

## Which Is Better to Prevent Cardiovascular Events, Only EPA or the Combination of EPA and DHA?

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Anti-atherosclerotic effects of n-3 fatty acids (FA) include reduction of serum triglyceride (TG), increase of serum high-density lipoprotein (HDL), anti-platelets effects, anti-inflammatory effects, improvement of endothelial function, increased stability of plaque and improvement of blood rheology [1].

Very recently, we studied the effects of the switching from high-purity eicosapentaenoic acid ester (hp-EPA) to n-3 FA formulation containing EPA and docosahexaenoic acid (DHA) on metabolic parameters [2]. In patients with baseline TG  $\geq$  150 mg/dL, TG tended to decrease. In the analysis of patients who underwent the switching to the formulation including the same daily dose of EPA and DHA, in patients with baseline TG  $\geq$  150 mg/dL, TG significantly decreased, indicating that the switching is more effective to reduce TG in patients with higher TG levels at baseline.

In the epidemiological study, the multivariate relative risk of coronary heart disease adjusting for coronary risk factors and time since last meal associated with a 1-mmol/L increase in TG was 1.29 (95% confidence interval (CI): 1.09 - 1.53;  $P = 0.004$ ) for men and 1.42 (95% CI: 1.15 - 1.75;  $P = 0.001$ ) for women, suggesting that elevation of serum TG is a crucial risk factor for cardiovascular events [3]. Considering that, together with our result, the combination of EPA and DHA is more effective to prevent cardiovascular events than only EPA.

Statins are the "gold standard" for the treatment to prevent cardiovascular diseases. To evaluate the cardio-protective effects of some drugs in clinical trials, we should consider whether trial participants take statins or not. In Japan EPA lipid intervention study (JELIS), all participants had taken statins (Table 1) [4-8]. The primary endpoint was detected in 262 (2.8%) patients in the EPA group and 324 (3.5%) in controls, a 19% relative reduction in major coronary events ( $P = 0.011$ ).

In the GISSI-Prevenzione (GISSI-P) trial, the treatment with n-3 FA (EPA + DHA) significantly lowered the risk of the primary endpoint (relative risk decrease 15% (95% CI, 2 - 26)) [5]. In the GISSI-HF trial, 955 (27%) patients died from any cause in the n-3 PUFA (EPA + DHA) group and 1,014 (29%) in the placebo group (adjusted hazard ratio (HR) 0.91 (95.5%

CI: 0.833 - 0.998),  $P = 0.041$ ) [6]. One thousand nine hundred eighty-one (57%) patients in the n-3 FA group and 2,053 (59%) in the placebo group died or were admitted to hospital for cardiovascular reasons (adjusted HR 0.92 (99% CI: 0.849 - 0.999),  $P = 0.009$ ). The percentages of subjects who had taken statins were only 4.7% and 22.6% in GISSI-P and GISSI-HF trials, respectively.

In the recent OMEGA study, the event rates were (n-3 FA (EPA + DHA) and control groups) as follows: sudden cardiac death, 1.5% and 1.5% ( $P = 0.84$ ); total mortality, 4.6% and 3.7% ( $P = 0.18$ ); major adverse cerebrovascular and cardiovascular events, 10.4% and 8.8% ( $P = 0.1$ ); and revascularization in survivors, 27.6% and 29.1% ( $P = 0.34$ ) [7]. In the ORIGIN trial, the incidence of the primary outcome was not significantly decreased among patients receiving n-3 FA (EPA + DHA), as compared with those receiving placebo (574 patients (9.1%) vs. 581 patients (9.3%); hazard ratio: 0.98; 95% CI: 0.87 - 1.10;  $P = 0.72$ ) [8].

In the previous two studies (GISSI-P and GISSI-HF), EPA + DHA may be effective to prevent cardiovascular events because of fewer combined use of statins. In the recent studies (OMEGA and ORIGIN) which included many participants who had taken statins, EPA + DHA failed to reduce cardiovascular events. However, EPA demonstrated a significant reduction of cardiovascular events in JELIS, in which all participants had taken statins.

We should consider how EPA or DHA reduces cardiovascular events independently of TG reduction. EPA or DHA may reduce cardiovascular events, due to decrease of inflammation and/or platelets activity, or the improvement of vascular integrity. Significant but slight differences in TG reduction between the n-3 FA group and controls in JELIS, GISSI-P and GISSI-HF support my hypothesis.

### Conflicts of Interest

The author declares no conflicts of interest concerning this article.

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**Table 1.** Clinical Trials to Test the Effects of n-3 Fatty Acids (FA) on Cardiovascular Events

| Trials       | Subjects  | Subjects who had taken statins (%) | EPA (mg/day) | DHA (mg/day) | Changes in TG  | Endpoints  | Risk reduction or increase by n-3 FA (P value)  |
|--------------|---|------------------------------------|--------------|--------------|--|--|---|
| JELIS [4]    | Hypercholesterolemic patients (n = 18,645)  | 100                                | 1800         | 0            | Decrease by 9% in the EPA group and by 4% in control (P < 0.0001 between groups)   | Sudden cardiac death, fatal and non-fatal myocardial infarction, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting | 19% reduction (P = 0.011)   |
| GISSI-P [5]  | Patients surviving recent ( $\leq 3$ months) myocardial infarction (n = 11,324)   | 4.7                                | 464 - 482    | 386 - 400    | Compared with controls (+1.4%), the small decrease in TG was significant in the n-3 FA group (-3.4%)   | Death, non-fatal myocardial infarction, non-fatal stroke   | 10% reduction (P = 0.048)   |
| GISSI-HF [6] | Patients with chronic heart failure (n = 6,975)   | 22.6                               | 464 - 482    | 386 - 400    | TG decreased slightly from a median value of 1.42 mmol/L at baseline to 1.36 mmol/L after 1 year and 1.34 mmol/L after 3 years, in the n-3 FA treatment group, but did not change in the placebo group | Death<br>Death or admission to hospital for cardiovascular reasons   | 9% reduction (P = 0.041)<br>8% reduction (P = 0.009)  |
| OMEGA [7]    | Patients surviving acute (3 - 14 days) myocardial infarction (n = 3,851)  | 94.2                               | 460          | 380          | Small difference in favor of the n-3 FA group (n-3 FA group, 1.37 mmol/L (1.00 - 2.01 mmol/L); control group, 1.43 mmol/L (1.05 - 2.09 mmol/L); P < 0.01)  | Sudden cardiac death<br>Total mortality<br>Major adverse cerebrovascular and cardiovascular events<br>Revascularization                              | 0% (P = 0.84)<br>19.6% increase (P = 0.18)<br>15.4% increase (P = 0.1)<br>5.4% reduction (P = 0.34) |
| ORIGIN [8]   | Patients who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance, or diabetes (n = 12,356) | 53.8                               | 465          | 375          | The n-3 FA group showed a mean reduction in the TG of 14.5 mg/dL, as compared with the placebo group (P < 0.001)   | Death from cardiovascular causes   | 2% reduction (P = 0.72)   |

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