Several studies have reported that consumption of fish and fish oil containing large amounts of n-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), lowers the risk of cardiovascular events and death.\(^1\)–\(^5\) A large-scale clinical trial also demonstrated that a preparation of pure EPA significantly decreased the incidence of coronary events by 19% in dyslipidemic patients (Japan EPA Lipid Intervention Study; JELIS).\(^6\) In addition, a subanalysis of secondary prevention subjects from JELIS found the risk of cardiovascular death and myocardial infarction (MI) to be significantly lower in the group with a high plasma EPA/alpha-linolenic acid (AA; n-6 PUFA) ratio compared with those with a low ratio.\(^7\) These findings indicated that EPA effectively suppressed cardiovascular events, and that serum EPA/AA ratio may potentially be a predictor of these events.

Both EPA and DHA are incorporated into the phospholipid component of the cell membrane and influence membrane-linked cellular processes.\(^8\) These n-3 PUFAs also suppress the progression of arteriosclerosis by inhibiting platelet aggregation,\(^9\) inflammatory cytokine production, and the expression of adhesion factors,\(^10\) among other properties. Pharmacological differences between EPA and DHA have become clearer in recent years,\(^11\),\(^12\) but it is still unclear as to which of these n-3 PUFAs has a stronger anti-arteriosclerotic effect in terms of pharmacological action.

Previous report showed an association between log AA, log EPA, and log AA/log EPA and prevalence of major adverse cardiac events (MACE) after acute MI (AMI).\(^13\) In addition, Lee et al reported that plasma EPA level, but not plasma DHA level, is a predictor of MACE in patients with AMI.\(^14\) The present study focused on secondary prevention by examining the relationship between MACE and serum PUFA parameters (levels of EPA, DHA, AA, and the ratio of n-3 S

**Background:** The relationship between major adverse cardiac events (MACE) and serum polyunsaturated fatty acid (PUFA) parameters has not been well documented in patients who have undergone percutaneous coronary intervention (PCI). The aim of the present study was to investigate this relationship.

**Methods and Results:** A total of 284 consecutive patients who underwent elective PCI were enrolled and stratified according to median serum levels of n-6 PUFAs (arachidonic acid [AA]), n-3 PUFAs (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), and serum EPA/AA and DHA/AA ratios. The relationship between these PUFA parameters and the incidence of MACE including cardiac death, acute coronary syndrome, PCI for de novo lesions, and coronary artery bypass grafting, was analyzed. Multivariate analysis showed that among the PUFA parameters, only a high serum EPA/AA ratio was significantly associated with a low incidence of MACE in all the models tested (model A, without adjusted variables: hazard ratio [HR], 0.52; 95% confidence interval [CI]: 0.27–0.99, \(P=0.048\); model B, adjusted for age and diabetes: HR, 0.51; 95%CI: 0.26–0.98, \(P=0.043\); model C, adjusted for age, sex, diabetes, hypertension, smoking, and low-density lipoprotein cholesterol: HR, 0.49; 95%CI: 0.25–0.94, \(P=0.033\)).

**Conclusions:** The incidence of MACE in patients who have undergone PCI is significantly associated with serum EPA/AA ratio. (Circ J 2012; 76: 423–429)

**Key Words:** Major adverse cardiac events; Percutaneous coronary intervention; Serum EPA/AA ratio
PUFAs to n-6 PUFA) that had a major effect on prognosis after elective percutaneous coronary intervention (PCI).

**Methods**

**Subjects**
A total of 284 consecutive patients who underwent elective PCI due to angina pectoris in Kokura Memorial Hospital from September 2007 to November 2007 were enrolled in the present study. Patients with AMI or unstable angina pectoris (UAP), and patients with failed PCI were excluded. The study was approved by the hospital’s ethics committee.

**Serum Fatty Acids**
The serum levels of EPA, DHA, and AA in fasting blood samples on the morning of PCI were analyzed at an external laboratory (SRL, Tokyo, Japan). In brief, plasma lipids were extracted by Folch’s procedure, and then fatty acids (tricosanoic acid, C23:0, as the internal standard) were methylated with boron trifluoride and methanol. The methylated fatty acids were then analyzed using a capillary gas chromatograph (GC-2010; Shimadzu, Kyoto, Japan).

**Other Variables**
Information on age, sex, and history of smoking, hypertension, lipid disorders, and diabetes mellitus was collected in self-administered questionnaires at baseline. Other serum lipid parameters, including the serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride, and HbA1c (diabetic parameter) were measured in the fasting state prior to PCI. Prescribed medication was checked at the time of discharge. At the time of admission, if the patients met the following criteria, these diseases were added to the baseline characteristics: hypertension, systemic arterial pressure >140 mmHg or diastolic pressure >90 mmHg or treatment with anti-hypertensive agents;
diabetes mellitus, diabetic criteria approved by the Japanese Diabetes Society or treatment with insulin or any oral hypoglycemic agents; dyslipidemia: LDL-cholesterol >140 mg/dl or HDL-cholesterol <40 mmHg or triglyceride >150 mg/dl or treatment with any lipid lowering agents.

Procedure
The patients were followed from September 2007 to June 2009. The average follow-up period was 537±126 days (range, 17–627 days).

The primary endpoint was the cumulative incidence of MACE, that is, cardiac death, acute coronary syndrome (ACS) including fatal/non-fatal MI or UAP, PCI for de novo lesions, and coronary artery bypass grafting (CABG).

PCI for de novo lesions or CABG was defined as coronary angioplasty in the case of recurrent angina with development of significant coronary stenosis. Patients who had difficulty visiting hospital (12 patients; 4% of all patients; eg, patients living too far away) were followed up via telephone interviews with the patients or their home doctors.

The subjects were stratified according to median serum levels of EPA, DHA, and AA, and EPA/AA and DHA/AA ratios; the relationship between these PUFA parameters and the incidence of MACE was analyzed.

Statistical Analysis
Continuous data are expressed as mean±SD or median (interquartile range) where appropriate. For univariate analysis, the Wilcoxon 2-sample test was used to compare continuous variables, and the chi-square test to compare categorical variables. Pearson’s test was used to estimate the correlation between serum PUFA parameters. The relationship between median PUFA parameters and the incidence of MACE was also investigated using Cox’s proportional hazards model. The cumulative probability of MACE was estimated using the Kaplan–Meier method with log-rank test. Statistical analyses were performed using JMP version 5.0.1a (SAS Institute, Cary, NC, USA). All reported P-values were 2-sided, and P<0.05 was regarded as statistically significant.

Results
Baseline Characteristics and Incidence of MACE
Subject baseline characteristics are listed in Table 1. Follow-up rate in the 284 patients was 100%, with 52 patients (124 per 1,000 person-years) experiencing MACE during the follow-up period (cardiac death, n=2; ACS, n=3; PCI for de novo lesions, n=38; CABG, n=9). Univariate Cox proportional hazards analysis of the association between the baseline characteristics and MACE is given in Table 2. The hazard ratio (HR) for the incidence of MACE was significantly lower in patients with higher serum EPA (HR, 0.54; 95% confidence interval [CI]: 0.30–0.95; P=0.031) and higher EPA/AA ratio (HR, 0.50; 95%CI: 0.27–0.87; P=0.013). In contrast, the HR was significantly higher in patients with diabetes (HR, 2.23; 95%CI: 1.27–4.03; P=0.005). The other variables, including the remaining lipid parameters, showed no significant relationship with the incidence of MACE (Table 2).

Table 2. MACE Univariate Analysis (Cox Proportional Hazards)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA &gt;150.4 μg/ml</td>
<td>1.06</td>
<td>0.61–1.83</td>
<td>0.840</td>
</tr>
<tr>
<td>EPA &gt;62.0 μg/ml</td>
<td>0.54</td>
<td>0.30–0.95</td>
<td>0.031</td>
</tr>
<tr>
<td>DHA &gt;134.1 μg/ml</td>
<td>0.59</td>
<td>0.33–1.02</td>
<td>0.060</td>
</tr>
<tr>
<td>EPA/AA &gt;0.4037</td>
<td>0.50</td>
<td>0.27–0.87</td>
<td>0.013</td>
</tr>
<tr>
<td>DHA/AA &gt;0.8716</td>
<td>0.65</td>
<td>0.37–1.13</td>
<td>0.127</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.61</td>
<td>0.84–3.40</td>
<td>0.155</td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.96–1.00</td>
<td>0.096</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02</td>
<td>0.55–2.03</td>
<td>0.951</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.23</td>
<td>1.27–4.03</td>
<td>0.005</td>
</tr>
<tr>
<td>CKD (eGFR &lt;60 ml/min/1.73m²)</td>
<td>1.00</td>
<td>0.57–1.73</td>
<td>0.995</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.50</td>
<td>0.80–2.67</td>
<td>0.201</td>
</tr>
<tr>
<td>BMI</td>
<td>0.99</td>
<td>0.92–1.07</td>
<td>0.806</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.00</td>
<td>0.99–1.01</td>
<td>0.735</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.00</td>
<td>0.98–1.02</td>
<td>0.867</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.638</td>
</tr>
</tbody>
</table>

MACE, major adverse cardiac events; HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease. Other abbreviations see in Table 1.

Table 3. Correlation of Serum PUFAs

<table>
<thead>
<tr>
<th></th>
<th>EPA</th>
<th>DHA</th>
<th>AA</th>
<th>EPA/AA</th>
<th>DHA/AA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P value</td>
<td>r</td>
<td>P value</td>
<td>r</td>
</tr>
<tr>
<td>EPA</td>
<td>0.65</td>
<td>&lt;0.0001</td>
<td>0.15</td>
<td>0.013</td>
<td>0.91</td>
</tr>
<tr>
<td>DHA</td>
<td>0.65</td>
<td>&lt;0.0001</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>0.45</td>
</tr>
<tr>
<td>AA</td>
<td>0.15</td>
<td>0.013</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>0.24</td>
</tr>
<tr>
<td>EPA/AA</td>
<td>0.91</td>
<td>&lt;0.0001</td>
<td>0.45</td>
<td>&lt;0.0001</td>
<td>0.24</td>
</tr>
<tr>
<td>DHA/AA</td>
<td>0.53</td>
<td>&lt;0.0001</td>
<td>0.73</td>
<td>&lt;0.0001</td>
<td>0.32</td>
</tr>
</tbody>
</table>

PUFA, polyunsaturated fatty acid. Other abbreviations see in Table 1.
Table 4. MACE Multivariate Analysis (Cox Proportional Hazards)

<table>
<thead>
<tr>
<th>Analysis 1</th>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher EPA (&gt;62.0 μg/ml)</td>
<td>HR (95%CI), P value</td>
<td>0.63 (0.33–1.16), 0.14</td>
<td>0.56 (0.29–1.07), 0.079</td>
</tr>
<tr>
<td>Higher DHA (&gt;134.1 μg/ml)</td>
<td>HR (95%CI), P value</td>
<td>0.71 (0.37–1.32), 0.28</td>
<td>0.78 (0.40–1.50), 0.46</td>
</tr>
<tr>
<td>Higher AA (&gt;150.4 μg/ml)</td>
<td>HR (95%CI), P value</td>
<td>1.16 (0.67–2.02), 0.60</td>
<td>1.08 (0.61–1.92), 0.78</td>
</tr>
</tbody>
</table>

Analysis 2

| Higher EPA/AA ratio (>0.4037) | HR (95%CI), P value | 0.52 (0.27–0.99), 0.048 | 0.51 (0.26–0.98), 0.043 | 0.49 (0.25–0.94), 0.033 |
| Higher DHA/AA ratio (>0.8716) | HR (95%CI), P value | 0.89 (0.47–1.66), 0.73 | 1.03 (0.54–1.94), 0.93 | 1.07 (0.55–2.03), 0.83 |

Model A, no adjusted factors; model B, adjusted for age, diabetes; model C, adjusted for age, gender, diabetes, hypertension, smoking, LDL-C.
Abbreviations see in Tables 1, 2.

Table 5. MACE vs. EPA/AA Ratio

<table>
<thead>
<tr>
<th>Lower EPA/AA (≤0.4037)</th>
<th>Higher EPA/AA (&gt;0.4037)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>34/142 (23.9)</td>
<td>18/142 (12.7)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2/142 (1.4)</td>
<td>0/142 (0)</td>
</tr>
<tr>
<td>ACS</td>
<td>2/142 (1.4)</td>
<td>1/142 (0.70)</td>
</tr>
<tr>
<td>PCI for de novo lesion</td>
<td>26/142 (18.3)</td>
<td>12/142 (8.5)</td>
</tr>
<tr>
<td>CABG</td>
<td>4/142 (2.8)</td>
<td>5/142 (3.5)</td>
</tr>
</tbody>
</table>

Data given as n (%).
ACS, acute coronary syndrome. Other abbreviations see in Table 1.
MACE include cardiac death, ACS, PCI for de novo lesion, and CABG.

Figure. Kaplan-Meier survival curves: lower vs. higher eicosapentaenoic acid/ arachidonic acid (EPA/AA) ratio. MACE, major adverse cardiac events.
Correlations Between PUFAs

Table 3 shows the correlations between serum PUFAs. Serum n-3 and n-6 PUFAs all showed significant positive correlation with each other. Serum EPA/AA and DHA/AA ratios were also significantly correlated (Table 3).

Multivariate Analysis of MACE

Based on the strong correlation between the PUFA parameters, a multivariate analysis of MACE prevalence was performed using 2 types of analysis: analysis 1 using EPA, DHA, and AA levels as covariants, and analysis 2 using EPA/AA and DHA/AA ratios as covariants. Three types of models were used in each analysis: model A, without adjusted variables; model B, adjusted for age and diabetes; and model C, adjusted for age, sex, diabetes, hypertension, smoking, and LDL-cholesterol. No significant relationship was observed between the incidence of MACE and serum EPA, DHA, or AA levels in all models (Table 4, analysis 1). In contrast, when analysis was carried out using serum EPA/AA and DHA/AA ratios, a higher serum EPA/AA ratio was found to have a significant association with a lower incidence of MACE in all models (model A: HR, 0.52; 95% CI: 0.27–0.99, P=0.048; model B: HR, 0.51; 95% CI: 0.26–0.98, P=0.043; model C: HR, 0.49; 95% CI: 0.25–0.94, P=0.033), while no significant association was seen between serum DHA/AA ratio and the incidence of MACE (Table 4, analysis 2).

Comparison of Higher and Lower EPA/AA Ratios Using Kaplan-Meier Survival Curves

With the exception of sex, there were no significant differences in baseline characteristics and medications between the lower and higher EPA/AA groups (Table 1). Figure shows Kaplan-Meier curves for MACE in the 2 groups. One hundred and sixty-eight people per 1,000 person-years (34/142) in the lower EPA/AA group and 83 people per 1,000 person-years (18/142) in the higher EPA/AA group experienced MACE (Figure). The lower EPA/AA group had a significantly higher incidence of MACE than the higher EPA/AA group (log-rank test; P=0.014).

Details of MACE

Comparison of the lower and higher EPA/AA groups showed that the incidence of PCI in de novo lesions was higher in the lower EPA/AA group (18.3% vs. 8.5%; P=0.015). The incidence of cardiac death, ACS, and CABGi, however, was not significantly different between the 2 groups (1.4% vs. 0%, P=0.16; 1.4% vs. 0.70%, P=0.56; 4% vs. 3.5%, P=0.73, respectively; Table 5).

Discussion

Univariate analysis of the present data has shown that diabetes, low serum EPA, and low serum EPA/AA ratio to be significant predictors of coronary artery disease (CAD) in patients undergoing elective PCI. As indicated in previous reports, blood levels of n-3 PUFAs such as EPA and DHA as well as their ratios to AA influenced the development of coronary atherosclerosis and CAD. In contrast, according to the present results, LDL-cholesterol and hypertension were not identified as risk factors for MACE, with HR of 1.00 and 1.02, respectively. This finding may be attributed to the fact that the present analysis was conducted in patients who underwent elective PCI, and whose conditions were already under control to some extent (ie, mean LDL-cholesterol, 113.2±30.2mg/dl; mean systolic pressure, 135.5±20.9mmHg; and mean diastolic pressure, 75.7±12.8mmHg). We analyzed the effect of fatty acids using the 3 multivariate analysis models. Serum EPA, DHA, and AA levels had no significant association with the incidence of MACE in all models. These multivariate analyses did not show serum EPA and DHA levels to be prognostic predictors of CAD in patients who had undergone elective PCI. In contrast, on multivariate analysis using serum EPA/AA and DHA/AA ratios, only high EPA/AA ratio was significantly associated with low risk for MACE in all models. Matsuzaki et al have previously reported that changes in the serum ratio of n-3 PUFAs to n-6 PUFAs, expressed as the ratio of EPA to AA, were predictive of coronary death and MI, and that cardioprotective effects, other than arrhythmia reduction, may be observed in populations such as the Japanese who consume large quantities of fish with higher doses of n-3 PUFAs.

Although accumulated evidence has demonstrated the efficacy of n-3 PUFAs in suppressing cardiovascular events, the parameter that is the best surrogate marker of PUFAs remains unclear. The present study found a lower EPA/AA ratio to be associated with a higher incidence of coronary events, indicating that serum EPA/AA ratio may play a key role in promoting atherosclerosis, and have the potential to be an important index for predicting cardiovascular events.

EPA has several cardioprotective effects such as antihyperlipidemic and anti-inflammatory actions, reduction of platelet aggregation, attenuation of myocardial ischemic reperfusion injury, a vasodilatory effect, enhancement of red cell deformability, and stabilization of atherosclerotic plaques. In contrast, oversupply of n-6 PUFA causes increased production of pro-inflammatory, proaggregative, and vasoconstrictive eicosanoids such as prostaglandin I2, E2, thromboxane A2, and leukotriene B4. Furthermore, n-3 and n-6 PUFAs compete in metabolic pathways that affect cellular responses to physiologic stress. In non-fish-eating populations, eicosanoids are derived mainly from AA, and the pro-inflammatory, proaggregative, and vasoconstrictive eicosanoid series such as prostaglandin I2/E2, thromboxane A2, and leukotriene B4 are involved in the physiologic responses in cell membranes. In populations with high intake of fish, the eicosanoid series derived from EPA (eg, prostaglandin I3/E3, thromboxane A3, and leukotriene B5), which are less inflammatory, aggregatory, and vasoconstrictive, play a greater role. These different metabolic effects of EPA and AA was one of the reasons why the serum EPA/AA ratio was related to the prevalence of MACE.

Three previous studies have examined the effect of fish oil supplementation on the fatty acid (EPA + DHA) composition of atherosclerotic plaques. Rapp et al found substantial incorporation of EPA and DHA into plaque lipids following consumption of a very high dose of fish oil (48–64 g/day providing 16–21 g EPA + DHA/day). In contrast, 2 other studies using considerably lower doses of EPA and DHA (0.81 g EPA and 0.675 g DHA/day) found significantly higher levels of EPA in atherosclerotic plaques than DHA. Moreover, plaques from patients treated with fish oil had fewer thin fibrous caps and signs of inflammation, with more plaques containing thick fibrous caps, no signs of inflammation, and lower levels of inflammatory agents and mRNA for matrix metalloproteinases (MMP-7 and -12), interleukin-6, and intercellular adhesion molecules. In fact, data on a Japanese sample showed that high serum EPA was significantly related to a low risk of coronary events, whereas serum DHA had no such relationship.

With regard to protection against atherosclerosis, these results indicate that plaque characteristics are different for EPA and DHA, with EPA being more easily incorporated into...
atherosclerotic plaques, resulting in a stronger protective effect against progression of atherosclerotic plaques compared to DHA. The present results confirm these findings in that the serum EPA/AA ratio was significantly related to incidence of MACE, while serum DHA/AA ratio was not.

The serum EPA levels and EPA/AA ratios measured in the present study were relatively low compared to those reported in the JELIS study conducted in Japanese patients (62 μg/ml vs. 95 μg/ml, 0.40 vs. 0.62, respectively). In addition, Itakura et al set the cut-off level of plasma EPA/AA ratio for MACE at 0.75 in their subanalysis of the JELIS data. Of the subjects enrolled in JELIS, however, 80% included cases of primary prevention, with EPA being analyzed in one-half of the subjects only. The background and study design of the JELIS study greatly differed from the present study in that it was an observational study and the subjects were confined to cases of secondary prevention without EPA treatment. Therefore, we considered this difference in patient characteristics to have led to the difference in serum EPA level and EPA/AA ratio measured in the 2 studies, and accordingly, it may be inappropriate to adopt the JELIS cut-off for risk stratification in high-risk populations for secondary prevention.

There is evidence, however, that EPA has greater efficacy especially in individuals with high risk of coronary events, such as those with multiple coronary risk factors and those with history of coronary events or peripheral artery disease. Taken together, these previous reports and the present data indicate that individuals at high risk for atherosclerotic disease, such as patients who undergo PCI, have a propensity for lower serum EPA and disturbed EPA/AA ratio. Consequently, giving EPA to this high-risk population would increase serum EPA level and EPA/AA ratio, resulting in improved clinical outcome. Although the use of drug-eluting stents (DES) dramatically decreases in-stent restenosis, the incidence of serious cardiac events, such as MI and death, has been shown to be similar to that with DES and bare metal stents, thereby introducing a new problem. As reported by Cutlip et al, coronary events in the second and subsequent years preferentially occur at new lesions than at the indwelling stent site. Therefore, in patients who have undergone PCI, attention should be paid not only to recurrent stenosis at the PCI site but also to the control of unstable plaques in other branches and the progression of atherosclerosis in the whole body. Even if conventional factors that suppress the onset of CAD after PCI, such as LDL-cholesterol, blood pressure, and diabetes, are well controlled, a residual risk for the recurrence of atherosclerotic disease still exists. Multivariate analysis indicated that serum EPA/AA ratio is an independent predictor of atherosclerotic events, which represents a current issue in patients undergoing PCI. Thus, in addition to the aforementioned factors that are important for reducing the risk of atherosclerotic events after PCI, the serum EPA/AA ratio should also be considered responsible for lowering this risk further, thereby improving long-term prognosis.

Study Limitations
Current data indicated that serum EPA/AA ratio could predict future coronary arterial events, and was useful for clinical treatment of CAD. The number of patients in the present study, however, was too small to determine the cut-off value for the ratio and to adequately examine its relationship with other cardiac events having lower incidences. A large-scale study should therefore be performed to determine the cut-off value, and to adequately evaluate the relationship between serum EPA/AA ratio and other cardiac events with lower incidence such as cardiac death, MI, or arrhythmias.

Conclusion
The incidence of MACE in patients who have undergone PCI is significantly associated with serum EPA/AA ratio.

Disclosures
Sources of financial support: Institutional support only. Conflicts of interest: None of the authors have any real or perceived conflicts of interest.

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