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Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS)

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Abstract

Background: Japan EPA Lipid Intervention Study (JELIS) was a large-scale clinical trial examining the effects of eicosapentaenoic acid (EPA) on coronary artery disease (CAD) in hypercholesterolemic patients. Herein, we focused on risk factors other than low-density lipoprotein cholesterol (LDL-C) to investigate the effects of EPA on CAD among JELIS primary prevention cases.

Methods: Hypercholesterolemic patients on statin therapy but without evidence of CAD ($n = 14{,}981$) were randomly assigned to an EPA group ($n = 7503$) or a control group ($n = 7478$). The relationships between incident CAD, the number of CAD risk factors (hypercholesterolemia; obesity; high triglyceride (TG) or low high-density lipoprotein cholesterol (HDL-C); diabetes; and hypertension) and EPA treatment were investigated.

Results: For the control and EPA groups combined, a higher number of risk factors was directly associated with an increased incidence of CAD. Incidence was lower for the EPA group than for the control group regardless of the numbers of risk factors. Compared to patients with normal serum TG and HDL-C levels, those with abnormal levels (TG ≥150 mg/dL; HDL-C <40 mg/dL) had significantly higher CAD hazard ratio (HR: 1.71; 95% CI: 1.11–2.64; $P = 0.014$). In this higher risk group, EPA treatment suppressed the risk of CAD by 53% (HR: 0.47; 95% CI: 0.23–0.98; $P = 0.043$).

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Conclusions: Multiple risk factors besides cholesterol are associated with markedly increased incidence of CAD. High TG with low HDL-C represents a particularly potent risk factor. EPA was effective in reducing the incidence of CAD events for patients with this dyslipidemic pattern, suggesting that EPA may be especially beneficial in patients who with abnormal TG and HDL-C levels (NCT00231738).

Keywords: JELIS; Eicosapentaenoic acid; Primary prevention; Coronary artery disease; Risk factors; HDL-C; Triglycerides

1. Introduction

Eicosapentaenoic acid (EPA) is one of the n-3 polyunsaturated fatty acids (PUFA) found large quantities in fish oil. Ever since Dyerberg and Bang reported that EPA levels were high in the blood and diets of Greenland Inuit (who have low prevalence of atherosclerotic diseases [1]), the preventive effects of n-3 PUFA, including EPA, has been examined in many epidemiological and clinical studies [2–6]. Most studies have found that intake of fish and fish oil are related to reduced risk for total mortality, sudden death and coronary artery disease (CAD). Furthermore, randomized controlled intervention trials have suggested the suppressive effects of fish and fish oil consumption on CAD [7].

Using a highly purified (≥98%) EPA, not a mixture of several fatty acids, i.e., fish oil, we conducted a randomized controlled trial, the Japan EPA Lipid Intervention Study (JELIS; ClinicalTrials.gov number, NCT00231738) [8], and reported that pure EPA suppressed CAD even in Japanese hypercholesterolemic patients who routinely consume a large amount of EPA and DHA from fish [5]. In the JELIS, EPA had no significant effect on total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) levels indicating that EPA can lower CAD risk by mechanisms other than LDL-C lowering.

Besides LDL-C, other risk factors for CAD include obesity, dislipidemia, impaired glucose metabolism and hypertension. When present together in the same patients, these risk markers constitute a syndrome called the visceral fat syndrome, syndrome X, insulin-resistant syndrome and the metabolic syndrome [9–14]. Compared to patients with only one of these risk factors, incidence of CAD in patients with multiple factors is higher [15,16]. In addition, we assumed that EPA would suppress CAD even in patients at high risk. The present study focused on CAD risk associated with increasing numbers of non-LDL-C risk factors in hypercholesterolemic patients and the effects of EPA on the risk for CAD in these patients.

2. Materials and methods

2.1. Study design and patients

The study design of the JELIS, including inclusion and exclusion criteria, has been reported in detail [17]. Briefly, hypercholesterolemic patients with serum TC levels ≥250 mg/dL (men: 40–75 years; women: postmenopausal-75 years) were followed for up to 5 years (mean: 4.6 years) using the prospective, randomized, open-label, blinded endpoint evaluation (PROBE) method. A total of 18,645 patients were registered and randomly assigned to either the EPA with statin (EPA group) or to statin alone (control group). Eighty percent ($n = 14{,}981$) of the patients had no history of CAD and are the subject of this report.

2.2. Procedures

Dietary guidance was provided for all patients before the start of and during the study. All patients received 10 mg of pravastatin or 5 mg of simvastatin administered once a day. In the EPA group, two 300-mg capsules containing EPA ethylester (EPA-E) with >98% purity were administered 3 times/day, for a total daily dose of 1800 mg.

2.3. Primary endpoint

The primary endpoint was major coronary events (MCE), comprising: sudden cardiac death; fatal myocardial infarction; nonfatal myocardial infarction; unstable angina pectoris including hospitalization for documented ischemic episodes; and angioplasty/stenting or coronary artery bypass grafting. MCE was reported by primary physicians and was examined by the case report committee without knowledge of groups' assignment.

2.4. Risk factors

The following five risk factors were of primary interest for this report and were defined as indicated at the time of registration:

A. *Hypercholesterolemia*: untreated serum TC ≥250 mg/dL (all subjects in JELIS had serum TC ≥250 mg/dL).
B. *Obesity*: body mass index (BMI) ≥25 kg/m^2.
C. *Dyslipidemia*: serum triglyceride (TG) ≥150 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL.
D. *Diabetes*: physician-diagnosis or fasting plasma glucose ≥126 mg/dL and/or hemoglobin A_{1C} ≥6.5%.
E. *Hypertension*: physician-diagnosis or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

Furthermore, all subjects were divided into the following four subgroups: based on the following serum TG and HDL-C levels at the time of registration:

1. TG <150 mg/dL and HDL-C ≥40 mg/dL (low TG/high HDL-C group).
2. TG ≥150 mg/dL and HDL-C ≥40 mg/dL (high TG/high HDL-C group).
3. TG <150 mg/dL and HDL-C <40 mg/dL (low TG/low HDL-C group).
4. TG ≥150 mg/dL and HDL-C <40 mg/dL (high TG/low HDL-C group).

2.5. Statistical analysis

All analyses were intention-to-treat with the level of significance set at $P < 0.05$ (two-sided). A Wilcoxon two-sample test was used to compare continuous variables. A chi-square test was used to compare class variables. Kaplan–Meier methods, the log-rank test, and the Cox proportional hazard model were used for survival analysis. The Cox proportional hazard model was adjusted for age, gender, smoking, diabetes and hypertension. However, we chose age, gender and smoking as adjusted factors to analyze the relationships between multiple risk factors and the incidence of MCE. We computed the power to detect the difference in CAD incidence between EPA and control groups for patients with high TG and low HDL-C. With a total of 957 patients in the high TG/low HDL-C group, we could detect a difference in MCE incidence of 1% vs. 0.5% with a power of 57%. The analysis plan for this sub-study was pre-specified according to the study hypothesis before the analysis was initiated. All analyses were conducted using SAS software (version 8.12; SAS Institute, Cary, NC).

3. Results

Subject characteristics have been previously reported [8]. The number of patients with hypertension and/or diabetes differed slightly from that originally published because the original designations were based only on physician-diagnosed diabetes or hypertension only. As a result, number of patients with diabetes was 1238 in control group, and 1258 in EPA group. In the same way, number of patients with hypertension was 4004 in control group, and 4015 in EPA group.

Risk for MCE increased in both the EPA and the control groups with increasing numbers of risk factors. The incidence of MCE was lower, but not statistically significant, for the EPA group than for the control group with each number of risk factors (Fig. 1).

Compared to the low TG/high HDL-C reference group, HR for MCE was increased only in the high TG/low HDL-C group (HR: 1.71; 95% CI: 1.11–2.64; $P = 0.014$; Fig. 2). Other risk factors were compared to the high TG/low HDL-C group, those in the low TG/high HDL-C group had no significant differences in TC or LDL-C but the proportions of male patients, smokers and drinkers; BMI; the prevalence of diabetes and high diastolic blood pressure. Furthermore,

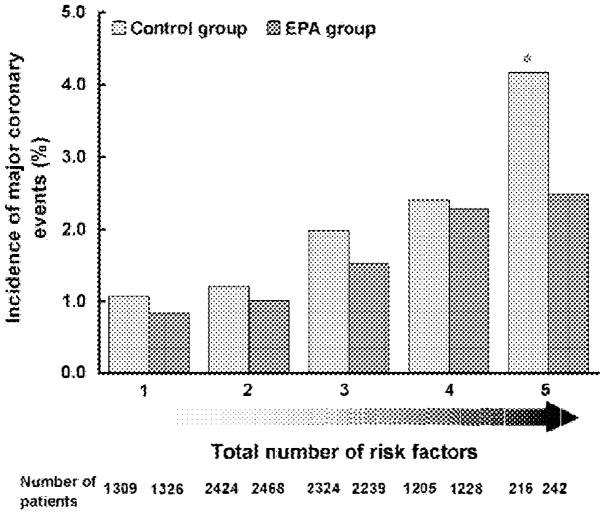
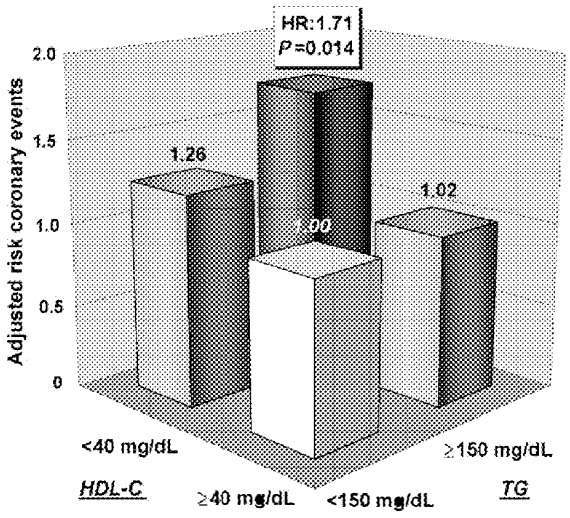


Fig. 1. Multiple risk factors and the incidence of MCE. Number of risk factors at the time of registration was counted: Risk A, hypercholesterolemia (all patients); Risk B, body mass index (BMI) ≥25; Risk C, triglyceride ≥150 mg/dL or HDL-cholesterol <40 mg/dL; Risk D, diabetes; Risk E, hypertension. The Cox proportional hazard model was adjusted for age, gender, smoking. *$P < 0.05$ vs. risk number 1 in the control group.



TG and HDL-C (mg/dL)	Events	(%)	P	HR	95%CI
TG<150 , HDL-C≥40	86 / 6614	1.3		1.00	
TG≥150 , HDL-C≥40	97 / 6095	1.6	0.923	1.02	0.75 - 1.37
TG<150 , HDL-C<40	4 / 196	2.0	0.653	1.26	0.46 - 3.45
TG≥150 , HDL-C<40	32 / 957	3.3	0.014	1.71	1.11 - 2.64

Fig. 2. Incidence of MCE and triglyceride and HDL-cholesterol levels at the time of registration for the combined EPA and control group. Hazard ratio and P value adjusted for age, gender, smoking, diabetes, and hypertension. HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HR, hazard ratio; CI, confidence interval.

Table 1
Patient background factors at time of registration and triglyceride and HDL-cholesterol levels

	TG < 150, HDL ≥ 40 (n = 6614)	TG ≥ 150, HDL < 40 (mg/dL) (n = 957)	P
Age (years)	61 ± 8	58 ± 9	<0.0001
Male (%)	1226 (19)	486 (51)	<0.0001
Smoker (%)[a]	697 (11)	312 (33)	<0.0001
Drinker (%)[a]	1170 (18)	336 (35)	<0.0001
BMI (kg/m^2)	23 ± 3	25 ± 3	<0.0001
Clinical history			
Diabetes[b] (%)	885 (13)	206 (22)	<0.0001
Hypertension[c] (%)	3297 (50)	508 (53)	0.062
Blood pressure			
Systolic (mmHg)	134 ± 18	135 ± 18	0.071
Diastolic (mmHg)	79 ± 11	80 ± 11	0.001
Lipid profile			
Total cholesterol (mg/dL)	274 ± 23	277 ± 30	0.779
LDL-cholesterol (mg/dL)	186 ± 28	186 ± 33	0.658
HDL-cholesterol (mg/dL)	67 ± 18	35 ± 4	<0.0001
Triglyceride (mg/dL)[d]	107 (85–128)	272 (207–399)	<0.0001
Fatty acid composition			
EPA (mol%)	3.1 ± 1.6	2.5 ± 1.5	<0.0001

Data represent number of patients (%) or mean (standard deviation), unless otherwise indicated.
[a] Self-reported information.
[b] Physician-diagnosed diabetes or fasting plasma glucose ≥126 mg/dL or hemoglobin A_{1C} ≥6.5%.
[c] Physician-diagnosed hypertension or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.
[d] Median (interquartile range). LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride.

in the high TG/low HDL-C group, EPA as a proportion of total plasma fatty acids at registration was lower than that in the reference group (Table 1). EPA treatment lowered the risk for MCE for the high-risk high TG/low HDL-C group by 53% (HR: 0.47; 95% CI: 0.23–0.98; P = 0.043; Fig. 3). For the high-risk group, EPA did not affect TC, LDL-C or HDL-C, but in did reduce TG (P = 0.012; Table 2). In addition, the mean plasma EPA levels in the high TG/low HDL-C group for the control group were 2.3 mol% at registration and 2.5 mol% during the observation period, whereas for the EPA group, mean plasma EPA levels markedly increased from 2.6 mol% at registration to 4.5 mol% during the observation period (Table 2), and the high EPA concentrations remained throughout the observation period.

4. Discussion

LDL-C is an important risk factor for CAD, and statins have been shown to lower both LDL-C levels and risk for CAD [18,19]. Besides LDL-C, other risk factors such as obesity, dislipidemia, impaired glucose metabolism and hypertension also increase risk for CAD [9–14]. This study examined the effects of EPA in the primary prevention sub-

Table 2
Risk factors in the high TG/low HDL-C group at follow-up

	TG ≥150 mg/dL and HDL-C <40 mg/dL						P
	Control group (n = 475)			EPA group (n = 482)			
	Baseline	Observation period	Change from baseline (%)	Baseline	Observation period	Change from baseline (%)	
Blood pressure							
Systolic (mmHg)	136 ± 18	134 ± 14	0	134 ± 17	134 ± 14	0	0.700
Diastolic (mmHg)	81 ± 11	79 ± 9	−2	79 ± 10	78 ± 9	−1	0.159
Lipid profile							
Total cholesterol (mg/dL)	277 ± 29	229 ± 37	−17	276 ± 32	229 ± 35	−17	0.522
LDL-cholesterol (mg/dL)	185 ± 30	140 ± 35	−22	187 ± 35	142 ± 35	−20	0.129
HDL-cholesterol (mg/dL)	35 ± 4	42 ± 9	22	35 ± 4	42 ± 9	22	0.776
Triglyceride (mg/dL)[a]	277 (215–400)	218 (166–291)	−18	269 (201–399)	202 (150–271)	−23	0.012
Fatty acid composition							
EPA (mol%)	2.3 ± 1.3	2.5 ± 1.2	28	2.6 ± 1.6	4.5 ± 1.9	120	<0.0001

Data represent mean (standard deviation), unless otherwise indicated.
[a] Median (interquartile range). LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride.

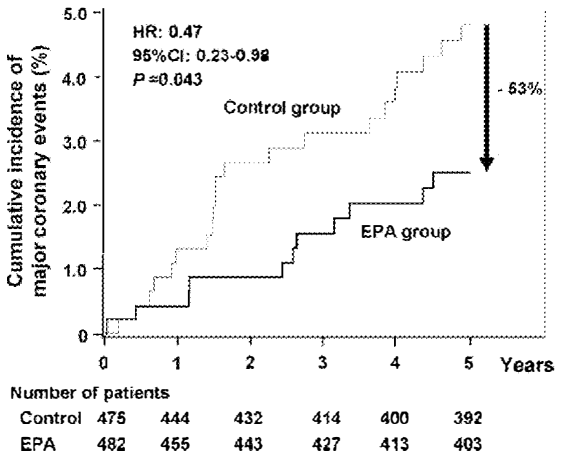


Fig. 3. Effects of EPA on the incidence of MCE for the high TG/low HDL-C group. Hazard ratio and *P* value adjusted for age, gender, smoking, diabetes, and hypertension. HR, hazard ratio; CI, confidence interval.

group of JELIS as a function of other CAD risk factors obesity; dislipidemia; diabetes; and hypertension. In both the control and EPA groups, greater number of risk factors was associated with increased incidence of MCE. This indicates that risk for MCE in the JELIS involved risk factors other than LDL-C. When dividing subjects with a number of risk accumulations among the 5 risk factors, incidence of MCE for the EPA group was lower than that for the control group for all subjects combined, regardless of the number of risk factors. But these differences were not statistically significant, most likely due to the low n in each subcategory.

EPA suppresses TG synthesis in the liver and thereby lowers serum TG levels and decreases atherogenic lipoproteins such as remnants and small dense LDL (sdLDL) [20]. Consequently, we compared MCE rates in the high TG/low HDL-C group to those in the low TG/high HDL-C reference group at the time of registration and found them to be increased by 71%. This shows that high TG/low HDL-C patients are at increased risk for MCE. Furthermore, within the high TG/low HDL-C group, EPA administration markedly reduced risk for MCE by 53%. When comparing patient background factors at the time of registration between these two groups, no significant differences in TC or LDL-C were seen, but the ratio of male patients, ratio of smokers and drinkers, BMI, incidence of diabetes and diastolic blood pressure for the high TG/low HDL-C group were all significantly higher. Thus, this group had many other features of the metabolic syndrome besides just high TG and low HDL-C. The present results also suggest that EPA is effective for suppressing onset of MCE in groups with multiple risk factors. Interestingly, plasma EPA level for the high TG/low HDL-C group at the time of registration was significantly lower when compared to the low TG/high HDL-C group. These results suggest some pre-existing baseline association between multiple risk factors and low plasma EPA levels, even in a Japanese population with high fish intake.

In the present study, EPA treatment had no effect on LDL-C in the high TG/low HDL-C group during the follow-up period, indicating that the lower MCE rates were the result of other effects of EPA than lowering LDL-C. EPA has many beneficial effects [21,22], including antiplatelet activity [23] and plaque-stabilizing properties [24,25], and thus these were likely responsible, at least in part, for the reductions in MCE.

While risk reduction in all primary prevention subjects of JELIS was 18% [8], risk reduction by 53% was achieved in high TG/low HDL-C group. This suggests that the factors that EPA appears to influence (plaque destabilization, rupture, and formation of occlusive thrombus) may be especially important mechanisms of MCE in patients with this form of dyslipidemia. EPA administration to the high TG/low HDL-C group slightly lowered TG and did not change in HDL-C. Although the effects of EPA on serum TG and HDL-C were limited, EPA markedly suppressed MCE in the high TG/low HDL-C group, and this suggests that EPA acts on mechanisms upstream of high TG/low HDL-C to suppress multiple risks.

Metabolic syndrome has been noted as a new risk factor for CAD [9,10]. Metabolic syndrome is characterized by accumulation of risk factors such as hypertension, dislipidemia and impaired glucose metabolism on the basis of visceral fat accumulation. In the present study, high TG and low HDL-C levels (the components of the metabolic syndrome) were shown to be important risk factors for MCE. EPA was most effective in the high TG/low HDL group in reducing incidence of MCE. Hence, this particular patient population may benefit the most from EPA treatment. Satoh et al. administered 1800 mg/day of EPA-E (the same dose as the JELIS) for 3 months to type II diabetics with the metabolic syndrome and reported that levels of sdLDL and remnant lipoproteins, which are risk factors for new cardiovascular events [26], decreased, and that levels of plasma C-reactive protein (CRP), a marker of inflammation that has been examined as a risk factor for cardiovascular events [27], also decreased [20]. In addition, Itoh et al. reported that the same regimen increased adiponectin [28], an adipocytokine known to improve arteriosclerosis [29] and diabetes [30].

The present results among JELIS primary prevention cases showed that multiple risk factors increase the risk of MCE. For the high TG/low HDL-C group, risk of MCE was particularly high, and EPA was shown to potently suppress MCE. In the high TG/low HDL-C group, level of plasma EPA at the time of registration was low, but EPA administration increased plasma levels, suggesting some correlation between plasma EPA level and MCE risk.

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