

Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS)[☆]

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ABSTRACT

Background: JELIS was a large-scale clinical trial that investigated the effects of eicosapentaenoic acid (EPA) on coronary artery disease (CAD). In this paper, the data of patients registered in JELIS were analysed to compare the incidence of CAD between patients with impaired glucose metabolism (IGM) and normoglycemic (NG) patients. The effect of EPA on the incidence of CAD in patients with IGM was also assessed.

Methods: The 18,645 hypercholesterolemic patients registered in JELIS were divided into two groups. One group consisted of patients with IGM ($n=4565$), which included the patients who had diabetes mellitus and patients who had a fasting plasma glucose of 110 mg/dL or higher, either at the time of registration or after 6 months. The other group consisted of NG patients ($n=14,080$). CAD incidence of the two groups over the average 4.6-year follow-up period was compared, and the effect of EPA was assessed.

Results: Compared to NG patients, IGM patients had a significantly higher CAD hazard ratio (1.71 in the non-EPA group and 1.63 in the EPA group). The treatment with EPA resulted in a 22% decrease in the CAD incidence ($P=0.048$) in IGM patients and an 18% decrease ($P=0.062$) in NG patients.

Conclusions: It was found that the CAD risk in IGM patients is higher than in NG patients, and that highly purified EPA is very effective in decreasing the incidence of CAD among Japanese IGM patients, even though the intake of fish is high.

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1. Introduction

Dyslipidemia is a major factor that is related to coronary artery disease (CAD) risk in diabetic patients [1]. Intervention studies of lipid management using HMG-CoA reductase inhibitors (statins) found that, on subgroup analysis of diabetic patients with dyslipi-

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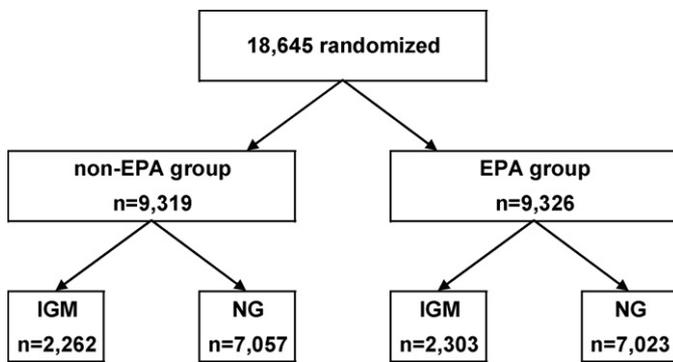


Fig. 1. Patient classification. IGM, impaired glucose metabolism; NG, normoglycemia. IGM criteria: (1) physician-diagnosed diabetes mellitus; (2) FPG \geq 110 mg/dL either at registration or after 6 month; (3) use of antidiabetic agents within the first year of investigation. The remainder were classified as NG (including 7443 participants with no FPG measurements).

demia, a decrease in LDL-C led to a reduction in their CAD risk [2–8]. The American Diabetes Association guidelines recommend that diabetic patients should have their lipid levels managed so that they reach target levels.

Recently, there have been several reports indicating that the intake of fish, fish oil and *n*-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduced the incidence of CAD [9–11].

The results of a 16-year follow-up survey involving more than 80,000 people showed that the CAD risk was lower in those who ate fish regularly and in those who consumed high quantities of *n*-3 fatty acids [10]. Cohort studies in Japan have also indicated that a high *n*-3 PUFA intake reduces the CAD risk [12]. However, no similar study has been done in patients with abnormal glucose metabolism (diabetic patients and those with abnormal serum glucose levels), who have been shown to have a CAD risk that is higher than non-diabetic patients.

Table 1
Patient background.

	NG (n = 14,080)		IGM (n = 4565)	
	Non-EPA (n = 7057)	EPA (n = 7023)	Non-EPA (n = 2262)	EPA (n = 2303)
Average age (year)	60	61	61 [†]	61 [†]
Male (%)	28	29	42 [†]	40 [†]
Smoker (%)	17	18	23 [†]	25 [†]
Drinker (%)	24	24	33 [†]	30 [†]
BMI \geq 25 (%)	34	33	42 [†]	45 [†]
Clinical history				
Coronary artery disease (%)	18	18	26 [†]	25 [†]
Hypertension (%)	33	33	43 [†]	43 [†]
Lipid profile				
Total cholesterol (mg/dL)	275 \pm 26	275 \pm 25	275 \pm 28	275 \pm 27
LDL-cholesterol (mg/dL)	182 \pm 29	182 \pm 30	180 \pm 29 [†]	180 \pm 29
HDL-cholesterol (mg/dL)	59 \pm 17	60 \pm 18	56 \pm 16 [†]	55 \pm 17 [†]
Triglyceride (median; mg/dL) ^a [25–75 percentile]	149 [107–211]	148 [105–207]	173 [124–252] [†]	175 [126–256] [†]
Fatty acid profile				
EPA (mol%)	2.7 \pm 1.5	2.9 \pm 1.6	2.8 \pm 1.6	2.9 \pm 1.6
Glucose metabolism				
FPG (mg/dL)	93 \pm 9	93 \pm 9	143 \pm 53 [†]	139 \pm 49 [†]
HbA _{1c} (%)	5.3 \pm 0.5	5.3 \pm 0.6	7.0 \pm 1.6 [†]	7.1 \pm 1.7 [†]
Blood pressure				
Systolic (mmHg)	135 \pm 18	135 \pm 18	139 \pm 19 [†]	139 \pm 19 [†]
Diastolic (mmHg)	80 \pm 11	79 \pm 11	80 \pm 11	80 \pm 11 [†]

Data are reported as percentage or mean \pm standard deviation, unless otherwise indicated. NG, normoglycemia; IGM, impaired glucose metabolism; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, fasting plasma glucose.

^a Median (interquartile range).

[†] $P < 0.05$ vs. NG.

[‡] $P < 0.01$ vs. NG.

A large-scale intervention clinical trial (Japan EPA Lipid Intervention Study: JELIS) that included hypercholesterolemic patients was done in Japan to study the effects of EPA, which was purified to >98%, as approved by the Ministry of Health, Labour and Welfare of Japan for use as a lipid-lowering agent. After an average of 4.6 years of follow-up of the 18,645 cases, including patients with a history of CAD, it was found that the incidence of CAD was reduced by 19% with EPA treatment [13]. Diabetic patients constituted 16% of the JELIS patients. The unadjusted hazard ratio for CAD by EPA treatment with or without diabetes were already indicated in the previous paper [13], and EPA treatment reduced the incidence of CAD in both absent and present diabetes groups, but it was not statistically significant in diabetic patients. Thus, in the present paper, the effects of EPA on the incidence of CAD in patients with impaired glucose metabolism, including diabetic patients and patients with hyperglycemia, were studied.

2. Subjects, materials and methods

2.1. Study design and patients

The JELIS trial design has been previously described in detail [14]. A Prospective Randomized Open-label Blinded-endpoint Evaluation (PROBE) method follow-up survey of hypercholesterolemic patients with a serum total cholesterol (TC) of 250 mg/dL or higher (males aged 40–75 years, and postmenopausal females aged up to 75 years) was conducted for a maximum of 5 years (average, 4.6 years). Using the central registration system, the cases registered in JELIS (18,645 cases) were divided randomly into two groups: one was treated with EPA (EPA group) and the other without EPA (non-EPA group). All of the patients were given dietary advice prior to and throughout the trial. All of the patients were prescribed pravastatin 10 mg or simvastatin 5 mg once daily. The patients in the EPA group were given capsules containing 300 mg of >98% pure EPA ethyl ester; they took 2 capsules orally 3 times daily, for a total

dose of 1800 mg. Data, including the serum lipid levels, the fasting plasma glucose (FPG) level, and the HbA_{1c} level, were assessed by accessing the patients' health care delivery organizations at the start of the trial, after 6 month, 12 month, and then annually. At the same time intervals, the levels of 24 plasma fatty acid fractions, including EPA, were measured by the central laboratory (BML Inc., Tokyo, Japan).

2.2. Primary endpoint

The primary endpoint was any major coronary events (MCE), including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, and coronary artery bypass grafting. The MCE reported by local physicians were verified by the endpoint committee in a group-blinded fashion.

2.3. Procedure

Patients were categorized into impaired glucose metabolism (IGM) and normoglycemia (NG) groups (Fig. 1). IGM criteria were shown as follows:

- (1) Physician-diagnosed diabetes mellitus.
- (2) FPG \geq 110 mg/dL, either at registration or after 6 month.
- (3) Patients using antidiabetic drugs (hypoglycemic agents, insulin, etc.) within the first year of investigation.

Patients who satisfied any of the above criteria were classified as IGM (non-EPA group, $n = 2262$; EPA group, $n = 2303$); the remainder were classified as NG (non-EPA group, $n = 7057$; EPA group, $n = 7023$).

The CAD risk of each of these groups was compared, and the effect of EPA on the incidence of CAD was investigated.

2.4. Statistical analysis

The power of sub-analysis was computed to be 58% under the assumption that EPA would suppress the incidence of major coronary events by 30% among the IGM patients.

A two-sided test was employed with a 5% level of significance. The Wilcoxon 2-sample test was used to compare continuous vari-

ables, and the chi-square test was used to compare categorical variables. Survival analysis was conducted using the Kaplan–Meier method, the log-rank test, and the Cox proportional hazards model. The Cox proportional hazards model was adjusted for age, gender, smoking, prior CAD, and hypertension. All analyses were performed using SAS statistical software (Version 8.12, SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Patient background

Age, ratio of males, smoking habit, drinking habit, BMI, CAD history, and hypertension were all significantly higher in IGM patients than in NG patients. It was also noted that high-density lipoprotein cholesterol (HDL-C) levels were lower, but triglyceride (TG), FPG, HbA_{1c}, and systolic blood pressure levels were significantly higher in IGM patients than in NG patients. No differences were found in TC and EPA levels at baseline between the IGM and NG patients (Table 1).

3.2. Effects of EPA on blood parameters and blood pressure

The effects of EPA on lipid profile, EPA concentration, glucose metabolism and blood pressure are shown in Table 2.

Plasma EPA concentrations were significantly higher in the EPA group than in the non-EPA group in both IGM and NG patients. Although EPA treatment produced statistically significant differences in TC and TG in both groups of patients and in HDL-C in the IGM group, none of these differences were likely to have been clinically significant.

3.3. MCE risk in IGM patients

IGM patients in the non-EPA group had a significantly higher MCE hazard ratio of 1.71 compared to NG patients (95% CI: 1.37–2.13; $P < 0.0001$). In the EPA group, IGM patients had a significantly higher MCE hazard ratio of 1.63 compared to NG patients (95% CI: 1.27–2.09; $P = 0.0001$).

Table 2

Effects of EPA on blood parameters and blood pressure.

	NG ($n = 14,080$)		IGM ($n = 4565$)	
	Non-EPA ($n = 7057$)	EPA ($n = 7023$)	Non-EPA ($n = 2262$)	EPA ($n = 2303$)
Lipid profile				
Total cholesterol (mg/dL)	228 \pm 29	226 \pm 29 [§]	224 \pm 31	223 \pm 34 [‡]
LDL-cholesterol (mg/dL)	138 \pm 28	137 \pm 29	133 \pm 29	134 \pm 32
HDL-cholesterol (mg/dL)	60 \pm 15	60 \pm 15	57 \pm 15	56 \pm 14 [†]
Triglyceride (median; mg/dL) ^a [25–75 percentile]	136 [103–183]	127 [95–171] [§]	153 [113–214]	143 [106–198] [§]
Fatty acid profile				
EPA (mol%)	2.8 \pm 1.3	5.3 \pm 2.2 [§]	2.9 \pm 1.4	5.3 \pm 2.2 [§]
Glucose metabolism				
FPG (mg/dL)	97 \pm 17	98 \pm 15	141 \pm 46	142 \pm 45
HbA _{1c} (%)	5.4 \pm 0.8	5.4 \pm 0.7	6.9 \pm 1.4	7.0 \pm 1.4
Blood pressure				
Systolic (mmHg)	133 \pm 13	133 \pm 13	136 \pm 14	136 \pm 15
Diastolic (mmHg)	78 \pm 8	78 \pm 8	78 \pm 8	78 \pm 9

Data are reported as percentage or mean \pm standard deviation, unless otherwise indicated. NG, normoglycemia; IGM, impaired glucose metabolism; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FPG, fasting plasma glucose.

^a Median (interquartile range).

[†] $P < 0.05$ vs. non-EPA.

[§] $P < 0.01$ vs. non-EPA.

	non-EPA		EPA		HR	95%CI	0	1	2	P
	Number of events (%)									
NG	185	7,057 (2.6%)	153	7,023 (2.2%)	0.82	0.66 - 1.01				0.062
IGM	139	2,262 (6.1%)	109	2,303 (4.7%)	0.78	0.60 - 0.998				0.048

Favours EPA Favours non-EPA

Interaction P=0.689

Fig. 2. Suppressive effects of EPA on MCE. NG, normoglycemia; IGM, impaired glucose metabolism; MCE, major coronary event; HR, hazard ratio; CI, confidence interval. HR and P value adjusted for age, gender, smoking, prior coronary artery disease, and hypertension.

3.4. Suppressive effect of EPA on MCE

As shown in Fig. 2, the EPA-treated NG patients had an MCE hazard ratio of 0.82 compared to the non-EPA-treated NG patients, but this difference was not significant (95% CI: 0.66–1.01; $P=0.062$). The EPA-treated IGM patients had a significantly lower MCE hazard ratio of 0.78 compared to the non-EPA-treated IGM patients (95% CI: 0.60–0.998; $P=0.048$); this demonstrates that EPA significantly suppressed MCE. The suppressive effects of EPA on MCE were not difference between NG and IGM (interaction $P=0.689$). The number needed to treat (NNT) for the suppression of MCE by EPA was 71 for IGM.

The Kaplan–Meier curves of MCE suppression by EPA in the NG and IGM patients are shown in Fig. 3.

4. Discussion

In the present sub-analysis, we found that IGM patients were at an increased risk for CAD compared to NG patients, and that this risk in IGM patients was reduced by EPA treatment. Recent epidemiological research has shown that patients with diabetes mellitus or individuals with a higher level of blood glucose have a high incidence of atherosclerotic diseases. The present study, which analysed the 4565 IGM patients included among the 18,645 cases enrolled in JELIS, also found an increased CAD risk in IGM patients compared to NG patients that was 1.7 times in non-EPA group and 1.6 times in EPA group.

Cohort studies such as the Framingham Study [15] and the Hisayama Study [16] have also reported that diabetic patients have a two to three times increased CAD risk. These indicate the need to actively prevent and treat patients who have abnormal glucose

metabolism. JELIS was an interventional study that assessed the use of highly purified EPA. The study protocol required that all patients be prescribed a statin. As a result, during the course of the study, LDL-C levels decreased from a baseline of 180 mg/dL to 137–138 mg/dL in NG patients and from a baseline of 180 mg/dL to 133–134 mg/dL in IGM patients, but an increased CAD risk have been remained in IGM patients. J-LIT, a large-scale study performed in Japan, has also reported that the CAD risk was significantly higher in diabetic patients than in non-diabetic patients, even if they received statin treatment [6]. These studies found an increased CAD risk in diabetic patients even though statin therapy reduced the LDL-C level by about 28%. The results of the present study concur with these results. The present analysis clarified that an abnormal glucose metabolism is a CAD risk factor that is independent of the LDL-C level.

In IGM patients, EPA significantly decreased the CAD risk by 22% compared to those not treated with EPA. On the other hand, the present analysis found no significant difference in FPG and HbA_{1c} levels during the treatment period between the non-EPA group and the EPA group in IGM patients. From these results, it is demonstrated that EPA significantly decreased the incidence of CAD in FPG and HbA_{1c} independent manner, indicating that the IGM population is an appropriate target for EPA treatment. The calculated NNT was 71, which was not so small.

A recent study of the effect of EPA in type-2 diabetic patients over an average follow-up of 2.1 years, which used carotid intima-media thickness (IMT) as an indicator of arteriosclerosis, found no change in lipid levels or serum glucose-related factors, but did find an improvement in the IMT [17].

Furthermore, in a 3-month study in patients with both type 2 diabetes and metabolic syndrome, EPA had no effect on LDL-C, HDL-C, or TG levels, but significantly reduced small dense LDL (sdLDL) [18]. This may indicate that EPA affects on the quality of serum lipid without affecting on lipid levels. It is well known that EPA has anti-inflammatory [19] and other beneficial effects, such as reduction of platelet aggregation [20], inhibition of cell proliferation [21], stabilisation of plaque [22,23]. These effects of EPA on atherosclerotic tissue may also contribute to decreasing the incidence of MCE in IGM patients.

Advances in molecular biology have led to the identification of molecules target of EPA, such as resolvin E1 for anti-inflammation [24] and SREBP-1c, whose inhibition ameliorates lipid metabolism disorder [25,26]. Further investigation will be needed to clarify the molecular mechanisms responsible for disrupted glucose and lipid metabolism in the pathogenesis of CAD in IGM patients.

The IGM patients studied in the present sub-analysis had abnormalities in indicators expected to improve with EPA, such as elevated TG, increased platelet activity, and decreased insulin sensitivity, which is a background factor for IGM. Therefore, EPA prescription to IGM patients can be considered rational [27].

The EPA concentration among Japanese individuals, given as the EPA concentration in the non-EPA-treated IGM patients, was 2.9 mol%, which was approximately 10-fold higher than that of white Americans [28]. In conclusion, EPA is very effective in

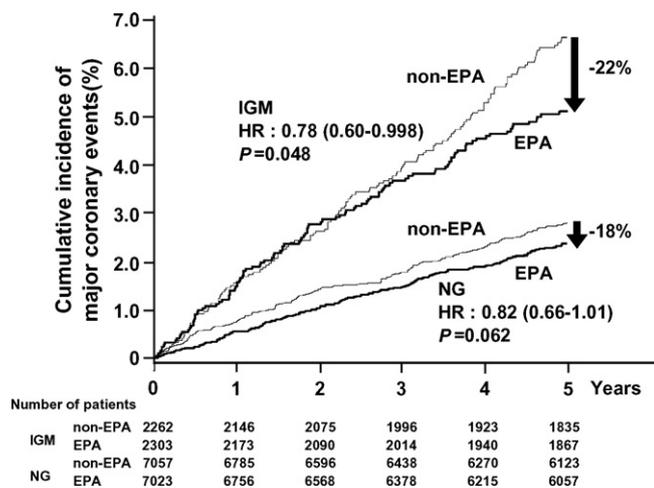


Fig. 3. Suppressive effects of EPA on MCE (Kaplan–Meier curves). NG, normoglycemia; IGM, impaired glucose metabolism; MCE, major coronary event; HR, hazard ratio; CI, confidence interval. HR and P value adjusted for age, gender, smoking, prior coronary artery disease, and hypertension.

decreasing the incidence of CAD among Japanese IGM patients, even though the intake of fish is high.

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