Incremental Effects of Eicosapentaenoic Acid on Cardiovascular Events in Statin-Treated Patients With Coronary Artery Disease

— Secondary Prevention Analysis From JELIS —

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Background: Results from JELIS (Japan EPA Lipid Intervention Study) demonstrated the efficacy of pure eicosapentaenoic acid (EPA) in preventing coronary artery disease (CAD) in hypercholesterolemic patients under statin treatment. The present study examined in detail whether EPA is effective for the secondary prevention of CAD.

Methods and Results: Patients with established CAD and a total cholesterol level ≥250 mg/dl were observed with a mean follow-up of 4.6 years. They were randomly assigned to receive either 1,800 mg of EPA + statin (EPA group) or statin alone (control group). The incidence of major coronary events (MCE) were compared in the 2 groups. The incidence of MCE was significantly lower in the EPA group (8.7% vs 10.7%, adjusted hazard ratio = 0.77, 95% confidence interval (CI) 0.63–0.96, P = 0.017, number needed to treat (NNT) = 49). Among 1,050 patients with prior myocardial infarction (MI), the incidence of MCE in the EPA group (15.0%) was significantly lower than that in the control group (20.1%, adjusted hazard ratio = 0.73, 95% CI 0.54–0.98, P = 0.033, NNT = 19).

Conclusions: EPA is effective for secondary prevention of CAD, especially in individuals with prior MI, and should be added to conventional treatment. (Circ J 2009; 73: 1283–1290)

Key Words: Acute coronary syndrome; Fatty acids; Lipids; Secondary prevention

Several interventional studies have reported the clinical benefits of fish oil administration or fish consumption in patients with coronary artery disease (CAD), suggesting that n-3 polyunsaturated fatty acids (PUFAs) can reduce the risk of coronary events. Two large-scale secondary prevention trials, the Diet and Reinfarction Trial (DART) and the Group Italiano per lo Studio della Sopravivenza nell’Infarto Miocardico-Prevenzione Trial (GISSI), reported that increased consumption of fish or fish-oil supplements reduced coronary death in postinfarction patients.

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However, those trials were performed in either United States or Europe, and different results might be obtained in the Japanese population, in which fish consumption is greater. In addition, assessment of individual fatty acids was not performed in the conventional trials because the intervention was performed with fish oil, which included various fatty acids, or with meals. Eicosapentaenoic acid (EPA) ethyl ester, which is purified from n-3 PUFAs present in fish oil, is approved by the Ministry of Health, Labour and Welfare of Japan as a treatment for hyperlipidemia and peripheral artery disease. The Japan EPA Lipid Intervention Study (JELIS) was a prospective, randomized, open-label, blinded...
endpoint trial that examined prevention of CAD by EPA (20:5 n-3) treatment in Japanese hypercholesterolemic patients. Secondary prevention strata of CAD were included in the trial population. To ensure that EPA was the only fatty acid tested, researchers administered a pure EPA capsule to patients in the active treatment group.

The biological effects of EPA include anti-arrhythmic effects, anti-inflammatory effects, decreased platelet aggregation, vasodilatory activity, and lipid-lowering effects. We began JELIS with the expectation that these effects of EPA, other than improvement of dyslipidemia, would reduce the risk of CAD.

The major findings of JELIS demonstrated 19% reduction by EPA treatment of major coronary events (MCE), including sudden cardiac death, fatal and non-fatal myocardial infarction (MI), and other non-fatal events, including unstable angina pectoris (AP), angioplasty, stenting, and coronary artery bypass grafting. In the present study, we performed an additional analysis of the JELIS data to determine whether EPA was effective for secondary prevention of CAD. We also examined a change in the ratio of plasma EPA to arachidonic acid (20:4 n-6) concentration and its relationship to the incidence of MCE.

Methods

Patient Population

A total of 18,645 patients with a total cholesterol (TC) level ≥250mg/dl, which corresponds to a low-density lipoprotein-cholesterol (LDL-C) level ≥170mg/dl at baseline, were examined in the JELIS trial. The design and inclusion and exclusion criteria are described in detail elsewhere. We used data from JELIS for 3,664 patients with established CAD defined as previous MI, coronary intervention, or confirmed AP for this analysis.

The exclusion criteria were acute MI within the past 6 months, unstable AP, a history of or complication by serious heart diseases, cerebrovascular disorder within the past 6 months, serious hepatic or renal disease, malignant tumor, uncontrollable diabetes mellitus, hyperlipidemia associated with effects of drugs such as steroid hormones, hemorrhage (hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptyisis, vitreous hemorrhage), hemorrhagic diathesis, hypersensitivity to the study drug formulation, planned surgery, or other condition judged inappropriate for inclusion in the study by the physician-in-charge.

Procedures

All patients received 10mg of pravastatin or 5mg of simvastatin once daily as the first-line treatment and were counseled to follow the National Cholesterol Education Program step I diet. The study population was randomly assigned to receive EPA with statin (EPA group) or statin alone (control group), after a 4- to 8-week washout from antihyperlipidemic drugs. In the EPA group, we administered a daily dose of 1,800mg of EPA as 6 capsules each containing 300mg of pure (≥98%) EPA ethyl ester. Statin administration was continued until trial termination in 1,311/1,652 (79%) cases in the control group and 1,282/1,620 (79%) in the EPA group. EPA administration was continued until trial termination in 1,234 (76%) cases. The planned duration of follow-up of the patients was 5 years. Local physicians monitored compliance with dietary instructions and medication use at each clinic visit. Reported clinical endpoints were reviewed by expert cardiologists belonging to the Event Evaluation Committee without knowledge of treatment allocation. The primary endpoint was the cumulative incidence of MCE, which included sudden cardiac death, fatal and nonfatal MI, and other non-fatal events including unstable AP, angioplasty, stenting, and coronary artery bypass grafting (CABG). We sampled blood to measure serum lipids at 6 and 12 months, and then every year until the final follow-up visit. Plasma total fatty acid concentrations were measured annually by a central laboratory (BML Inc, Tokyo, Japan) for all patients who gave informed consent for blood sampling.

Statistical Analysis

All analyses were based on the intention-to-treat principle. The Wilcoxon 2-sample test was used for comparisons involving continuous variables, and the chi-square test for those involving categorical variables. Time-to-event data were analyzed using the Kaplan-Meier method. The hazard ratio (HR) and its 95% confidence interval (CI) were computed with the Cox proportional hazard model adjusted for age, sex, smoking, prior MI, diabetes, and hypertension. Number needed to treat (NNT) was simply computed as the inverse of the absolute difference between 2 groups in terms

Figure 1. Trial profile. EPA, eicosapentaenoic acid.
Results

Baseline Characteristics

Figure 1 shows the trial profile. Data from all 3,664 patients in the secondary prevention strata were used for the analysis. Patients were followed for a mean of 4.6 years, and the 5-year follow-up rate was >92% in both groups. Baseline characteristics of the study population are shown in Table 1. Of the 3,664 (1,823 in the EPA group and 1,841 in the control group) individuals with documented CAD, 1,050 had a history of MI, 2,903 with AP, and 895 of percutaneous transluminal coronary angioplasty (PTCA) or CABG. The rate of prior MI was higher, though not significantly so, in the EPA group; in contrast, AP was significantly less frequent in this group. There were more tobacco smokers in the EPA group. Except for these variables, the 2 treatment groups were well-matched at baseline, and the pattern of use of concomitant medications was similar between them (Table 1).

Primary Endpoint

In the population for analysis comprising all 3,664 patients, 355 patients (158 in the EPA group, 197 in the control group) reached the composite primary endpoint. Kaplan-Meier curves for the primary endpoint showed that the 5-year cumulative total MCE rate was 8.7% in the EPA group and 10.7% in the control group (Figure 2a), with a significant relative risk reduction of 23% in the EPA group (P=0.017; NNT =49). As shown in Figure 3, EPA therapy was associated with a significant reduction of 30% in the incidence of unstable AP. The incidence of coronary death or MI was 30% lower in the EPA group than in the control group; this difference was not significant. In addition, the incidence of fatal or nonfatal MI was 30% lower in the EPA group; this difference, as well, was not significant. However, the incidence of nonfatal coronary events (nonfatal MI, unstable AP, and angioplasty/stenting or CABG) was 21%, and significantly lower in the EPA group than in the control group.

Ancillary Analysis

Among the 895 patients with prior coronary intervention (PTCA or CABG), the incidence of MCE in the EPA group (14.7%) was significantly lower than that in the control group (22.0%, adjusted HR 0.65, P=0.007, NNT=13, Figure 2b). Among the 1,050 patients with prior MI, the incidence of MCE in the EPA group (15.0%) was significantly lower than that in the control group (20.1%, adjusted HR 0.73, P=0.033, NNT=19, Figure 2c). Among the 537 patients with...
prior MI and coronary intervention, the incidence of MCE in the EPA group (15.2%) was also significantly lower than that in the control group (24.7%, adjusted HR 0.59, P=0.008, NNT=10, Figure 2d). Among the 2,903 patients with stable AP, the incidence of MCE in the EPA group (7.8%) was significantly lower than that in the control group (9.4%, adjusted HR 0.76, P=0.036, NNT=62, Figure 2e). Furthermore, among the 484 patients with stable AP and a coronary intervention, the incidence of MCE in the EPA group (16.8%) was also significantly lower than that in the control group (24.6%, adjusted HR 0.66, P=0.044, NNT=13, Figure 2f).

**Changes in Serum Lipid Values**

Figure 4 summarizes the post-treatment lipid profiles of
Figure 3. Incidence of primary endpoints and hazard ratios (HRs) with 95% confidence intervals (CIs). EPA, eicosapentaenoic acid; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction.

Figure 4. Percentage change and on-treatment average levels (SD) in serum lipid profile in the eicosapentaenoic acid (EPA) group and Control group. TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

Figure 5. Trends in mean eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio during observation. Points represent mean ± SD.
the 2 treatment groups. TC and LDL-C levels decreased by 21% and 27% from baseline, respectively, in both groups. There were minimal changes in high-density lipoprotein-cholesterol (HDL-C) levels above the baseline in both treatment groups. These changes did not differ significantly between the 2 groups. Triglyceride levels decreased 11% from baseline in the EPA group and 6% in the control group. Triglyceride levels exhibited greater decrease in the group with levels above 150 mg/dl at registration, at 27% from baseline in the EPA group and 21% in the control group. A significant decrease was observed in the EPA group.

Relationships Among EPA, AA, and EPA/AA Ratio, and the Incidence of CAD

The mean value of the ratio of plasma EPA to arachidonic acid (AA, 20:4 n-6) at baseline was 0.6 in both treatment groups. The ratio did not change in the control group, but increased to 1.3 at 1 year in the EPA group and remained at that level through the follow-up period (P<0.001 in Figure 5). We divided the patients into 3 groups with approximately equal numbers of cases according to their on-treatment EPA and AA levels and EPA/AA ratio (Table 2). The incidence of MCE was lower, but not significantly so, in the group with highest EPA/AA ratio (≥1.06) (HR 0.80) compared with that in the group with lowest ratio (≤0.55) group, and the incidence of cardiac death or MI was significantly lower (adjusted HR 0.58, P=0.038) in the patient group with the highest EPA/AA ratio than in that with the lowest ratio.

Discussion

The beneficial effects of EPA were remarkable in the secondary prevention subgroup in JELIS. The inclusion of larger numbers of patients in the EPA group who were smokers or had a history of MI was the principal reason for the reduction in the HR after adjustment for risk factors. Analysis of combined endpoints showed that EPA treatment led to a significant reduction of 21% in the incidence of nonfatal coronary events. Although the incidence of fatal or nonfatal MI was 30% lower in the EPA group, this difference was not significant, possibly because of insufficient statistical power (only a small number of patients with MI were included).

GISSI-Prevenzione is another large-scale clinical trial that demonstrated prevention of cardiovascular events by n-3 PUFAs. However, the n-3 PUFAs used in GISSI reduced mortality because of coronary events, though the same finding was not clearly obtained in JELIS. In the control group, the cardiac death rate per 1,000 person-years was 2.5 in JELIS compared with 17 in GISSI-Prevenzione. We suspect that a difference in dietary fish consumption was responsible for this difference in results. Our findings suggest that the number of all coronary events can be reduced by administration of EPA, even in Japanese who consume an abundance of fish. Furthermore, GISSI-Prevenzione evaluated the recurrence of acute coronary events in patients within 3 months after acute coronary syndrome, whereas we evaluated the recurrence of acute coronary events in stable patients more than 6 months after acute coronary syndrome. In addition, the difference in the inclusion criteria of the trials might have influenced the results.

Although previous epidemiological studies reported that the incidence of CAD in the Japanese population is lower than that in Western countries,23,24 a high LDL-C level is a risk factor for CAD in Japanese, as in the United States and Europe. Results from a clinical trial involving administration of simvastatin to Japanese patients with hypercholesterolemia have shown that lowering LDL-C can reduce the incidence of CAD.25,26 Although it is known that treatment with EPA has a LDL-C lowering effect18,19 in JELIS only the triglyceride level, and not the LDL-C level, differed between the treatment groups. EPA had a weak LDL-C lowering effect beyond that of statins alone. The efficacy of EPA in reducing MCEs in this study design might have been independent of its control of LDL-C levels. Recently, a post hoc analysis of the Treating to New Targets (TNT) study reported that the LDL-C level was predictive of MCEs in patients with LDL-C level below 70 mg/dl.27 That finding suggests that strategies providing benefits beyond LDL-C lowering may also be important. In some recent clinical studies designed to increase HDL-C levels, negative results have been reported with acyl-coenzyme A:cholesterol acyl-transferase inhibitors28 and cholesterol ester transfer protein inhibitors,29 and succinobucol30 in reversing progression of coronary atherosclerosis. Using EPA is thus a successful strategy for decreasing the risk of coronary artery events beyond the effect of statin treatment. In fact, changes in triglyceride-rich lipoproteins may also be important. In addition, administration of EPA leads to changes in membrane

Table 2. Relationships Between On-Treatment EPA, AA, and EPA/AA Ratio, and Adjusted Risk of Coronary Events

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Major coronary events</th>
<th>Sudden cardiac death or fatal/nonfatal MI</th>
<th>Unstable angina</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPA (mol%)</strong></td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>No. of patients</td>
<td>1,047</td>
<td>1,125</td>
<td>1,089</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.00</td>
<td>1.02 (0.78–1.35)</td>
<td>0.82 (0.62–1.09)</td>
</tr>
<tr>
<td><strong>AA (mol%)</strong></td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>No. of patients</td>
<td>1,050</td>
<td>1,032</td>
<td>1,179</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.00</td>
<td>1.09 (0.87–1.31)</td>
<td>1.18 (0.91–1.55)</td>
</tr>
<tr>
<td><strong>P value vs Low</strong></td>
<td>0.854</td>
<td>0.28</td>
<td>0.172</td>
</tr>
<tr>
<td><strong>EPA/AA ratio</strong></td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>No. of patients</td>
<td>1,064</td>
<td>1,108</td>
<td>1,089</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.00</td>
<td>1.00 (0.73–1.26)</td>
<td>0.80 (0.61–1.06)</td>
</tr>
<tr>
<td><strong>P value vs Low</strong></td>
<td>0.759</td>
<td>0.85</td>
<td>0.258</td>
</tr>
</tbody>
</table>

HRs with 95% CIs were compared and P values determined by comparison with the Low group. Cox proportional hazard model was used to compute them. AA, arachidonic acid; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval. Other abbreviation see in Table 1.

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fatty acid composition and function that could also improve cardiovascular function, independent of any changes in lipoprotein levels.

As noted, the benefits of n-3 PUFA's on cardiovascular events include its antiarrhythmic effect\textsuperscript{10,11} anti-inflammatory effect\textsuperscript{12–14} decreased platelet aggregation\textsuperscript{15} vasodilatory activities\textsuperscript{16,17} triglyceride-lowering effect\textsuperscript{18,19} and increase in adiponectin\textsuperscript{13,20}. A randomized controlled trial that measured the concentrations of EPA, DHA, and docosahexaenoic acid in carotid artery plaque lipid fractions reported that fish oil increased plaque stability. Thies et al\textsuperscript{21} reported that higher proportions of EPA and DHA and decreased numbers of macrophages in carotid plaque were observed in the fish oil treatment group than in the group treated with a blend of palm and soybean oil and the group treated with sunflower oil. Furthermore, fewer atheromatous plaques and thin fibrous cap atheromas were observed in the fish oil-treated group than in the other groups. A clinical observation study that used multidetector spiral computed tomography reported that there was an inverse correlation between serum n-3 PUFA (EPA and DHA) levels and the extent of coronary soft plaques and calcification in acute MI patients\textsuperscript{22}. Those findings suggest that EPA and DHA may have anti-atherosclerotic effects.

In conclusion, the findings for the secondary prevention strata of JELIS were that EPA administration yielded a 23% reduction in the incidence of MCE. Notably, patients with prior MI exhibited a 27% reduction, and those with prior MI and an intervention (PTCA or CABG) exhibited a 41% reduction. These findings strongly suggest that the addition of EPA to conventional treatment should be considered for secondary prevention of CAD, and also suggest that n-3 PUFA's should be considered to reduce secondary prevention of CAD, which according to the results of this trial, might also include EPA alone.

Study Limitation

The efficacy of preventing restenosis and acute coronary syndrome for acute-phase treatment of CAD could not be tested, because patients were excluded from this trial if the onset of CAD had been within 6 months.

When we devised the protocol for JELIS approximately 10 years ago, no target level of LDL-C had been clearly defined. The mean LDL-C value during the observation period of this study was 130 mg/dl, and high levels were controlled rather than meeting a current treatment target value. Though the control of LDL-C level was not satisfactory in this study, we considered the reduction of the risk of CAD with use of EPA to be clinically important. It appears possible that the prevention by EPA of CAD is independent of its control of the LDL-C level. We planned to emulate an evaluation in the real world of medical care, so we did not use a placebo in the control group, and for ethical reason we adopted the additional design parameter of treatment of hypercholesterolemia for all patients by statin administration.

Acknowledgments

We are indebted to all the trial participants; to the large number of physicians, nurses, and hospital staff for their long-term commitment to the study, and to all the patients who participated in the trial.

Disclosure

This study was supported by grants from Mochida Pharmaceutical Co Ltd, Tokyo, Japan. The marketed capsules containing 300 mg EPA ethyl ester were supplied by Mochida Pharmaceutical Co Ltd. The results of this study were presented at the American Heart Association Annual Meeting, Chicago, IL, USA, November, 12–15, 2006. M Matsuzaki received travel costs from Mochida Pharmaceutical Co Ltd, Tokyo, Japan, to participate in the annual scientific meeting. None of the other committee members or investigators received remuneration for performing the study. Clinical trial registration information: NCT00231738 (http://www.clinicaltrials.gov).

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