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Does treatment with eicosapentaenoic acid prevent major coronary events in patients with hypercholesterolemia?

Original article Yokoyama M *et al.* for the Japan EPA lipid intervention study Investigators (2007) Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* **369:** 1090–1098

SYNOPSIS

KEYWORDS coronary artery disease, eicosapentaenoic acid, fatty acids, fish oil, hypercholesterolemia

BACKGROUND

Eicosapentaenoic acid (EPA) ethyl ester is derived from long-chain n-3 polyunsaturated fatty acids that occur naturally in fish oil. EPA is licensed in Japan for the treatment of hyperlipidemia and peripheral artery disease, but it is not known whether this agent is effective for the prevention of major coronary events.

OBJECTIVE

To determine whether EPA effectively reduces major coronary events in statin-treated patients with hypercholesterolemia.

OUTCOME MEASURE

The primary, composite end point was the occurrence of a major coronary event (unstable angina, fatal or nonfatal myocardial infarction [MI], sudden cardiac death, angioplasty, or CABG surgery).

DESIGN

The Japan EPA lipid intervention study (JELIS) was a prospective, open-label, randomized trial with blinded end points. The study population consisted of Japanese men and women with hypercholesterolemia (total cholesterol concentration ≥6.5 mmol/l), with or without a history of coronary artery disease. Exclusion criteria included acute MI, cerebrovascular events or cardiovascular reconstruction within the 6 months before enrollment, a history of unstable angina or serious heart disease, malignancy, uncontrolled diabetes, drug-related hyperlipidemia, and hemorrhage.

INTERVENTION

All patients received 10 mg pravastatin or 5 mg simvastatin daily and those in the EPA group also received 600 mg highly purified EPA ethyl ester (Epadel, Mochida Pharmaceuticals, Tokyo, Japan) three times daily. Patients were monitored for medication compliance by their local physician. Serum lipid concentrations were measured at 6 and 12 months after study initiation, and annually thereafter.

RESULTS

Between November 1996 and November 1999, 19,466 patients were recruited to the study, of whom 18,645 were eligible for randomization. Male patients (31.4%) were aged between 40 and 75 years and female patients (68.6%) were postmenopausal and aged up to 75 years. The mean age across the study population was 61 years. In total, 9,326 patients were randomly assigned to the EPA group; the remaining 9,319 patients received statins alone (control group). After a mean follow-up period of 4.6 years, the primary end point had occurred in 586 patients (EPA = 262, controls = 324). The 5-year cumulative event rate was significantly lower in patients who received EPA than in those who did not (2.8% vs 3.5%; $P = 0.011$), which constituted a 19% reduction in major coronary events in those receiving EPA treatment. Patients who received EPA also had significantly lower rates of unstable angina (1.6% vs 2.1; $P = 0.014$) and nonfatal coronary events (3.2% vs 2.6%, $P = 0.015$) than did controls. By contrast, there was no significant difference in the rates of sudden cardiac death, MI, or coronary death between the two groups. Notably, EPA was associated with a higher rate of adverse events than statins alone (25.3% vs 21.7%; $P < 0.0001$).

CONCLUSION

A daily EPA dose of 1,800 mg is potentially effective for the prophylaxis of nonfatal coronary events in patients with hypercholesterolemia.

COMMENTARY

William S Harris

JELIS is the largest and longest omega-3 fatty acid intervention study yet reported. In this trial, more than 18,600 hypercholesterolemic men and women from Japan were followed for cardiac events for 5 years after being randomly assigned to receive statin monotherapy or a statin plus 1,800 mg of EPA ethyl esters. Although Japanese individuals already have an omega-3 fatty acid intake approximately eight times higher than is typical in Western cultures,[1] the addition of EPA to statin therapy resulted in a 19% reduction in major adverse cardiac events. The primary effects of EPA were seen not on mortality or sudden death (for which there were few events and no differences between treatment groups), but on 'softer' end points, such as unstable angina and nonfatal cardiac events. The effect of EPA was similar in both the primary and secondary-prevention setting, although statistically significant only in the latter. EPA had no significant impact on serum lipid parameters.

There were significantly more adverse events in the EPA group than in the control group, possibly because this was an open label, nonplacebo-controlled trial. EPA treatment was associated with more gastric disturbances, skin complaints, and bleeding episodes, but fewer reports of pain. These side effects were, however, described as mild by the authors and EPA therapy, therefore, seems to be safe, even in this high omega-3 population.

Although the authors reported the effects of treatment on serum concentrations of EPA (the active agent), they did not give full serum fatty acid profiles. These data would have been helpful in the ongoing discussion of the relative value of omega-3 fatty acid levels in serum or red blood cells versus ratios as predictors of coronary heart disease (CHD) risk. In noting that the ratio of omega-6 arachidonic acid (AA) to EPA decreased with treatment, the authors do not state whether AA levels were actually lowered, which might have mechanistic implications, or if the only change was an increase in EPA. Although omega-3 levels have predictive power for CHD end points,[2] metrics such as omega-3:omega-6 or AA:EPA ratios have recently been criticized for failing to add to the risk profile provided by omega-3 levels alone, and for confusing the public-health message regarding how best to alter fatty acid intake in order to reduce CHD risk.[3] The answer seems to be that increasing omega-3 intake is far more important than lowering omega-6 intake. This simple message, if heeded and not clouded by discussions of target ratios, would clearly reduce CHD risk, particularly in Western populations.

This study is important for several reasons. Firstly, it indicates that, even with a background of high omega-3 intake (800–1,000 mg/day), additional EPA can further reduce the risk for cardiac events without altering lipoprotein levels. Secondly, the effects of EPA are additive to that of statins. Thirdly, since there was no effect on arrhythmias, the reduction in cardiac events could have been mediated by an EPA-induced reduction in inflammatory plaques, as suggested by Theis *et al.*[4] Fourthly, the effects of EPA manifested very soon after initiation of therapy and were of essentially the same magnitude in both secondary and primary prevention settings. Thus, JELIS provides support for the hypothesis that increased omega-3 fatty acid intake reduces CHD risk, apparently regardless of dietary background.

References

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Competing interests
The author declared associations with the following companies: Monsanto and Reliant Pharmaceuticals. See the article online for full details of the relationships.

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PRACTICE POINT
JELIS underscores the need to ensure that all patients at high risk of cardiovascular disease increase their intake of long-chain omega-3 fatty acids by at least 1.0 g/day, as recommended by the AHA