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## Fish Oil Added to Statin Therapy Reduces Risk For Major Coronary Events

**CME**

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from [Heartwire](#) — a professional news service of WebMD

April 3, 2007 — Results of the Japan EPA Lipid Intervention Study (JELIS), first presented at the American Heart Association's 2005 Scientific Sessions, have now been published in the March 31 issue of *The Lancet*. As previously reported by [heartwire](#), the addition of eicosapentaenoic acid (EPA) to low-dose statin therapy significantly reduced the incidence of major coronary events, largely driven by a reduction in unstable angina, when compared with statins alone.

A subgroup analysis of the study, which involved a large number of primary-prevention patients, revealed that statin-treated secondary-prevention patients gained the most benefit from fish-oil supplementation.

The investigators, led by Mitsuhiro Yokoyama, MD, from Kobe University Graduate School of Medicine in Kobe, Japan, believe the benefit provided by the addition of EPA, a long-chain, n-3 polyunsaturated fatty acid, to statin therapy does not appear to be mediated by the effects of cholesterol lowering. In both treatment groups, there was a 26% reduction in levels of low-density lipoprotein (LDL) cholesterol.

"The beneficial effects of EPA could have stemmed from many biological effects that lead to the attenuation of thrombosis, inflammation, and arrhythmia, in addition to a reduction of triglycerides," write the authors. "Overall, this study shows that EPA, at a dose of 1800 mg per day, is a very promising regimen for prevention of major coronary events, especially since EPA seems to act through several biological mechanisms."

In an accompanying editorial, Dariush Mozaffarian, MD, DrPH, from the Harvard Medical School in Boston, Massachusetts, commends the efforts of the JELIS investigators. He notes that the current study should inspire other clinical trials of the effects of fish oil and other dietary factors and habits on cardiovascular health.

"Compared with drugs, invasive procedures, and devices, modest dietary changes are low risk, inexpensive, and widely available," writes Dr. Mozaffarian. "We must curb our infatuation with downstream risk factors and treatments, and focus on the fundamental risk factors for cardiovascular disease: dietary habits, smoking, and physical activity. If the millions of heart attacks occurring each year were not a clarion call, the obesity epidemic certainly should be."

### 19% Reduction in Major Coronary Events

The JELIS study enrolled more than 18,000 patients, of whom 9326 were given 1800 mg/day of highly purified EPA capsules and 9319 served as controls. In Japan, this high-dose EPA has been available since 1990 for treating lipid abnormalities and peripheral artery disease and is considerably higher than the dose available over the counter in North America.

Patients in the trial were all taking low-dose statins, with more than 90% treated with pravastatin (10 mg) and simvastatin (5 mg). At baseline, LDL cholesterol levels in the control group (statin alone) and the study group (statin plus EPA) were approximately 183 mg/dL.

After a mean follow-up of 4.6 years, the addition of EPA to low-dose statin therapy resulted in a statistically significant 19% reduction in the risk for major coronary events, defined as sudden cardiac death, fatal or nonfatal myocardial infarction (MI), unstable angina, or the need for revascularization.

**Table. JELIS: Hazard Ratios of Clinical Endpoints\***

Outcome	Statin Alone, % of Patients	Statin Plus EPA, % of Patients	Hazard Ratio (95% CI)
<b>All Patients</b>			
Major coronary events	3.5	2.8	.81 (0.69 - 0.95)
Sudden cardiac death	0.2	0.2	1.06 (0.55 - 2.07)
Fatal MI	0.2	0.1	.79 (0.36 - 1.74)
Nonfatal MI	0.9	0.7	.75 (0.54 - 1.04)
Unstable Angina	2.1	1.6	.76 (0.62 - 0.95)
CABG or PTCA	2.4	2.1	.86 (0.71 - 1.05)
<b>Primary Prevention of CAD</b>			
Major coronary events	1.7	1.4	.82 (0.63 - 1.06)
Sudden cardiac death	0.1	0.1	1.25 (0.34 - 4.67)
Fatal MI	0.1	0.1	1.00 (0.32 - 3.11)
Nonfatal MI	0.6	0.5	.80 (0.52 - 1.24)
Unstable Angina	0.9	0.8	.85 (0.60 - 1.19)
CABG or PTCA	1.0	0.9	.87 (0.62 - 1.21)
<b>Secondary Prevention of CAD</b>			
Major coronary events	10.7	8.7	.81 (0.66 - 1.00)
Sudden cardiac death	0.7	0.7	1.02 (0.47 - 2.19)
Fatal MI	0.4	0.3	.64 (0.21 - 1.94)
Nonfatal MI	2.1	1.4	.70 (0.42 - 1.14)
Unstable Angina	6.7	4.8	.72 (0.55 - 0.95)
CABG or PTCA	8.0	7.0	.87 (0.69 - 1.10)

\*JELIS indicates Japan EPA Lipid Intervention Study; EPA, eicosapentaenoic acid; CI, confidence interval; MI, myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; and CAD, coronary artery disease.  
Source: *Lancet*. 2007;369:1062-1063, 1090-1098.

Commenting on the findings, Dr. Mozaffarian writes that the absence of effect on cardiac death is to be expected because the benefit of fish or fish-oil consumption for this endpoint is nonlinear. Most risk reduction, he writes, occurs with modest intake, typically around 250 mg of EPA per day, which corresponds to 1 to 2 serving of fish per week. In Japan, average fish consumption is 1 serving per day and 90% of individuals eat fish once a week. As a result, most of the population is already above the threshold for preventing cardiac death, he notes.

What is surprising, Dr. Mozaffarian continues, is the significant reduction in nonfatal coronary events, with subjects taking EPA having 19% fewer events than controls, a finding not observed in most US and European studies. Although the trial was open-label, and such soft endpoints as unstable angina and coronary revascularization could have been the result of patients' behaviour, clinicians' treatment, or event ascertainment, these findings should not be discounted, writes Dr. Mozaffarian.

"In view of the diverse physiological effects of fish oil and their differing dose-response curves, the main benefit at lower levels of consumption might be prevention of primary ventricular arrhythmia, whereas at high levels of consumption (eg, more than 1 g per day of EPA or DHA [docosahexaenoic acid]), modest benefits for nonfatal coronary events could also begin to occur because of, for example, triglyceride-lowering, antihypertensive, or anti-inflammatory effects," writes Dr. Mozaffarian.

*Lancet.* 2007;369:1062-1063, 1090-1098.

The complete contents of [Heartwire](#), a professional news service of WebMD, can be found at [www.theheart.org](http://www.theheart.org), a Web site for cardiovascular healthcare professionals.

## Learning Objectives for This Educational Activity

Upon completion of this activity, participants will be able to:

- Describe the effect of fish oil supplementation on nonfatal coronary events in patients with hypercholesterolemia who are receiving statins.
- Describe the effect of fish oil supplementation on fatal coronary artery disease in patients with hypercholesterolemia.

## Clinical Context

Intake of only once or twice a week (200 - 400 g weekly) or supplemental intake of EPA plus docosahexaenoic acid (1 g daily) has been shown to reduce coronary mortality by 20% to 30% in patients with a history of MI. And, it is postulated that fish intake may have an anti-arrhythmic effect. Another hypothesis is that fish oil may lower serum lipids, in particular, triglycerides.

This is an open-label, randomized trial with blinded endpoint evaluation, comparing coronary artery disease outcomes in patients already receiving statins for hypercholesterolemia in Japan where coronary artery disease rates are low and dietary fish intake is relatively high compared with other countries.

## Study Highlights

- Included were 19,466 patients with hypercholesterolemia recruited through clinicians in all regions of Japan: 5859 men (age, 40 - 59 years) and 12,786 postmenopausal women (age, up to 75 years) with or without coronary artery disease.
- *Coronary artery disease* was defined as previous MI, coronary interventions, or confirmed angina pectoris.
- Inclusion criteria were total cholesterol level of 6.5 mmol/L or greater and LDL cholesterol level of 4.4 mmol/L or greater.
- Exclusion criteria were acute MI within 6 months, serious heart or cerebrovascular disease, renal or hepatic disease, cancer, poorly controlled diabetes, and planned surgery.
- Primary endpoint was any major coronary event including sudden cardiac death and fatal and nonfatal events.
- All patients received either pravastatin (10 mg) or simvastatin (5 mg) once daily as first-line treatment, and the dose was doubled for refractory hyperlipidemia.
- No other anticholesterolemic agent was permitted.
- Follow-up was for 4.6 years.
- EPA was given at a dose of 600 mg 3 times daily (1800 mg daily) using capsules containing highly purified EPA ethyl ester.
- 9326 patients received EPA, and 9319 were in the control group.
- Serum lipids were measured at 6 and 12 months then annually, and adverse events were monitored by the clinician during visits.
- Mean age was 61 years, 69% were women, mean total cholesterol level was 7.1 mmol/L, triglyceride level was 1.7 mmol/L, LDL cholesterol level was 4.7 mmol/L, and high-density lipoprotein cholesterol level was 1.5 mmol/L.
- 90% of patients took pravastatin (10 mg) or simvastatin (5 mg) daily.
- Compliance was 73% for controls, 71% for EPA, and 74% for statins.
- 586 patients reached the primary endpoint, and 5-year cumulative rate of major coronary events was 2.8% in the EPA group

and 3.5% in the controls.

- EPA treatment was associated with a significant 19% decrease in major coronary events.
- EPA treatment was associated with a significant 24% reduction in the frequency of unstable angina.
- Coronary death and fatal and nonfatal MI were not significantly lower in the EPA group.
- Incidence of nonfatal coronary events (including procedures such as stenting, angioplasty, and bypass grafting) were significantly lower (19%) in the EPA group.
- In the primary prevention group, there was a nonsignificant 18% decrease in major coronary events vs a significant 19% decrease for the secondary prevention group.
- LDL cholesterol level was not an important factor contributing to risk reduction for major coronary events.
- Total and LDL cholesterol levels decreased significantly from baseline by 19% and 25%, respectively, in both groups with no significant differences between the groups.
- Triglycerides decreased by 9% in the EPA group and 4% in the control group ( $P < .0001$  between groups).
- Plasma EPA concentration at year 5 was 169 mg/L in the EPA group, a 70% increase from baseline.
- Discontinuation rate resulting from adverse events was 11.7% in the EPA group and 7.2% in the control group.
- Adverse events were mild and consisted of abnormal laboratory values, gastrointestinal disturbance (nausea, diarrhea, or epigastric discomfort), and skin abnormalities.
- Frequency of new cancers was similar between the 2 groups.

## Pearls for Practice

- In Japanese patients with hypercholesterolemia, EPA treatment in addition to statins is associated with a reduction in major nonfatal coronary events for 5 years.
- Use of EPA in addition to statins is not associated with reduced coronary death or sudden cardiac death for 5 years in Japanese patients with hypercholesterolemia.

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## Target Audience

This article is intended for primary care clinicians, cardiologists, and other specialists who care for patients at risk for coronary artery disease.

## Goal

The goal of this activity is to provide medical news to primary care clinicians and other healthcare professionals in order to enhance patient care.

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