**Eicosapentaenoic Acid Added to Strong Statin Therapy**  
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### Beneficial Effects of EPA

Statin monotherapy is widely prescribed to treat elevated levels of low-density lipoprotein (LDL) cholesterol and the beneficial effects on clinical outcomes in patients with cardiovascular diseases are recognized worldwide. However, patients have a residual risk despite highly effective statin therapy. A number of studies have been conducted over 10 years to explore the effects of adding other treatments to statins, called ‘Beyond Statin’, such as niacin, cholesteryl ester transfer protein inhibitors, ezetimibe, and eicosapentaenoic acid (EPA).

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The JELIS trial reported that EPA was a promising treatment for the prevention of major coronary events in Japanese hypercholesterolemic patients. In that study, 18,645 patients (14,981 in primary prevention and 3,664 in secondary prevention) with hypercholesterolemia were randomly assigned to receive either 1,800 mg of EPA daily with a statin (EPA group; n=9,326) or a statin only (controls; n=9,319) with a 5-year follow-up. A 19% relative reduction in major coronary events was observed in the EPA group (P=0.011), and serum LDL cholesterol was not a significant factor in the reduction of risk for major coronary events. In the secondary prevention subgroup given EPA treatment, major coronary events were reduced by 19% (P=0.048). However, the JELIS trial did not include patients treated with strong statins.

It has been reported that in the patients with coronary artery disease treated with a strong statin, the changes in destabilized components of coronary artery plaques evaluated by virtual histology intravascular ultrasound correlated negatively with the EPA to arachidonic acid (EPA/AA) ratio independently of LDL cholesterol. In this issue of the Journal, Niki et al report the first study to evaluate the changes in coronary plaque components and local inflammatory cytokines when EPA was given to dyslipidemic patients treated with strong statins. In their study, integrated backscatter intravascular ultrasound (IB-IVUS) was used for the evaluation of coronary artery plaques. IB-IVUS can identify plaques with a high prevalence of thin cap fibroatheroma detected by optical coherence tomography. A significant reduction of lipid volume and a significant increase of fibrous tissue volume were observed in the EPA group, with no change in the total plaque volume. These findings suggest that EPA treatment in addition to a strong statin could further stabilize coronary artery plaque within 6 months. As stabilization of coronary artery plaque is generally followed by a reduction in its volume, the results of this study are consistent with the findings of the previous study. In terms of inflammatory markers, coronary sinus levels of pentraxin (PTX) 3 and monocyte chemoattractant protein (MCP)-1 were reduced by treatment with EPA. These 2 markers are known to be associated with the mechanism of many inflammatory diseases. In particular, the PTX3 level might reflect atherosclerotic activity, local inflammatory status, and plaque instability at the coronary culprit site more directly than other biomarkers. In addition to the changes in plaque components, coronary vessel volumes were reduced in the EPA group more than in the control group, which also reflected the anti-inflammatory effect of EPA.

Regarding the anti-inflammatory effects of EPA, Niki et al explain that its mechanisms were associated with prostaglandins, leukotrienes, nuclear factor-κB, and peroxisome proliferator activated receptor 3. PTX3 and MCP-1 levels were reduced in coronary sinus samples after EPA treatment, but not in femoral vein samples. These results suggest that EPA could improve the inflammation of coronary artery plaques. Recent studies have documented the efficacy of EPA in diseases other than coronary artery disease through improvement of inflammation. EPA prevented abdominal aortic aneurysm.

### Recommendation of EPA Intake in Each Category

<table>
<thead>
<tr>
<th>EPA/AA</th>
<th>&lt;0.4</th>
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<th>0.75-1.0</th>
<th>&gt;1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td>SR</td>
<td>SR</td>
<td>MR</td>
<td>UK</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>SR</td>
<td>MR</td>
<td>UK</td>
<td>NN</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td>MR</td>
<td>UK</td>
<td>NN</td>
<td>NN</td>
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**Figure.** High-risk patients with low EPA/AA ratio need EPA, whereas low-risk patients with high EPA/AA ratio may not need EPA. High risk: secondary prevention with ≥3 risk factors, polyvascular disease or recurrence; Moderate risk: secondary prevention or primary prevention with ≥3 risk factors; Low risk: primary prevention with ≤2 risk factors. AA, arachidonic acid; EPA, eicosapentaenoic acid; MR, moderately recommended; NN, not needed; SR, strongly recommended; UK, unknown.
development through the inhibition of macrophage-mediated inflammation, including MCP-1. Moreover, inflammation may contribute to both the occurrence/maintenance of atrial fibrillation and its thromboembolic complications, and oral intake of EPA may partly prevent atrial fibrillation through anti-inflammatory and anti-oxidative stress effects.

Clinical Use of EPA

When considering candidates for EPA treatment in the present clinical settings, there are 3 important clinical studies. Itakura et al showed that the risk of cardiovascular events in groups with an EPA/AA ratio above 0.75 and 1.0 was significantly lower than in groups with a ratio less than 0.75 (hazard ratio with an EPA/AA ratio above 0.75 and 1.0 was significantly lower than in groups with a ratio less than 0.75 (hazard ratio [HR]=0.83, P=0.031) and 1.0 (HR=0.080, P=0.021). However, there was no significant difference above and below a ratio of 0.5 in the 15,534 patients including both primary and secondary prevention. Next, according to the results of multivariate logistic regression analyses of the study participants, which consisted of 1,037 patients without acute coronary syndrome (ACS) and 72 patients with ACS, the patients in the group with the lowest EPA/AA ratio (<0.33) were more likely to have ACS than the group with a ratio greater than 0.55 (odds ratio [OR]=3.14). Finally, Domei et al measured the serum concentrations of various fatty acids and evaluated their associations with major adverse cardiac events in 284 patients who underwent elective percutaneous coronary intervention. They reported that the patients with a higher EPA/AA ratio (>0.40) had a significantly lower incidence of major adverse cardiac events than those with a lower EPA/AA ratio (<0.40) (P=0.014). From these studies, high-risk patients with lower EPA/AA ratios (<0.40) should be recommended to take EPA, whereas low-risk patients with higher ratios (>1.0) do not need to.

Dietary Management

Lifestyle education is important for patients with cardiovascular diseases. Although scientific evidence indicates that oily fish consumption or dietary supplements containing EPA decrease the risk of mortality from coronary artery disease, serum trans-fatty acid concentrations have been increasing in young patients with coronary artery disease and/or metabolic syndrome in Japan. The Japanese government and physicians should emphasize the importance of dietary treatment, not only the taking of drugs.

References