Fish Oil Augments the Cardiac Benefits of Statins

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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.

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. ■