergo a glucose tolerance test, wrote Dr. Mellen, a cardiologist at Wake Forest University in Winston-Salem, N.C.

The study involved 51 postmenopausal women with angiographically documented coronary artery disease and no history of diabetes. Their average age was 65 years. Their fasting levels of serum glucose were all within the normal range of 100 mg/dL or less, and their serum level of glucose 2 hours following an oral glucose challenge was also in the normal range of 140 mg/dL or less.

All of the participants underwent repeat coronary angiography 3 years later, and the change in their minimal lumen diameter in an affected coronary artery was correlated with their baseline glucose levels following an oral glucose challenge.

Patients with a serum glucose level of less than 87 mg/dL after challenge at baseline had atherosclerosis regression during follow-up, with their coronary lumen diameter increasing by an average of 0.044 mm.

Patients with a serum glucose level of 87-106 mg/dL after challenge at baseline showed an average 0.039 mm loss in lumen diameter during follow-up.

Patients whose serum glucose level was 107-123 mg/dL after challenge at baseline had an average 0.140-mm loss in coronary lumen diameter, and patients whose serum glucose level was 124-140 mg/dL or more after challenge at baseline had an average 0.185-mm loss in lumen diameter.

The trend of increased progression of atherosclerosis in women with higher serum glucose levels following challenge was statistically significant.

In contrast, no correlation was seen between fasting levels of serum glucose and progression of atherosclerosis. ■